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Observational study

Total sleep deprivation and pain perception during cold noxious stimuli in humans

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HIGHLIGHTS

- 24-h sleep deprivation augments perceived pain to cold pressor test.
- Our findings are consistent for both mean and peak pain responses.
- Gender does not appear to significantly impact our findings.

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ABSTRACT

Background and aims: A substantial portion of the population suffers from chronic pain leading to significant health care costs and lost productivity. Loss of sleep duration and quality are widely reported in patients suffering from a variety of acute or chronic pain conditions. Conversely, sleep loss has been known to elevate pain perception; thus a potential bi-directional relationship exists between sleep deprivation and pain. To date, the majority of studies examining the relationship between experimentally induced pain and sleep loss have focused on the measurement of pain *threshold*. Additionally, despite evidence of sex differences in ratings of perceived pain, previous studies examining pain following sleep loss have not probed for sex differences. We examined the effects of 24-h total sleep deprivation (TSD) on perceived pain during a 2-min cold pressor test (CPT). We hypothesized that TSD would augment perceived pain and that women would demonstrate an elevated pain response compared to men.

Methods: Testing was carried out in 14 men and 13 women. All subjects reported to be nonsmokers with no history of cardiovascular disease, autonomic dysfunction, asthma, or diabetes. All female subjects were free of oral contraceptive use, and were tested during the early follicular phase of the menstrual cycle. Trial order was randomized and testing sessions (Normal sleep (NS) and TSD) were separated by approximately one month. Subjects immersed their left hand, up to the wrist, in an ice water bath (~1 °C), and perceived pain was recorded every 15 s from a modified Borg scale (6–20 arbitrary units a.u.).

Results: Perceived pain responses during CPT were augmented following TSD (Δ1.2 a.u.; time × condition, $p < 0.05$). The augmented pain response following TSD was noted when perceived pain was expressed as mean (NS Δ7.0 ± 0.5 vs. TSD Δ8.2 ± 0.5 a.u.; $p < 0.05$) or peak (NS Δ8.9 ± 0.6 vs. TSD Δ10.2 ± 0.5 a.u.; $p < 0.05$) perceived pain. The effects of TSD on perceived pain were similar in both men and women (condition × time × sex, $p > 0.05$).

Conclusions and implications: We conclude that TSD significantly augments perceived pain during CPT, but this response was not sex dependent. These findings support emerging evidence that adequate sleep represents a relevant, and cost effective, preventative/therapeutic strategy to reduce self-perceived pain in both men and women.

1. Introduction

Approximately 19% of adult Americans suffer from some form of persistant pain [1]. The economic cost of chronic pain in terms of health care and lost productivity in the United States is estimated somewhere between $560 and $635 billion per year [2]. Understanding the processes involved in pain sensation, and developing

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cost-effective strategies for the management of pain are of clinical and economic importance.

Most humans spend nearly one-third of their lives sleeping, and proper sleep hygiene is critical to overall health and wellness. Unfortunately, there has been a steady decline in both sleep duration and quality in humans of all ages over the past 30 years. Epidemiological studies report an association between chronic pain and sleep loss [3–8], and it is widely accepted that the relationship between pain and sleep loss is bidirectional. As such, treatment strategies remain complex and dependent upon which condition (pain vs. sleep deprivation) is believed to be the primary modulator. Nevertheless, sleep represents a cost-effective, nonpharmaceutical strategy for pain management.

Cooperman et al. [9] was the first to report a decrease in cutaneous pain threshold as measured with von Frey hairs in six male subjects during a 60 h sleep deprivation protocol. In more recent years, the observations made by Cooperman et al. [9] have been supported using a variety sleep loss paradigms and methods of stimuli in humans [10–13]. However, these studies have primarily focused on assessment of *pain threshold*. In contrast to pain threshold analyses, sustained cold noxious stimuli have been shown to produce greater pain ratings that more closely mimic clinical pain conditions than pain threshold analysis [14]. To our knowledge, no studies have examined the influence of experimentally-induced 24-h total sleep deprivation (TSD) on sustained pain elicited by a classic cold pressor test.

Finally, while several studies have examined the influence of sleep deprivation on pain threshold [9–11,15], these studies have not probed into potential sex differences. This is surprising because there is considerable evidence indicating sex differences in pain ratings with women generally reporting elevated sensitivity to experimentally induced pain than men [16–18]. Furthermore, studies suggest that reports of clinical or chronic pain are more prevalent in women compared to men [19,20]. Despite evidence of sex differences in both experimental and clinical pain, the relations between sleep deprivation, pain, and sex remain equivocal.

The purpose of the present study was to (1) examine the influence of sleep deprivation on pain perception to cold noxious stimuli in humans, and (2) determine if the effects of TSD on perceived pain produce a differential response between men and women. We hypothesized that TSD would augment pain perception elicited via the classic cold pressor test, and that this augmentation would be more dramatic in women compared to men.

2. Materials and methods

2.1. Subjects

Thirty healthy subjects (15 men and 15 women) enrolled in the study. Autonomic and cardiovascular responses at rest [21] and during acute stress [22] have been previously reported. All subjects reported to be nonsmokers with no history of cardiovascular disease, autonomic dysfunction, asthma, or diabetes. All female subjects were free of oral contraceptive use, reported regular menstrual cycles (range 26–30 days), and were tested during the early follicular phase (2–5 days after the onset of menstruation) of the menstrual cycle. One female subject was excluded from the study when estradiol and progesterone levels indicated she was not in the early follicular phase for one testing session. All subjects were screened for obstructive sleep apnea by a board certified sleep physician using the at home ApneaLink (Resmed, San Diego, CA). Exclusion from the study occurred when the apnea-hypopnea index was $\geq$10 episodes per hr., and one male subject was excluded on this basis. Additionally, one female subject was excluded due to failure to complete the CPT session resulting in a total sample size of 27 (14 men: 22 ± 1 years, 176 ± 2 cm, 79 ± 4 kg; 13 women: 22 ± 1 years, 165 ± 2 cm, 63 ± 3 kg). All subjects participated in an orientation session before providing written informed consent. This study was approved by the Michigan Technological University Institutional Review Board.

Table 1
Modified Borg scale used to assess perceived pain.

6	
7	Very low pain
8	
9	Low pain
10	
11	Fairly painful
12	
13	Somewhat painful
14	
15	Painful
16	
17	Very painful
18	
19	Almost unbearable
20	

2.2. Experimental Design

Two experimental testing sessions were performed: one following a normal night of sleep (NS), and one following 24-h TSD. Subjects were tested approximately one month apart to ensure females were tested during the early follicular (EF) phase of the menstrual cycle. Trial order (NS vs. TSD) was randomized using a crossover design. Specifically, 7 women and 5 men were assigned to the NS trial first, while the remaining subjects (7 women and 9 men) were assigned the TSD trial first. Sleep time for 3 days preceding the study was monitored with wrist actigraphy (Actiwatch 64 Respironics Inc, Bend OR) to ensure subjects were getting adequate sleep.

The day prior to the TSD trial, subjects were contacted at 7:30 a.m. and instructed to refrain from napping during the day. They reported to the laboratory at 11:00 p.m. where two assistants ensured they did not sleep or close their eyes during the night. Subjects participated in light activities including reading, studying, and games with the assistants during the TSD protocol. Subjects refrained from caffeine, alcohol and exercise for 12 h, and fasted for 8 h prior to testing.

2.3. Protocol

On each day of testing (i.e., NS and TSD), 3 consecutive recordings of resting blood pressure (~1 min apart) were taken with an automated sphygmomanometer (Omron HEM-907XL, Omron Health Care) following 5 min of seated rest. Following a standard breakfast, subjects assumed a supine position on the testing table for instrumentation. Beat-to-beat blood pressure, heart rate, and muscle sympathetic nerve activity (MSNA) were continuously recorded during a 10 min baseline, 5 min mental stress trial, and 2 min cold pressor trial; the autonomic and cardiovascular responses in these various sessions have been previously reported [21,22]. The present study specifically focuses on the self-reported pain ratings obtained during the cold pressor test. Briefly, the cold pressor test (CPT) trial consisted of a 3-min resting supine baseline, 2 min CPT, and 3 min recovery. During CPT, subject's immersed their left hand up to the wrist in a mixture of ice and water (~1 °C). Ratings of perceived pain were recorded every 15 s when one research assistant would instruct the subject to verbally identify a pain rating from a modified Borg scale for pain (6–20 arbitrary units) situated in the subject's field of view. As depicted in Table 1,