Emotional control of nociceptive reactions (ECON): Do affective valence and arousal play a role?

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Abstract

Prior research suggests emotional picture-viewing modulates motoric (nociceptive flexion reflex), autonomic (skin conductance response, heart rate acceleration), and subjective (pain rating) reactions to noxious electrodermal stimulation. The present study sought to determine whether emotional valence and arousal contribute to nociception modulation. To do so, pictures varying in emotional content (erotica, food, neutral, loss, attack) were chosen to manipulate emotional valence (pleasant = erotic and food; unpleasant = loss and attack) and arousal (low = food and loss; moderate = erotica and attack). Pictures were presented in pseudorandom order to elicit emotional processing while noxious electric stimulations were delivered to the sural nerve. Nociceptive flexion reflex (NFR) magnitude, skin conductance response (SCR), heart rate (HR) acceleration, and subjective pain ratings to each stimulation were measured, standardized, averaged by picture content, and analyzed. Results suggested that picture-viewing explained 52% of the variance in the multivariate combination of the nociceptive reactions and modulated them in parallel. Pleasant pictures inhibited reactions, whereas unpleasant pictures enhanced them. However, only erotica and attack pictures elicited significant modulation relative to neutral pictures, suggesting arousal also contributed. An exploratory multilevel analysis also supported this conclusion. Together, these data suggest emotional control of nociceptive reactions (ECON) is associated with a valence-by-arousal interaction. Implications of these findings for how emotional picture-viewing can be used to study supraspinal modulation are discussed.

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1. Introduction

Emotional processing influences subjective pain (e.g., de Wied and Verbaten, 2001; Keefe et al., 2001; Meagher et al., 2001; Villemure et al., 2003) and physiological reactions to noxious stimulation (nociceptive flexion reflex, skin conductance response, heart rate acceleration, cortical potentials) (Kenntner-Mabiala and Pauli, 2005; Rainville et al., 2005; Rhudy et al., 2005, 2006, 2007b). Unfortunately, little research has been conducted to elucidate factors that determine the emotion–pain relationship.

We have used motivational priming theory (MPT; Lang, 1995) as a conceptual framework to make predictions about the influence of emotional processing on pain (Rhudy and Meagher, 2001). MPT purports two central opponent motive systems are responsible for emotional processing (Lang and Davis, 2006). The appetitive system is activated by appetitive stimuli (e.g., sex, food) and results in positively valenced emotions. The defensive system is activated by harmful or potentially harmful stimuli (e.g., threat, noxious stimuli) and results in negatively valenced emotion. Thus, measures of

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valence/pleasure have been used to assess which motive system is activated.

The imminence of appetitive consummation (appetitive system) or threat (defensive system) determines the strength/intensity of motive system activation and promotes action via metabolic arousal (Bradley, 2000). Thus, measures of arousal are used to assess the degree of system activation. Not surprisingly, stimuli with greater motivational-relevance, such as sexual objects and threatening stimuli, lead to strong appetitive and defensive system activation (and arousal), respectively (Bradley et al., 2001).

MPT predicts that if a motive system is activated (primed), future responses emanating from that system will be facilitated, whereas responses from the opposing system will be inhibited (Lang, 1995). For example, defensive system activation facilitates subsequent defensive responses, while inhibiting appetitive responses. Further, MPT predicts the degree of system activation determines the degree of facilitation/inhibition (Cuthbert et al., 1996): greater activation = greater modulation. Therefore, defensive reactions to nociceptive input should be inhibited by appetitive activation (positive emotions) and facilitated by defensive activation (negative emotions). Moreover, nociception modulation should be greater when systems are strongly activated (indirectly assessed from higher arousal). No single study, however, has tested this hypothesis by independently manipulating the system activated (valence) and the degree of activation (arousal). Based on MPT, it is predicted that the motive system (emotional valence) determines the direction, and emotional activation (arousal) determines the degree, of nociception modulation.

The present study used a picture-viewing paradigm to study the emotion–pain relationship. Pictures varying in content (attack, loss/grief, neutral objects, food, erotica) were used to manipulate motive system activation (valence: unpleasant, neutral, pleasant) and activation level (arousal: low vs. moderate). During picture-viewing, noxious electric stimulations were delivered to the sural nerve and nociceptive reactions were assessed (nociceptive flexion reflex, heart rate acceleration, subjective pain). It was predicted that unpleasant pictures would facilitate nociceptive reactions and pleasant pictures would inhibit them (Rhudy et al., 2005, 2006, 2007b). However, modulation was expected to be greatest during erotic and attack pictures because they elicit the greatest activation/ arousal.

2. Method

2.1. Participants

All procedures were fully approved by The University of Tulsa Ethics Review Board and participants recruited from the psychology department gave informed consent after details of the experiment were described to them. Participants were excluded for: <18 yrs old, cardiovascular, neurological, and/or circulatory problems, recent use of analgesic, anxiolytic, or antidepressant medication, psychological trauma as defined by the DSM-IV (APA, 2000), specific phobia of snakes or spiders, or Raynaud’s disease. Twenty-five healthy participants (10 male, 15 female) completed the study and were included in the analyses; however, an additional male participant was excluded for equipment failure and three others (2 female, 1 male) were excluded because a nociceptive flexion reflex could not be obtained (see Section 2.6.1). Of the total 29 participants, most were female (59%), White non-Hispanic (55.2%), single (89.7%), and unemployed (55.6%), with an average age of 21.81 yrs (SD = 5.50).

2.2. Apparatus

A computer running LabVIEW software (National Instruments, Austin, TX) equipped with dual monitors and A/D board (National Instruments, PCI-6036E) controlled all stimuli, questionnaire presentation, and data acquisition, and was used for offline data reduction. One 17" flat panel monitor was used by the experimenter to monitor physiological signals and experimental timing. The other 17" flat panel monitor (positioned .5 m from the participant) presented visual stimuli and questionnaires. Electrophysiological stimulations were delivered by a Grass Instruments stimulator (Model S88, West Warwick, RI), stimulus isolation unit (Model SIU8T), constant current unit (Model CCU1), and bipolar stimulating electrode (Nicolet, 019-401400, Madison, WI). The stimulating electrode was attached to the left ankle over the retromalleolar pathway of the sural nerve. The onset/offset of the stimulator was controlled by computer, and a computer-controlled voltage regulator varied the current to the participant (max current = 40 mA). All psychophysiological signals were sampled at 1000 Hz and collected/filtered using a Grass Instruments Model 15LT Bipolar Amplifier with Quad AC (15A54) and Dual DC (15A12) modules. Skin conductance response (SCR) was measured using an adaptor (Grass, Model SCA1) for the 15A12 amplifier and electrodes filled with isotonic paste (EC33, Grass Instruments).

To apply all EMG, ECG, and stimulating electrodes, first the skin was degreased with alcohol, slightly abraded using NuPrep gel to achieve impedances below 10 KΩ, and then conductive gel (EC60, Grass Instruments) was applied. All recording electrodes were Ag–AgCl. Psychophysiological signals were sampled in 11 s trials: 3 s before picture presentation and 8 s after picture onset. Throughout testing, participants were seated in a recliner with a small pillow positioned under their left ankle to facilitate relaxation. Sound attenuating headphones and a video camera allowed the experimenter to communicate with and monitor the participant from an adjacent room.

2.3. Emotion-induction: picture-viewing

Emotion elicited by picture-viewing has been shown to reliably alter pain and nociception (de Wied and Verbaten, 2001; Meagher et al., 2001; Wunsch et al., 2003; Kenntner-Mabiala and Pauli, 2005; Rhudy et al., 2005, 2006, 2007b). Therefore,
60 digital pictures\(^1\) from five picture contents (12 pictures per content) were chosen from the International Affective Picture System (CSEA, 1999; Lang et al., 1999) that should manipulate emotional valence and arousal. Valence was manipulated by two pleasant picture contents (couples in erotic poses, food), two unpleasant picture contents (depictions of loss/grieving, animal and human attack scenes), and neutral pictures (household objects, mushrooms). Erotic and attack picture contents were chosen to elicit moderate motive system activation and arousal, whereas food and loss contents were chosen to elicit low motive system activation and arousal. Mean normative valence/pleasure and arousal ratings for each picture content were: erotic couples (valence: \(M = 6.66\), arousal: \(M = 6.10\)), food (valence: \(M = 6.88\), arousal: \(M = 4.82\)), neutral (valence: \(M = 4.93\), arousal: \(M = 2.53\)), loss (valence: \(M = 2.65\), arousal: \(M = 4.56\)), and human and animal attack (valence: \(M = 3.00\), arousal: \(M = 6.35\) ) (See section entitled “Subjective reactions to picture-viewing” below for description of rating scales) (Lang et al., 1999). Thus, pictures containing erotic and food contents were roughly equivalent in normative pleasure/valence ratings, as were attack and loss contents. Moreover, erotic and attack contents were roughly equivalent in normative arousal ratings, but higher than loss and food contents which were roughly equivalent. Therefore, pictures containing erotica, food, loss, and attack contents were chosen to independently manipulate affective valence and arousal, and neutral pictures served as controls.\(^2\) Pictures were presented by computer in a dimly lit room. The order of presentation was randomized across participants with the limitation that not more than two pictures of similar content were shown consecutively. Picture duration was also manipulated. Half of the pictures were presented for 500 ms and the other half 6 s (duration balanced across content) because these durations have been shown to effectively modulate the defensive acoustic startle reflex (Codispoti et al., 2001). Picture duration did not have a significant influence on nociceptive reactivity; thus, the picture duration IV was removed from the final statistical models predicting nociceptive outcomes.

To examine the effect of picture-viewing on nociceptive reactions, electric stimulations at 120% NFR threshold (see Section 2.6.1) were delivered randomly during 50% of pictures, with the limitation that stimulations were equally distributed across picture content and picture duration. Therefore, six stimulations were delivered during each picture content. To minimize conditioning to the pictures, 10 stimulations were also delivered during randomly chosen inter-picture intervals, for a total of 40 stimulations during the picture-viewing procedure.

2.4. Subjective reactions to picture-viewing

Subjective emotional evaluations of pictures were assessed using the Self-Assessment Manikin (SAM; Bradley and Lang, 1994). The SAM is a two item questionnaire that consists of two sets of five pictographs depicting affective valence/pleasure (unpleasant–pleasant) and arousal (calm-excited). A computerized version of the SAM was used to rate affective valence and arousal following each picture (Rhudy et al., 2005). To respond, participants dragged an indicator on or between any of the five pictographs for each scale and submitted their answers by computer mouse. This yielded ratings between 1 and 9 for each dimension, with higher scores indicating greater pleasure or arousal, depending on the scale. Pictures were expected to vary in emotional valence, with erotic and food pictures eliciting the greatest pleasure, neutral pictures intermediate, and loss and attack pictures the least pleasure (Lang et al., 1999). Erotic and food pictures were expected to elicit equivalent pleasure, whereas loss and attack were expected to elicit equivalent displeasure (low pleasure). Arousal was expected to be highest in response to erotic and attack pictures, intermediate for food and loss, and lowest for neutral (Lang et al., 1999).  

2.5. Psychophysiological reactions to picture-viewing

In paradigms using picture-viewing to evoke emotions, psychophysiological reactions are typically used in conjunction with subjective reactions to verify emotion-induction. SCR is used as a physiologic correlate of subjective arousal and HR as a correlate of subjective valence (Lang et al., 1993; Bradley et al., 2001). However, we have failed to observe these picture-evoked ANS responses when shocks are delivered throughout picture-viewing, even from pictures not receiving a shock (Rhudy et al., 2005, 2006). We argue this is likely due to the masking of subtle picture-evoked ANS reactions when pictures are viewed in a threatening context (i.e., during randomly delivered shocks) (Rhudy et al., 2005, 2006). Nonetheless, these measures were recorded and analyzed to facilitate comparisons with other picture-viewing studies. However, we do not predict SCR or HR will covary significantly with subjective arousal or valence, respectively.

SCR was measured by placing electrodes filled with isotonic paste (EC33, Grass Instruments) on the volar surface of the middle and ring fingers after participants washed and dried their hands (Venables and Christie, 1980). Electrocardiogram (ECG) was measured using Ag–AgCl electrodes that were filled with conductive gel (EC60, Grass Instruments) and applied to the left and right forearms. ECG was converted offline to heart rate (HR) in beats-per-minute in half-second bins by determining the interbeat interval in milliseconds using LabVIEW software. Picture-evoked reactions in SCR and HR were calculated by subtracting mean activity in the 1 s

\(^1\) Image numbers were: erotic couples (4607, 4611, 4651, 4666, 4669, 4670, 4690, 4810, 4606, 4608, 4623, 4653), food (7230, 7270, 7283, 7320, 7330, 7350, 7390, 7400, 7430, 7450, 7470, 7475), neutral (7000, 7004, 7010, 7025, 7030, 7040, 7080, 7090, 7150, 7175, 7235, 5551), loss (2141, 2205, 2276, 2455, 2700, 2800, 2810, 2900, 9000, 9001, 9220, 9421), and human and animal attack scenes (1052, 1111, 1205, 1301, 1525, 1932, 3500, 6230, 6242, 6250, 6520, 6550, 6560).  

\(^2\) Although these picture contents were chosen to independently manipulate emotional valence and arousal, it must be pointed out that valence and arousal manipulations are by definition confounded with picture content. Thus, it is possible that modulatory differences noted between attack and loss, or erotic and food contents may reflect differences due to content rather than arousal/intensity. Indeed, a recent study attempted to manipulate valence and arousal independent of content and found that picture content, emotional valence, and emotional arousal all had independent modulatory effects on the acoustic startle reflex (Bernat et al., 2006). Specifically, erotic and threat pictures had the greatest modulatory influences that appeared independent of reported arousal.
prior to picture presentation from 12 half-second bins following picture onset (Bradley et al., 2001). Picture-evoked SCR was determined by finding the maximum change that occurred 1–4 s after picture onset. Picture-evoked HR was calculated in two ways: (1) maximum deceleration from baseline in the first 3 s of picture-viewing and (2) peak acceleration during the last 3 s of picture-viewing (Bradley et al., 2001). To eliminate stimulus artifact due to shocks, picture-evoked SCR and HR reactions were only calculated for pictures in which a shock was not presented.

2.6. Nociceptive reactions

2.6.1. Nociceptive flexion reflex (NFR)

The NFR is a protective withdrawal reflex in response to a noxious stimulus (Skljarevski and Ramirez, 2002; Sandrini et al., 2005). Experimentally, the NFR is typically elicited by electrodermal stimulation over the sural nerve that activates primary nociceptors (Aβ and C fibers). Nociceptor activation results in a nociceptive signal to the spinal cord that subsequently elicits a withdrawal response in the leg that can be quantified using electromyography (EMG) (Wiesenfeld-Hallin et al., 1984; Sandrini et al., 2005). The NFR is a spinal reflex because supraspinal regions are not necessary for its elicitation (e.g., Sandrini et al., 1999). The stimulation intensity necessary to reliably elicit the NFR (i.e., NFR threshold) correlates with subjective report of pain threshold, and the magnitude of the NFR correlates with subjective pain intensity (Chan and Dallaire, 1989; Guieu et al., 1992; Rhudy et al., 2005). Thus, the NFR is used as an objective, indirect measure of spinal nociception.

Two active recording electrodes were placed over the left biceps femoris muscle 10 cm superior to the popliteal fossa to assess EMG activity associated with the NFR. A common ground electrode was placed over the left lateral epicondyle of the femur. Biceps femoris EMG activity 90–150 ms post-stimulation was used to define the NFR. Prior research has shown that using the 90–150 ms timeframe avoids potential contamination by the non-nociceptive RII reflex, startle responses, and/or voluntary movements (Dowman, 1992; France and Suchowiecki, 2001). The raw biceps femoris signal was amplified by 20,000, bandpass filtered (10–300 Hz), and rectified.

The intensity of electrodermal stimulation delivered throughout picture-viewing was set at 120% NFR threshold. To determine NFR threshold, procedures were adapted from France and colleagues (France et al., 2002). During threshold assessment, NFR was defined as a mean EMG response in the 90–150 ms post-stimulus interval that exceeded mean EMG activity during the 60 ms pre-electrical stimulus baseline interval by at least 1.0 standard deviation. Stimulation of the sural nerve for threshold determination proceeded using an up-down staircase method with a variable interval of 8–12 s while the participant sat comfortably in a recliner with their leg outstretched (knee angle approximately 180°; e.g., Chan and Tsang, 1985). Each stimulation consisted of five rectangular wave pulses of 1 ms duration and 3 ms interstimulus interval (250 Hz). The threshold assessment procedure started at 0 mA (current) and increased in 1.5 mA steps until a NFR was detected. Stimulus intensity was then decreased in .75 mA steps until a reflex was no longer detected. This up-down procedure was repeated two more times with .5 mA steps. The average stimulus intensity of the last two peaks and troughs was increased 20% to generate the intensity of stimulation used during picture-viewing (120% NFR threshold). This intensity minimizes ceiling and floor effects (Danziger et al., 1998). Participants for which a NFR could not be reliably obtained before tolerance was achieved were given the choice of repeating the threshold assessment procedure or discontinuing the experiment (three discontinued as noted in the Section 2.1).

To examine the influence of picture-viewing on NFR, within-subject changes in NFR magnitude were examined. NFR magnitude was calculated for stimulations delivered during picture-viewing by subtracting mean activity in the 60 ms prior to electric stimulation from mean activity in the 90–150 ms post-stimulation window.

2.6.2. Subjective pain ratings

To rate each electric stimulation, a computer-presented rating scale oriented vertically was used (France et al., 2002; Rhudy et al., 2005). Bottom-to-top, the scale was labeled: 0 (no sensation), 1 (just noticeable), 25 (uncomfortable), 50 (painful), 75 (very painful), and 100 (maximum tolerable). To respond, participants moved an indicator anywhere along the scale and submitted their answers by computer mouse. These ratings were used as a measure of subjective pain.

2.6.3. Autonomic reactions

Research from our laboratory has found that peak autonomic reactions (skin conductance response [SCR]; peak heart rate [HR] acceleration) to noxious stimulation are modulated by emotional processing (Rhudy et al., 2007b). Specifically, peak SCR and HR acceleration following noxious shock are diminished by appetitive activation and enhanced by defensive activation. Therefore, we chose to focus only on these autonomic measures.3 SC activity was first averaged by .5 s epochs, and then the mean activity in the 1 s pre-shock interval was subtracted from each .5 s post-shock epoch (Bradley et al., 2001). SCR was defined as the maximum skin conductance increase in the 1–4 s post-shock interval (Dawson et al., 2001). These methods of scoring SCR and HR acceleration have been used in previous emotion research to determine picture-evoked reactions (Bradley et al., 2001). However, these scoring methods may lead to artificially high values, because they base responses on peak values in a narrow scoring window. To determine whether the emotional modulation effects noted in this study were artifacts of our scoring methods we also calculated HR as the mean change in the 1–5 s post-stimulus window and SC as the mean change in the 1–4 s post-stimulus window. These change scores were then standardized and compared to the standardized versions of our original HR acceleration and SCR variables. The two scoring methods were highly correlated with each other (SCR, r = .90; HR, r = .59; p < .001). Analyses of the effect of picture-viewing on these new variables resulted in nearly identical results as those reported using the HR acceleration and SCR variables. Picture content explained 36% of the variance in SC change and 23% in HR change. The pattern of SC change means and HR change means for each picture content were the same as those noted for SCR and HR acceleration, thus we chose to keep our original variables in the manuscript to be consistent with our previous study (Rhudy et al., 2007b).
Therefore, the .5 s post-shock epoch (in the 1–4 s post-shock interval) with the greatest positive change was used as the response definition (Bradley et al., 2001). ECG was converted offline to HR in beats-per-minute from interbeat intervals and visually inspected for errors. Like SC, the HR waveform was first averaged by .5 s epochs and the mean activity in the 1 s pre-shock interval was subtracted from each .5 s post-shock epoch. Peak HR acceleration was defined as the .5 s post-shock epoch (in the 1–5 s post-shock interval) with the greatest positive change.

2.7. Procedure

Health status of all participants was determined using a brief health questionnaire and interview to determine eligibility. If eligible, electrodes were applied, the participant was seated comfortably in a reclining chair, and then familiarized with the rating scales used throughout testing (SAM, pain rating scale). Ratings were made using a computer mouse positioned on a lap desk. Participants were told that there were two phases to the experiment. Phase 1 (NFR threshold assessment) involved sending electric pulses to the ankle to determine the stimulus intensity necessary to elicit the NFR. During this phase, the participant viewed the pain rating scale positioned next to a digital green light (both were continuously displayed on the computer monitor). The light indicated when the participant was to make a rating (following every stimulus). The participant was told to make a rating whenever the light came on, regardless of whether the stimulus was perceived. During phase 2, the participant was instructed to view every picture presented on the computer monitor, and told that electric stimuli would be delivered randomly during and in between pictures. Picture duration was varied in a pseudorandom manner, with half of the pictures having 500 ms duration and the other half 6 s duration. Picture durations were equally distributed across picture contents. Inter-picture intervals varied randomly from 12 to 22 s. Electric stimuli (at 120% NFR threshold) were delivered during 50% of the pictures (six for each picture content, balanced across picture duration) and 10 inter-trial intervals. Thus, a total of 40 stimulations were delivered during phase 2. During phase 2, electric stimuli were randomly delivered 3–5 s after picture onset and 11–21 s after inter-picture interval onset to reduce predictability (shock onset intervals were always an integer). The 3–5 s post-picture-offset interval was chosen because it has been shown to produce the largest emotional modulation effects on the acoustic startle reflex (Bradley et al., 1993; Codispoti et al., 2001). Following each picture, the SAM was administered to assess emotional responses to the pictures. The pain rating scale was administered following pictures and inter-picture intervals in which an electric stimulus was delivered. At the end of the experiment, the participant was debriefed and thanked for their participation.

2.8. Data reduction and analyses

All self-report and psychophysiological variables were averaged across pictures with similar content (attack, loss, neutral, food, erotic). Before averaging, SCR, HR acceleration, NFR, and pain ratings were standardized within-individuals by converting to $z$ scores. Standardizing has the effect of eliminating between-subject variability (by setting each participant’s mean response to zero), while retaining within-subject variability due to picture-viewing. Therefore, individual differences in the absolute magnitude of each variable are removed and the effect of picture-viewing (a within-subject effect) is retained. Furthermore, standardizing has the beneficial effect of placing all nociceptive reactions in a common metric (standard deviation units) thus facilitating the interpretation of analyses that collapse across reaction type (analyzing all reactions simultaneously, see below).

Although analyses were conducted to examine the independent influence of affective valence and arousal, a single independent variable (picture content) was used to model the influence of valence and arousal rather than separate independent variables. This allowed statistical models to make comparisons to neutral pictures (which could not be done if valence and arousal were separate independent variables). Analyses on manipulation checks for emotion-induction were conducted using a 5 (Picture Content) × 2 (Picture Duration) × 2 (Participant Sex) repeated measures MANOVA. To examine the influence of picture-viewing on nociceptive reactions, a 4 (Reaction Type) × 5 (Picture Content) repeated measures MANOVA was conducted. Initially, participant sex and picture duration were also included as independent variables in the model predicting nociceptive reactions, but these effects were not significant (Fs < 2.10, ps > .16). Thus, for parsimony, they were dropped from the final model. Follow-up comparisons were conducted with Bonferroni adjusted means tests to control for Type I error rate, except a priori hypotheses of nociceptive outcomes were one-tailed Fisher LSD tests. Unless noted, analyses were conducted using the GLM procedure within SPSS 14.0. Partial eta-squared ($\eta^2$) was used as the effect size for $F$ tests and Cohen’s $d$ was used for mean comparisons. Cohen (1977) provides guidelines for interpreting $\eta^2$ (small = .01, medium = .06, large = .14) and $d$ (small = .2, medium = .5, large = .8). Wilks’ $\lambda$ are the multivariate statistics interpreted but are not presented given the redundancy with partial eta-squared.

2.8.1. Hypotheses

It was predicted that nociceptive reactions would be modulated in parallel and influenced by emotional valence and arousal (valence-by-arousal interaction). Specifically, nociceptive reactions were expected to be facilitated by unpleasant pictures and inhibited by pleasant pictures. However, pictures eliciting greater arousal were expected to show stronger modulation – attack pictures were expected to elicit the greatest facilitation and erotic pictures the greatest inhibition. Therefore, only a main effect of picture content was predicted to be significant in the analysis of nociceptive reactions. Reactions during

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4 It is important to note that within-subject $z$ transformations can have the beneficial effect of minimizing the impact of outlier values, because means are centered at zero and the within-subject variability is put on a common metric (in this case standard deviation units). Therefore, the standardized means will “rein in” the outlier. At times, this can cause a mean to change its magnitude relative to other means. This is most obvious when comparing unstandardized means to standardized means.
attack and erotic pictures were expected to be significantly different (higher and lower, respectively) than reactions during neutral pictures, whereas reactions during loss and food pictures were not expected to differ significantly from reactions during neutral pictures.

3. Results

3.1. Subjective reactions to picture-viewing

Table 1 depicts subjective valence and arousal ratings by picture content, picture duration, and participant sex. Analysis of valence/pleasure ratings found a main effect of picture content, $F(4,20) = 35.13$, $p < .001$, $\eta^2 = .88$. Erotic and food pictures elicited similar pleasure ($p = 1.00, d = .13$) that was greater than neutral pictures ($ps < .001, ds > 2.24$). Attack and loss pictures were similar in pleasure ($p = 1.00, d = .11$) and lower than neutral pictures ($ps < .001, ds > 1.41$). However, this main effect was qualified by significant interactions of Picture Content $\times$ Participant Sex [$F(4,20) = 3.45$, $p = .027$, $\eta^2 = .41$] and Picture Content $\times$ Picture Duration [$F(4,20) = 8.01$, $p = .001$, $\eta^2 = .62$]. To decompose the Picture Content $\times$ Participant Sex interaction, the simple effect of sex was examined. Only the simple effect of sex for the neutral pictures was significant. Men rated neutral pictures as slightly less pleasurable than women ($M_M = 4.54$ vs. $4.88$; $p = .036$, $d = .63$). To decompose the Picture Content $\times$ Picture Duration interaction, the simple effect of picture duration was examined for each picture content. The only effect of duration noted was for ratings of loss content, with 6 s pictures eliciting greater displeasure than 500 ms pictures ($M_M = 2.45$ vs. $3.13$; $p < .001$, $d = .81$).

Analysis of arousal ratings revealed main effects of picture content [$F(4,20) = 12.99$, $p < .001$, $\eta^2 = .72$] and picture duration [$F(1,23) = 7.18$, $p = .01$, $\eta^2 = .24$].

For unpleasant contents, loss ($p = .001$, $d = .89$) and attack pictures ($p < .001, d = 1.74$) were more arousing than neutral, and attack pictures were more arousing than loss ($p < .001, d = .92$). For pleasant contents, food ($p = .001$, $d = .93$) and erotic ($p < .001, d = 1.46$) pictures were more arousing than neutral, but the comparison between erotic and food pictures eluded significance ($p = .10$, $d = .57$). The main effect of picture duration suggested 6 s pictures elicited greater arousal than 500 ms pictures, albeit a small difference in subjective arousal. Together, these data suggest that valence and arousal were independently manipulated, although erotic pictures evoked less subjective arousal than expected.

3.2. Psychophysiological reactions to picture-viewing

Table 2 depicts psychophysiological reactions to picture-viewing by picture content and picture duration. As predicted, picture contents did not lead to differential psychophysiological reactions. For picture-evoked SCR, only the main effect of picture duration was significant [$F(4,23) = 7.07$, $p = .01$, $\eta^2 = .24$], but not the main effect of picture content ($p = .42$) or the Picture Content $\times$ Picture Duration interaction ($p = .23$). Brief pictures led to slightly greater SCR (0.13 μS vs. 0.18 μS). For picture-evoked HR acceleration, the main effects of picture content ($p = .14$) and picture duration ($p = .63$) and the Picture Content $\times$ Picture Duration interaction ($p = .23$) were all non-significant. For picture-evoked HR deceleration, the main effects of picture content ($p = .10$) and picture duration ($p = .06$), and the Picture Content $\times$ Picture Duration interaction ($p = .10$) were all marginally significant. HR acceleration tended to be higher during brief pictures. However, exploratory Bonferroni comparisons for the main effect of picture content and the simple effects of picture duration were all non-significant ($ps > .05$). Thus, these data are con-

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consistent with our previous research suggesting subtle physiological responses to pictures are not observed when shocks are randomly delivered during picture-viewing (Rhudy et al., 2005, 2006).

### 3.3. The effect of picture-viewing on nociceptive reactions

As predicted, only a significant main effect of picture content was found that explained 52% of the variance in the multivariate combination of the standardized reactions ($F (4, 21) = 5.76, p = .003, \eta^2 = .52$). Fig. 1 depicts standardized nociceptive reactions by picture content. Standardized reactions during attack pictures were significantly larger than during neutral ($p = .032, d = .59$), but not loss pictures ($p = .10, d = .38$). Alternatively, standardized reactions during erotic pictures were significantly smaller than all other picture contents ($p < .02, d = .68–1.55$). Although reactions during loss and food pictures were in the predicted directions, these pictures did not lead to significant modulation relative to neutral pictures ($p s > .16, d s < .30$). Importantly, the Reaction Type $\times$ Picture Content interaction was not significant ($F = .45, p = .91$). This suggests reactions were modulated in parallel by picture contents. Nonetheless, to provide a more stringent test of parallel modulation, the simple effect of reaction type was examined at each level of picture content using exploratory Bonferroni comparisons. Reactions were not significantly different during attack ($p s > .12$), loss ($p s > .70$), neutral ($p s > .35$), food ($p s > .30$), or erotic ($p s > .26$) pictures. To determine the variance explained by picture content in each separate reaction, partial $\eta^2$ was calculated from the simple effect of picture content. Picture content explained 15% of the variance in NFR, 42% of the variance in pain ratings, 37% of the variance in SCR, and 32% of the variance in HR acceleration. For reference purposes, Table 3 presents unstandardized means for each nociceptive reaction by picture content. However, it is important to point out that standardization of variables can cause changes in the relative magnitude of the means and are thus not directly comparable to unstandardized variables.

### 3.4. Exploratory analyses

#### 3.4.1. Potential confounds

Given that NFR, SCR, and HR reactions are all calculated as a change from baseline, there is the potential for picture-viewing to alter baseline physiological activity, and thus confound the interpretation of these variables (even though prior analyses suggested pictures did not lead to differential psychophysiological responses). For example, an incorrect inference of SCR inhibition could result if erotic pictures, but not attack pictures, significantly increased baseline skin conductance level, causing the response magnitude to

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Table 3
Means and standard deviations of unstandardized nociceptive reactions by picture content

<table>
<thead>
<tr>
<th></th>
<th>ITI</th>
<th>Attack</th>
<th>Loss</th>
<th>Neutral</th>
<th>Food</th>
<th>Erotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFR magnitude (ΔμV) Mean SD</td>
<td>5.49 3.24</td>
<td>7.16 8.09</td>
<td>6.59 6.22</td>
<td>6.88 7.53</td>
<td>6.30 5.40</td>
<td>5.65 4.58</td>
</tr>
<tr>
<td>Pain rating (0–100) Mean SD</td>
<td>43.49 23.46</td>
<td>47.45 24.73</td>
<td>47.29 25.41</td>
<td>45.81 23.06</td>
<td>45.17 24.93</td>
<td>43.51 24.38</td>
</tr>
<tr>
<td>SCR (ΔμS) Mean SD</td>
<td>1.26 1.20</td>
<td>1.32 1.32</td>
<td>1.21 1.07</td>
<td>1.20 1.16</td>
<td>1.14 1.23</td>
<td>1.06 1.09</td>
</tr>
<tr>
<td>HR acceleration (Δbpm) Mean SD</td>
<td>7.90 3.82</td>
<td>8.41 4.04</td>
<td>7.88 4.43</td>
<td>7.22 4.45</td>
<td>7.30 4.63</td>
<td>6.20 4.95</td>
</tr>
</tbody>
</table>

Note: NFR, nociceptive flexion reflex; SCR, skin conductance response; HR, heart rate; bpm, beats-per-minute.

appear smaller after the baseline activity is subtracted (although the actual response magnitude might not have changed). To ensure that this was not the case, the average local baselines used to calculate the change scores for each physiological reaction were analyzed using 5 (Picture Content) × 2 (Picture Duration) ANOVAs. Fig. 2 depicts local baselines averaged by picture content for each of the physiological reactions as well as post-shock waveforms of each reaction averaged by picture content. No significant effects were found, suggesting baselines were not significantly altered by the content or duration of pictures. Therefore, change scores are a valid method of quantifying the magnitude of these responses.

3.4.2. The relationship between self-reported emotion and nociceptive reactions

Although it is assumed that subjective emotion (valence, arousal, Valence × Arousal interaction) at least partially mediates the relationship between picture content and nociceptive reactivity, MANOVA models do not directly test the relationship between subjective emotion and nociception. To examine this relationship, a multilevel model (hierarchical) correlational approach was conducted using the SPSS 14.0 MIXED procedure to examine covariation between trial-by-trial valence and arousal ratings and trial-by-trial nociceptive reactions. Thus, a benefit of this approach is that it takes into account inter- and intra-individual variability in reactions to each picture and each shock. A custom model with REML estimation was built that included reaction type, valence, arousal, Valence × Arousal interaction, and a Valence × Arousal × Reaction Type interaction as fixed effects and subject number as a random effect. Significant effects of arousal \( F(1,2967)=11.48, p = .001 \) and a Valence × Arousal interaction \( F(1,2967)=9.76, p = .002 \) were found. The effect of valence just eluded significance \( F(1,2967)=3.47, p = .063 \). The main effect of reaction type \( F(3,2967)=.93, p = .42 \) and the interaction of Valence × Arousal × Reaction Type \( F(1,2967)=1.27, p = .28 \) were non-significant. This suggests that subjective emotion does covary with nociception modulation. Further, the analysis provides additional evidence that a valence-by-arousal interaction is associated with nociception modulation, and that reactions were modulated in parallel.

4. Discussion

The present study used picture-viewing to study supraspinal modulation of objective (NFR magnitude, SCR, HR acceleration) and subjective (pain ratings) reactions to noxious sural nerve stimulation – a paradigm referred to as emotional control of nociceptive reactions (ECON). Extending prior research, this study used different picture contents to vary valence and arousal. Moreover, this was the first study to evaluate the influence of picture-viewing on four nociceptive reactions simultaneously. Pictures effectively manipulated valence, with erotic and food pictures eliciting the greatest pleasure, attack and loss pictures the lowest pleasure, and neutral intermediate. Pictures also manipulated emotional arousal, with erotic and attack pictures eliciting the greatest arousal, loss and food pictures intermediate arousal, and neutral pictures the lowest arousal. Surprisingly, erotic pictures did not elicit significantly greater arousal than food pictures, as was predicted from normative ratings. It is tempting to speculate that sexual arousal may have been underreported in our sample due to geographic social norms. However, there is no way to verify this given that objective picture-evoked psychophysiological reactions are masked when pictures are viewed in a threatening context (Rhudy et al., 2005, 2006).

Analyses suggested valence and arousal contributed to modulation of nociceptive reactions. Reactions were larger during unpleasant pictures and smaller during pleasant pictures. But, only reactions elicited during erotic and attack pictures were significantly modulated relative to neutral pictures. This was supported by an exploratory multilevel analysis suggesting self-reported arousal and the valence-by-arousal interaction were significant predictors of nociceptive reactions.

Consistent with prior research (Rhudy et al., 2005, 2006, 2007b), the present study found nociceptive reactions were modulated in parallel. To test this, all reactions were placed on a common metric and analyzed using a Reaction Type × Picture Content interaction within MANOVA (minimizing Type I error). The interaction effect, exploratory simple effects tests of reaction type, as well as the multilevel analysis all suggested reactions were modulated in parallel. Importantly, picture content explained 52% of the variance in the multivari-
Fig. 2. Local baselines used to calculate physiological nociceptive reactions and the time course of physiological nociceptive reactions following noxious sural nerve stimulation. Panels on the left depict local baselines averaged by picture content for each of the physiological reactions (Att, attack; Neu, neutral; Ero, erotic). Panels on the right are the post-shock waveforms of each reaction averaged by picture content (NFR waveforms for loss and food pictures are not depicted in the top right panel to improve readability). The top panels are the nociceptive flexion reflex (NFR), the middle panels are skin conductance response (SCR), and the bottom panels are heart rate (HR). Erotic pictures reduced physiological reactivity and attack pictures enhanced physiological reactivity. (Note: Individual trials depicting NFR waveforms are characterized by a phasic response in the 90–150 ms post-stimulation interval. In the present figure, however, the waveforms in the upper right panel appear “plateau-like,” with activity beginning in the 90–150 ms interval and extending beyond it. This is due to grand averaging across individuals and trials that obscures the “silent period” that typically occurs after the NFR (RIII component), but before startle and voluntary movements in individual trials. In the present graph, this averaging artifact is particularly prominent, because there were participants who demonstrated large absolute EMG responses after the 90–150 ms interval, and grand averages (means) are heavily influenced by outliers. This large individual variability in response magnitude is an important reason for standardizing biceps femoris EMG (NFR magnitude) when the effect of interest is a within-subject effect, i.e., emotional modulation.)

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ate combination of the reactions, and considerable variance in individual reactions (15% NFR, 42% pain ratings, 37% SCR, 32% HR acceleration).

As noted here, picture content generally explains more variance in pain report than other nociceptive reactions (Rhudy et al., 2005, 2006, 2007b). One potential explanation could be report bias, because pain ratings and picture (emotion) ratings are made together. Contrary to this hypothesis, the picture content IV explains greater variance in pain than emotion ratings (Rhudy et al., 2005, 2006). Alternatively, different nociceptive responses may be modulated by different processes. Supporting this, emotional modulation of the NFR is abolished when noxious shocks are predictable, despite intact modulation of subjective pain (Rhudy et al., 2006). Thus cortico-cortical circuits may continue to modulate subjective pain even when brain-to-spinal cord circuits are disengaged. This would explain why some cognitive-emotional factors (catastrophizing, self-efficacy) modulate subjective pain but not NFR (France et al., 2002; Brant et al., 2007; Rhudy et al., 2007a). Although compelling, the reason for modulatory differences across responses cannot be determined at this time.

4.1. Relation to prior research

This is the fourth study from our laboratory to examine the influence of emotional picture-viewing on nociceptive reactions. Rhudy and colleagues (2005) were the first to demonstrate emotional processes can activate descending circuits that influence spinal nociception. In that study, erotic, neutral, and attack pictures modulated the spinally-mediated NFR and subjective pain. NFR magnitudes and pain ratings were greater during attack pictures and smaller during erotic pictures. As a result, we argued ECON procedures represent novel, non-invasive methods for engaging descending modulation in humans.

Rhudy et al. (2006) examined whether reactions to predictable noxious shocks were also modulated by picture-viewing. Hypothetically, if nociceptive reactions to predictable shocks were also modulated, then employing predictable shocks could reduce participant stress given the preference for noxious events to be predictable (Miller, 1981; Mineka and Henderson, 1985). In that study, half of the participants received cued (predictable) shocks during picture-viewing, and the other half received uncued (unpredictable) shocks. Data from the uncued shock group replicated the first study. However, pain ratings, but not NFR, were modulated in the cued shock group. Thus, it was concluded that unpredictable shocks should be used to observe NFR modulation (and ensure brain-to-spinal cord circuitry is activated).

The third study combined data from the first two studies to examine the impact of picture-viewing on autonomic reactions to noxious shocks (Rhudy et al., 2007b). Skin conductance and heart rate had been recorded in the prior experiments as a physiological manipulation check for emotion-induction. These signals were rescored to calculate shock-evoked change (nociceptive reaction), rather than picture-evoked (emotion-induction). As predicted, autonomic nociceptive reactions were also modulated by emotion. Shock-evoked SCR and HR acceleration were smaller during pleasant pictures than during unpleasant pictures. Thus, converging evidence suggests ECON can be used to study modulation of nociceptive reactions assessed from multiple response systems (motoric, autonomic, subjective), mediated by circuits at spinal (NFR) and supraspinal (SCR, HR) levels.

4.2. The emotion–pain relationship

This study provides preliminary support for the hypothesis that the emotion–pain relationship is determined by a valence-by-arousal interaction. Specifically, valence determines the direction of the modulation and arousal the magnitude. This hypothesis may not extend to highly arousing emotions, however. Animal and human studies (e.g., Fanselow, 1994; Rhudy and Meagher, 2000) suggest nociceptive reactions are inhibited by events that elicit intense defensive activation (highly arousing negative emotion) – a reversal of the direction of modulation compared to negative emotions with low-to-moderate arousal. However, the direction of modulation does not appear to reverse during highly arousing positive emotions. The current study suggests positive emotions with low-to-moderate arousal inhibit pain, whereas other studies suggest intense appetitive activation (e.g., genital stimulation) that elicits highly arousing positive emotion (e.g., orgasmic bliss) leads to profound pain inhibition (Komisaruk and Whipple, 1986). When all data are considered, a valence-by-arousal interaction may still characterize the emotion–pain relationship (Fig. 3). Picture-viewing would not be expected to induce negative emotions capable of producing pain inhibition, however. Inhibition is expected only when negative emotions accompany imminent threat (Fanselow, 1994) and pictures are only likely to represent an imminent threat for certain clinical populations (e.g., specific phobia of snakes).

4.3. Limitations

The present study was limited by a small sample. Fortunately, picture-viewing exerts a large statistical effect on nociceptive reactivity. However, other predictors in the model (participant sex, picture duration) may have achieved significance with a larger sample. Although the Reaction Type × Picture Content interaction did not achieve significance, exploratory simple effects tests provided some confidence low power was not responsible.
It is noteworthy that modulation of subjective pain was a clinically small effect, despite being a statistically large effect. Thus, emotional picture-viewing may prove better for studying nociceptive processing than for coping with chronic pain (Seminowicz and Davis, 2007). Before this conclusion can be drawn though, the effects of picture-viewing on clinical pain must be established (c.f., Montoya et al., 2005).

In the present study respiration rate was not measured. Thus, picture-evoked breathing changes may have modulated shock-evoked HR (respiratory sinus arrhythmia) rather than pain modulatory circuits. However, given that ANS reactions may contribute to pain perception (Chapman et al., 2002), respiration may represent another mechanism by which emotion can indirectly influence pain and nociceptive reactions. Nonetheless, our HR outcomes should be interpreted with caution.

A final limitation is due to the method of manipulating arousal. Given the arousal manipulation is confounded with picture content, we are unable to determine whether quantitative differences in activation/arousal are responsible for our results, or whether something qualitatively different about attack and erotic pictures enabled them to modulate nociception. Additional research is needed to manipulate arousal within a picture content to provide additional support for the independent influence of arousal. Indeed, a recent study found that valence, arousal, and picture content all contributed uniquely to emotional modulation of the acoustic startle reflex (Bernat et al., 2006). Despite our confounding between picture content and arousal, exploratory multilevel analysis of subjective emotion ratings suggested that a valence-by-arousal interaction did significantly predict nociceptive reactions.

4.4. Implications

This represents the third independent test of ECON procedures. Nociception modulation has been reliably elicited across all three samples, and picture content consistently explained large proportions of variance in nociceptive outcomes. Thus, ECON appears to be a valid method of engaging supraspinal modulation. Although it is important that future studies determine whether individual differences (e.g., participant sex) influence which pictures elicit greatest modulation, these results suggest the greatest modulation is evoked by erotic and attack pictures. Thus, researchers should be cautious when averaging reactions across pictures of similar valence (but that vary in content/arousal) as this may attenuate the modulation observed.

4.5. Summary

This study found emotional valence and arousal contribute to modulation of nociceptive reactions (NFR, subjective pain, SCR, and HR acceleration), with modulation being associated with a valence-by-arousal interaction. The combined influence of valence and arousal had a coordinating effect, with picture content explaining 52% of the variance in the four reactions. Together, these data suggest the ECON paradigm is a reliable tool for studying supraspinal modulation.

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