Habituation, sensitization, and emotional valence modulation of pain responses

Jamie L. Rhudy*, Emily J. Bartley, Amy E. Williams

Department of Psychology, The University of Tulsa, USA

ARTICLE INFO

Article history:
Received 9 October 2009
Received in revised form 13 November 2009
Accepted 19 November 2009

Keywords:
Emotion
Habituation
Sensitization
Nociceptive flexion reflex
Autonomic response
Electrocutaneous stimulation

Abstract

The Emotional Controls of Nociception (ECON) paradigm involves the presentation of emotionally-charged pictures during which painful stimuli are delivered. Across several ECON studies, unpleasant pictures enhanced pain and nociception, whereas pleasant pictures inhibited pain and nociception. However, at this time it is unknown whether emotional valence (unpleasant, neutral, pleasant) influences the habituation or sensitization of pain responses that occurs within a testing session. Indeed, ECON assumes that emotional valence modulation of pain is consistent throughout testing; otherwise the interpretation of valence modulation (unpleasant > neutral > pleasant) could be threatened. To address this issue, the present study (N = 120) presented 108 pictures that varied in emotional valence. During and in between pictures, 52 suprathreshold electrocutaneous stimuli were delivered to evoke pain, the nociceptive flexion reflex [NFR], and pain-evoked skin conductance response [SCR]. Mixed effects ANOVAs verified that within-subject changes in pain responses were influenced by stimulus repetition (NFR and SCR habituated, pain ratings sensitized) and emotional valence (responses were highest during unpleasant pictures, intermediate during neutral pictures, and lowest during pleasant pictures). However, habituation/sensitization slopes were unaffected by emotional valence, thus indicating emotional valence modulation was consistently observed throughout the testing session. These results provide additional validation for the ECON paradigm and suggest that the circuit responsible for emotional modulation of pain and nociception is less susceptible to habituation or sensitization than the circuits responsible for responses to suprathreshold shocks.

© 2009 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

1. Introduction

Pain is a dynamic experience influenced by nociceptive input, but also modulatory factors that regulate pain responding [16,31]. One important modulatory factor is emotion [23,26,37]. Emotional processing is associated with a supraspinal circuit [29] that has substantial overlap with, and connections to, nociceptive systems [37]. As a result, emotion plays an integral role in the experience and modulation of pain, and a dysfunction of one system is often linked to negative consequences in the other system (e.g., comorbidity between chronic pain and depression) [24,41]. Given the inextricable relations between pain and emotion, it is important to have valid experimental models to study their associations.

The Emotional Controls of Nociception (ECON) paradigm involves the presentation of emotionally-charged pictures during which constant-intensity suprathreshold stimuli are delivered. Using this paradigm, pleasant pictures have been shown to reliably inhibit pain and nociception, whereas unpleasant pictures reliably enhance pain and nociception [36,38–40,47]. Importantly, this modulation involves brain-to-spinal cord circuitry because the spinally-mediated nociceptive flexion reflex (NFR) is influenced. However, the validity of the ECON paradigm is dependent on being able to attribute within-subject changes in pain responses to emotional picture-viewing. Over the course of a testing session, the magnitude of pain responses can be affected by factors unrelated to pictures (e.g., habituation/sensitization from repeated stimulation [71]). To assuage this potential problem, pictures of different valences (unpleasant, neutral, pleasant) are pseudorandomly distributed across the testing session. Further, painful stimulations are pseudorandomly distributed across the testing session, as well as being equally distributed across picture valences. These methodological strategies should wash out any effects of habituation/sensitization as long as the slopes are not influenced by emotional picture valence (i.e., the response slope should be parallel for pleasant, neutral, and unpleasant pictures; Fig. 1 A). By contrast, if the slopes are influenced by emotional valence, then this could pose a problem (Fig. 1 B). Indeed, ECON assumes that emotional valence modulation of pain responses is consistently observed throughout the testing session. The present study addressed this issue by presenting 36 unpleasant, 36 neutral, and 36 pleasant pictures during which 52 suprathreshold stimuli were delivered to evoke pain, the nociceptive...
five participants were enrolled, but not included in the analyses. Twenty participants acknowledged a recent psychological trauma as defined by the DSM-IV [1]; or were diagnosed with Raynaud’s disease. Twenty-five participants were enrolled, but not included in the analyses due to reaching 40 mA maximum stimulation before NFR obtained (n = 7), reaching pain tolerance before NFR obtained (n = 13), or equipment problems (n = 5). One-hundred and twenty participants (61% women, n = 73) completed the study and are included in analyses. Average age of completers was 35 years (SD = 15) and a majority were White (76%, n = 91), single (57%, n = 68), and employed (76%, n = 91), with an average of 15 years of education (SD = 2.66). All participants provided informed consent after study procedures were fully described to them.

2.2. Procedure

All procedures were fully approved by the University of Tulsa ethics review board and were administered in a single session. During the session, the researcher provided a thorough overview of the experiment and obtained informed consent. A demographics form and brief interview were used to obtain background information and assess inclusion/exclusion criteria. Participants were then instructed on the use of the pain ratings scale and the Self-Assessment Manikin scales for rating emotional responses (both described below), were instrumented for physiological recording, and then filled out several psychosocial questionnaires. These tasks lasted about 1.5–2 h.

The testing session consisted of three major testing phases: (1) startle modulation assessment (~1 h), (2) basal pain sensitivity assessment (20–30 min), and (3) emotional controls of nociception (ECON) (~2 h). Throughout all phases, participants were seated comfortably in a recliner with a small pillow placed under the left ankle to facilitate relaxation of the leg muscles. Questionnaires and picture stimuli were presented by an LCD projector onto a large screen mounted approximately 3 m in front of the participant. Participants were offered breaks in between testing sessions to minimize fatigue.

During startle modulation assessment, participants viewed emotionally-charged pictures during which 105-dB white noise bursts were delivered over headphones (these pictures were different than those during ECON). Basal pain sensitivity testing involved NFR threshold and electrocutaneous pain tolerance assessment. NFR threshold was obtained using the ascending-descending staircase method described elsewhere [35]. Pain tolerance assessment involved a single ascending staircase of electrocutaneous stimuli that ended when the participant rated a stimulus as 100 (maximum tolerable) on the pain rating scale. Startle modulation and pain sensitivity data are not presented in the current report. Intensity of electrical stimulations delivered during ECON testing was set at 120% NFR threshold. During ECON, 108 emotionally-charged pictures not used during startle testing were presented in four blocks of 27 pictures balanced for affective valence (9 pleasant, 9 neutral, 9 unpleasant). Each picture was presented for 6 s and inter-picture intervals varied randomly from 12 to 22 s. 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. Noxious stimulations were trains of five 1-ms rectangular wave pulses at 250 Hz (i.e., 3 ms ITI) that were delivered over the retromalleolar pathway of the sural nerve at an intensity of 120% NFR threshold. Electric stimulations were equally distributed across the four blocks and delivered during one-third of pictures (12 stimulations per valence) and 16 inter-picture intervals. Thus, a total of 52 stimulations were delivered during the picture-viewing phase, but only 36 were delivered while pictures were displayed. To reduce predictability, electric stimulations were randomly delivered 3–5 s after picture onset and 11 to 21 s after inter-picture interval onset. The 3–5 s post-picture-onset interval was chosen because it has been shown to produce the largest emotional valence modulation effects on the acoustic startle reflex.
[4,10]. The Self-Assessment Manikin was administered after each picture to assess subjective responses to pictures. The pain rating scale was administered following every electrocutaneous stimulation (but, after picture offset if necessary). When participants were responding to SAM and pain scales, experimental timing was paused. After each picture block, participants were offered an optional short break and filled out a questionnaire on their personality (3–5 min per break). At study completion, participants were thanked and paid for their participation.

2.3. Apparatus and signal processing

Experimenter 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. Data acquisition, stimulus presentation, and questionnaire presentation were controlled by a PC equipped with dual monitors, A/D board (PCI-6036E or PCI-6031E; National Instruments, Austin, TX), and LabVIEW software (National Instruments, Austin, TX). One monitor output was used to present questionnaires and pictures via an LCD projector and the other monitor output was used to view physiological signals and track experimental timing on a 17” flat panel monitor.

An electric stimulator (Grass Technologies, West Warwick, RI; Model S88 or Model S48), stimulus isolation unit (Grass, Model SIUT), constant current unit (Grass, 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 computer-controlled voltage regulator varied the current to the participant (max current = 40 mA). Psychophysiological signals were sampled in 9 s trials during inter-picture intervals (3 s pre-shock, 6 s post-shock) and 14 s trials during pictures (3 s pre-picture, 6 s during picture, and 5 s post-picture) at 1000 Hz and collected/filtered using a Grass Technologies Model 15LT Bipolar Amplifier with one Dual DC (15A12) and two Quad AC (15A54) modules. Skin conductance response (SCR) was measured using an adaptor (Grass, Model SCA1) for the 15A12 amplifier. All recording electrodes were Ag–AgCl.

To apply EMG and stimulating electrodes, the skin was first degreased with alcohol, slightly abraded using NuPrep gel to achieve impedances below 5 KΩ, and then electrodes were filled with conductive gel (Grass Technologies, EC50) before they were secured to the skin using adhesive collars. To measure skin conductance, electrodes were filled with isotonic paste (EC33, Grass Technologies) and secured to the volar distal tips of the index and middle finger. For NFR recording, two electrodes were placed over the biceps femoris muscle of the left leg 10 cm superio to the popliteal fossa and a common reference electrode was placed over the lateral epicondyle of the femur. The raw biceps femoris signal was amplified, bandpass filtered (10–300 Hz), and rectified.

2.4. Emotion induction

2.4.1. Picture stimuli

In the present study 108 digital pictures were chosen from the International Affective Picture System [27] that varied in affective valence (36 unpleasant, 36 neutral, 36 pleasant; see Table 1). Pleasant contents included erotica, families/babys, and adventure/sports. Unpleasant contents included depictions of death/grieving, attack scenes, and mutilated bodies/injuries. Neutral picture contents included household objects, mushrooms, neutral faces, and neutral designs. The pictures were delivered in 4 blocks of 27 pictures, with each block containing 9 pleasant (3 erotic, 3 family, 3 adventure), 9 neutral, and 9 unpleasant (3 death, 3 attack, 3 mutilation) pictures. Normative IAPS ratings [27] were used to match pictures across blocks on valence and arousal ratings. Picture order was randomized within blocks (across participants) with the limitation that not more than 3 pictures of similar valence were shown consecutively. Randomizing within blocks that contained equal numbers of pleasant, neutral, and unpleasant pictures ensured that picture valence was evenly distributed across the testing session. Pictures were presented by LCD projector onto a large screen in a dimly lit room.

2.4.2. Subjective emotion ratings

Picture-evoked subjective responses were assessed using the Self-Assessment Manikin (SAM) [5], a 2-item questionnaire that assesses pleasure, arousal, valence/pleasure (unpleasant-pleasant) and arousal (calm-excited). Each item is comprised of sets of five cartoon figures that yielded ratings between 1 and 9 for each dimension, with higher scores indicating greater pleasure or arousal, respectively. After each picture, a computerized version of the SAM [38] was used to make ratings, with instructions for participants to “rate your emotional reaction to the picture.”

2.5. Nociceptive outcomes

Nociceptive reactivity (shock-evoked responses) was assessed from subjective ratings, NFR magnitude, and skin conductance response. Although pain-evoked heart rate acceleration and pain-evoked blink reflexes were also measured in this study, analyses found that these responses do not show reliable valence modulation (unpleasant > neutral > pleasant) and that picture-evoked responding in ECG and orbicularis oculi EMG may have influenced the baseline (pre-shock) activity used to calculate these responses [32]. Thus, pain-evoked HR and pain-evoked blinks were not examined in the present study.

2.5.1. Subjective ratings of electrocutaneous stimuli

A computer-presented rating scale oriented vertically was used to rate electric stimulations [17,38]. This scale has been used in our previous ECON studies and numerous other NFR studies [15,18,38–40]. The scale was labeled: 0 (no sensation), 1 (just noticeable), 25 (uncomfortable), 50 (painful), 75 (very painful), and 100 (maximum tolerable). Participants moved an indicator anywhere along the scale and submitted their answers by computer mouse. These ratings were used as a measure of pain experience.

2.5.2. Nociceptive flexion reflex (NFR) magnitude

The NFR is a spinal reflex elicited by Aβ fiber activation [43,44] and NFR magnitude correlates with subjective pain intensity [8,21,35,38]. Thus, NFR magnitude was used in the current study to assess within-subject changes in spinal nociceptive responding [43,44]. NFR magnitude was defined as the mean biceps femoris EMG response in the 90–150 ms post-electric stimulus interval minus the mean EMG response in the 60–0 ms pre-electric stimulus baseline divided by the pooled standard deviation of the two intervals (Cohen’s d). This response definition was chosen because empirical evidence suggests Cohen’s d optimizes the correlation of NFR magnitude with pain ratings and it has better distributional properties [33,35]. Using the 90–150 ms post-stimulation interval timeframe reduces potential contamination by the non-nociceptive RII reflex, startle responses, and/or voluntary movements [14].
2.5.3. Pain-evoked skin conductance response (SCR)

Skin conductance was first averaged by 0.5 s epochs, and then the mean activity in the 1 s pre-electric stimulus interval was subtracted from each 0.5 s post-electric stimulus epoch [3]. SCR was defined as the maximum skin conductance increase in the 1–4 s post-electric stimulus interval [3,11,36,40]. Therefore, the 0.5 s post-electric stimulus epoch (in the 1–4 s post-electric stimulus interval) with the greatest positive change was used as the response definition [3,36,40]. This response definition for SCR has been shown to be modulated by emotional picture-viewing [36,40].

2.6. Data analysis

Analyses were conducted using the MIXED procedure in SPSS 14.01. Data were analyzed at the trial level, such that every participant had 120 rows of data corresponding to each picture (n = 108) and each shocked inter-picture interval (n = 16). For all models, subject ID number was used as the grouping variable to model between-subject variability and the covariance of repeated measures was modeled using a first-order autocorrelation (AR1) error structure. Unlike our previous studies [38–40], the current study analyzed unstandardized pain responses in order to illustrate habituation/sensitization in the original units of the pain-related variables. Picture Valence (unpleasant, neutral, pleasant) was entered into the models as a nominal within-subject variable and Stimulation Sequence (order of shocks) was entered into the models as a continuous within-subject variable. The Picture Valence main effect was found for valence/pleasure ratings (F[2, 4018.90] = 2921.80, p < 0.001) and arousal ratings (F[2, 3223.81] = 758.88, p < 0.001). The linear and quadratic trends were significant for both valence and arousal ratings (all ps < 0.001). Thus, to further explore these trends, Bonferroni mean comparisons were conducted. Compared to neutral and pleasant pictures, unpleasant pictures were rated as less pleasurable and more arousing (ps < 0.001), and pleasant pictures were rated as more pleasurable and more arousing than neutral pictures (ps < 0.001). Thus, results suggest emotion was manipulated as expected by pictures.

One-hundred and eight different pictures were presented during ECON to minimize emotional habituation that could occur with repeated exposure to pictures. To test whether we were successful, Picture Sequence (36 trials per Picture Valence) was entered into the mixed effect ANOVAs noted above. The effect of Picture Sequence was significant for both valence and arousal ratings (all ps < 0.001). Rather, valence ratings increased on average by +0.00366 with each subsequent picture during ECON and arousal increased by +0.00691 with each subsequent picture.
To determine whether each pain outcome demonstrated significant change in response magnitude over the 52 stimulations, the effect of Picture Valence was initially ignored and a mixed effects ANOVA was conducted with Stimulus Sequence (shocks ordered 1–52) entered as a continuous predictor. These data are depicted in Fig. 3. The main effect of Stimulation Sequence was significant for pain ratings \( F(1,1021.80) = 9.079, p = 0.003 \), NFR magnitude \( F(1,1732.29) = 166.92, p < 0.001 \), and pain-evoked SCR \( F(1,914.74) = 8.39, p = 0.004 \). The parameter estimates from these models suggested that with each subsequent stimulus, pain ratings increased on average by 0.047 units, NFR decreased on average by 0.00246 units, and pain-evoked SCR decreased on average by 0.000246 μS.

Participant sex and age were entered as predictors in the models above to determine whether habituation/sensitization was moderated by these variables. The interactions of Sex \( \times \) Stimulus Sequence and Age \( \times \) Stimulus Sequence were non-significant in all analyses (all \( p > 0.11 \)). Thus, given that age and sex do not influence emotional modulation \([13,45]\) or habituation/sensitization, age and sex were not included in models examining emotional modulation of nociceptive reactions.

### 3.3. Habituation/sensitization and emotional modulation of pain responses

**Fig. 4** illustrates these results. To examine whether habituation/sensitization slopes were influenced by emotional valence, mixed effects ANOVAs were conducted that entered Picture Valence (unpleasant, neutral, pleasant) as a nominal variable and Stimulation Sequence as a continuous predictor to model the habituation or sensitization slope. A distinction between these analyses and those in Section 3.2 is that Stimulation Sequence ranged from 1 to 12, representing the order of the 12 shocks delivered during pictures of a given valence (12 during unpleasant, 12 during neutral, 12 during pleasant). For these analyses, main effects (Picture Valence, Stimulation Sequence) were entered first and then the Picture Valence \( \times \) Stimulation Sequence interaction was entered in a second step. To determine whether the addition of the interaction improved model fit, the chi-square difference test was conducted \([22]\). Interactions that were non-significant and did not improve fit according to the chi-square difference test were dropped from the model for parsimony.

For pain ratings, the main effects of Picture Valence \( F(2, 3197.47) = 47.12, p < 0.001 \) and Stimulation Sequence \( F(1, 969.88) = 6.43, p = 0.011 \) were both significant. The main effect of Stimulation Sequence confirms the analysis in Section 3.2 indicating pain ratings showed significant sensitization with repeated stimulation. The trend analyses used as a follow-up test for the main effect of Picture Valence indicated the linear trend was significant \( (p < 0.001) \), but not the quadratic trend \( (p = 0.78) \). Pain ratings were highest during unpleasant pictures, intermediate during neutral pictures, and lowest during pleasant pictures (Fig. 4, top bar graph). The addition of the Picture Valence \( \times \) Stimulation Sequence interaction did not improve model fit \( (\Delta \chi^2 \left[ df = 2 \right] = 4.82, p = 0.18) \), nor was it a significant effect in the model \( (p = 0.09) \). Together, this suggests pain sensitization was similar across
pleasant, neutral, and unpleasant pictures (Fig. 4, top scatterplot) and that NFR modulation was consistent across the testing session.

For NFR magnitude, the main effects of Picture Valence $[\text{df} = 2, 3829.07, p = 0.001]$ and Stimulus Sequence $[\text{df} = 1, 1476.96, p = 0.001]$ were both significant. The main effect of Stimulus Sequence confirms the analysis in Section 3.2 suggesting pain-evoked SCR habituated with repeated stimulation. The trend analyses used as a follow-up test for the main effect of Picture Valence indicated the linear trend was significant ($p = 0.001$), but not the quadratic trend ($p = 0.28$). Pain-evoked SCRs were highest during unpleasant pictures, intermediate during neutral pictures, and lowest during pleasant pictures (Fig. 4, lower bar graph). The addition of the Picture Valence $\times$ Stimulus Sequence interaction did not improve model fit ($\chi^2 [\text{df} = 2] = 1.62, p = 0.88$), nor was it a significant effect in the model ($p = 0.45$). Together, this suggests SCR habituation was similar across pleasant, neutral, and unpleasant pictures (Fig. 4, lower scatterplot) and that SCR modulation was consistent across the testing session.

4. Discussion

3.4. Exploratory analyses: attention to pictures

Additional issues that the present data allow us to address are whether attention/distraction influences pain responses and whether attention/distraction alters habituation or sensitization processes. To address these issues, data collected during the neutral pictures (attention directed toward visual stimulus) and the inter-picture intervals (attention not directed) were examined. Attention (Neutral Picture vs. No Picture) and Stimulus Sequence were entered as predictors into mixed effect ANOVAs. Results indicated a significant main effect of Attention for pain ratings $[\text{df} = 1, 2545.25, p = 0.003]$ and pain-evoked SCR $[\text{df} = 1, 2511.81, p = 0.001]$, but not NFR $[\text{df} = 1, 2740.81, p = 0.384]$. Attention toward pictures decreased pain ratings and increased pain-evoked SCR (Fig. 4, bar graphs). Moreover, the Attention X Stimulus Sequence interaction was significant for pain ratings $[\text{df} = 1, 2741.68, p = 4.14, p = 0.042]$ and pain-evoked SCR $[\text{df} = 1, 2716.62, p = 4.20, p = 0.041]$, but not NFR $[\text{df} = 1, 2625.88, p = 0.798]$. Relative to no pictures, attention to pictures was associated with a more positive slope for pain ratings (greater sensitization; $\Delta$slope $= +0.25$) and a more negative slope for SCR (greater habituation; $\Delta$slope $= -0.013$). Thus, attention to pictures enhanced stimulus repetition effects for pain and SCR.

The present study examined whether habituation or sensitization slopes were influenced by emotional picture valence. As predicted, we found NFR and SCR habituated over repeated stimulations, but we also found that pain perception sensitized. This divergence between SCR, NFR, and pain could be due to a number of factors, including differences in the response circuits. For example, habituation of flexion reflexes can be observed in spinalized animals [20]. Therefore, response decrements in NFR (and maybe SCR) could be due to changes in the reflex pathways that are not involved in pain perception. Moreover, it is not surprising that SCR would diverge from pain, given that SCR can be evoked by non-noxious stimuli and is strongly potentiated by stimulus novelty [6]. Alternatively, the dissociation between SCR, NFR, and pain may be due to differences in the factors that modulate them. Using simultaneous EEG-fMRI, Christmann and colleagues [9] found dipole strength in the anterior cingulate cortex (ACC) was stronger at the end of a block of painful electric stimulations than at the beginning. Given that the ACC is associated with emotional reactions and pain unpleasantness, this could provide a
mechanism by which negative affect due to the prolonged testing session selectively sensitized pain perception in the current study. Whatever the underlying mechanisms, an important implication is that the different response slopes will attenuate correlations among NFR, SCR, and pain in studies that use them to assess within-subject changes in nociceptive responding over time. Thus, this issue should be considered in the research design.

4.2. Emotional modulation of pain responses

Emotional modulation was noted for all pain responses, an effect that appeared to be independent of habituation or sensitization. Relative to neutral pictures, pleasant pictures increased subjective pleasure, increased subjective arousal, and inhibited pain responses. By contrast, unpleasant pictures decreased subjective pleasure, increased subjective arousal, and facilitated pain responses. These findings are consistent with the notion that emotional valence, rather than emotional arousal, led to this pattern of pain modulation. Indeed, we have previously shown that picture-evoked valence determines the direction of modulation (pleasant = inhibition, unpleasant = facilitation), whereas picture-evoked arousal determines the degree of modulation (greater arousal = greater inhibition/facilitation) [40]. While subjective arousal was slightly higher for unpleasant pictures than pleasant pictures, this difference in arousal would not be expected to elicit the pattern of pain modulation we observed. Rather, if arousal were responsible, then one would expect pain modulation to follow a different pattern (e.g., neutral < pleasant < unpleasant; [pleasant and unpleasant] < neutral). Moreover, these findings are consistent with prior reports of emotional valence modulation of cold pressor pain [12,30,34], contact heat pain [49], and subjective and physiological responses to electrotactile pain [2,25,36,38–40,42,47,48].

In the present study only four suprathreshold stimuli were delivered per picture content, which precluded us from adequately modeling the habituation and sensitization slopes for the most arousing pictures (e.g., erotica, mutilation). Given that emotional arousal influences the magnitude of inhibition/facilitation, this means emotional valence modulation would have been stronger had we been able to average by these contents. Nonetheless, the unpleasant > neutral > pleasant modulation pattern was observed for every pain response (Fig. 4, bar graphs).

4.3. Attentional Influences

Exploratory analyses that compared pain responses during neutral pictures to responses during inter-picture intervals found that pain ratings were lower and pain-evoked SCRs were larger during pictures. This is consistent with reports of reduced pain [46] and increased SCR [19] during tasks that require greater attention. Interestingly, slopes for pain sensitization and SCR habituation were steeper when attention was directed toward pictures. While these findings are intriguing and suggest a role of attention in the modulation of habituation/sensitization, they should be interpreted with caution until replicated by a study designed to specifically address attentional factors (e.g., specific attentional instructions given; no emotional pictures interleaved).

4.4. Implications

The major finding of the current study is that, despite changes in pain responses associated with repetitive stimulation, emotional valence modulation was constant throughout the ECON testing session (Fig. 4, scatters). To maximize this modulatory effect, we chose to present each emotional picture only once to eliminate emotional habituation to the pictures. In a study by Bradley and colleagues [6], six emotional pictures (2 pleasant, 2 neutral, 2 unpleasant) were presented repeatedly to human participants, during which acoustic startle probes were delivered to elicit the startle eyeblink response. They found that physiological–emotional reactions to the repeated pictures (e.g., corrugator EMG, skin conductance, heart rate) habituated across trials, as did startle eyeblink magnitude. Notably, emotional valence modulation of the startle response was observed throughout the testing session. They interpreted their results to mean that the emotional modulation circuit is less subject to habituation than the primary startle reflex pathway or emotional responses from somatic and autonomic systems. Likewise, our results suggest the circuit responsible for emotional modulation of pain and nociception is less subject to habituation or sensitization than the circuits responsible for somatic (NFR), autonomic (SCR), and perceptual responses to shock. The similarity of our findings to the Bradley et al. study is not surprising though, given that the circuitry responsible for startle modulation and pain modulation have several supraspinal regions in common (e.g., amygdala, periaqueductal gray) [16,28]. Nevertheless, to specify whether emotional valence modulation of pain/nociception is constant throughout the ECON testing session even when emotional responses to pictures habituate (e.g., ratings, skin conductance), future studies are needed in which the same set of emotional pictures are repeated like the Bradley et al. study.

The present study found that some of the within-subject changes in pain reactivity are due to factors independent of emotional pictures, namely habituation and sensitization processes. Given that the habituation/sensitization slopes were unaffected by emotional pictures, this supports the practice of using research methodologies to wash out their effects. Specifically, picture contents should be dispersed evenly throughout the testing session, and suprathreshold stimuli should be evenly distributed throughout the testing session and across picture valence. But in addition, it is beneficial for statistical analyses to take into account stimulus repetition effects because this variability in the dependent variable will be removed from the error term of the ANOVA model thereby increasing statistical power.

4.5. Study limitations

Despite numerous strengths (e.g., large sample, multiple pain responses assessed, powerful statistical methods), a few study limitations must be noted. First, prior exposure to emotional pictures during startle testing may have influenced responses during ECON. Indeed, when subjective ratings of pictures are compared between the startle and ECON phases, valence ratings were slightly lower during ECON (pleasantStartle = 6.77, pleasantECON = 6.71; neutralStartle = 5.35, neutralECON = 5.24, unpleasantStartle = 2.79, unpleasantECON = 2.58) and arousal ratings were slightly higher during ECON (pleasantStartle = 4.55, pleasantECON = 4.82; neutralStartle = 2.24, neutralECON = 2.77, unpleasantStartle = 5.05, unpleasantECON = 5.28). However, as we mentioned above, Bradley and colleagues [6] found that changes in emotional responses to pictures can occur without significant influence on emotional valence modulation of startle. Therefore, if their findings can be generalized to emotional valence modulation of pain, then any effect of pre-exposure to pictures during startle is not likely to have influenced ECON. Nonetheless, future work should determine whether our results can be replicated without pre-exposure to emotional pictures. A second limitation is that the habituation/sensitization slopes may have been influenced by the fact that intervals between electric stimuli were not equivalent (due to pseudorandom delivery). While slopes may have been influenced, this should not affect the primary conclusion of this study. Specifically, emotional valence modulation was not influenced by habituation and sensitization when pictures were distributed equally across testing session and electrotactile stimuli were distributed equally across testing session and picture valence. Thus,
our conclusions should be valid for ECON studies that follow the suggestions outlined in Section 4.4. A third limitation is that results may not generalize to longer testing sessions with more supra-threshold stimuli. Although future studies should address this issue, long testing sessions are not necessary to evoke robust emotional valence modulation, because our previous ECON studies presented 8 pleasant, 8 neutral, and 8 unpleasant pictures with noxious stimuli during 50% of pictures [38,39]. And finally, our results may not generalize to non-healthy participants. Indeed, emotional valence may influence the habituation or sensitization slopes in populations for which stimulus-response pathways and/or descending modulation circuits are sensitized or otherwise altered (e.g., chronic pain patients).

Despite these limitations, the present study provides further evidence that ECON is a valid procedure for studying emotional modulation of pain. Thus, we believe these procedures can be used to better elucidate the emotion–pain relationship, but to also study individual differences that influence descending, brain-to-spinal cord control of pain.

Acknowledgements

This work was funded by a Grant (HR06-177) from the Oklahoma Center for the Advancement of Science and Technology and Faculty Development Summer Fellowships from The University of Tulsa awarded to Jamie L. Rhudy, Ph.D. Portions of this paper were presented at the 2008 and 2009 American Pain Society conferences held in Tampa, FL and San Diego, CA. The authors would like to thank Klanci McCabe, Jennifer Russell, Carl Lattimore III, Ashley Vincent, Jennifer DelVentura, Ellen Terry, Emily Main, Mary Chandler, Kara Kerr, and Fred Kurzban for their help with data collection and data processing. In addition, we thank all of the participants that contributed to this work. The authors have no conflicts of interest to report.

References