The Effects of Sleep Deprivation on Pain Inhibition and Spontaneous Pain in Women

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Impaired central pain modulation is implicated in the pathophysiology of chronic pain. In this controlled experiment, we evaluated whether partial sleep loss altered endogenous pain inhibition and reports of spontaneous pain. Thirty-two healthy females were studied polysomnographically for 7 nights. On Nights 1-2 (Baseline), subjects slept undisturbed for 8 hours. After Night 2, subjects were randomized to Control (N = 12), Forced Awakening (FA, N = 10), or Restricted Sleep Opportunity (RSO, N = 10) conditions. Controls continued to sleep undisturbed. FA underwent 8 forced awakenings (one per hour) on Nights 3-5. RSO subjects were yoked to FA on total sleep time (TST), receiving partial sleep deprivation by delayed bedtime. On Night 6, both FA & RSO underwent 36 hours total sleep deprivation (TSD), followed by 11-hour recovery sleep (Night 7). Subjects completed twice-daily psychophysical assessments of mechanical pain thresholds and pain inhibition (Diffuse Noxious Inhibitory Controls), via use of a conditioning stimulus (i.e., cold pressor) paradigm. FA and RSO demonstrated 50% reductions in total sleep time and increases in non-painful somatic symptoms during partial sleep deprivation. While sleep deprivation had no effect on pain thresholds, during partial sleep deprivation the FA group demonstrated a significant loss of pain inhibition and an increase in spontaneous pain; neither of the other 2 groups showed changes in pain inhibition or spontaneous pain during partial sleep deprivation. These data suggest that sleep continuity disturbance, but not simple sleep restriction, impairs endogenous pain-inhibitory function and increases spontaneous pain, supporting a possible pathophysiologic role of sleep disturbance in chronic pain.

Keywords: Sleep, pain, sleep deprivation, pain inhibition, insomnia, diffuse noxious inhibitory controls

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INTRODUCTION

INSOMNIA AND SLEEP LOSS ARE NEARLY UBIQUITOUS FEATURES OF MANY CHRONIC PAIN DISORDERS.[1] PROLONGED MIDDLE OF THE NIGHT AWAKENINGS ARE particularly common complaints reported by pain patients.[2] Polysomnographic (PSG) studies have confirmed that chronic pain is associated with poor sleep continuity and reduced total sleep time.[3] Several PSG studies have also found alterations in sleep architecture.[4,5] Both chronic pain and insomnia have increased incidence in late life, differentially affect women,[6,7] and are increasingly conceptualized as neurologic diseases.[8,9] With respect to chronic pain, there is substantial evidence that dysregulation of supraspinal mechanisms, which facilitate and/or inhibit afferent nociceptive transmission, may drive a state of central sensitization that contributes to amplified and prolonged pain states.[10]

Longitudinal research and preliminary experimental work suggest that while disturbed sleep is a consequence of pain, sleep disruption might also contribute directly to hyperalgesia.[11] Classic uncontrolled studies, for example, have reported that selective slow wave sleep deprivation decreases mechanical pain thresholds.[12,13] Recently, a well-controlled study found that REM sleep deprivation increased thermal pain sensitivity.[14] Other studies of selective sleep stage deprivation, however, have reported minimal effects on pain thresholds.[15-17] With respect to total sleep deprivation, 2 investigations have found evidence of deprivation-induced hyperalgesia,[17,18] while another study reported a negative finding.[19]

Although these studies support the possibility that sleep deprivation directly influences pain and thereby exacerbates or increases risk for chronic pain, the data are not unequivocal. Most of the studies are limited by small sample sizes (total sample sizes range from 6-20) and a lack of control groups. Furthermore, most relied on either selective sleep stage deprivation paradigms that do not reduce total sleep time, or on total sleep deprivation. While these designs provide important information, more recent approaches have highlighted the need to model partial sleep deprivation induced by prolonged nightly awakenings.[14] Chronic pain syndromes often involve multiple forms of sleep disruption, including bouts of prolonged wakefulness that require study. Prior work has not explored possible mechanisms of sleep disturbance - hyperalgesia. It is unknown whether sleep deprivation alters measures of central pain processing, i.e., descending pain facilitatory or inhibitory processes; this information would elucidate possible mechanisms of sleep disturbance-induced hyperalgesia. For example, it is unclear whether any form of sleep deprivation impairs endogenous pain-inhibitory processes, which play an important role in shaping responses to noxious stimuli and in potentially preventing the development of persistent pain conditions.[8] Sleep deprivation, is known, however, to degrade performance on cognitive tasks of executive function that rely on inhibiting irrelevant responses,[20] suggesting a potential disinhibiting effect of sleep deprivation.

One well-studied pain-inhibitory process with demonstrated clinical relevance is Diffuse Noxious Inhibitory Controls (DNIC). DNIC is a phenomenon in which one noxious stimulus inhibits the perception of pain produced by a second noxious stimulus ap-

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plied to a distant anatomic site.[21] DNIC effects are demonstrated by assessing responses to a phasic noxious stimulus before and then during application of a tonic noxious stimulus; the tonic noxious stimulus is applied to an anatomic site innervated by a different dermatome than the phasic stimulus. A normal pain inhibitory effect is demonstrated as a significant decrease in pain sensitivity from baseline (typically a 20%-30% increase in pain threshold) at the phasic site during and immediately after application of the tonic stimulus.

Animal and some human research using morphine and naloxone challenges have shown that DNIC and similar descending pain inhibitory processes may depend on endogenous opioid-mediated supraspinal mechanisms that inhibit nociception at the spinal level.[22-24] Impaired DNIC has been demonstrated in numerous chronic pain disorders with high rates of comorbid sleep disturbance including: fibromyalgia,[24-26] tempormandibular joint disorder,[27] back pain,[28] irritable bowel syndrome,[29] and chronic tension headache.[30]

In this experiment, we extend the literature linking sleep deprivation and hyperalgesia by: 1) evaluating for the first time whether sleep continuity disturbance and associated sleep loss impairs DNIC, and 2) determining whether partial sleep deprivation is associated with increased reports of spontaneous clinical pain, which would be predicted by a loss of efficacy of endogenous pain-inhibitory systems.[31] Because of the exploratory nature of the study aims, we sought to reduce error variance and establish an effect of sleep deprivation on a well-controlled, homogeneous sample. We therefore restricted this initial investigation to healthy females, because female sex is consistently associated with both pain sensitivity and higher rates of chronic pain.[32] Planned follow-up studies with males are ongoing.

METHODS

Subjects: Inclusion/Exclusion Criteria

Healthy, adult, female good sleepers, free from medical or psychiatric illnesses were eligible. Screening involved completing a medical history, physical exam, and laboratory blood testing (including complete blood count and toxicology testing for recreational drugs, stimulants, opioids, benzodiazepines, etc.). To be eligible, subjects were required to be nonsmokers/non-nicotine users and low caffeine users (≤2 cups of coffee or equivalent /day). Additional good sleeper inclusion requirements were: 1) a Pittsburgh Sleep Quality Index Total Score[33] <five; 2) a usual sleep latency and wake after sleep onset time ≤15 minutes; 3) a stable preferred sleep phase within 22:00 and 08:00; 3) usual total sleep time between 7 and 8.5 hours/night. These criteria were confirmed via averages of 2 weeks of sleep diary and actigraphy monitoring. Exclusion criteria were: 1) significant medical/psychiatric history within the past 6 months, or lifetime history of Raynaud syndrome, bipolar disorder, psychotic disorder, or recurrent major depression; 2) life time history of alcohol or substance abuse problem; 3) use of antidepressant medications within 6 months; 4) significant symptoms of psychological distress (T-scores >64 on the Brief Symptom Inventory[34]); 5) history of chronic pain disorder (lifetime history of persistent pain for ≥6 months); 6) acute pain (measured via the McGill Pain Questionnaire and via 2-week baseline diaries); 7) current or lifetime history of sleep disorders; 8) current daytime sleepiness (Epworth Sleepiness Scale[35] ≥10); 9) history of head injury with loss of consciousness; 10) abnormal or positive blood chemistries, including a positive pregnancy test. The protocol was approved by the institutional review board and all subjects completed informed consent prior to participation.

Screening Measures

Medical/Psychiatric History Form

This 51-item form was developed by the authors to elicit general health history information, including menstrual cycle information and hormonal contraception usage.

The Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a widely used, well-validated 19-item measure of sleep quality.[33]

Epworth Sleepiness Scale (ESS)

The ESS is an 8-item index that measures the likelihood of falling asleep in certain situations, such as sitting and reading, etc.[35]

PRIME-MD-PHQ

This is a patient questionnaire for use in medical settings to diagnose common DSM-IV psychiatric disorders. It demonstrates good accuracy, sensitivity, and specificity compared to mental health expert interviews.[36]

The Brief Symptom Inventory (BSI)

The BSI is a well-normed, 53-item, self-report measure of multiple dimensions of psychological symptoms that generates 8 subscales.[34] This well-validated measure also yields 3 global scales indexing overall psychological distress. The BSI was used to screen out individuals reporting significant psychological distress relative to norms for healthy adults on all 11 scales.

McGill Pain Questionnaire-Short Form (MPQ-SF)37

The MPQ-SF assesses the multidimensional nature of pain and has been demonstrated to be reliable and valid. Any positive responses to any of the items were followed up to determine whether the patient had an acute pain condition, which would render them ineligible to participate in the study.

Wrist Actigraphy

Mini Mitter Actiwatch-Score actigraphs were worn during the screening phases of the study to provide an index of pre-experimental sleep parameters and circadian rhythm.[38] They were worn during the experimental phase to supplement nursing observation, verifying that subjects did not nap.

Sleep and Pain Diaries

During the 2-week screening phase and on all 7 mornings following each study night, subjects completed a sleep and pain diary to assess subjective impressions of sleep.[39] The diary has

an evening section that is completed before going to bed that includes data on daytime pain, napping, use of analgesics, contraception, menstruation, and use of centrally acting substances such as stimulants.

Nocturnal Polysomnography (PSG)

PSGs were performed on all 7 experimental nights at the Johns Hopkins Bayview Medical Center-GCRC Sleep Research Core facilities, according to standard PSG procedures.[40] Subjects slept in a private room designed for sleep studies. The montage included the following: 1) 4 EEG channels (C4-A1, C3-A2, O1-A2, O2-A1); 2) right and left electro-oculograms (EOGs); 3) three bipolar EMGs (submental, and right and left anterior tibialis muscles; 4) respiratory monitoring via pulse oximetry, thermister, and cannula measures of oral and nasal airflow, and abdominal and thoracic strain gauges measuring respiratory effort; and 5) a standard EKG montage. Electrodes were affixed shortly after evening pain testing procedures. PSG records from all nights were scored according to standard procedures,[40] by 2 independent raters (one board-certified in Sleep Medicine) who were unaware of study aims, formal group assignment, or study night. Clinical polysomnographic indices as defined in the International Classification of Sleep Disorders-Revised (ICSD-R)[41] were scored on the first night to rule out subjects with occult intrinsic sleep disorders, such as sleep apnea, etc.

Outcome Measures

Laboratory Pain Assessment

On the evening prior to their first study night, subjects were familiarized with the pain testing equipment and task instructions, followed by practice trials of the procedures (data not recorded). Participants subsequently underwent assessment of responses to noxious stimuli twice per day during the 8 day study period: one session was completed each morning, approximately 30 minutes after awakening, and one administered in the late afternoon, between 16:00 and 17:00. Testing was performed by technicians who were required to maintain and periodically (monthly) demonstrate adequate inter-tester reliability (i.e., pressure pain threshold values were required to be within 1 lbs/cm^2 on at least 80% of reliability trials).

Each pain testing session included the sequential assessment of pressure pain threshold (PPTh), thermal sensitivity, and pain inhibition (DNIC). The order of pressure and thermal testing procedures were randomized. The DNIC test was conducted last due to potentially prolonged pain sensations stimulated by the cold pressor task. Baseline data reporting on the thermal procedures are described elsewhere.[42] In an effort to maintain a focused scope on the effects of sleep deprivation on pain-inhibitory capacity, we report on novel results for pressure pain threshold and DNIC only.

Pressure Pain Threshold (PPTh)

A Somedic algometer was used to assess PPTh similar to previous studies.[25] The algometer's 1-cm^2 rubber probe was placed over the muscle belly; the pressure then increased steadily at a constant rate (30kPA/Sec) until the subject indicated that she "first felt pain." PPTh was assessed 2 times each at the following 3 body sites, bilaterally, in a randomized order: trapezius muscle, masseter muscle, and the proximal third of the brachioradialis muscle (forearm). At least 30 s were maintained between successive stimuli. To formally evaluate test-retest reliability of our algometric procedures, we calculated standard reliability estimates between morning and evening testing for all subjects on Day 3. Both Chronbach's alpha (r = 0.92) and Spearman-Brown (r = 0.91) coefficients indicated adequate reliability. To further evaluate stability over time, we calculated Cronbach's alpha, Spearman-Brown coefficients and Gutman Split-Half reliability coefficients for morning and evening ratings in the control group over the entire 7-day experiment. All coefficients ranged between 0.87 and 0.92, indicating good test-retest reliability.

Diffuse Noxious Inhibitory Controls (DNIC)

DNIC is a noninvasive test of endogenous pain-inhibitory systems that involves the simultaneous application of 2 types of noxious stimuli (tonic and phasic) to distant anatomic regions.[8,43] Baseline PPTh was reassessed on the right brachioradialis or right trapezius in a random order. Immediately following this "baseline" assessment, participants underwent a cold pressor task, similar to previous DNIC studies.[44,45] During each cold pressor task, each participant immersed her contralateral hand (left) up to the wrist in a circulating ice water bath maintained at 4°C. Twenty seconds after commencing hand immersion, PPTh was reassessed on either the right brachioradialis or right trapezius (same site as baseline assessment). During each morning or afternoon pain testing session, a total of 4 DNIC tasks were performed: 2 trials at each anatomical site (right trapezius and right forearm). Two-min intervals were maintained between each cold pressor task. The instructions for the procedure directed each participant to keep her left hand in the water for the duration of the PPTh assessment. DNIC was measured as the percent change in PPTh during the cold pressor tasks relative to baseline PPTh. An increase in PPTh during cold pressor reflects normal functioning of pain-inhibitory processes.

Pennebaker Inventory of Limbic Languidness (PILL)

The PILL is 54-item questionnaire, which measures a variety of somatic and frankly painful symptoms.[46] It has high internal consistency (alpha = 0.88), adequate test-retest reliability (0.70), and has been found to distinguish fibromyalgia patients from pain-free controls.[47] This measure was selected and adapted for use in this study, both for its clinical relevance and because it provides an exceptionally broad scope of possible symptoms. We modified the time frame so that patients completed the questionnaire each night and rated the presence of symptoms over the course of the day. The PILL instructs subjects to indicate the degree to which a symptom was experienced on 5-point Likert scale ("0- not at all," "1-a little," "2- somewhat," "3- moderately," and "4- very much"). Similar to other investigators, we examined items reflecting frankly painful symptoms separately from nonpainful somatic items.[48] A painful somatic symptoms scale was used in the analyses, which was composed of the sum of 10 items (back pains, headaches, chest pains, cramps, toothaches, heartburn, severe pains or cramps in the stomach, joint pain, sore muscles, and sore throat). A nonpainful somatic symptoms scale was similarly calculated based on the remaining 44 items (e.g., severe itching, nausea, vision problems, twitching).

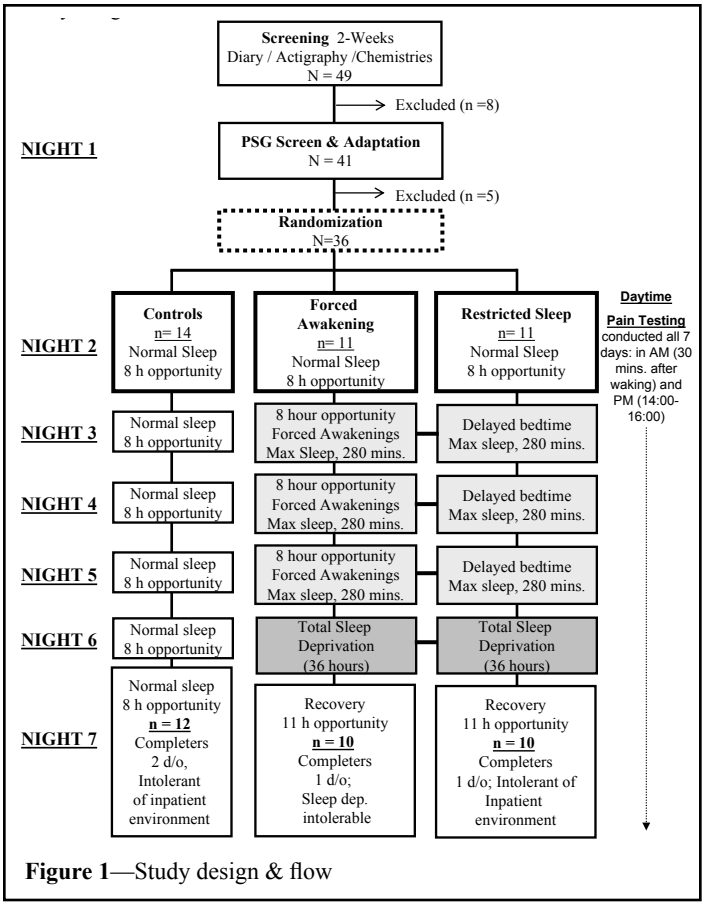

Figure 1—Study design & flow

Stanford Sleepiness Scale (SSS)

The SSS[49] is a widely used, 7-item measure, designed to evaluate subjective changes in sleepiness using a 7-point scale. Items range from (1) "Feeling active, vital, alert, or wide awake" to (7) "No longer fighting sleep, sleep onset soon; having dream-like thoughts."

Experimental Design and Procedures

Figure 1 schematically represents the study design. After completing the 2-week screening period, during which subjects were not permitted to take centrally acting agents such as sympathomimetics or caffeine, subjects were admitted to the clinical research unit for 7 consecutive nights. **Night 1** served to adapt subjects to the polysomnographic procedures, familiarize and train subjects on the pain testing protocol, and rule out individuals with sleep disorders. **Night 2** served as a baseline night; all subjects were provided an 8-hour opportunity to sleep undisturbed. After Night 2, subjects were randomly assigned in blocks of 3 to one of three groups: Control, Forced Awakening (FA), or Restricted Sleep Opportunity (RSO), such that either an RSO or Control Subject always followed an FA subject.

Controls

Subjects continued to sleep undisturbed with an 8-hour sleep opportunity for the remaining 5 nights.

Forced Awakening Condition

Subjects underwent 3 consecutive nights (3-5) of partial sleep deprivation via a forced awakening protocol. The night was divided into 8 one-hour intervals. One of the hour long intervals was randomly determined as a 60-minute forced awaking, during which no sleep was permitted. The remaining seven 60-minute intervals were subdivided into thirds (20-minute intervals). One 20-minute block in each of these 7 remaining intervals, was randomly determined to be a 20-minute forced awakening, during which subjects were not permitted to sleep. During assigned forced awaking periods, nursing staff awakened subjects and kept them awake for the entire interval. Subjects were asked to sit up in bed to reduce the chance of microsleep. Polysomnographic monitoring was maintained for the entire sleep period. Given the 8 forced awakenings implemented during the night (seven 20-minute awakenings and one 60-minute awakening), the maximum total sleep time possible (if the subject slept 100% of the time when not forced to be awake) was 280 minutes. After the 3 nights of partial sleep deprivation, subjects then remained awake for a 36-hour **Total Sleep Deprivation Period (Night 6).** After completing afternoon pain testing on Day 7, subjects were then permitted an 11-hour recovery sleep, during which they slept undisturbed. After recovery sleep (Day 8), subjects completed morning pain testing procedures and were permitted to leave the unit. Subjects continued to wear actigraphs and returned to the unit for the final afternoon pain testing session on Day 8. Subjects were not permitted to the leave the inpatient unit during sleep deprivation periods and were under continuous nursing supervision/monitoring (day and night) to prevent naps and ensure safety.

Restricted Sleep Condition (RSO)

This condition served as a comparison condition, permitting the evaluation of whether sleep loss via disrupted sleep continuity affects pain sensitivity beyond simple sleep loss. During Nights 3-5, subjects assigned to the RSO condition had total sleep opportunity restricted and yoked to the amount of total sleep time achieved by a subject in the FA group. This was accomplished by delaying the RSO subject's bedtime and keeping a fixed wake time. For example, if an FA subject achieved 210 minutes of total sleep time on Night 3, the yoked RSO subject would be provided a 210-minute opportunity for undisturbed sleep (bedtime 03:30, wake time 07:00) on Night 3. Subjects in the RSO condition were monitored polysomnographically for an entire 8-hour period to precisely verify that the subjects did not sleep prior to the designated lights-out time. The aim was to closely match the 2 groups on total sleep time and achieve a condition in which one group had disrupted sleep continuity (FA), while the RSO group had consolidated sleep. Like FA subjects, RSO subjects underwent 36 hours of total sleep deprivation after the 3 partial deprivation nights, followed by the 11-hour recovery period sleep period (Night7).

Because no prior work has sought to evaluate whether any form of sleep deprivation alters pain inhibition, we included one night of total sleep deprivation at the end of the 2 partial deprivation conditions in order to maximize the possibility of identifying an effect of sleep deprivation on DNIC. While the design adopted for this purpose is efficient, in light of the exploratory nature of the hypotheses, it should be noted that it limited our ability to understand the independent effects of total sleep deprivation and subsequent recovery sleep on DNIC, because these conditions are confounded by the prior effects of the partial sleep deprivation. Positive findings on DNIC and the profile of DNIC during total

sleep deprivation, will guide future designs to determine the utility of treating total sleep deprivation as a stand alone condition.

Statistical Analyses

In order to consolidate the number of analyses, baseline pain response data (Day 3) were first analyzed to determine whether there was an effect of time of day on pain threshold or the DNIC Index. Paired sample *t*-tests revealed no time of day effects (P>0.05, 2-tailed), therefore the data were averaged across time of day. To further to reduce Type I error rate and provide a more stable estimate of pain responsivity, PPTh data were averaged across the 3 body sites, and over the left and right sides. Thus, an individual's PPTh on a given day reflects a mean of 24 values (3 sites x 2 sides x 2 trials x 2 times of day). PPTh values are presented as lbs/cm^2.

A DNIC Index was calculated as the average percentage change in PPTh during the cold pressor task within the testing session (i.e., [mean PPTh for the trapezius and forearm during the cold pressor task / mean PPTh for the trapezius and forearm prior to cold pressor] *100). Because there was no time of day effect or difference in DNIC effect by anatomic site, morning and afternoon values and anatomic sites were averaged. Thus, an overall DNIC score for each day reflected a total of 8 trials (2 body sites (trapezius and bronchioradialis), each assessed twice during 2 testing sessions (morning and afternoon). DNIC index scores that are greater than 100 reflect increases in PPTh during the cold pressor task and represent an expected pain-inhibitory effect. For example, an index of 120, a typical score for healthy subjects, reflects a 20% increase in PPTh during the cold pressure task.

To determine potential covariates for the longitudinal analyses, we conducted preliminary analyses assessing baseline group differences on relevant pain-related variables, polysomnographic parameters (total sleep time), and demographic characteristics (age, BMI, race, menstrual phase [estimated via diary], and use of oral contraceptives), using analysis of variance (ANOVA) with follow-up comparisons for continuous variables or chi-square tests for categorical variables.

We undertook longitudinal analyses to determine whether pain responses and somatic symptoms changed over time as a function of condition. We conducted 4 mixed factorial ANCOVAs/ANOVAs, with Group (3 levels: Control, Restricted Sleep, Forced Awakening) as the between-subjects factor, and Day (6 levels: Day 3 [baseline] through Day 8 [recovery]) as the within-subjects factor. The 4 dependent measures used in the mixed models were PPTh, DNIC index, spontaneous painful somatic symptoms on the PILL, and PILL spontaneous nonpainful somatic symptoms. As depicted in Table 1, all 3 groups showed a significant and comparable DNIC effect on Day 3 (21.4% overall increase in PPTh during cold pressor). Because the groups did not differ on

Table 1—Comparison of groups at baseline: clinical, sleep, and pain testing parameters (N=32)

Variable	Controls n = 12		Restricted Sleep n = 10		Forced Awakening n = 10		P[a]
Age	25.3 ± 6.2		26. 5 ± 4.7		24.2 ± 3.9		0.61
Body mass index	22.3 ± 5.2		22.9 ± 3.2		23.1 ± 2.8		0.88
% on oral contraceptives	41.7%		30.0%		40.0%		0.84
Polysomnographic Sleep (Night 2)	**% Sleep**	**Minutes**	**% Sleep**	**Minutes**	**% Sleep**	**Minutes**	
NREM Stage 1	1.7±1.2	7.8±5.4	2.1±2.0	9.5±8.5	2.5±1.8	11.2±8.0	0.56/0.56
NREM Stage 2	60.6±7.3	282.3±34.5	61.0±6.8	280.2±38.7	61.2±6.8	283.0±30.8	0.98/0.98
NREM Stage 3/4	17.1±4.0	79.6±18.7	15.2±8.7	69.9±40.2	14.5±6.8	68.2±32.9	0.65/0.65
Stage REM	20.6±4.2	96.2±20.1	21.8±4.0	98.8±18.6	21.8±3.9	100.5±15.6	0.75/0.84
Sleep Latency (Min.)	6.7±3.4		9.1±4.9		10.9±13.3		0.46
Wake After Sleep Onset (Min.)	8.2±8.3		10.0±11.7		10.2±8.7		0.86
Total Sleep Time (Min.)	465.9±13.4		459.8±14.5		462.9±21.1		0.69
Sleep Efficiency[b]	97.0%±2.2		95.8%±2.4		95.8%±3.1		0.45
Lab Pain Testing (Day 3)							
Pressure Pain Threshold[c] (PPTh), lbs/cm^2	5.9±1.7		5.6 ± 1.5		5.9 ± 2.0		0.89
Pain Inhibition (DNIC)							
PPTh prior Cold Pressor[d]	7.5 ± 2.6		7.2 ± 1.9		6.6 ± 2.3		0.62
PPTh with Cold Pressor[d]	8.8 ±3.2		8.5 ±2.9		8.5 ±4.5		0.98
Cold Pressor Pain Rating (Mean, 0 to 100)	69.9 ±25.8		78.3 ±16.2		69.0 ±21.7		0.58
DNIC Index[e]	117.3 ± 15.4[f]		118.1 ± 13.5[f]		128.8 ± 32.3[f]		0.43

[a] One-way ANOVA, P value
± = standard deviation
[b] Total Sleep Time / Time in Bed * 100
[c] PPTh, lbs/cm^2. Mean for all body sites, bilaterally, i.e., masseter, trapezius, bronchioradialis
[d] mean threshold for body sites assessed during DNIC procedure, i.e. right trapezius & bronchioradialis
[e] = DNIC Index (Diffuse Noxious Inhibitory Controls) = PPTh during Cold Pressor / PPTh prior to cold Pressor *100
[f] Significant DNIC Effect (Increase in PPTh during cold pressor) determined by comparing the observed DNIC Index against a DNIC Index = 100 (no DNIC), 1 sample t-test, P<0.001 for the entire sample, P< 0.03 for each group analyzed individually

PPTh or DNIC prior to sleep deprivation (Table 1), and consistent with prior data analysis for longitudinal studies of changes in pain sensitivity,[17] we normalized PPTh and DNIC data using baseline scores (i.e., the value for each subsequent day was divided by the DNIC Index for Day 3) to facilitate interpretation of change over time. Group-level data for PPTh and DNIC thus are presented as the percentage change in the DNIC index from Day 3, i.e., ([% increase in PPTh during cold pressor on Day X] – [% increase in PPTh during cold pressor on Day 3] / (% increase in PPTh during cold pressor on Day 3). For example, a group mean of -78 for DNIC on Day 5 of the study indicates that DNIC decreased by 78% of the baseline value.

In order to characterize significant omnibus effects (see the Results section), follow-up tests to determine the nature of group differences in DNIC were performed in 2 ways. First, planned contrasts (i.e., using ANOVAs) were performed in which the FA group was compared to the other 2 groups following partial sleep deprivation, and the Control group was compared to the 2 sleep deprivation groups following the nights of total sleep deprivation and recovery sleep. Second, we determined whether statistically significant DNIC effects were present on each day by performing 1-sample *t*-tests, comparing whether the observed unnormalized DNIC index value for that day was significantly greater than 100 (e.g., a score of 100 indicates no DNIC effect, in that PPTh during the cold pressor is identical to the PPTh value prior to cold pressor). Together, this set of analyses permitted examination of how DNIC changed as a function of specific sleep manipulations, and assessment of whether DNIC was abolished by any of the sleep manipulations as hypothesized. Given the exploratory nature of this work, we followed the suggestion of Nakagawa et al [50] and did not conduct corrections for multiple comparisons. Nakagawa et al argue that Type II error hinders the development of novel hypotheses.

RESULTS

As shown in Figure 1, 36 subjects were randomized to Control (C;n = 14), Forced Awakening (FA; n = 11) and Restricted Sleep Opportunity (RSO; n = 11) conditions. Four subjects dropped out prior to completing all 7 nights (2 controls, 1 FA, and 1 RSO). Data from the 32 subjects who completed the testing were retained for subsequent analyses. Mean age of the completers was 25.34 (SD = 5.03. min = 18, max = 36). Ninety-four percent were single (n=30). Self-described racial composition was as follows: 53% Caucasian (n=17), 25% African American (n = 8), 15% Asian American (n = 5), 9% Latina (n = 3), and 6% multiracial (n = 2). Forty-seven percent of the subjects were students. Thirty-four percent had earned a master's degree or higher (n = 11), and an additional 34% reported having earned a bachelor's degree (n=11). The remaining 10 subjects all reported having completed some college education. Thirty-seven percent worked full time (n = 12). Two subjects were unemployed, and 2 worked part time.

At baseline, the 3 groups did not differ in age, race, BMI, use of oral contraceptives, or menstrual cycle phase; these variables were not associated with PPTh or measures of DNIC (P >0.05) and were thus not included as covariates in the longitudinal ANOVAs. PPTh and DNIC, however, were positively correlated with each other at baseline (Pearson's r = 0.36, P = 0.04), suggesting that individuals with higher mechanical pain thresholds had larger DNIC responses (increased PPTh) during the cold pressor test. Baseline PPTh was therefore used as a covariate in the analyses of DNIC effects over time, as recommended for the analysis of outcomes data.[51]

In terms of sleep parameters, no baseline differences emerged for measures of sleep continuity or sleep architecture, and all variables were observed to be within the normal range in each group. Similarly, no group differences were observed for PPTh or DNIC at baseline and all 3 groups showed a significant DNIC effect, demonstrating an average 21% increase in PPTh during cold pressor (Table 1).

Effects of Sleep Condition on PSG Sleep and Daytime Sleepiness

Figure 2 describes the effects of the experimental manipulations on mean sleep parameters. TST, NREM S1, NREM S2, NREM S3+4, and Stage REM all demonstrated a significant (P <0.001) within subjects Group x Night interaction, indicating that changes in these PSG sleep parameters differed by group across consecutive nights ($F_{10,140}$ test values for PSG parameters, respectively = 47.3, 12.02, 37.3, 19.4, 13.3). Due to PSG equipment failure for one of the Control subjects, Night 4 analyses were based on N=31. For Daytime Sleepiness (SSS), Mauchly's test indicated that the sphericity assumption was not met. Therefore, a Greenhouse-Geisser correction was implemented. A significant (P <0.001) within-subjects Group x Day interaction was found for Daytime Sleepiness ratings (ESS [Days 3-8], $F_{7.3,91.3}$ = 7.9). Figure 2 depicts group means, SEM data, and the results of follow-up post hoc comparisons tests (LSD), across baseline (Night 2), partial sleep deprivation (Nights 3-5), total sleep deprivation (Night 6) and recovery nights (Night 7).

To summarize the key sleep findings, both FA and RSO demonstrated an equivalent, approximate, 50% reduction in total sleep time during all 3 partial sleep deprivation nights (3-5). Similarly, during partial deprivation, both FA and RSO also showed equivalent reductions in NREM S2 and Stage REM. During partial sleep deprivation nights, FA showed significant increases in NREM S1 compared to controls, whereas RSO showed significant reductions in NREM S1. FA demonstrated a significant (P <0.05), approximate 50% decrease in NREM S3+S4 on the first night of partial sleep deprivation compared to both RSO and Controls, but no detectable reductions on the remaining partial deprivation nights. Unlike FA, RSO did not lose any detectable amounts of NREM S3+S4 during all 3 partial sleep deprivation nights. Both FA and RSO demonstrated equivalent, steady increases in subject daytime sleepiness through total sleep deprivation, which normalized after recovery sleep. See Figure 2.

Pressure Pain Threshold (PPTh)

The ANOVA assessing changes over study days in PPTh as a function of group yielded a near-significant between-subjects effect of group ($F_{2,29}$ = 3.0; P = 0.07), with the restricted sleep group trending toward elevations from baseline in PPTh across study days, relative to the other groups. However, the interaction of Group x Day was not significant, ($F_{10,145}$ = 0.9; P = 0.56), suggesting no reliable differences between groups in patterns of post-baseline changes in PPTh. There was no significant overall main effect for time on PPTh ($F_{5,145}$ = 0.9; P = 0.50).

Diffuse Noxious Inhibitory Controls (DNIC)

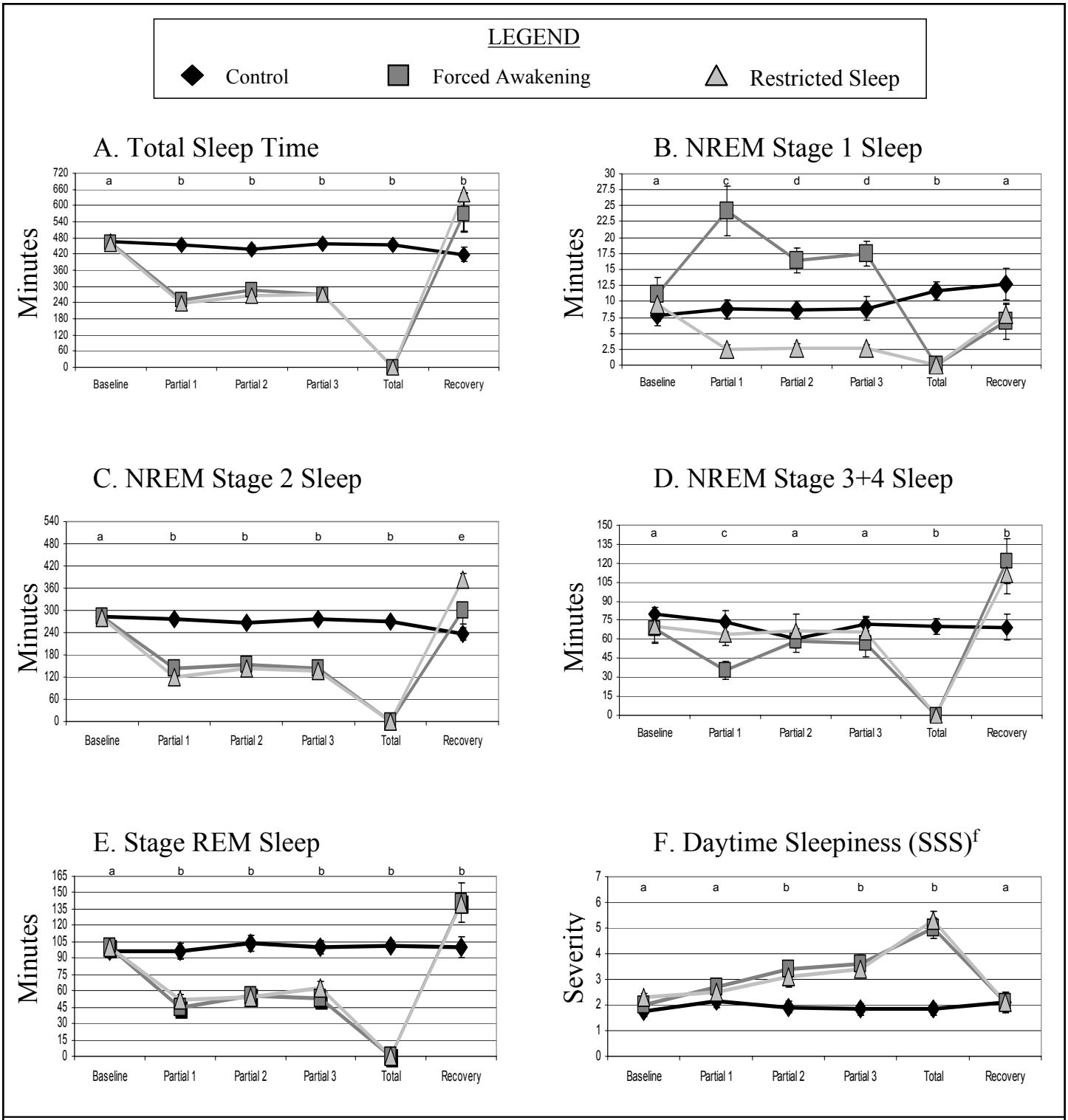

Figure 2—The Effects of the Experimental Manipulations (Group) on Polysomnographic Total Sleep Time (A), Sleep Architecture (B-E), and Subjective Daytime Sleepiness (F)

NOTES: Control (n=12), slept undisturbed all 7 nights; Forced Awakening Group (n = 10), 8 forced awakenings during 8 hour sleep period; Restricted sleep opportunity (n = 10), consolidated, but curtailed sleep with total sleep time yoked to FA group

Baseline = Night 2 (undisturbed sleep); Partial = partial sleep deprivation, Total = 36 hours sleep deprivation, Recovery = 11 hour recovery sleep period

[a] No difference between groups, P>0.05, One way ANOVA

[b] FA = RSO ≠ Control , LSD post hoc multiple comparison test, P<0.05

[c] FA ≠ Control=RSO, LSD post hoc multiple comparison test, P<0.05

[d] FA ≠ RSO ≠ Control, LSD post hoc multiple comparison tests, P<0.05

[e] FA = Control ≠ RSO, LSD post hoc multiple comparison tests, P<0.05

[f] SSS = Stanford Sleepiness Scale, higher values indicate increased sleepiness

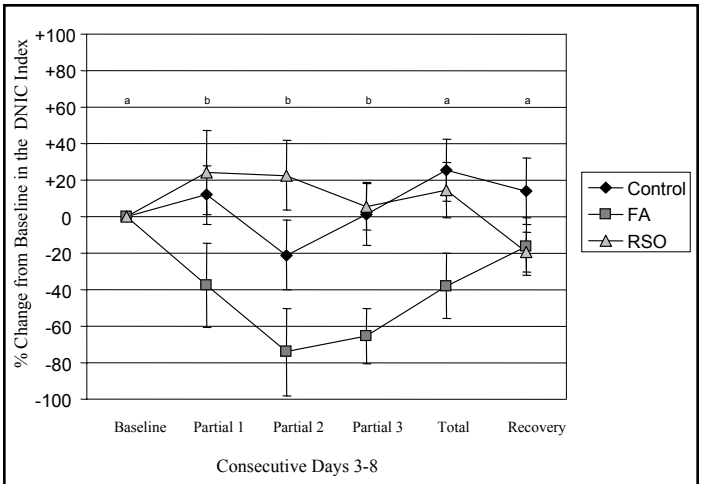

Figure 3—The Effects of Partial Sleep Deprivation Type on Pain Inhibition (N=32) (mean ± SEM)
NOTES: DNIC Index = (PPTh Cold Pressor – PPTh prior cold pressor)*100 / DNIC Index for Baseline (Day 3)
Control (n=12), slept undisturbed all 7 nights; FA (n= 10) = Forced Awakening Group, 8 forced awakenings during 8 hour sleep period; RSO (n=10) = Restricted sleep opportunity, consolidated, but curtailed sleep with total sleep time yoked to FA group
Baseline = Day 3; Partial = partial sleep deprivation; Total = 36 Hours sleep deprivation; Recovery = 11 hour recovery sleep period
[a] No difference between groups, P>0.05, One way ANOVA
[b] FA ≠ Control=RSO, LSD post hoc multiple comparison test, P<0.05

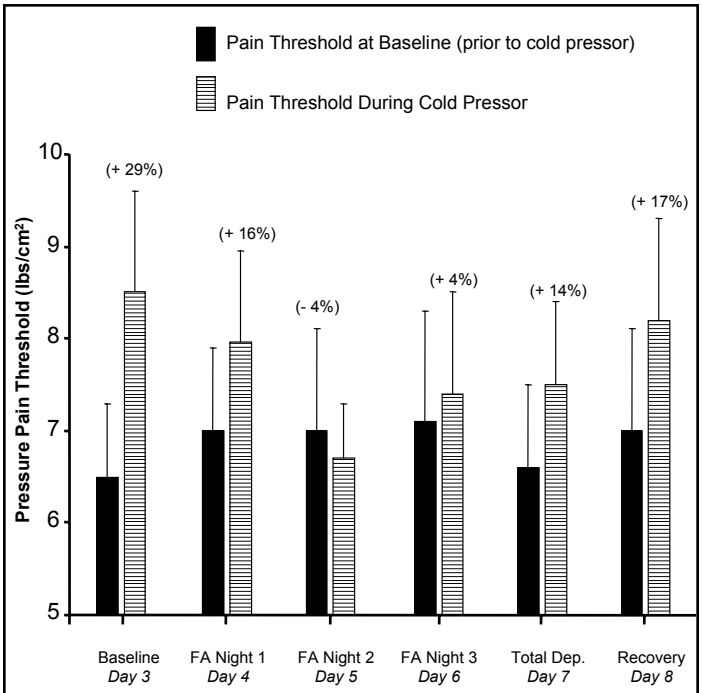

Figure 4—Pressure Pain Threshold Values for the DNIC Procedure in the Forced Awakening (FA) Group (mean ± SEM)

Results of the ANCOVA for DNIC indicated significant between-subjects effects of group ($F_{2,26}$ = 5.2; P = 0.01) and baseline PPTh ($F_{1,26}$ = 8.1; P = 0.01), but these were qualified by a significant Group x Day interaction ($F_{10,130}$ = 2.9; P <0.01), and a 3-way interaction between Day, Group, and baseline PPTh ($F_{10,130}$ = 3.3; P <0.01). Follow-up ANCOVAs with Fisher's LSD comparisons were performed at each study day following baseline, in order to evaluate differences between groups in DNIC. On days 4, 5, and 6 (i.e., the days following each of the 3 nights of partial sleep deprivation), the Forced Awakening group had significantly lower normalized DNIC scores than the other 2 groups (*F* values= 4.7, 5.1, 5.0; P's <0.05 for the planned contrast ANOVAs on days 4, 5, and 6, respectively). However, the Forced Awakening and Restricted groups did not differ from Controls either after total sleep deprivation or following recovery sleep (P values all >0.10). A within-group analysis of DNIC values using single sample tests revealed that the forced awakening group showed a significant (P <0.05) DNIC effect at baseline (i.e., PPThs were significantly increased from baseline during the cold pressor task), but no significant DNIC effect after any of the 3 partial sleep deprivation nights (P values all >0.05). DNIC increased modestly following total sleep deprivation and was fully restored after recovery sleep (P <0.05 for the test of the DNIC effect). In the control and restricted sleep groups, significant DNIC effects were present on every study day (all P values <0.05).

In the overall ANCOVA model testing the effects of the sleep manipulations on DNIC, there were 2 significant effects involving baseline PPTh. The first, a between-subjects effect of baseline PPTh, was a function of the fact that individuals with relatively higher baseline pressure pain thresholds also had relatively greater DNIC. The 3-way interaction between group, time, and baseline PPTh was a function of the following effect: in the forced awakening group, it was subjects with the highest baseline PPTh, and the highest DNIC scores at baseline, who were most likely to show the largest decrements in DNIC following the nights of partial sleep deprivation. Unfortunately, the relatively small sample size (n = 10) in the Forced Awakening group precludes us from effectively subdividing the group for the purposes of analyzing this 3-way interaction, which will require replication in larger samples.

Figure 4 depicts the raw PPTh values for the FA group before and during the cold pressor task for each day of the experiment. As depicted in this figure, during the partial sleep deprivation days (4-6), the DNIC effect averaged across the 3 partial sleep deprivation days was only a 5.3% increase in PPTh during cold pressor (compared with the 28.8% increase observed at the pre-intervention baseline (i.e., Day 3). This reduction, during partial sleep deprivation, reflects an 81.6% decrease in inhibitory capacity.

Spontaneous Painful and Nonpainful Somatic Symptoms (PILL)

As shown in Figure 5, we found significant Group x Day interactions for the PILL painful and nonpainful somatic scales[1] ($F_{10,130}$ values = 2.2 [p = 0.02] and 3.02 [p = 0.002]). Both Omnibus F Tests for the painful and nonpainful somatic symptoms scales showed no between group differences for the day, after the Baseline (Night 2), the first partial deprivation night (Night 3), and the Recovery Night 7 (P >0.07). Omnibus between group differences on both scales were found for days following the remaining partial and total sleep deprivation nights as follows. For the Painful Symptom Index, between group differences were found for days following Nights 5-7 ($F_{2,29}$ = 4.9, 3.9, and 4.7, respectively, P values <0.05). Similarly, for the Non-painful Somatic Symptom Index, between group differences were found for Days 5-7 ($F_{2,29}$ = 5.2, 4.1, and 6.7, respectively; all P values <0.05). As depicted in Figure 5, for the Painful Symptom Index, only the FA group

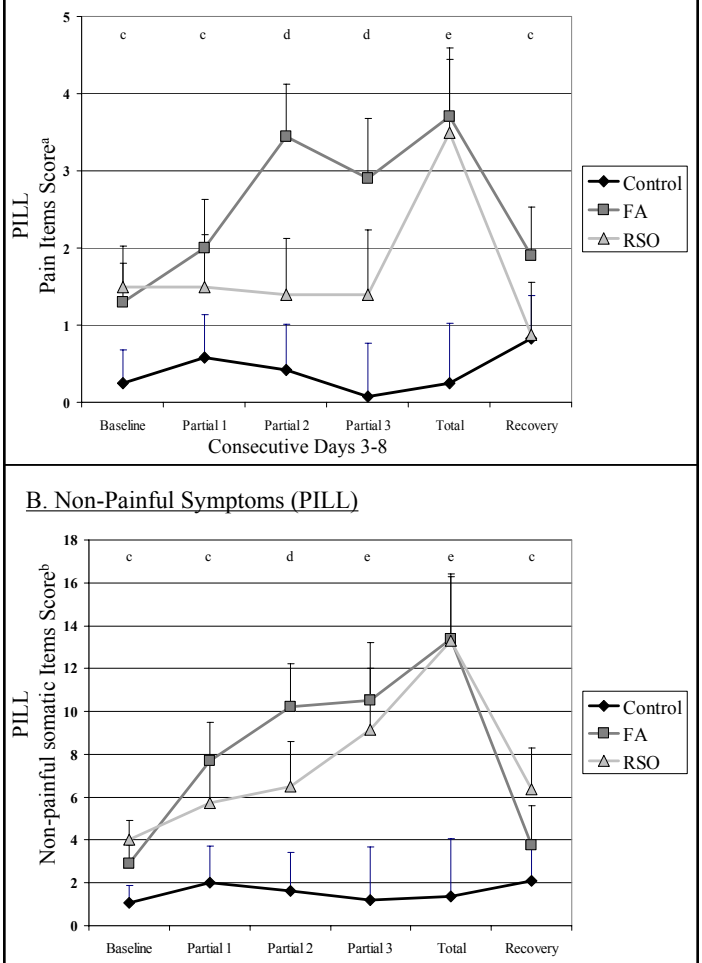

Figure 5—The Effects of Partial & Total Sleep Deprivation on the Report of Spontaneous Painful and Non-Pain Somatic Symptoms (N=32, Mean & SEM plots)

[a] PILL = Pennebaker Inventory of Limbic Languidness: Higher scores indicate increased frequency/severity of spontaneous painful symptoms; possible scale range = 0-40; 1 = "a little" degree of pain in 1 of 10 painful symptoms (e.g., back pain), 40 = "very much pain" for all 10 symptoms.

[b] PILL Non-Painful Somatic Items: Higher scores indicate increased frequency/severity of spontaneous non-painful somatic symptoms; possible scale range = 0-96; a score of 1 = "a little degree" of experiencing at least 1 out of 44 non-painful somatic symptoms (e.g., twitching of the eyelids); 96 = experiencing all 44 symptoms, "very much."

[c] No difference between groups, P>0.05, One way ANOVA

[d] FA ≠ Control=RSO, LSD post hoc multiple comparison test, P<0.05

[e] FA = RSO ≠ Control , LSD post hoc multiple comparison test, P<0.05

showed a differential increase in spontaneous pain after partial sleep deprivation (Days 4-6), with the RSO group demonstrating symptom levels similar to controls. Both FA and RSO reported similarly higher levels of spontaneous pain after Total Sleep Deprivation compared to Controls, which normalized after recovery sleep. As described in Figure 5, Panel B, on Day 5 (after second night of partial deprivation) the FA group also showed a differential, albeit less dramatic increase in nonpainful somatic symptoms relative to RSO and Controls. Post hoc comparisons found that RSO and Controls were not different in nonpainful somatic symptom report for Day 5. This differential increase in nonpainful somatic symptoms for the FA group was not observed after the third night of partial deprivation or after total sleep deprivation, however. On these days (6 and 7), both RSO and FA showed an equivalent increase in nonpainful somatic symptoms relative to Control, which disappeared after Recovery.

DISCUSSION

In this experiment, we evaluated whether partial sleep loss associated with sleep disruption versus partial sleep loss achieved by sleep restriction altered psychophysical measures of pressure pain threshold, pain inhibitory capacity, and spontaneous reports of painful versus non-painful somatic symptoms. Although both partial sleep deprivation groups lost comparable amounts of polysomnographically recorded sleep over 3 consecutive days (50% reduction in total sleep time), only the FA condition demonstrated robust decrements in pain-inhibitory function (i.e. a loss of the DNIC effect), and a differential increase in spontaneous painful symptoms, which returned to baseline levels after recovery sleep. Somewhat surprisingly, although both partial sleep deprivation groups showed comparable increases in daytime sleepiness and spontaneous somatic symptoms after 36 hours of total sleep deprivation, neither group, showed abnormal DNIC or PPT following total sleep deprivation. The FA group did, however, trend toward continued reductions in DNIC during total sleep deprivation, which might have proven to be significant with a larger sample size. Caution should be observed in interpreting the "Total" and "Recovery" data, because they are confounded by the prior effects of the partial deprivation conditions.

Analysis of the differences in sleep architecture between the FA and RSO groups during partial deprivation suggests that the perturbation of slow wave sleep (Night 3) and subsequent "lightening" of NREM sleep (increased NREM S1) may be factors associated with impaired DNIC. This possibility is consistent with uncontrolled studies demonstrating that selective slow wave sleep deprivation, implemented via noxious auditory stimuli, enhances threshold measures of pain sensitivity.[12,13] In contrast to these studies, we did not find any threshold changes after any form of sleep deprivation. This negative finding, however, is consistent with several other studies.[15,16] These mixed findings with respect to simple threshold measures, suggests the possibility that measures of pain modulation such as DNIC or suprathreshold measures of pain might provide a more sensitive index of pain processing impairments.[8] The apparent inconsistencies in the literature with respect to the effects of sleep loss on PPTh may also be a function of the different sleep deprivation paradigms used and/or the differential degree of slow wave sleep loss generated across studies. Our data would suggest that higher order pain-modulatory processes such as DNIC may be more sensitive than simple threshold measures to partial slow wave sleep loss associated with sleep disruption. This is underscored by the finding that our restricted sleep group was spared virtually any slow wave sleep loss/disruption across the 3 partial deprivation days and demonstrated no loss in DNIC, despite losing significant and comparable amounts of REM and NREM Stage 2. Future work will be necessary to determine whether DNIC impairments occur in a dose dependent fashion relative to selective slow wave sleep disruption or whether they are dependent on a more complex per-

turbation of the entire sleep cycling process caused by our forced awakening paradigm.

The lack of effect of the subsequent 36 hours of total sleep deprivation on any of the psychophysical measures of pain responses is a puzzling finding that will also require follow up investigation. Because the total sleep deprivation condition occurred after 3 consecutive nights of partial sleep deprivation, it remains unclear whether the lack of decrement in DNIC following total deprivation reflects an adaptive compensatory process, overriding transient effects of sleep loss, or whether DNIC impairments are primarily a function of sleep perturbation (i.e., the disruption of active cerebral processes that regulate sleep). Future work involving total sleep deprivation as a stand-alone condition will be necessary to resolve this issue. Additional studies extending the duration of the forced awaking paradigm beyond 3 days will be needed to clarify whether impairment in pain inhibition recovers in a compensatory fashion in healthy subjects and individuals with pain disorders.

With respect to total sleep deprivation, our lack of an effect on PPTh is consistent with a study by Drewes et al that found that total sleep deprivation did not alter experimental joint pain sensitivity in healthy subjects.[19] Two other studies have, however, reported enhanced pain sensitivity after total sleep deprivation. First, Onen and colleagues reported a significant reduction in pressure pain tolerance in a paradigm involving 2 nights of selective slow wave/REM deprivation, followed by total sleep deprivation.[17] This contrast may be a function of differences between laboratory measures of pain threshold versus pain tolerance and/or differences in the degree of prior SWS loss between the present study and the Onen et al study. Second, Kundermann and colleagues[18] reported decreased thermal threshold after 2 nights of total sleep deprivation. Apparent differences in the present study versus the Kundermann et al study might be a function of the modality of noxious stimulation (mechanical versus thermal).

Our finding that disrupted sleep continuity caused a loss of DNIC and subsequent development of spontaneous pain has several clinical implications. It provides, for the first time, mechanistic support for the longitudinal findings that sleep disturbance is a risk factor for exacerbation of chronic pain.[52-54] Impaired or absent DNIC effects have been found in numerous chronic pain conditions ranging from tension headache to fibromyalgia.[26,30,55] The extent to which altered pain inhibition in these clinical populations is directly related to sleep continuity disturbances remains to be determined. Our findings would support aggressive efforts to treat insomnia (particularly in patients demonstrating multiple nocturnal awakenings) early in the course of a pain condition to determine whether sleep consolidation has prophylactic benefit.

Several limitations should be noted when interpreting the current findings. By virtue of the sleep manipulation, this study, like other sleep deprivation studies, could only be single blinded and it remains possible that the observed effects might be partially attributable to subject expectancies. Several aspects of our data, however, argue against a demand characteristic explanation. Unlike prior work that measured only pain threshold and tolerance, in which a clear expectancy of increased sensitivity is likely, our measure of DNIC is a calculated difference score in PPTh during the application of another painful stimulus. We would argue that this type of procedure is less susceptible to clear expectancy effects. Furthermore, our finding that both RSO and FA showed similar increases in nonpainful somatic symptoms across partial deprivation, but that only the FA condition showed a differential increase in somatic symptoms, argues against a global expectancy that the forced awakening condition should yield more negative outcomes. When interpreting these data, it should be noted that both painful and nonpainful somatic symptoms increased after total sleep deprivation in both groups. This suggests that factors in addition to reduced DNIC appear to underlie sleep loss related symptoms. Another limitation of this work pertains to generalizability. In an effort to maintain maximal experimental control, we studied selected young healthy women. It will be necessary to extend this work to other populations to determine generalizability, most notably males and older adults. Finally, although we used diaries to estimate menstrual phase and neither menstrual phase nor hormonal contraception use differed by groups, future studies could be enhanced by conducting hormone level testing and studying all women at the same point in the menstrual cycle.

Future studies using this forced awakening model of partial sleep deprivation are warranted; this study highlights the insufficiency of studying partial sleep deprivation via simple sleep restriction. Combining this model, which arguably has ecological validity for the type of sleep loss associated with insomnia or individuals whose job involves frequent multiple awakenings (e.g., physicians or parents with infants), with traditional models of selective partial sleep deprivation will expand the understanding of the functions of sleep and it deleterious effects on central nervous system. This preliminary work supports a promising line of inquiry aimed at determining how sleep loss and perturbation may directly contribute to or aggravate chronic pain syndromes. These psychophysical data suggest one possible pathway: sleep continuity disturbance impairs brainstem, opioidergic descending systems,[23,56] which are implicated in central sensitization models of hyperalgesia and chronic pain.[57]

ACKNOWLEDGMENTS

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FOOTNOTE

[1] Sample size for analyses: Control = 12, FA = 9, and RSO = 8, due to missing data.

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