Are There Sex Differences in Affective Modulation of Spinal Nociception and Pain?

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Abstract: Sex differences in the processing and experience of emotion exist. The present study examined whether sex differences in emotion lead to sex differences in affective modulation of pain and spinal nociception (assessed by nociceptive flexion reflex, NFR). Participants were healthy men (n = 47) and women (n = 73). Prior to affective modulation testing, electrocutaneous pain sensitivity was assessed (NFR threshold, pain threshold, pain tolerance). Affective modulation of pain and NFR was then assessed by presenting pictures that vary in emotional valence and arousal (mutilation, attack, death, neutral, families, adventure, erotica) during which suprathreshold electrocutaneous stimulations were delivered. Subjective emotional reactions were assessed after every picture, and nociceptive reactions were assessed after every suprathreshold stimulus. Results indicated women had greater pain sensitivity and also responded more negatively to attack pictures and less positively to erotic pictures. But despite these differences, affective modulation of pain/NFR was not moderated by sex: erotic pictures inhibited pain/NFR and mutilation pictures enhanced pain/NFR. Together, this implies subjective emotional experience does not completely mediate picture-evoked modulation of pain/NFR, a supposition that was further supported by exploratory analyses that demonstrated picture-evoked modulation of pain/NFR was present even after controlling for intra- and inter-individual differences in emotional reactions to pictures. Implications and limitations of these findings are discussed.

Perspective: Evidence suggests that women are more sensitive to experimental and clinical pain, but the mechanisms contributing to these sex differences are poorly understood. Affective processes are known to play a role in regulating pain signaling and pain experience; therefore, the present study examined whether sex differences in affective experience contribute to sex differences in pain. Results indicate that in healthy individuals affective processes may not contribute to sex differences in pain.

Key words: Emotion, pain, pain modulation, nociceptive flexion reflex, sex differences.

Pain has a negative impact on men and women, but women suffer from more chronic pain conditions and report clinical pain more frequently, with longer duration and greater severity. Similarly, laboratory research suggests women have greater pain sensitivity and greater physiological nocireactivity to noxious stimuli. While the mechanisms responsible for sex differences in pain are likely manifold, sex differences in affective modulation of pain could contribute. Evidence suggests affective experiences influence pain according to a valence-by-arousal interaction (Fig 1). Valence refers to the pleasantness-unpleasantness of emotions and is related to the direction of modulation (pleasant = pain inhibition, unpleasant = pain facilitation; see Rhudy and Williams for a caveat regarding low base rate, intense negative emotions). Arousal is associated with the intensity/activation of emotions and is related to the degree of pain modulation (greater arousal = greater inhibition/facilitation). Supporting this, arousing pleasant pictures (erotica) inhibit pain and arousing unpleasant pictures (threat) facilitate pain, but pleasant and unpleasant pictures with low arousal (food, grieving) do not significantly modulate...
rate emotions so the current figure depicts the influence of stimuli (especially erotic). These differences in emotional reactivity to unpleasant stimuli (especially threat) and less reactivity to pleasant stimuli, low statistical power, failure to consider valence manipulation checks, use of unstandardized emotional stimuli, and methodological problems that limit the conclusions. However, much of this research suffers from methodological problems that limit the conclusions (eg, reliance on pain self-report, between-subject emotion manipulation or no emotion manipulation, lack of manipulation checks, use of unstandardized emotional stimuli, low statistical power, failure to consider valence and arousal). To address these concerns, the present study used a large sample (n = 120; 73 women) and state-of-the-art methods for emotion-induction, nociception measurement, and statistical analysis (multilevel modeling). First, pain sensitivity was assessed (NFR threshold, pain threshold, pain tolerance) and then pictures that varied in valence and arousal (mutilation, attack, death, neutral, families, adventure, erotica) were presented during which suprathreshold nociceptive stimuli were randomly delivered. We predicted that

1) women would have greater pain sensitivity;
2) women would respond with greater displeasure to unpleasant pictures (especially threat), leading to greater pain/NFR facilitation relative to men;
3) men would respond with greater pleasure to pleasant pictures (especially erotic), leading to greater pain/NFR inhibition relative to women.

Further, exploratory analyses were conducted to determine whether emotional reactions to pictures mediated the relationship between picture viewing and pain/NFR. While plausible, pain/NFR modulation may not depend on conscious emotional experience because emotional experience evoked by pictures may be processed in supraspinal regions (eg, hippocampus, orbitofrontal cortex) distinct from those critical for affective modulation of nociception (eg, amygdala). Portions of this paper were presented at the 2009 American Pain Society meeting.

Methods

Participants

All participants provided written and verbal informed consent after the study procedures were fully described to them. Participants were recruited from the community by newspaper advertisements, email distribution, and fliers. Participants were excluded if they were <18 years old; self-reported a history of neurological, cardiovascular, and/or circulatory problems; reported recent use of analgesic, antidepressant, anxiolytic, or antihypertensive medications; had a specific phobia of snakes or spiders (shown during picture viewing); reported any diagnosis of chronic pain; acknowledged a recent psychological trauma as defined by the DSM-IV; or were diagnosed with Raynaud’s disease. Twenty-five participants were enrolled, but not included in the final analyses due to: equipment problems (n = 5), reaching 40 mA maximum stimulation before NFR obtained (n = 7), and reaching pain tolerance before NFR obtained (n = 13). One hundred and twenty participants (73 women) completed the study and are included in analyses. Average age was 35 years (SD = 15) and most participants were Caucasian (n = 91), single (n = 68), and employed (n = 91), with an average of 15 years of education (SD = 2.66). Of the 73 women who completed the study, 19 reported taking hormone preparations for birth control and 16 women reported being menopausal or postmenopausal (or were assumed to be so because they were ≥49 years and had not menstruated for at least 90 days). Women were asked to report the number

Figure 1. The proposed valence by arousal interaction that characterizes the influence of emotion on pain. Emotional valence (pleasant versus unpleasant) is associated with the direction of modulation (inhibition versus facilitation), whereas emotional arousal is associated with the degree of modulation (greater arousal = greater inhibition or facilitation). It should be noted that intense negative emotions can inhibit pain (fear-induced hypoalgesia); however, these are low base rate emotions so the current figure depicts the influence of most emotions on pain.

Importantly, a physiological correlate of spinal nociception (nociceptive flexion reflex, NFR) is similarly modulated, suggesting affective pictures engage corticospinal modulatory mechanisms. Interestingly, the amygdala, a region critical for nociception modulation, is activated by emotional stimuli according to a valence-by-arousal interaction, suggesting it may play a role in affective modulation of pain.

Compared to men, women experience more negative affect and less positive affect. They also show greater physiological/emotional reactivity to unpleasant stimuli (especially threat) and less reactivity to pleasant stimuli (especially erotic). These differences in emotion could contribute to sex differences in pain. For example, women’s greater tendency to experience unpleasant emotions could contribute to relatively greater pain facilitation, whereas their tendency to experience less pleasant emotions could lead to relatively less pain inhibition. The net result would be a tendency for enhanced pain in females, relative to males. Pain itself is threatening and evokes negative emotions; therefore, sex differences in emotional reactivity could contribute to sex differences in pain even in the absence of another emotional stimulus. Supporting this, sex differences in experimental pain are greater when the absence of another emotional stimulus. While a few studies have failed to demonstrate these proposed sex differences in affective modulation of pain, many others have. However, much of this research suffers from methodological problems that limit the conclusions (eg, reliance on pain self-report, between-subject emotion manipulation or no emotion manipulation, lack of manipulation checks, use of unstandardized emotional stimuli, low statistical power, failure to consider valence and arousal). To address these concerns, the present study used a large sample (n = 120; 73 women) and state-of-the-art methods for emotion-induction, nociception measurement, and statistical analysis (multilevel modeling). First, pain sensitivity was assessed (NFR threshold, pain threshold, pain tolerance) and then pictures that varied in valence and arousal (mutilation, attack, death, neutral, families, adventure, erotica) were presented during which suprathreshold nociceptive stimuli were randomly delivered. We predicted that

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of days since the start of their last menstrual period and their average cycle length. \(^\text{28,31}\) Using methods based upon Fehring et al,\(^\text{21}\) these reports were used to estimate the menstrual phase at the time of testing. Of the 38 women not taking hormone birth control and who were not menopausal/postmenopausal, 21 were in the follicular phase, 16 were in the luteal phase, and 1 woman was considered oligomenorrheic (because she was 19 years old, had not menstruated in over 35 days, and was not taking hormone birth control). Participants were paid $100 for study completion.

**Apparatus, Signal Acquisition, and Electrode Application**

Experimenteres monitored physiological signals, experimental timing, and participant behavior from an adjacent room. A video camera with a microphone allowed the experimenter to monitor and hear the participant, whereas a microphone connected to a 40 W audio amplifier (Radio Shack, Fort Worth, TX; Part #32-2054) allowed the experimenter to communicate with the participant, who was wearing sound-attenuating headphones. All data acquisition, as well as stimuli and questionnaire presentation, were controlled by a PC equipped with dual monitors, A/D board (PCI-6036 or PCI-6031E; National Instruments, Austin, TX), and LabVIEW (National Instruments) software. One video output from the computer was used to present questionnaires and pictures via an LCD projector onto a large screen in front of the participant. A second video output was displayed to a 17” flat panel monitor so that an experimenter could monitor physiological signals and experimental timing.

A Grass instruments stimulator (Model S88 or Model S48, West Warwick, RI), stimulus isolation unit (Model SIU8T), constant current unit (Model CCU1), and bipolar stimulating electrode (Nicolet, 019-401400, Madison, WI) were used to deliver noxious electrocutaneous stimuli to the left ankle over the retromalleolar pathway of the sural nerve. The onset/offset of the stimulator was controlled by computer and a custom-built computer-controlled voltage regulator varied the current to the participant (max current = 40 mA). During NFR threshold testing, psychophysiological signals were sampled in 7-second trials (1-second preshock, 6-second postshock), whereas during affective modulation testing, signals were sampled in 9-second trials during interpicture intervals (3-second preshock, 6-second postshock) and 14-second trials during pictures (3-second prepicture, 6-second during picture, and 5-second postpicture). Sampling rate was set at 1,000 Hz and signals were collected/filtered using a Grass Instruments Model 15LT Bipolar Amplifier with 1 Dual DC (15A12) and 2 Quad AC (15A54) modules. All recording electrodes were Ag-AgCl.

To apply electromyographic (EMG) and stimulating electrodes, the skin was first degreased with alcohol, slightly abraded using NuPrep gel to achieve impedances below 5 K\(\Omega\), and then electrodes were filled with conductive gel (EC60, Grass Instruments, West Warwick, RI) before they were secured to the skin using adhesive collars. For recording NFR, 2 electrodes were placed over the biceps femoris muscle of the left leg 10 cm superior to the popliteal fossa and a common reference electrode was placed over the lateral epicondyle of the femur. The raw signal was amplified (× 20,000), bandpass filtered (10–300 Hz), and rectified.

**Basal Pain/Nociceptive Sensitivity Testing**

Electrocutaneous pain and nociceptive sensitivity were assessed from NFR threshold, ratings of suprathreshold stimuli, pain threshold, and pain tolerance.

**Nociceptive Flexion Reflex (NFR) Threshold**

The NFR is a spinally-mediated withdrawal reflex, dependent on activation of A-delta nociceptors,\(^\text{70,80}\) with a threshold that is highly correlated with pain threshold.\(^\text{70}\) Supraspinal regions are not necessary for its elicitation; therefore, NFR is used to assess spinal nociceptive processes.\(^\text{70,72}\) To facilitate relaxation of the leg muscles, participants were seated comfortably in a recliner, with a small pillow situated under the left ankle. The procedures for assessing NFR threshold were adapted from France et al\(^\text{24}\) and used in previous studies.\(^\text{63,64}\) Trains of 5, 1-ms rectangular wave pulses at 250 Hz (ie, 3-ms ITI) were delivered to the sural nerve with a varying intertrain interval of 8 to 12 seconds to reduce stimulus predictability. The first train started at 0 mA (current) and was increased in steps of 1.5 mA until an NFR was detected. The NFR was defined as a mean biceps femoris EMG response in the 90- to 150-ms poststimulus interval that exceeded mean EMG activity during the 60-ms prestimulus baseline interval by 1.4 SD as suggested by empirical evidence.\(^\text{57}\) Using the 90- to 150-ms timeframe reduces potential contamination by the non-nociceptive RII reflex, startle responses, and/or voluntary movements.\(^\text{19}\) The stimulus intensity was then decreased in .75-mA steps until an NFR was no longer observed. This up-down staircase process was repeated 2 more times, but with the use of .5-mA steps. NFR threshold was defined as the average stimulation intensity (in mA) of the last 2 peaks and troughs of the up-down staircase procedure.

**Ratings of Suprathreshold Stimuli**

Following every electrocutaneous stimulus, participants rated their experience using a computer-presented numerical rating scale (NRS).\(^\text{63}\) The scale ranged from 0 to 100 with the following labels: 0 (no sensation), 1 (just noticeable), 25 (uncomfortable), 50 (painful), 75 (very painful), and 100 (maximum tolerable). Participants responded by moving an indicator to a position along the line that corresponded to their rating and submitted their answer by computer mouse. Ratings of suprathreshold stimuli were assessed from the average ratings of the 4 stimuli corresponding to the last 2 peaks and 2 troughs from the NFR threshold assessment.

**Electrocutaneous Pain Threshold and Tolerance**

Immediately following NFR threshold assessment, pain threshold and tolerance were assessed. Electric
stimulation over the sural nerve (using the same pulse train parameters as NFR threshold procedures) was increased in 1.5-mA steps (variable 8–12 s ITI) until pain tolerance (intensity corresponding to 100 rating on the NRS) or the 40-mA maximum was achieved. Pain threshold was defined as the first stimulus intensity rated ≥50 on the NRS rating scale. Pain tolerance was defined as the stimulus intensity rated 100 (or 40 mA if the maximum was reached).

**Emotional Controls of Nociception (ECON) Paradigm**

The ECON paradigm is used to assess affective modulation of pain and nociception by delivering suprathreshold stimuli while participants view affectively charged pictures.

**Picture Stimuli**

In the present study, 108 digital pictures were chosen from the International Affective Picture System (IAPS) that varied in affective valence (36 unpleasant, 36 neutral, 36 pleasant). Pleasant-picture contents included couples in erotic poses, families, and adventure (eg, motorcycle racing, hang-gliding). Unpleasant-picture contents included death (eg, people grieving, cemetery scenes), mutilation (eg, injured bodies), and attack scenes (eg, humans attacking other humans, animals/people attacking viewer). Neutral-picture contents included household objects, mushrooms, designs, and neutral faces. These contents were chosen because they also differ in emotional arousal. The pictures were split into 4 blocks of 27 pictures, with each block containing 9 pleasant (3 erotic, 3 families, 3 adventure), 9 neutral, and 9 unpleasant (3 death, 3 attack, 3 mutilation) pictures. Normative IAPS ratings were used to ensure that blocks were equivalent in valence/pleasure and arousal ratings (see description of SAM ratings below). IAPS picture numbers for the contents were: mutilation (3062, 3110, 3250, 3064, 9252, 9253, 3068, 9405, 2800, 9440, 7205, 9480, 2205, 2810, 9000), attack (1931, 6250, 6350, 1050, 1932, 6510, 1321, 3530, 6550, 1120, 1525, 6260), death (2141, 9421, 9440, 2800, 9220, 9490, 2276, 9430, 9480, 2285, 2810, 9000), neutral (2190, 5390, 5500, 6150, 7205, 7280, 5520, 7000, 7038, 7040, 7110, 7705, 2480, 5534, 7010, 7020, 7235, 7900, 5350, 5530, 7004, 7060, 7100, 7234, 2580, 2880, 7034, 7050, 7187, 7190, 5531, 5533, 7030, 7080, 7090, 7224), families (2208, 2310, 2311, 2165, 2170, 2224, 2303, 2395, 2660, 2340, 2341, 2655), adventure (5626, 8260, 8470, 5470, 8193, 8340, 5460, 8192, 8300, 2216, 8116, 8161), erotica (4651, 4658, 4659, 4652, 4681, 4689, 4647, 4670, 4687, 4664, 4672, 4683).

**Subjective Responses to Pictures**

Picture-evoked emotional responses were assessed using a custom-built, computerized version of the

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**Figure 2.** Procedural diagram for the Emotional Controls of Nociception (ECON) paradigm.
defined by NFR Cohen’s d\(^2\) (*Indicates significant difference between men and women*). Neu, neutral; Fam, families; Adv, adventure; Ero, erotica. Abbreviations: Mut, mutilation; Att, attack scenes; Dea, death; pictures were similar in men and women. Error bars are SEM. The bottom panel depicts arousal ratings. Arousal ratings of pictures were similar in men and women. (P < .05).

**Figure 3.** Subjective valence and arousal responses to emotional-picture contents in men and women. Filled bars represent men and open bars represent women. The top panel depicts valence/pleasure ratings. Men rated the erotica as more pleasurable, whereas women rated attack as less pleasurable. Women also rated families as more pleasurable than men did. The bottom panel depicts arousal ratings. Arousal ratings of pictures were similar in men and women. Error bars are SEM. Abbreviations: Mut, mutilation; Att, attack scenes; Dea, death; Neu, neutral; Fam, families; Adv, adventure; Ero, erotica. *Indicates significant difference between men and women.*

Self-Assessment Manikin (SAM\(^1\), a 2-item questionnaire that yields valence/pleasure (unpleasant-pleasant) and arousal (calm-excited) ratings that range from 1 to 9. Higher scores indicate greater pleasure or arousal, respectively. Participants rated each picture immediately after it was presented.\(^7\)

**Nociceptive Outcomes During Picture Viewing**

Electrocutaneous stimulations set at 120% NFR threshold were randomly delivered throughout picture viewing to elicit nociceptive responding. The numerical rating scale that was used during pain sensitivity testing was also used to assess subjective reactions to the supra-threshold electrocutaneous stimuli delivered during picture viewing. NFR magnitude was used to assess within-subject changes in spinal nociceptive processes during picture viewing.\(^14,32,58,63\) NFR magnitude was defined by NFR Cohen’s d\(^2\) (\(d = \frac{\text{[mean EMG in the 90- to 150-ms postshock interval] - mean EMG response in the –60- to 0-ms preshock baseline]}{\text{pooled standard deviation of the 2 intervals}}\)). This scoring method was based on evidence that it produces a normal distribution and has a stronger correlation with subjective pain ratings than other scoring methods (eg, peak response, area under the curve).\(^54,55\) Trials with excessive activity in the preshock baseline EMG activity were rejected (4% rejected).

**Psychosocial Variables**

Pain catastrophizing and depressive symptoms were assessed to determine if men and women differed on these variables known to influence pain.

**Pain Catastrophizing Scale (PCS)**

The PCS is a reliable and valid 13-item scale that assesses catastrophic thinking in response to pain.\(^73\) Responses are made on a 5-point scale that ranges from 0 (not at all) to 4 (all of the time). For the present study, the PCS was administered prior to pain testing using traditional instructions, and items were summed to achieve a PCS total score that can range from 0 to 52, with higher scores indicating greater catastrophizing about pain.

**Center for Epidemiological Studies-Depression Scale (CES-D)**

The CES-D is a reliable and valid 20-item questionnaire in which participants respond on a 4-point scale that ranges from 0 (rarely or none of the time) to 3 (most or all of the time) with instructions to rate their symptoms during the past week.\(^51\) The CES-D was administered prior to pain testing, and items were summed to achieve a total score that can range from 0 to 60, with higher scores indicating greater symptomatology.

**Procedure**

All procedures were fully approved by the University of Tulsa ethics review board. At the testing session, the experimenter provided a thorough overview of the experiment and obtained informed consent. A demographics form and brief interview was administered to attain background information and assess inclusion/exclusion criteria. Participants were then instructed on the use of the 0 to 100 numerical rating scale and the Self-Assessment Manikin. After being fully instrumented for physiological recording, psychosocial questionnaires were administered.

The complete testing session consisted of 3 phases: 1) startle modulation testing; 2) basal pain sensitivity testing; and 3) affective modulation of pain/nociception (ECON). Throughout all phases, participants were seated comfortably in a recliner chair with the footrest up and a small pillow placed under the left ankle to facilitate relaxation of the leg muscles. The room was dimly lit, and questionnaires and picture stimuli were presented by an LCD projector onto a large screen mounted approximately 3 m in front of the participant.

During startle testing, participants viewed a set of 54 affectively charged pictures during which 105-dB white noise bursts were delivered over headphones. These pictures were different from those presented during ECON. Results from startle modulation testing are being analyzed for another report, so they are not discussed further. Basal-pain-sensitivity testing involved the assessment of NFR threshold followed by assessment of electrocutaneous pain threshold and tolerance.

**Fig 2** depicts ECON procedures which were similar to previously published studies,\(^63-65\) except that 108 affectively charged pictures were presented in 4 blocks.
of 27 pictures, with each block containing 9 pleasant (3 erotic, 3 adventure, 3 families), 9 neutral, and 9 unpleasant (3 mutilation, 3 attack, 3 death) pictures. Pictures were randomized within the block for each participant with the limitation that the same picture content was not shown more than twice consecutively. Each picture was presented for 6 seconds and interpicture intervals varied randomly from 12 to 22 seconds. The participant was instructed to view every picture presented on the projector screen and told that electric stimuli would be delivered randomly during and in between pictures. Suprathreshold electric stimulations (set at 120% NFR threshold) were trains of 5, 1-ms rectangular wave pulses at 250 Hz that were delivered over the sural nerve. These stimuli were delivered during 1/3 of the pictures (balanced across picture valence and contents), thus resulting in 4 stimuli being delivered during each emotional content and 12 stimuli delivered during neutral content. We have previously shown that 3 to 4 suprathreshold stimuli per content are adequate to achieve a reliable estimate of noxious responding. Suprathreshold stimuli were also delivered during 16 intertrial intervals to reduce predictability. Thus, a total of 52 stimulations were delivered during ECON. Suprathreshold stimuli were randomly delivered 3 to 5 seconds after picture onset and 11 to 21 seconds after interpicture interval onset, also to reduce predictability. Moreover, the 3- to 5-second postpicture-onset interval was chosen because it has been shown to produce the largest affective modulation effects on the acoustic startle reflex (a protective reflex like the NFR). Following every picture, the Self-Assessment Manikin was administered to assess subjective emotional responses to the pictures. The numerical rating scale was administered following pictures and interpicture intervals in which a suprathreshold stimulus was delivered. During rating periods, experimental timing was paused to ensure another picture or electric stimulus was not delivered. After each block of 27 pictures, participants were offered a short break. At study completion, participants were thanked and paid their honorarium.

**Data Analysis**

For the present study, women were initially split up into 4 groups based on hormonal status (follicular phase, luteal phase, hormone birth control, menopausal/postmenopausal). The 1 woman who was determined to be oligomenorrheic was excluded from these analyses. Consistent with a recent study from our laboratory that examined menstrual cycle effects and verified hormonal status, there were no differences between groups of women on any measure of basal pain sensitivity or affective modulation of pain/NFR. Therefore, to simplify the presentation of these data, the four groups of women were combined in order to examine the influence of sex (ie, women were collapsed across hormonal status).

Chi-square or independent samples t-tests were conducted to examine whether there were sex differences in demographic characteristics, psychosocial variables, and basal-pain sensitivity. For analysis of ECON data, all outcome variables were analyzed using a 2 (Sex) × 7 (Picture Content) multilevel model using the SPSS 14.01 MIXED procedure (SPSS Inc, Chicago, IL). Data were analyzed at the trial/picture level, such that every participant had 108 rows of data corresponding to each picture (trials were nested within participants). Subject ID number was used as the grouping variable to model between-subject variability, and the covariance structure of the repeated measures was a first-order autoregressive structure with a moving average structure (ARMA11) to control for autocorrelation among the errors. The MIXED approach has a number of advantages including increased statistical power and the fact that it does not eliminate cases with missing data. It is also important to note that SPSS MIXED uses Satterthwaite estimations procedures that produce noninteger values for the denominator degrees of freedom that vary from analysis to analysis.

To be consistent with our previous studies, pain ratings and NFR magnitudes were first converted to within-subject z scores ($z = [\text{raw score} – \text{participant’s overall mean response}] / \text{participant’s overall standard deviation}$). This removes arbitrary between-subject variability in response magnitude while leaving all of the within-subject variability that can be analyzed to determine whether it is due to affective modulation and/or group differences in affective modulation. Moreover, standardizing improves statistical power and the distributional properties of the variables. It is noteworthy that analyses of unstandardized pain outcomes resulted in the same general conclusions. (The only sex difference in unstandardized response magnitude during ECON was that men’s unstandardized NFR magnitudes tended to be larger than women’s [M = 1.16 versus 1.00, $P = .02$], regardless of picture content.) For comparison, unstandardized nociceptive responses are also reported.

Participant Sex (males versus females) was a between-subject variable and Picture Content (mutilation, attack, death, neutral, families, adventure, erotica) was a within-subject variable. The order/sequence of the suprathreshold stimulations delivered during pictures was entered as a continuous predictor in all models of pain outcomes to control for any within-subject changes in pain/NFR response magnitude that occur from exposure to repeated stimulations (eg, habituation/sensitization) and not picture-evoked modulation. Follow-up mean comparisons for significant main effects were conducted with 2-tailed Fisher’s LSD tests. In the event of a significant interaction, first the omnibus F-test for the simple effect was examined and if significant, then Fisher’s LSD tests were conducted. If the Picture Content effect was significant for pain outcomes, Fisher’s tests were limited to comparisons with neutral pictures (to minimize family-wise Type I error rate) unless otherwise noted. Given the considerable variability in age, preliminary analyses examined whether age also moderated emotional modulation of pain/NFR. While these analyses indicated that age was related to participants’ emotional reactions to pictures, age was unrelated to emotional
modulation of pain or NFR. Therefore, to simplify the presentation, we chose to keep the focus of the paper on sex and pain/NFR modulation.

There is an ongoing debate regarding methods for calculating effect sizes for omnibus effects in multilevel models (eg, Picture Content main effect) when repeated measures are included. Thus, to obtain effect size estimates associated with \( F \)-tests, partial eta-squared (\( \eta^2 \)) was calculated from traditional GLM analyses. Cohen’s \( d \) was reported as the effect size for mean comparisons and Cramer’s Phi was reported as the effect size for chi-square tests. Significance was set at \( P \leq .05 \) (2-tailed).

### Hypotheses

Sex differences in emotional reactions to pictures were expected. Specifically, it was predicted that women would have greater negative emotional reactions (lower valence/pleasure ratings) to threat-related stimuli and men would have greater positive emotional reactions (higher valence/pleasure ratings) to sexual stimuli. Picture Content was expected to modulate nociceptive responses. Specifically, unpleasant pictures were expected to augment pain responses and pleasant pictures were expected to inhibit responses, and arousing pictures (eg, erotica, attack, mutilation) were expected to evoke greater modulation than less arousing pictures. Participant sex was expected to moderate this affective modulation.

### Results

#### Participant Demographics

Table 1 presents participant demographics. Men and women did not differ on any demographic variable except ethnicity. Women were more likely to be Caucasian than men were.

#### Psychosocial Variables

Men and women did not differ on pain catastrophizing or depressive symptoms (Table 1); therefore, any sex differences in affective modulation of pain cannot be attributed to these variables.

#### Basal Pain/Nociceptive Sensitivity

Electrocutaneous pain threshold and pain tolerance were significantly lower in women, suggesting greater pain sensitivity (Table 2). The lack of group differences in NFR threshold is particularly important, because supra-threshold stimulation intensity was set to 120% NFR threshold. This means men and women did not differ in the intensity of suprathreshold stimuli delivered during ECON procedures, and any differences in affective modulation of pain or NFR. Therefore, to simplify the presentation, we chose to keep the focus of the paper on sex and pain/NFR modulation.
modulation of pain/nociception cannot be attributed to stimulus intensity.

**Affective Modulation of Pain and Nociception**

**Subjective Responses to Pictures**

Figure 3 presents means and standard errors for valence/pleasure and arousal ratings by sex.

For valence ratings, there was a significant main effect of Picture Content [F(6, 4088.71) = 1086.79, P < .001, η² = .93]. Fisher’s mean comparisons indicated all contents were significantly different from one another, except the comparisons for adventure versus erotica (P = .29) and death versus attack (P = .12). Pleasant contents led to higher valence ratings and unpleasant contents led to lower valence ratings, with mutilation leading to the lowest ratings and families the highest ratings. The main effect of Sex was nonsignificant [F(1, 127.19) = 1.93, P = .17, η² = .03], but there was a significant Sex × Picture Content interaction [F(6, 4088.76) = 12.50, P < .001, η² = .26, see Fig 3]. As expected, Fisher’s comparisons indicated men rated the erotic pictures as more pleasurable (P < .001, d = .48), whereas women rated the attack pictures as less pleasurable than men did (P = .001, d = .45). Moreover, women rated families as more pleasurable than men did (P < .001, d = .56).

For arousal ratings, the main effect of Picture Content was significant [F(6, 4026.32) = 442.19, P < .001, η² = .79]. Fisher’s mean comparisons indicated all contents were significantly different from one another, except the comparisons for attack versus erotica (P = .75). Among the pleasant contents, erotica led to the greatest arousal followed by adventure and then families. Among the unpleasant contents, mutilation led to the greatest arousal followed by attack and then death. The Sex main effect [F(1, 121.26) = .41, P = .52, η² = .001] and the Sex × Picture Content interaction [F(6, 4026.67) = 1.46, P = .19, η² = .06] were both nonsignificant. Thus, men and women reacted with similar subjective arousal to each of the different emotional-picture contents.

**Nociceptive Outcomes**

Standardized pain ratings are illustrated in Fig 4 and standardized NFR magnitudes are illustrated in Fig 5. For comparison purposes, unstandardized means and standard errors of the mean for pain outcomes are reported in Table 3. For pain ratings, a significant main effect of Picture Content was found [F(6, 3617.91) = 21.38, P < .001, η² = .44]. Compared to neutral pictures, mutilation (P < .001, d = .72) and attack (P = .01, d = .32) pictures facilitated pain ratings, whereas families (P = .02, d = .27), adventure (P = .05, d = .22), and erotic (P < .001, d = .74) pictures inhibited pain ratings. The Sex × Picture Content interaction was nonsignificant [F(6, 3617.97) = .83, F(6, 4026.76) = 12.50, P < .001, η² = .26, see Fig 3]. As expected, Fisher’s comparisons indicated men rated the erotic pictures as more pleasurable (P < .001, d = .48), whereas women rated the attack pictures as less pleasurable than men did (P = .001, d = .45). Moreover, women rated families as more pleasurable than men did (P < .001, d = .56).

Figure 4. Affective modulation of standardized pain ratings of suprathreshold electrocutaneous stimuli. The top panel depicts the main effect of Picture Content (responses collapsed across men and women). Relative to pain elicited during neutral pictures, pain was higher during mutilation and attack pictures, and pain was lower during families, adventure, and erotic pictures. The bottom panel depicts the Sex × Picture Content interaction, which was nonsignificant. Filled bars represent men and open bars represent women. Error bars are SEM. Abbreviations: Mut, mutilation; Att, attack scenes; Dea, death; Neu, neutral; Fam, families; Adv, adventure; Ero, erotica. *Indicates significant mean comparison relative to neutral (P ≤ .05).

Figure 5. Affective modulation of standardized nociceptive flexion reflex (NFR) magnitudes. The top panel depicts the main effect of Picture Content (responses collapsed across men and women). Relative to NFRs elicited during neutral pictures, NFRs were larger during mutilation pictures and smaller during erotic pictures. The bottom panel depicts the Sex × Picture Content interaction, which was nonsignificant. Filled bars represent men and open bars represent women. Error bars are SEM. Abbreviations: Mut, mutilation; Att, attack scenes; Dea, death; Neu, neutral; Fam, families; Adv, adventure; Ero, erotica. *Indicates significant mean comparison relative to neutral (P ≤ .05).
For NFR magnitude, a significant main effect of Picture Content was found \([F(6, 3891.53) = 6.85, P < .001, \eta^2 = .22]\). Compared to neutral pictures, mutilation pictures facilitated NFR \((P < .001, d = .63)\) and erotic pictures inhibited NFR \((P = .03, d = .38)\). The Sex \(\times\) Picture Content interaction was nonsignificant \([F(6, 3891.66) = 1.31, P = .25, \eta^2 = .06]\). To rule out the possibility that our lack of sex differences in affective modulation of pain was due to an imbalance in the number of men and women, we randomly selected 47 women to make the groups even and conducted the analyses again. These analyses resulted in identical conclusions.

**Exploratory Analyses: Does Conscious Emotional Experience Mediate Affective Modulation of Pain/Nociception?**

Analyses indicated that emotional pictures modulated pain and nociception similarly in men and women despite there being sex differences in the subjective reactions to the pictures. This suggests subjective emotion may not completely mediate the effect of emotional pictures on pain responses. The present analyses were conducted to formally test whether mediation occurred. If mediation is present, 4 steps must be satisfied. First, there must be a relationship between the IV (picture content) and the DV (pain outcome). This was established in the section of this article entitled Nociceptive Outcomes. Second, there must be a relationship between the IV (Picture Content) and the mediators (valence and arousal ratings). This criterion was met in the section entitled Subjective Responses to Pictures. The current exploratory analysis simultaneously examined the third (mediators must be related to the DV) and fourth (the effect of the IV is no longer significant when the mediators are added to the model) criteria. To do so, valence ratings, arousal ratings, and the Valence \(\times\) Arousal product term associated with the 36 pictures during which an electrical stimulation was presented were entered as time-varying covariates in the multilevel models described in the section entitled Nociceptive Outcomes. This specifically allowed us to examine the relationship between inter- and intra-individual variability in emotional experience and pain outcomes.

Analyses of standardized pain ratings found that valence ratings \([F(1, 3925.76) = 8.50, P = .004]\) and arousal ratings \([F(1, 2945.78) = 5.62, P = .018]\) were significant covariates in the model. This meets the third criterion noted above. Importantly, the Picture Content main effect was still significant \([F(6, 4029.79) = 3.66, P = .001]\); thus, the fourth criterion was not met. The Sex main effect and Sex \(\times\) Picture Content interaction were still nonsignificant \((Fs < 1)\).

**Table 3. Unstandardized Nociceptive Outcomes During Picture Viewing by Picture Content and Participant Sex**

<table>
<thead>
<tr>
<th>Emotional-Picture Contents</th>
<th>Mutlitation</th>
<th>Attack</th>
<th>Death</th>
<th>Neutral</th>
<th>Families</th>
<th>Adventure</th>
<th>Erotica</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Ratings (0–100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>49.09</td>
<td>47.08</td>
<td>47.02</td>
<td>46.07</td>
<td>44.65</td>
<td>44.85</td>
<td>43.36</td>
</tr>
<tr>
<td>SEM</td>
<td>3.16</td>
<td>3.16</td>
<td>3.16</td>
<td>3.11</td>
<td>3.16</td>
<td>3.16</td>
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<tr>
<td>Women</td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>55.67</td>
<td>54.78</td>
<td>53.87</td>
<td>52.90</td>
<td>51.60</td>
<td>52.68</td>
<td>49.65</td>
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<tr>
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<td>2.53</td>
<td>2.53</td>
<td>2.49</td>
<td>2.53</td>
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<tr>
<td>Mean</td>
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<td>50.45</td>
<td>49.49</td>
<td>48.13</td>
<td>48.77</td>
<td>46.50</td>
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<tr>
<td>SEM</td>
<td>2.02</td>
<td>2.02</td>
<td>2.02</td>
<td>1.99</td>
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<td>2.02</td>
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<tr>
<td>NFR Magnitude (d score)</td>
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<tr>
<td>Men</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.25</td>
<td>1.11</td>
<td>1.18</td>
<td>1.14</td>
<td>1.14</td>
<td>1.15</td>
<td>1.13</td>
</tr>
<tr>
<td>SEM</td>
<td>.06</td>
<td>.06</td>
<td>.06</td>
<td>.05</td>
<td>.06</td>
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<td>.06</td>
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<tr>
<td>Women</td>
<td></td>
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<tr>
<td>Mean</td>
<td>1.07</td>
<td>1.01</td>
<td>1.02</td>
<td>1.00</td>
<td>.99</td>
<td>1.00</td>
<td>.92</td>
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<tr>
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<td>.05</td>
<td>.05</td>
<td>.05</td>
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<td>.05</td>
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<tr>
<td>All Participants</td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.16</td>
<td>1.06</td>
<td>1.10</td>
<td>1.07</td>
<td>1.07</td>
<td>1.08</td>
<td>1.02</td>
</tr>
<tr>
<td>SEM</td>
<td>.04</td>
<td>.04</td>
<td>.04</td>
<td>.03</td>
<td>.04</td>
<td>.04</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: NFR, nociceptive flexion reflex; SEM, standard error of the mean.
subjective emotional experience does not completely mediate affective modulation of pain and NFR.

Discussion

The present study examined sex differences in pain sensitivity and affective modulation of pain and nociception. Consistent with prior research, women were more pain sensitive as assessed from electrotactile pain threshold and tolerance. However, NFR thresholds were similar in men and women implying that differences in pain perception in the present study were not due to spinal nociceptive processes.

Affective modulation of pain and NFR was assessed by delivering suprathreshold electric stimulations during affectively charged pictures, a procedure we have referred to as Emotional Controls of Nociception (ECON). While the present study found sex differences in emotional responses to pictures, sex differences in affective modulation of pain and NFR were not found. Compared to men, women rated the attack pictures as less pleasurable and family pictures as more pleasurable, whereas compared to women, men rated erotic pictures as more pleasurable. But, the Sex × Picture Content interaction was nonsignificant in analyses of pain ratings or NFR, indicating similar modulation in men and women. These findings suggest sex differences in pain sensitivity are not explained by differential engagement of affective modulation of nociception due to sex differences in emotional reactivity.

Although sex differences in affective modulation were not observed, pain report was inhibited by pleasant pictures (families, adventure, erotica), and enhanced by unpleasant pictures (attack, mutilation). Moreover, modulation was strongest when viewing the most arousing contents. Cohen’s $d$ effect size for modulation by mutilation was $d = .72$ and erotica was $d = .74$, which were more than double the size of the next largest effect (attack: $d = .32$). This was paralleled by NFR modulation in which erotica was the only content to evoke significant inhibition and mutilation was the only content to evoke significant facilitation. Thus, only the most arousing pictures engaged corticospinal mechanisms to modulate spinal nociception. These data are consistent with the valence-by-arousal interaction that is thought to characterize the influence of emotion on pain. Indeed, the direction of modulation was determined by emotional valence, whereas the degree of modulation was determined by emotional arousal. (Note that if pleasant and unpleasant pictures in Figs 4 and 5 were depicted as separate lines, and the picture contents were ordered from lowest to highest arousal level, the graphs would look like our hypothetical model in Fig 1.)

It is noteworthy that modulation of pain experience is a clinically small effect in our ECON studies (see unstandardized pain ratings in Table 3), which brings up an important point. ECON is not intended to be an intervention for coping with pain; rather, it is a reliable tool for studying pain modulatory processes. Indeed, this is the sixth independent study to verify the ECON effects. The importance of ECON stems from the fact that pictures presented for only 6 seconds can engage corticospinal mechanisms to regulate spinal nociceptive processes and pain experience in parallel. Thus, these procedures can be used to examine inter- and intra-individual differences in modulatory capacity. The present study found affective pictures modulated pain and NFR equally well in men and women, hence the capacity to engage corticospinal processes via emotion was present in both sexes.

There could be alternative explanations for our data, however. For example, there may be sexually dimorphic physiological mechanisms for affective modulation that produce similar outcomes. The current study suggests corticospinal mechanisms are involved given that NFR is modulated, but imaging studies are needed to determine the exact neurocircuitry. Alternatively, sex differences in affective modulation may be more pronounced in populations for which emotion and/or pain systems are altered. Without a doubt, it will be important to determine whether our results extend to clinical populations for which these systems are known to be dysregulated (eg, fibromyalgia, major depression). Our failure to find sex differences could also stem from our specific experimental methods. For example, the use of odors and noise to induce emotions has led to sex differences in affective modulation of pain, and there may be a sex-specific relationship between trait anxiety and pain. Moreover, our choice of pain stimuli could have contributed. We used electrical stimulation because it allows measurement of NFR. But a study that used the cold pressor, a stimulus known to evoke pain with a stronger affective-motivational component than electrical stimulation, found that erotic pictures led to hypoalgesia in men, but not women. However, it is important to note that all of the studies that have found sex differences have relied on subjective pain responses. A major advance of the present study was the use of the physiologically assessed NFR. So, it is unclear whether firm conclusions can be drawn from these prior studies, given the potential for report bias. Report bias could be especially problematic in studies of affective modulation of pain because participants are likely to guess the study hypotheses.

Conscious Emotional Experience and Affective Picture Modulation of Pain

The current results support the notion that a valence-by-arousal interaction characterizes emotional modulation of pain/NFR. Relative to other unpleasant pictures, mutilation pictures evoked displeasure, the highest arousal, and the strongest nociception facilitation. By contrast, relative to other pleasant pictures, erotic pictures evoked pleasure, the highest arousal, and the strongest nociception inhibition. Pleasant and unpleasant pictures that evoked less arousal had minimal influence on pain/NFR. Interestingly, exploratory analyses suggested that subjective valence and arousal ratings did not mediate the relationship between picture viewing and pain/NFR. This suggests the mechanisms responsible for modulation of pain and NFR by affective
pictures do not correlate well with conscious emotional experience. Our laboratory and others have argued that affective modulation of nociception likely includes the amygdala and its projections to brainstem regions.44,49,52,61,79 Interestingly, a recent fMRI study found that viewing affectively charged pictures activated the amygdala, but that amygdala activation by pictures did not correlate with the subjective emotional appraisal of the pictures.27 Rather, emotional experience correlated with activation in the hippocampus and orbitofrontal cortex. These findings are consistent with evidence from patients with amygdala lesions that indicates these individuals show normal appraisals of affective pictures and normal appraisals of their own emotions.82 Thus, the capacity for affective pictures to modulate pain/NFR may not depend on the conscious experience evoked by the pictures, but rather on amygdala activation elicited by affective picture processing. However, this is speculative until future studies can address this hypothesis.

Limitations

This study had a number of strengths over prior studies, including a large sample size, well-validated methods to study affective modulation, powerful statistical procedures, and the assessment of both subjective and physiological pain outcomes. However, a few limitations should be noted. First, although pain-sensitivity outcomes were not the main focus, the method of limits used to assess pain threshold and tolerance could produce response bias. Therefore, future studies should consider using a multiple random staircase procedure.30 Second, testing sessions were not counterbalanced such that pain testing was always conducted after startle modulation testing, which also included emotional-picture presentation.

While this could have resulted in fatigue or habituation of emotional reactivity, we have shown elsewhere that fatigue and habituation to pictures is minimal.36 Moreover, the present study was able to observe affective modulation of pain/NFR in both sexes with effect sizes that were similar to our previous studies even though affective modulation of pain/NFR was always tested at the end of the testing day. Third, we did not objectively measure hormone status of women and our groups associated with hormone status were small, so our preliminary analyses of hormone effects may have suffered from Type II errors. However, we have assessed affective modulation of pain/NFR in a group of 41 healthy women during their midfollicular and late luteal phases (verified by ovulation tests) and found that menstrual phase had no effect.3,55 Thus, sex hormones may not play a significant role in affective modulation of pain in healthy women. And finally, we used pictures with different contents to evoke different levels of arousal. Given that content was confounded with arousal, we cannot determine whether picture content and affective arousal exert independent and/or unique effects on pain/NFR modulation.6

In sum, affective pictures modulated pain similarly in men and women, despite evoking sex-specific emotional reactions. Together, these findings suggest that sex differences in emotional processing are not likely to contribute to sex differences in pain sensitivity.

Acknowledgments

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