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Emotional modulation of pain and spinal nociception in persons with severe insomnia symptoms

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Abstract

Background—Impaired sleep enhances pain, perhaps by disrupting pain modulation.

Purpose—Given that emotion modulates pain, the present study examined whether emotional modulation of pain and nociception is impaired in persons with severe insomnia symptoms relative to controls.

Methods—Insomnia group (n=12) met ICD-10 symptoms for primary insomnia and controls (n=13) reported no sleep impairment. Participants were shown emotionally-evocative pictures (mutilation, neutral, erotica) during which suprathreshold pain stimuli were delivered to evoke pain and the nociceptive flexion reflex (NFR; physiological correlate of spinal nociception).

Results—Emotional responses to pictures were similar in both groups, except that subjective valence/pleasure ratings were blunted in insomnia. Emotional modulation of pain and NFR was observed in controls, but only emotional modulation of NFR was observed in insomnia.

Conclusions—Consistent with previous findings, pain modulation is disrupted in insomnia which might promote pain. This may stem from disrupted supraspinal circuits not disrupted brain-to-spinal cord circuits.

Keywords

insomnia; pain modulation; sleep; psychophysiology; descending modulation; affect

Introduction

Sleep impairment has a high degree of co-occurrence with pain. Indeed, the majority of chronic pain sufferers report impairments in sleep, including insomnia-like symptomatology (1-4). Interestingly, several studies suggest that sleep disturbance may not only be a consequence of pain, but may also enhance clinical pain (3-5). Thus, sleep problems may promote and maintain clinical pain. What is more, sleep disturbance might actually initiate pain. Poor sleep has been shown to be related to the development of chronic widespread

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pain symptoms (6), and experimentally disrupted sleep has been associated with increased sensitivity to mechanical (7) and thermal pain (8, 9), and in some cases, increased spontaneous pain complaints (7, 10). Taken together, it appears that disturbed sleep can alter pain processing.

At this time however, the mechanisms contributing to the sleep-pain relationship are poorly understood. One hypothesis is that sleep disturbance disrupts pain modulation – central processes that regulate pain signaling (nociception) at supraspinal and spinal levels (11-13). This could be an important underlying mechanism because impairments in pain modulation can promote chronic pain. Indeed, several chronic pain conditions are associated with impaired pain modulation (14-17), and impaired pain modulation may predict future pain problems (18). Thus, sleep problems may place individuals at risk for chronic pain by impairing pain modulation.

Manipulation of emotion is one method of modulating pain and nociception (19). Emotion circuits are highly interconnected with the pain and pain modulation circuitries (19-21) and emotions can reliably up- and down-regulate pain and spinal nociception (19, 22). This emotion-pain relationship is believed to be important for survival in that it allows organisms to respond adaptively to a changing environment (19, 23, 24). Given this overlap between emotion and pain systems, disruptions in emotional processing have the potential to negatively impact pain processing.

Not surprisingly, there is evidence that disturbed sleep disrupts emotional processing. For example, 30% of patients presenting with insomnia also suffer from depression (25), and sleep problems are observed in nearly all mood and anxiety disorders (26). Additionally, sleep loss has been shown to increase negative affect and impair emotional coping (27), and imaging research indicates that sleep deprivation may disrupt activity in brain regions associated with emotion, pain, and pain modulation (e.g., amgydala, medial prefrontal cortex)(28). Thus, sleep disturbance may promote pain by disrupting supraspinal circuits involved with emotion regulation and emotional modulation of pain.

Given that impaired sleep can lead to a disruption in modulation of pain as well as disruptions in emotion, and that emotion is one pathway by which pain may be modulated at the supraspinal and spinal levels, then otherwise healthy and pain-free individuals with sleep problems (e.g., severe insomnia symptoms) may exhibit disruptions in emotional modulation of pain and nociception. If true, this might represent another mechanism that promotes the deleterious effects of sleep on pain.

Assessment of Emotional Modulation of Pain and Spinal Nociception

To assess emotional modulation of pain and spinal nociception, emotionally charged pictures that vary in content (mutilation, neutral, erotica) can be presented during which suprathreshold electric stimuli are delivered to the ankle to evoke pain and the nociceptive flexion reflex (NFR). The NFR is a spinally-mediated withdrawal response with a simple reflex arc that is activated by noxious stimuli (i.e., noxious stimulus→A-delta fibers→dorsal horn neurons→motoneurons→limb withdrawal) (29). The stimulus intensity that elicits the NFR typically occurs near pain threshold and the magnitude/size of the NFR

is correlated with suprathreshold stimulus intensity and subjective pain ratings (29). As a result, the NFR is used as a correlate of spinal nociception (pain signaling in the spinal cord). Despite being spinally-mediated, this reflex can be influenced by descending pain modulation circuitry, including brain-to-spinal cord pathways activated by emotion (22). In studies of healthy humans, viewing emotional pictures generally modulates pain and NFR according to a picture valence linear trend. Specifically, pain and NFR magnitudes are greatest during unpleasant pictures, intermediate during neutral pictures, and lowest during pleasant pictures (although comparisons with neutral are not always significant) (22, 30, 31). Given evidence that there are separate circuits that govern emotional modulation of pain vs. NFR (a supraspinal circuit that modulates pain and a brain-to-spinal cord circuit that modulates NFR)(13, 32), this paradigm provides a means of testing two different pain modulation circuits activated by emotion.

For the present study, emotional modulation of pain and NFR was assessed in otherwise healthy individuals with severe insomnia symptoms and controls without sleep problems. Given recent evidence that a failure to emotionally modulate pain (but intact NFR modulation) may be associated with chronic pain risk (17, 33, 34), we hypothesized that the insomnia group would exhibit disrupted emotional modulation of pain (i.e., a failure to observe a valence linear trend in pain), but intact NFR modulation. Given that physiological-emotional reactions were assessed in response to emotional pictures (i.e., valence ratings, arousal ratings, facial [corrugator] muscle activity, skin conductance, startle reflex modulation), a secondary goal was to assess group differences in emotional processing.

Methods

Participants

Participants were individuals suffering from severe insomnia symptoms and healthy controls without sleep problems. Both were recruited from the community through newspaper, radio, and online advertisements as well as flyers placed in a local sleep clinic. All participants provided written and verbal informed consent prior to participation. Participants were excluded for: < 18 years of age, chronic pain, cardiovascular or neurological disorders, severe circulatory problems, recent use of pain or sleep medications, antihypertensives, antidepressants, or anxiolytics, recent psychological trauma, poor vision (unless corrected with glasses or contacts), and body mass index (BMI) > 35 (due to difficulty getting an NFR in persons with high adiposity). Insomnia participants had to meet ICD-10 criteria for insomnia and have an Insomnia Severity Index (measure of sleep impairment) score ≥ 10 (35). Further, control participants were excluded if they had any current or history of Axis I disorders and participants with insomnia symptoms were excluded if they had any current Axis I disorders[1]. One participant met criteria for current specific phobia and alcohol abuse. These diagnoses were deemed unlikely to confound testing, because specific phobias only induce anxiety in response to phobia-specific stimuli (36) and none of the stimuli used were the participant's phobic stimuli. Further, evidence suggests that emotional modulation of

[1]Initially, medical chart review was used to exclude insomnia participants with an Axis I diagnosis. However, this approach was replaced with the SCID-I after one insomnia participant was tested. Thus, the first insomnia participant did not receive a SCID-I, but did not have a current or past Axis I diagnosis according to their medical record.

pain is not affected by chronic alcohol use (i.e., alcohol dependence) (37), so it was assumed it would also not be affected by alcohol abuse. One insomnia participant met criteria for past major depressive disorder (single episode, >10 years ago), one met criteria for past obsessive compulsive disorder, five met criteria for past alcohol/substance abuse, and two met criteria for past substance dependence. Given evidence that history of major depressive disorder might influence pain perception (e.g., 38, 39), analyses were conducted with and without the participant with past major depression. Conclusions did not differ appreciably in the two sets of analyses, so results from the full sample are reported. Thus, 25 participants (*N*=13 controls and *N*=12 insomnia) completed the study and were included in analyses (Table 1).

Determination of Insomnia

A phone interview was first conducted with interested participants to get a preliminary assessment of insomnia symptoms as delineated by the ICD-10. During the initial phone interview, each participant was asked to describe his or her sleep difficulties in detail. Participants were excluded if the symptoms described did not appear to be due to insomnia-like pathology (e.g., due to other sleep disorders such as narcolepsy or sleep apnea). Additionally, each participant was asked if he or she was aware of any identifiable causes that may be resulting in his or her sleep problems (e.g., illness, other medical conditions, recent traumatic or stressful life event, substance-use-related sleep problems). Participants who reported that they were aware of such causes were not included. We did not conduct polysomnography to rule out other occult sleep disorders; however, obese participants (BMI>35) were excluded which likely minimized the chance that sleep problems in the insomnia group were due to obstructive sleep apnea (40). Participants who met initial screening criteria for insomnia were then asked to come into the laboratory and fill out several measures assessing sleep.

Sleep symptoms assessment—All participants were asked to complete a questionnaire assessing presence or absence of symptoms of primary insomnia according to the ICD-10 criteria. All assessments were made by graduate students in clinical psychology with training in clinical diagnosis. To meet criteria for primary (non-organic) insomnia, participants must have reported difficulty falling asleep, maintaining sleep, or poor quality sleep, occurring at least 3 times per week for the past month. Additionally, they had to report concern about their sleep problems and impairment in functioning due to poor sleep and sleep problems could not be clearly attributed to another mental disorder, general medical condition or recent life stressors (41). All participants in the insomnia group met these criteria and all participants in the control group did not.

Insomnia Severity Index—All participants were asked to fill out the Insomnia Severity Index. The Insomnia Severity Index is a reliable and valid 7-item, brief screening tool used to assess the patient's perception of the severity of his or her sleep problems, with a particular focus on reported symptoms, their consequences, and resulting level of distress (42). Each item is answered on a Likert-type 0-4 scale. Total scores range from 0 to 28, with higher scores indicating greater insomnia severity (42). Scores greater than or equal to 10 on the Insomnia Severity Index have been shown to produce good sensitivity and specificity for identifying insomnia in community participants (35, 42).

Fatigue Severity Scale—On the day of testing, all participants were asked to fill out the Fatigue Severity Scale. The Fatigue Severity Scale is a reliable and valid 9-item self-report measure assessing level of fatigue and its consequences over the past week (43). Responses are made on a Likert-type 1-7 scale, with total scores ranging from 9 to 63 (higher scores indicating more severe fatigue). The Fatigue Severity Scale was used to confirm the presence of daytime fatigue, a primary symptom associated with insomnia.

Structured Clinical Interview for the DSM-IV (SCID-I)—The SCID-I is a structured clinical interview assessing for the presence of Axis I conditions. The SCID-I was given to all participants to assess for the presence and/or history of psychopathology. Participants with insomnia could not currently meet criteria for mood or anxiety disorders (except one person met criteria for specific phobia), substance dependence, or any Axis I condition that may better account for their sleep impairment. Healthy controls could not currently meet criteria for any Axis I DSM-IV conditions, or substance dependence, nor could they have a history of significant mood or anxiety problems.

General Health and Functioning (SF-36)

The Short-Form Health Survey (SF-36) was used to assess group differences in health (44, 45). There are eight subscales (physical functioning, role limitations due to physical functioning, role limitations due to emotional functioning, vitality/energy, mental health, social functioning, bodily pain, and general health perceptions). Subscales range from 0 to 100 with higher scores reflecting better health.

Apparatus

A PC with dual monitors and LabVIEW software was set up in a control room adjacent to an experiment room. An experimenter controlled the initiation of the experiment and monitored the physiological signals from the control room. Participants viewed all pictures and questionnaires on a 1.8 m × 1.8 m screen located 3.2 m away. Participants utilized a lap desk and a computer mouse to complete questionnaires and proceed through the experiment. Participants wore headphones (TDH-49, Telephonics, Farmingdale, New York) throughout the experiment which allowed them to hear the computer-administered instructions as well as to communicate with the experimenter and hear the startle noise bursts. Acoustic sound bursts to elicit startle responses were produced via a Coulbourn Instruments (Model A12-33, Allentown, PA) audio signal generator and amplified by a RadioShack 40 Watt PA amplifier to 105 dB. Startle probes had a near instantaneous rise time and were 50 ms in duration. All physiological signals were collected and amplified by a Grass Technologies Physiodata Amplifier System (Model 15LT, Warwick, RI). An adaptor (Grass, Model SCA1) was used to measure skin conductance response (SCR). Electric stimuli to assess pain/NFR were generated by a Digitimer stimulator (DS5; Hertfordshire, England) and delivered using a bipolar surface stimulating electrode (Nicolet, Madison, WI; 30 mm inter-electrode distance) attached to the left leg over the retromalleolar pathway of the sural nerve. The computer controlled the timing and intensity of the stimulations (max intensity used = 50 mA to ensure safety). Each electric stimulus was a train of 1 ms square wave pulses delivered at 250 Hz. A mechanical scale with attached height rod (Detecto, Webb City, MO) was used to assess weight and height in order to calculate BMI.

Emotion-Induction: Picture-Viewing

Pictures were chosen from the International Affective Picture System (46), a database of pictures normed and standardized by valence and arousal ratings. Pictures were selected from three categories: unpleasant (mutilation), neutral (household items) and pleasant (erotica). Mutilation and erotica picture contents were used because they elicit the most robust modulation of pain and NFR (30). Pictures were divided into four blocks, with two blocks assessing emotional processing in the absence of pain and two blocks assessing emotional modulation of pain and NFR. Block 1 always assessed emotional processing in the absence of pain (and included startle modulation), because the startle reflex may be influenced by shock exposure (47). Thereafter, blocks alternated in what they assessed: emotion processing (Block 1), pain/NFR modulation (Block 2), emotion processing (Block 3), pain/NFR modulation (Block 4). Normative ratings of valence and arousal were used to ensure pictures evoked similar emotional responses across all 4 blocks.[2] Picture order within each block was randomized with the limitation that not more than two pictures of similar content were shown consecutively. Each picture was presented for 6 s with a 12 to 22 s inter-picture interval.

Emotional Reactions to Pictures

Emotional reactivity was assessed from two continuous dimensions: valence and arousal (48, 49). Valence measures the unpleasantness/pleasantness of emotion, whereas arousal measures emotional activation/intensity. Five measures were employed in the current study. Self-reported valence and arousal were assessed, corrugator EMG and startle modulation were assessed as physiological correlates of valence, and SCR was assessed as a physiological correlate of arousal. It is important to note that although measures of valence correlate with each other and measures of arousal correlate with each other, they can diverge (48, 50). Moreover, they are mediated by different physiological mechanisms (51-53) Measures of subjective emotional experience correlate with hippocampus and orbitofrontal cortex activation, startle modulation is mediated by the amygdala and PAG (52, 54, 55), SCR is mediated by the hypothalamus, brainstem and sympathetic nervous system (56), and corrugator EMG activity correlates with hippocampus, insula, and the superior temporal sulcus activity (57). Further, some measures are more under voluntary control (subjective ratings, facial EMG) whereas others are more involuntary (startle, SCR). Thus, these five measures provide unique indices of valence and arousal to comprehensively assess emotion processing. Although emotional reactions to pictures were assessed in all four testing blocks, only those from the blocks without pain evocation are presented because conclusions from pain and no pain blocks were identical.

[2]Image numbers by Block were: Block 1 – mutilation (3010, 3030, 3069, 3102, 9253, 9405; $M_{Valence}$=1.76, $M_{Arousal}$=6.52), neutral (7002, 7035, 7041, 7050, 7090, 7150; $M_{Valence}$= 4.96, $M_{Arousal}$=2.73), and erotica (4599, 4607, 4609, 4659, 4669, 4687; $M_{Valence}$= 6.76, $M_{Arousal}$=6.19); Block 2 - mutilation (3015, 3060, 3061, 3068, 3071, 3130; $M_{Valence}$= 1.82, $M_{Arousal}$=6.48), neutral (7009, 7020, 7038, 7080, 7170, 7950; $M_{Valence}$= 5.01, $M_{Arousal}$=2.67), and erotica (4611, 4650, 4660, 4672, 4676, 4695; $M_{Valence}$= 6.77, $M_{Arousal}$=6.21); Block 3 - mutilation (3000, 3053, 3062, 3101, 3120, 3150; $M_{Valence}$= 1.75, $M_{Arousal}$=6.50), neutral (6150, 7004, 7006, 7034, 7100, 7705; $M_{Valence}$= 4.99, $M_{Arousal}$=2.69), and erotica (4608, 4624, 4658, 4689, 4690, 4800; $M_{Valence}$= 6.78, $M_{Arousal}$=6.22); Block 4 – mutilation (3051, 3064, 3080, 3100, 3110, 3140; $M_{Valence}$= 1.74, $M_{Arousal}$=6.47), neutral (7000, 7175, 7211, 7217, 7233, 7235; $M_{Valence}$= 4.93, $M_{Arousal}$=2.73), and erotica (4623, 4643, 4652, 4666, 4670, 4694; $M_{Valence}$= 6.78, $M_{Arousal}$=6.22).

Subjective valence and arousal—The Self-Assessment Manikin (SAM) uses two sets of five pictographs to measure valence (pleasant-unpleasant) and arousal (excited-calm) (58). Participants viewed the SAM on the screen after the presentation of each picture and were asked to rate their emotional reactions to the picture by dragging an indicator on or between the pictographs. Emotion reactions were scored on a scale from 1 to 9, with higher numbers representing greater pleasure or arousal. The SAM is a highly valid and reliable measure of subjective emotional reactions (58).

Corrugator supercilii activity—Two Ag/AgCl electrodes filled with conductive gel were affixed over the left corrugator supercilii muscle which contracts to pull the brow down during a frown. Corrugator activity is a facial display of emotion, thus it can be influenced by voluntary facial movements as well as individual differences in facial expressiveness (59). Corrugator electromyogram (EMG) was amplified × 20,000 and bandpass filtered (30 Hz-1000 Hz) online. Corrugator activity is greatest during unpleasant pictures and therefore inversely correlated with subjective valence (48, 50). Corrugator responding was calculated by subtracting the mean rectified EMG (in μV) in the 1 s prior to picture onset from the mean rectified EMG during the 6 s of picture presentation (48).

Startle reflex magnitude—Startle is a reflexive response to an abrupt, unexpected stimulus (60). In humans, startle is quantified from the eyeblink response (via orbicularis oculi EMG) that occurs 21-120 milliseconds after an abrupt noise stimulus. Startle magnitude is generally smallest during pleasant pictures and greatest during unpleasant pictures (although comparisons with neutral are not always significant) (60, 61); therefore, startle inversely correlates with subjective reports of valence. Because startle is a rapid reflex mediated by a simple neurocircuit (55), it is an involuntary response. Startle eyeblink magnitude was scored by subtracting the mean rectified and integrated EMG of the 60 ms prior to startle probe onset from the peak rectified and integrated (8 ms time constant) EMG response with an onset 21 to 120 ms following startle-probe onset (48).

SCR—SCR was used as a physiological measure of picture-evoked sympathetic arousal and correlates with subjective reports of arousal (48, 50). SCR was assessed via placement of two Ag/AgCl electrodes filled with isotonic paste (EC33, Grass Technologies) on the volar surface of the index and middle fingers of the non-dominant hand. Participants were asked to thoroughly wash and dry their hands prior to the study to remove dirt and oils and to control for individual differences in exposure to moisture. Because SCR is mediated by the sympathetic nervous system, it is less likely to be influenced by voluntary control. SCR was calculated by subtracting the mean skin conductance (in μS) in the 1 s prior to picture onset from the peak skin conductance that occurred in the 2 - 6 s interval after picture onset (48).

Determination of Suprathreshold Stimulus Intensity used During Picture Viewing

The suprathreshold stimulation intensity used during emotional picture viewing was set to 120% NFR threshold to minimize ceiling and floor effects (62). NFR threshold procedures were identical to those used previously (17). NFR threshold was assessed using 3 ascending-descending staircases of electric stimuli. The first ascending staircase started at 0 mA and increased in 2 mA steps until an NFR was detected. NFR was defined as a mean rectified

biceps femoris EMG response in the 90-150 ms post-stimulus interval that exceeded the mean rectified biceps femoris EMG activity during the 60 ms pre-stimulus baseline interval by at least 1 standard deviation (17). This criterion was chosen because it increased sensitivity for detecting an NFR which reduced the burden on the participants, but also retained adequate specificity (63, 64). After an NFR was obtained, the current was decreased in 1 mA steps until an NFR was no longer detected. The second and third ascending-descending staircases used 1 mA steps. The interval between electric stimulations varied randomly between 8-12 s to reduce predictability and reflex habituation. The average stimulus intensity of the last two peaks and troughs were used to define NFR threshold.

Assessment of Pain and Nociception during Picture-Viewing

Pain ratings—Pain ratings in response to suprathreshold stimulations were assessed via a computer-presented numerical rating scale similar to that used in numerous prior studies (e.g., 22, 65-70). Pain ratings ranged from 0 to 100, with labels at 0 (no sensation), 50 (painful), and 100 (maximum tolerable). Participants used a computer mouse to drag an indicator vertically along the scale to make each rating. It is worth noting that although a rating of 50 corresponds to “pain” we regularly observe that participants use values below 50 to indicate mild pain (17, 22, 31, 32). This numerical rating scale behaves similarly to the “gold standard” visual analog scale (VAS) that uses anchors of “no pain” and “the most intense pain sensation imaginable,” with mild pain occurring near a rating of 30 units (71).

NFR magnitude—The size of the NFR (i.e., NFR magnitude) correlates with stimulus intensity and pain perception (29). Thus, changes in NFR can be used to index changes in spinal nociception during picture-viewing. NFR magnitude was calculated from a *d*-score (*d* = [mean rectified EMG during 90-150 ms post-stimulus interval – mean rectified EMG during 60 ms prestimulus interval] / [average standard deviations of EMG from the −60 to 0 ms prestimulus baseline and 90-150 ms post-stimulus intervals]). Research has shown that calculating NFR magnitude from a *d*-score produces a stronger correlation with pain ratings than other methods of scoring NFR magnitude and improves the distributional qualities of the NFR variable (ie, distribution is normal in shape) (72, 73).

Procedure

All procedures were approved by the University of Tulsa Institutional Review Board (IRB). Once the participant arrived for the experimental session, verbal and written informed consent was obtained. A demographics/health status questionnaire (that included a question on number of hours slept the previous night), sleep questionnaires, and the SCID-I were administered to further assess the participant's health status and eligibility. The numerical rating scale and Self-Assessment Manikin were explained and participants practiced using them. After completion of the forms, the experimenter applied the physiological sensors. To apply sensors, the location was prepped with alcohol to remove dirt and sebum, and NuPrep exfoliant gel was used to remove the outer layers of dead skin cells. Impedances at or below 5 kΩ were obtained for each site, except for the stimulating electrode which was set at or below 2 kΩ. Sensors were then applied using adhesive collars. Participants sat in an upright position in a reclining chair (PC-6 Perfect Chair, Human Touch, Long Beach, CA) in a

dimly lit room with their knee angle set at approximately 160 degrees. Participants were then instructed, by the computer, on the picture-viewing procedure.

Block 1 assessed emotion processing in the absence of pain. Affectively-charged pictures were presented in a random order, with the limitation that no more than 2 pictures of the same category could be shown consecutively. Each picture was shown for 6 s and inter-picture intervals varied randomly from 12-22 s. Startle probes (50 ms duration, 105 dB intensity) were delivered during 9 pictures (3 per content). Probes were also delivered during 4 randomly determined inter-picture intervals to minimize the predictability of their delivery. Thus, a total of 13 probes were delivered during each Block. Each probe started 3 to 5 s after picture onset and 11 to 21 s after inter-picture interval onset in order to reduce predictability. After the presentation of each picture, participants rated their emotional response on the SAM. To ensure that a picture or probe was not delivered during a rating period, the computer automatically paused the experiment during presentation of a rating scale until the participant submitted their ratings by computer mouse.

After the first block, NFR threshold was assessed. Block 2 assessed emotional modulation of pain and NFR. Procedures were identical to those used to assess emotional reactivity in the absence of pain, except that electric stimulations set at 120% NFR threshold were delivered instead of startle probes, and pain NRSs were administered. Before the third block there was a 5-min mandatory break period during which participants were asked to sit quietly and relax. Blocks 3 and 4 used procedures identical to Blocks 1 and 2, respectively. Optional breaks (e.g., 1-5 min) were offered in between blocks if participants requested them. After all procedures were completed, the participant was provided an honorarium.

Data Reduction and Analyses

Physiological data were scored offline via LabVIEW software and visually reviewed for errors. All participants completed all phases of the study. Sixteen trials (1.1%) of startle were excluded due to excessive activity or blinks in the prestimulus baseline (i.e., >20μV), otherwise all trials from other physiological variables were included in the analyses. Data was analyzed using 2 Group (Insomnia, Healthy controls) × 3 Content (Mutilation, Neutral, Erotica) linear mixed model analyses. NFR and pain analyses included stimulus order as a covariate to control for habituation/sensitization to the electric stimuli over repeated presentations (17, 74). Specifically, a variable was created that coded for the order of the 9 electric stimulations that occurred in each block (i.e., order = 1–9), and this variable was entered as a covariate into the analyses. Thus, if the regression slope for this variable is negative then the dependent variable habituated over the 9 stimulations in the block and if it is positive it sensitized. Similarly, startle analyses included acoustic probe order as a covariate to control for startle habituation over time (17). Importantly, habituation and sensitization effects in response to electric stimuli and startle probes do not vary by picture content (74, 75). Emotional reaction analyses included picture order as a covariate to control for habituation to picture content over time. Controlling for these order effects improves statistical power and improves the validity of the statistical models by removing potential habituation/sensitization variance that is unrelated to emotional modulation (74).

Outcomes assessed during emotional reactivity and pain modulation were analyzed separately using the SPSS 17.0 MIXED procedure to increase power and also because cases with missing data are not excluded (76). Each block contained 18 pictures and electric stimulations/startle probes were delivered during 9 pictures in each block; therefore, each participant contributed 36 responses (2 blocks × 18 pictures = 36) for analysis of valence and arousal ratings, 18 responses (2 blocks × 9 unprobed pictures = 18) for analysis of corrugator EMG and SCR, and 18 responses (2 blocks × 9 stimulations or probes = 18) for analysis of reactions to stimulations/probes (startle, pain, NFR). Analyzing the data in this manner (i.e., keeping the data in "long form"), enhances power by increasing the denominator degrees of freedom (*df*) for *F*-tests of within-subject effects. For example, each participant contributes 18 within-subject responses (one for each stimulation/probe) instead of only 3 (one for each picture content); therefore, this means the *df*s are increased 6-fold which has the same effect on statistical power as increasing our sample size 6-fold (72 participants with insomnia symptoms, 78 controls) had we used a traditional general linear model (GLM) ANOVA. This provides power > .99 to detect a very small effect size (i.e., partial $\eta^2 \geq .009$ for pain and NFR) on the Picture Content main effects, Group × Picture Content interactions, and Picture Content simple effects (all of which are the most important for assessing emotional modulation effects).

Subject ID was used as the grouping variable to designate the Level 2 units (i.e., to account for non-independence of observations given that each participant contributed multiple rows of data). Level 1 units were responses to pictures (valence/arousal ratings, corrugator EMG, SCR) or stimulations/probes (pain, NFR, startle). The variance-covariance structure of the repeated measures was modeled using an autocorrelation matrix (AR1). All models included a random intercept to allow outcomes to vary across individuals (Level 2 units). Non-integer Satterthwaite-estimated denominator *df*'*s* were rounded for ease of reporting. Follow-up mean comparisons to significant *F*-tests were conducted using mean contrasts. Significance was set at $p < 0.05$ (two tailed). Corrections for multiple comparisons (e.g., Bonferroni) were not carried out because: 1) the effects of emotional picture viewing on pain, NFR, and emotional reactions are well established therefore mean comparisons were a priori hypothesis-driven and 2) doing so would result in loss of power and the potential for increased Type II error.

Results

Participant Characteristics

To compare groups on background variables, independent samples t-tests and chi-square (or continuity correction in the event that the chi square was not appropriate due to cells with low frequency counts) analyses were conducted (Table 1). Groups had significantly different rates of employment and years of education, however these variables were not expected to significantly influence findings. Groups did not differ significantly in age, sex, race, marital status, or BMI. They also did not differ on most SF-36 scales except vitality, but there were marginally significant differences for role limitations due to emotional functioning, mental health, and social functioning. Further, groups differed on self-reported number of hours slept the previous night, the Insomnia Severity Index, and the Fatigue Severity Scale.

Compared to the control group, the insomnia group reported less vitality/energy and fewer hours slept, but more insomnia symptoms and fatigue.

Emotional Reactions during Non-Pain Blocks (Blocks 1 & 3)

Results of linear mixed model ANOVAs are presented in Table 2 whereas means and SEMs are presented in Table 3.

Valence ratings—A significant main effect of picture content indicated that mutilation was rated as less pleasurable (reduced valence ratings) than neutral and erotica, and erotica was rated as more pleasurable (increased valence ratings) than neutral (all *ps*<.001). However, this was qualified by a significant picture content by group interaction that indicated the insomnia group exhibited less displeasure to mutilation pictures (*p*<.01) and less pleasure to erotic pictures (*p*=.02) than healthy controls. There was no main effect of group.

Corrugator EMG—There was a main effect of picture content, such that corrugator activity was highest during mutilation, intermediate during neutral, and lowest during erotica (all *ps*<.02). There was no main effect or interaction with group.

Startle reflex modulation—There was a main effect of picture content, such that startle was largest during mutilation, intermediate during neutral, and smallest during erotica (all *p*s < .05). There was no main effect or interaction with group. Probe order was significant, indicating that magnitude of blinks habituated within each block ($B = -1.77$, $p<.001$).

Arousal ratings—There was a main effect of picture content, such that mutilation and erotic pictures were rated as more arousing than neutral images (*ps*<.01). There was no main effect or interaction with group.

SCR—There were no group or picture content effects for SCR, but picture order was significant, indicating that the magnitude of SCR habituated within a block ($B = -0.002$, $p=.045$).

NFR Threshold

NFR threshold did not differ between healthy controls ($M=16.50$, $SD=13.47$) and insomnia patients ($M=15.17$, $SD=12.72$), $t(23)=0.26$, $p=.80$, $d=0.10$. Importantly, this means that suprathreshold stimulation intensities used during emotional modulation were not significantly different across groups.

Emotional Modulation of Pain and Spinal Nociception (Blocks 2 & 4)

Results of linear mixed model ANOVAs for pain and NFR are presented in Table 2.

Modulation of pain ratings—A main effect of picture content was observed, but this was qualified by a significant interaction of group by content. The interaction indicated that the insomnia group did not exhibit modulation of pain ratings by picture content (all *p*s>.11), whereas the typical linear trend was noted in controls (Fig 1). Pain ratings were higher

during mutilation than neutral and erotica (*p*s<.001), suggesting they emotionally modulated pain.

Modulation of NFR—A significant main effect of picture content was observed, but the main effect and interaction with group was non-significant. This indicates that both groups demonstrated the typical linear trend, such that mutilation pictures elicited greater NFRs than erotic pictures ($p<.01$). Other comparisons were not significant. Stimulation order was significant ($p<.01$) indicating that NFR magnitudes habituated within blocks ($B = -0.02$, $p=.001$).

Exploratory Analysis—Given our observation that pain modulation and NFR modulation diverged in the insomnia group, we conducted an exploratory linear mixed model regression analysis to examine whether the relationship between pain and NFR varied by group. To do so, pain was entered as the dependent variable and NFR magnitude, Group, and the Group × NFR magnitude interaction were entered as predictors. As expected, there was a significant Group × NFR magnitude interaction, $F(1, 587) = 5.36$, $p = .02$. Consistent with the emotional modulation results, examination of the unstandardized regression coefficients indicated the strength of the relationship between NFR and pain was significantly weaker in the insomnia group ($B = 2.19$) than in the control group ($B = 4.79$, comparison significant at $p = .02$).

Discussion

Emotional Processing in Persons with Severe Insomnia Symptoms

Physiological-emotional responding to pictures generally followed the expected pattern noted in prior studies of healthy persons (48). Compared to neutral, the unpleasant mutilation pictures elicited greater displeasure (lower valence), subjective arousal, corrugator EMG activity, and startle magnitudes. By contrast, compared with neutral pictures, pleasant erotic pictures elicited greater pleasure (valence) and subjective arousal, but lower corrugator EMG activity and startle magnitudes. As we have noted in some of our previous pain studies (e.g., 22), SCR did not vary by picture content likely because pain and pain anticipation evoke sympathetic activation that can overshadow the picture-evoked SCR.

One important group difference in emotional reactivity was noted. Participants in the insomnia group reported less displeasure to the mutilation pictures and less pleasure to erotic pictures compared with the healthy controls. The emotional blunting to pleasant stimuli is consistent with a number of previous studies (for a review, 77). By contrast, emotional blunting in response to unpleasant stimuli is somewhat surprising given that studies have found negative emotions are enhanced by sleep disturbance (77). But, given that Wagner, et al. (78) found that displeasure ratings in response to unpleasant pictures were enhanced by REM sleep, then negative emotional blunting might stem from impaired REM sleep in the insomnia group (79).

Given that we only observed a group difference in subjective valence (pleasure), the effect might be mediated by supraspinal circuits involved with conscious emotional experience. Indeed, some supraspinal regions (e.g., hippocampus, orbitofrontal cortex) correlate with

conscious emotional appraisal, whereas others (e.g., amygdala) correlate with the non-conscious detection and processing of emotional stimuli (52, 54). Therefore, it is possible that hippocampus and/or orbitofrontal responsivity plays a role in the emotional valence blunting. Alternatively, it could result from disruptions in top-down control from the medial prefrontal cortex, as has been noted previously in sleep deprived individuals (28).

Emotional Modulation of Pain and NFR in Persons with Severe Insomnia Symptoms

As predicted, individuals with insomnia symptoms, in comparison with healthy controls, failed to emotionally modulate pain perception. This is consistent with two prior studies that examined a different pain modulatory process in persons with disrupted sleep. Specifically, Smith, et al. (10) found that repeated awakening of healthy women led to increased spontaneous pain complaints and a reduced capacity to inhibit pain as assessed via conditioned pain modulation (CPM; using a painful stimulus to inhibit pain evoked at a distant location). Similarly, Haack, et al. (80) found that otherwise healthy individuals with insomnia had increased spontaneous pain, enhanced pain sensitivity (lower heat and pressure pain thresholds), and a deficit in CPM-related pain inhibition. These studies suggest that disturbed sleep impairs the body's ability to inhibit pain in the presence of other pain (i.e., counterirritation). When taken together, these data imply that sleep disruption may affect multiple pain modulatory circuits because emotional modulation of pain is believed to be mediated by neurocircuitry distinct from CPM (12, 13, 81, 82). This may cause a global failure to down-regulate pain that results in an inability to keep pain in check when necessary.

Interestingly, the present study also suggests that disrupted sleep is associated with a failure to up-regulate pain in the presence of unpleasant affective stimuli. At first glance this might seem advantageous; however, in some circumstances it is adaptive to enhance pain in order to improve detection of somatic threat and/or promote recuperation from injury (23). So, a failure to emotionally up-regulate pain might also place individuals at risk for pain and/or injury.

Our failure to find a group difference in suprathreshold pain ratings was somewhat surprising given prior evidence that sleep disturbance is associated with hyperalgesia (7-9, 80). However, suprathreshold stimulus intensities were tailored to each individual and that might have obscured our ability to observe hyperalgesia on pain ratings of these stimuli. Moreover, suprathreshold stimulus intensity was (non-significantly) lower in the insomnia group which might account for the non-significant trend for their suprathreshold pain ratings to be lower (Fig 1).

As predicted, we did not find a group difference in emotional modulation of NFR even though there was a group differences in pain modulation. Indeed, both groups showed the valence linear trend modulation of NFR. This is consistent with our finding that groups did not differ in NFR threshold. Given that NFR provides information about spinal nociceptive processes that is unique from information provided by measures of pain perception (29), these observations imply that insomnia-related pain risk and hyperalgesia likely stem from a disruption of pain processing at the supraspinal level, not the spinal level.

Does a Failure to Emotionally Modulate Pain Confer Risk for Chronic Pain?

The present data on persons suffering from severe insomnia symptoms parallel those found in recent studies of fibromyalgia and major depressive disorder (17, 33). Specifically, all three groups failed to emotionally modulate pain, but had intact emotional modulation of NFR. Notably, fibromyalgia and major depression groups were not associated with reduced displeasure to mutilation, even though (like insomnia) they showed reduced pleasure ratings to erotica. Given this, it is possible that a general emotional blunting associated with insomnia led to a failure to engage pain modulation. However, a general failure to respond to the pictures cannot completely explain our findings in participants with insomnia symptoms because: 1) there were no group differences on any other emotion variable (including the physiological measures of valence) and 2) emotional modulation of NFR was observed.

Thus, the similarities in emotional modulation of pain and NFR across fibromyalgia, major depression, and insomnia symptom sufferers may suggest a similar disruption of supraspinal circuitry in these groups. At least two different modulatory circuits are engaged by emotional picture-viewing (13). Emotional modulation of NFR is associated with activity in the dorsolateral prefrontal cortex, parahippocampal gyrus, thalamus, amygdala, and brainstem nuclei, whereas emotional modulation of pain is associated with activity in the orbitofrontal cortex, subgenual anterior cingulate cortex, cuneus, and insula (13). As a result, a failure to emotionally modulate pain may be a phenotype for the disruption of the emotional modulation of pain circuit. A disruption of this circuit might confer risk for pain by impairing a person's ability to flexibly modulate the pain signal once it reaches the brain, even though the pain signal is modulated at the spinal level. If this hypothesis is true, it suggests that teaching these individuals to regulate pain via standard cognitive-behavioral strategies (e.g., increase positive emotions, decrease negative emotions) may not be effective until disruptions in the supraspinal circuit are corrected. However, it is important to note that the linkage between emotional modulation of pain and future chronic pain risk is currently speculation. Longitudinal prospective studies are needed to identify whether a causal relationship exists.

Limitations

The present study has a few limitations to be considered. First, our small sample size may have reduced statistical power, thereby obscuring some group differences. However, this is likely to have the greatest negative impact on between-subject contrasts (i.e., main effect of group in linear mixed models, independent samples t-tests), because the power of within-subject effects is increased by the use of linear mixed ANOVAs (note the large denominator degrees of freedom in the main effect of picture content and the Group × Picture Content interaction, Table 2). Indeed, statistical power was >.99 to detect very small within-subject effects which were the primary effects of interest (i.e., emotional modulation of pain/NFR). Further, to increase confidence that Type II errors were not a problem, the simple effect of picture content (the well-powered within-subject effect) was examined within each group even when the Group × Picture Content interaction was non-significant. This resulted in the same conclusions. Nonetheless, our failure to find group differences on some variables (e.g.,

suprathreshold pain ratings, the degree of emotional modulation of NFR) may have resulted from our small sample and therefore null findings should be interpreted with caution.

Second, occult sleep disorders (e.g., sleep apnea, periodic limb movement) could not explicitly be ruled out. We relied exclusively on self-report of symptoms to verify participants met criteria for a diagnosis of primary insomnia. Although self-report is often used to establish an insomnia diagnosis (e.g., 35, 42), it is not very effective for ruling out other potentially confounding sleep problems. Therefore, future studies are needed to replicate these findings using polysomnography to exclude for occult sleep diagnoses and/or in a study of healthy participants who have undergone experimental disruption of sleep.

Third, the majority of insomnia participants had histories of psychiatric diagnoses while none of the healthy controls had such histories. Thus, it is possible that a history of psychiatric problems may have accounted for some of the observed group differences. To address this, future studies should match groups on current and past psychiatric diagnoses. Matching should also be conducted to ensure that groups do not differ on background variables (e.g., years of education, employment status).

Conclusions

In sum, severe insomnia symptoms were associated with emotional blunting (subjective ratings of valence) and a disruption of emotional modulation of pain, but intact emotional modulation of spinal nociception (i.e., NFR). Therefore, this study extends prior work to show that sleep disturbance has a negative effect on pain regulatory processes other than conditioned pain modulation. Given that similar findings have been observed in fibromyalgia and major depressive disorder, a failure to emotionally modulate pain (but not NFR) may be a phenotype for chronic pain risk. However, future research is needed to confirm this hypothesis.

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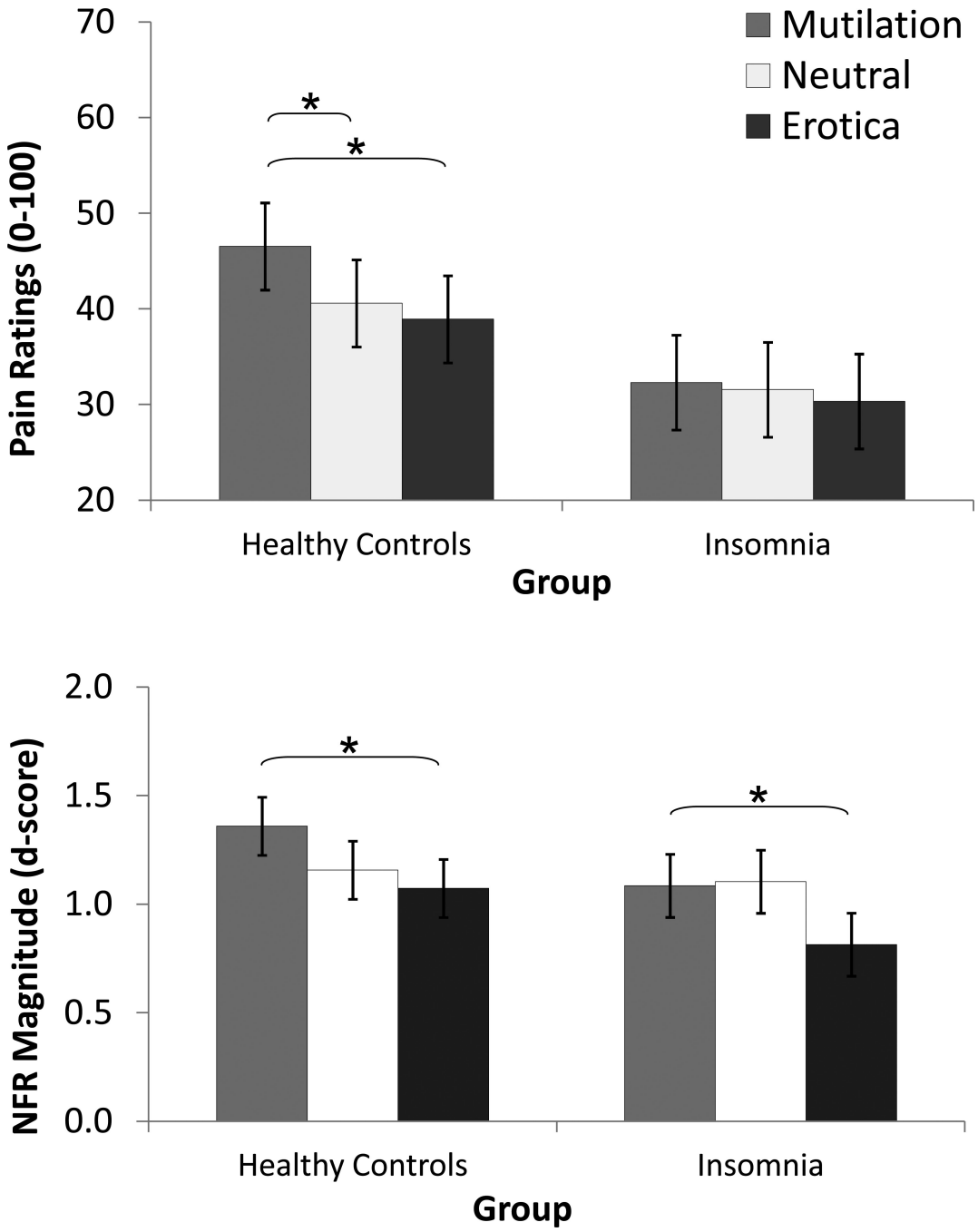

Figure 1.

Emotional modulation of pain (top graph) and nociceptive flexion reflex (bottom graph) across picture contents and groups. Emotional modulation of pain was observed in healthy controls but not participants with insomnia symptoms But, emotional modulation of spinal nociception (NFR) was observed in both groups.

Table 1

Participant Characteristics by Group

	Healthy Controls (*n*=13)		Insomnia (*n*=12)				
Characteristics (units)	***M / n***	***SD / %***	***M / n***	***SD / %***		***t* / χ^2**	***p*-value**
Age (years)	37.23	13.96	36.75	14.35		0.85	0.933
Sex (% Female)	7	53.8%	5	41.7%		0.37	0.543
Race (% Caucasian)	13	100%	9	75%		1.71	0.192
Marital Status (% Married)	7	53.8%	2	16.7%		2.30	0.129
Employed (% full or part-time)	9	69.2%	4	33.3%		4.41	0.041
Years of Education (years)	15.53	2.26	12.32	4.73		2.18	0.040
Body Mass Index (kg /m^2)	26.06	3.97	23.88	4.67		1.26	0.224
SF-36 Physical Functioning (0-100)	93.85	7.12	90.42	18.40		0.62	0.539
SF-36 Role Physical (0-100)	94.87	18.49	89.58	16.71		0.75	0.462
SF-36 Role Emotional (0-100)	100.00	0.00	80.56	36.12	1	1.87	0.089
SF-36 Vitality (0-100)	68.46	12.65	52.08	13.22		3.17	0.004
SF-36 Mental Health (0-100)	84.00	8.94	75.67	11.50		2.03	0.054
SF-36 Social Functioning (0-100)	96.15	7.88	85.42	16.71		2.03	0.060
SF-36 Bodily Pain (0-100)	84.62	17.20	83.75	18.07		0.12	0.903
SF-36 General Health (0-100)	79.23	11.70	79.58	12.70		0.07	0.943
Amount Slept Previous Night (hours)	7.41	1.20	4.32	1.55		5.22	<0.001
Insomnia Severity Index (0-28)	7.23	7.00	27.42	4.52		7.99	<0.001
Fatigue Severity Scale (9-63)	21.38	11.29	39.42	8.48		4.48	<0.001

Table 2

Results of linear mixed model ANOVAs for emotion and pain outcomes

	Valence Ratings		Corrugator EMG		Startle Magnitude		Arousal Ratings		SCR		Pain Ratings		NFR	
Fixed Effects	***df***	***F***	***df***	***F***	***df***	***F***	***df***	***F***	***df***	***F***	***df***	***F***	***df***	***F***
Group	1,25	0.03	1, 25	1.21	1, 25	0.64	1,25	0.18	1,25	0.92	1, 25	2.19	1, 25	1.19
Content	2, 716	673.05*	2, 322	12.91*	2, 353	8.71*	2,718	232.62*	2, 319	1.20	2, 314	16.13*	2, 330	12.97*
Group × Content	2, 715	18.27*	2, 318	0.37	2, 350	1.75	2, 717	2.61	2, 314	2.65	2, 316	6.59*	2, 331	2.42
Order	1, 413	0.01	1, 252	0.31	1, 270	18.19*	1, 415	0.27	1, 253	4.07*	1, 306	0.0003	1, 263	12.08*

Note:

NFR=Nociceptive flexion reflex

*p<.05

Table 3

Means and SEMs for emotion outcomes in Insomnia (*n*=12) and Healthy Controls (*n*=13)

	Picture Contents							
DV by Group	**Mutilation**			**Neutral**			**Erotica**	
	M	***SEM***		***M***	***SEM***		***M***	***SEM***
Valence Ratings (1-9)								
Healthy Controls	1.61*	0.17		5.23	0.17		6.56*	0.17
Insomnia	2.40*	0.17		4.98	0.17		5.97*	0.17
All participants	2.00[a]	0.12	a	5.13[b]	0.12	b	6.27[c]	0.12
Corrugator EMG (ΔμV)								
Healthy Controls	1.06	0.26		0.48	0.26		−0.12	0.26
Insomnia	1.24	0.27		0.78	0.27		0.39	0.27
All participants	1.15[a]	0.19	a	0.63[b]	0.19	b	0.14[c]	0.19
Startle Magnitude (ΔμV)								
Healthy Controls	69.28	13.20		58.35	13.19		57.19	13.18
Insomnia	83.99	13.86		80.23	13.79		65.27	28.15
All participants	76.63[a]	9.57	a	69.29[b]	9.54	b	61.23[c]	9.56
Arousal Ratings (1-9)								
Healthy Controls	5.17	0.36		2.73	0.36		5.41	0.36
Insomnia	5.24	0.38		2.13	0.38		5.30	0.38
All participants	5.21[a]	0.26	a	2.43[b]	0.26	b	5.35[a]	0.26
SCR (ΔμS)								
Healthy Controls	0.04	0.02		0.02	0.02		0.02	0.02
Insomnia	0.05	0.02		0.03	0.02		0.07	0.02
All participants	0.05[a]	0.01	a	0.03[a]	0.01	a	0.05[a]	0.01

Note. SCR = skin conductance response. NFR = nociceptive flexion reflex. “All participants” refers to means for the main effect of picture content. Means in the “all participants” rows that have different superscripts are significantly different at $p<.05$.

*simple effect of group is significant at $p<.05$. If there was no main effect of group or no Group × Picture Content interaction, then no superscripts are reported for the simple effect of picture content within each group.