Affective modulation of autonomic reactions to noxious stimulation

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Abstract

Research suggests that emotion modulates spinal nociception and pain; however, there is limited evidence that other objective, nociceptive reactions are modulated. This study examined the impact of affective picture-viewing on autonomic reactions (skin conductance response, heart rate acceleration) resulting from noxious electric stimulations to the sural nerve. Pictures varying in affective valence (unpleasant, neutral, pleasant) were presented during which noxious stimulations were delivered. Skin conductance response and short-latency heart rate acceleration following each stimulation was calculated and averaged by picture valence. Results suggested that autonomic reactions were modulated in parallel. Specifically, reactions were smaller during pleasant pictures than unpleasant pictures, although unpleasant pictures did not result in significant facilitation relative to neutral pictures. The valence linear trend explained 26% of the variance in the multivariate combination of the reactions, suggesting emotion does modulate autonomic reactions to nociception. These results suggest that SCR and HR acceleration are outcomes that can be assessed together with NFR and pain report during picture-viewing to study affective modulation of spinal (NFR), supraspinal (SCR, HR acceleration), and subjective (pain report) nociceptive reactions.

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1. Introduction

Motivational priming theory posits that reactions to aversive stimuli are inhibited by pleasant stimuli and facilitated by unpleasant stimuli (Lang et al., 1990). Numerous studies examining the acoustic startle reflex (ASR) have supported this claim (Grillon and Baas, 2003); however, little has been done to extend these findings to other averingly motivated reactions (cf., Vrana, 1995).

Using methodology similar to studies of ASR, our laboratory recently demonstrated that affective valence also modulates nociceptive reactions (Rhudy et al., 2005; in press). During affective picture-viewing, noxious electric shocks were randomly delivered and measures of spinal nociception (nociceptive flexion reflex, NFR) and subjective pain were recorded. As predicted, nociceptive reactions were facilitated by unpleasant pictures and inhibited by pleasant pictures (i.e., significant valence linear trend). In these studies, skin conductance and heart rate were recorded during picture-viewing as a means to verify emotion-induction (i.e., picture-evoked autonomic reactions). From these data, it is possible to calculate shock-evoked skin conductance response (SCR) and heart rate (HR) acceleration. Doing so will allow us to examine the influence of emotion on these supraspinally-mediated (i.e., hypothalamus–brainstem) reactions to nociception.

The present study pooled data from two recent investigations of the influence of picture-viewing on pain and the NFR resulting from noxious electric stimulation to the sural nerve (Rhudy et al., 2005, in press). The studies were identical, with the exception that half of the participants in the second study received predictable noxious shocks during picture-viewing (Rhudy et al., in press). These participants were omitted from analyses to ensure that data analyzed in the present study were collected under identical conditions. SCR and short latency heart rate acceleration resulting from noxious shocks were calculated and averaged by pictures of similar valence. It was predicted that autonomic reactions would be modulated in parallel, with larger reactions during unpleasant pictures and smaller reactions during pleasant pictures. As a result, the valence linear trend was expected to be significant and explain a...
large percentage of variance in the multivariate combination of the reactions.

2. Materials and methods

Only those methods directly relevant to the present study are described. A thorough explanation of study methods is published elsewhere (Rhudy et al., 2005).

2.1. Participants

Participants were 53 healthy male (28.3%) and female students who received course credit for their participation. Most were White–non Hispanic (75.5%), single (86.8%), and employed (60.4%) with an average age of 22.04 years (S.D. = 5.64 years). All procedures were fully approved by The University of Tulsa ethics review board and participants gave informed consent before participating.

2.2. Apparatus

Stimulus presentation and data acquisition were computer controlled using a PC equipped with dual monitors, A/D board (National Instruments, PCI-6036E, Austin, TX), and LabVIEW software. Noxious electrical stimuli were delivered using a Grass Instruments stimulator (Model S88, West Warwick, RI), stimulus isolation unit (Model SIU8T), constant current unit (Model CCU1), and a bipolar stimulating electrode (Nicolet, 019-401400, Madison, WI) attached to the left ankle over the retromalleolar pathway of the sural nerve. The maximum intensity was set at 40 mA. All psychophysiologic signals were sampled at 1000 Hz and collected/filtered with Grass Instruments Model 15LT Bipolar Amplifier with Quad AC (15A54) and Dual DC (15A12) modules. An adaptor (Grass, Model SCA1) allowed skin conductance measurement. Experimenters monitored participants by video from an adjacent room.

2.3. Picture-viewing: emotion-induction

Pictures from the International Affective Picture System (IAPS; CSEA, 1999) were used to manipulate affective valence: unpleasant (human and animal attack), neutral (mushrooms, household objects), and pleasant (erotic).1 Pictures were presented on a 17 in. flat panel monitor positioned .5 m from the participant in a dimly lit room. The order of picture presentation was random, with the limitation that not more than two pictures of similar valence were shown consecutively. Therefore, on average, unpleasant, neutral, and pleasant pictures were distributed equally throughout picture-viewing, minimizing the influence of habituation/sensitization to repeated shocks.

2.4. Noxious electric stimulation

The bipolar stimulating electrode was attached to the left ankle over the retromalleolar pathway of the sural nerve after skin was cleaned with alcohol and slightly abraded with NuPrep to reduce impedance ≤ 10 kΩ. Stimulations were 5 rectangular wave pulses of 1 ms duration at 250 Hz delivered randomly during and in between pictures (balanced across picture valence). Stimulus intensity was set at 1.2 times the nociceptive flexion reflex (NFR) threshold. The NFR is a withdrawal response in the lower limb elicited by activation of Aδ fibers, and NFR threshold is used as an objective measure of nociceptive threshold (Sandrini et al., 2005; Skljarevski and Ramadan, 2002). To determine NFR threshold, stimulus intensity began at 0 mA and increased in 1.5 mA steps (with a varying 8–12 s interval) until a reflex was detected. A reflex was defined as a mean biceps femoris EMG response in the 91–150 ms post-stimulus interval that exceeded mean EMG activity during the 60 ms pre-stimulus interval by at least 1.0 S.D. (for full description, Rhudy et al., 2005). Once the reflex was detected, then stimulus intensity was decreased in .75 mA steps until it was no longer detected. Continuing from this intensity, this up-down staircase procedure was repeated two more times, but with .5 mA steps. The average intensity of the last two peaks and troughs was multiplied by 1.2 and used throughout picture-viewing.

2.5. Autonomic reactions to noxious stimuli2

Skin conductance (SC) was measured by placing electrodes filled with isotonic paste (EC33, Grass Instruments) on the volar surface of the index and middle 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 after the skin was degreased with alcohol and slightly abraded using NuPrep gel to lower impedance. SC and ECG were sampled in 11 s epochs (3 s before, 6 s during picture presentation, and 2 s after picture offset). ECG was converted offline to heart rate (HR) in beats-per-minute from interbeat interval. Each 11 s epoch of SC and HR was averaged by .5 s bins and the mean activity in the 1 s pre-stimulation interval was subtracted from each post-stimulation .5 s bin (Bradley et al., 2001). This method of computer scoring provides a reliable and efficient

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1 Image numbers were: erotica (4658, 4659, 4660, 4670, 4681, 4687, 4689, 4800), human and animal attack (1050, 1120, 1300, 1930, 3530, 6260, 6350, 6510), and neutral (5500, 5510, 5520, 5530, 7010, 7030, 7040, 7080). Mean normative valence and arousal ratings across categories were: attack (valence = 2.90, arousal = 6.88), neutral (valence = 5.11, arousal = 2.68), and erotic (valence = 6.85, arousal = 6.65) (Lang et al., 2001).

2 The 1-s pre-shock baseline used to calculate autonomic reactions to shock were recorded during pictures (shocks were delivered 3–5 s following picture onset). Therefore, it is possible that picture-evoked changes in SCR and HR altered these local (pre-shock) baselines, confounding assessment of SCR and HR acceleration. Indeed, picture-viewing is known to evoke autonomic responses (Lang et al., 1993). There are at least two reasons suggesting that this was not a problem in the current study. First, change scores for autonomic reactions were also calculated using a pre-picture baseline (1 s prior to picture onset). Conclusions were the same when those change scores were analyzed. Second, picture-evoked SCR and HR was not influenced by picture valence (heart rate acceleration: p = .70, η² = .01; skin conductance: p = .82, η² = .008); therefore, local baselines were not significantly altered by picture-viewing.
way of creating change from pre-stimulation baseline scores for every post-stimulation .5 s epoch. As recommended by others (Dawson et al., 2000), skin conductance response (SCR) was defined as the maximum skin conductance increase in the 1–4 s post-stimulation interval. Therefore, the .5 s post-stimulation epoch (in the 1–4 s post-stimulation interval) with the greatest positive change was used as the response definition (Bradley et al., 2001).

A similar procedure was used to calculate HR. Although the functional significance is subject to debate (cf., Turpin, 1986), two HR accelerative components have been observed following abrupt, intense stimulation (Ramirez et al., 2005) – one that peaks around 4 s and another near 30 s. We were only able to calculate the early accelerative response from the current data, and did so using an algorithm based on the work of others (Bradley et al., 2001). Using the change scores described above, peak HR acceleration was defined as the .5 s post-stimulation epoch (in the 1–5 s post-stimulation interval) with the greatest positive change. Together, the SCR and HR acceleration definitions provide a means of assessing maximum autonomic response following noxious stimulation.

2.6. Manipulation checks: Self-Assessment Manikin ratings

Affective responses to picture-viewing were rated using a computerized version of the Self-Assessment Manikin (SAM; Lang, 1980). The SAM consists of two sets of five pictographs depicting affective valence/pleasure (unpleasant–pleasant) and arousal (calm–excited). Participants dragged an indicator on or between any of the five pictographs for each scale and submitted their answers by pressing a button. This yielded ratings between 1 and 9 for each dimension (higher scores = greater pleasure or arousal).

2.7. Procedure

Participants were provided an overview of the experiment, informed consent was obtained, and then electrodes were applied. Participants were then told that there would be two phases to the experiment. Phase 1 (stimulus intensity determination) involved sending electric stimuli to the ankle to determine the intensity for use during picture-viewing (i.e., 1.2× NFR threshold). During phase 2, the participant was instructed to pay close attention to the pictures presented and told that electric stimuli would be delivered randomly during and in between pictures. Electric stimuli were delivered during 50% of the pictures (4 per picture valence) and 6 inter-picture intervals, for a total of 18 stimulations in phase 2. This number of stimulations was chosen to minimize participant stress and stimulus predictability. The number of stimuli was balanced across picture type. Each picture was presented for 6 s and inter-picture intervals varied randomly (12–22 s). Noxious stimuli were delivered 3–5 s after picture onset and 11–21 s after inter-picture interval onset (onset time randomly determined). The SAM was administered after each picture. Once the experiment was completed, the participant was debriefed and thanked.

2.8. Data analysis

All variables (SCR, HR, valence ratings, arousal ratings) were averaged by picture valence (unpleasant, neutral, pleasant). Valence/pleasure and arousal ratings were analyzed using two repeated-measures ANOVAs with picture valence (unpleasant, neutral, pleasant) as the within-subject factor and participant sex as a between-subject factor. Before averaging by picture valence, SCR and HR acceleration were standardized within individuals by converting to z scores. Standardization removes arbitrary between-subject variability and places variables on a common metric (standard deviation units) to facilitate interpretation of multivariate analysis. Autonomic reactions were analyzed using a repeated-measures MANOVA with picture valence and response-type (SCR, HR acceleration) as within-subject variables. Participant sex was also initially included as a predictor; however, it was removed from the final model because it was not significant (main effect and interactions, p values>.47) and effects sizes were small (≤1.3% variance explained). Bonferroni corrected multiple comparisons and polynomial trend analyses were used to follow-up all significant effects. Wilk’s Lambda is reported to overcome potential sphericity problems. 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).

2.9. Hypotheses

It is predicted that autonomic reactions to noxious stimulations will be larger during unpleasant pictures and smaller during pleasant pictures. Moreover, there will be strong congruence between the two reactions. Specifically, the main effect of picture valence will be significant but not the Response-Type × Picture Valence interaction. The valence linear trend is expected to explain a large percentage of the variance in the multivariate combination of autonomic reactions.

3. Results

3.1. Self-Assessment Manikin (SAM) ratings

Table 1 presents results from SAM ratings. The picture valence main effect was significant for valence ratings.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Unpleasant</th>
<th>Neutral</th>
<th>Pleasant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
</tr>
<tr>
<td>Valence ratings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2.73 1.17</td>
<td>4.28 1.12</td>
<td>6.57 1.50</td>
</tr>
<tr>
<td>Women</td>
<td>2.30 1.22</td>
<td>4.84 0.86</td>
<td>5.34 1.41</td>
</tr>
<tr>
<td>Total</td>
<td>2.42 1.21</td>
<td>4.68 0.97</td>
<td>5.69 1.53</td>
</tr>
<tr>
<td>Arousal ratings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>5.85 2.34</td>
<td>2.80 1.95</td>
<td>5.10 2.29</td>
</tr>
<tr>
<td>Women</td>
<td>5.75 1.70</td>
<td>2.49 1.67</td>
<td>4.58 2.12</td>
</tr>
<tr>
<td>Total</td>
<td>5.78 1.88</td>
<td>2.58 1.74</td>
<td>4.73 2.16</td>
</tr>
</tbody>
</table>
Valence ratings were lower for unpleasant pictures ($d=1.47, p<.001$) and pleasant pictures ($d=.94, p<.001$) relative to neutral pictures. No gender effects were noted for arousal ($p$ values $>.50$). Together, these data suggest that affect was effectively manipulated.

### 3.2. Autonomic reactions to noxious stimulation

MANOVA suggested the picture valence main effect was significant [Lambda=.70, $F(2,51)=10.99, p<.001$, $\eta^2=.30$] (see Fig. 1), but not the Response-Type × Picture Valence interaction ($p>.16$). A significant linear trend explained 26% of the variance in the multivariate combination of the reactions. Autonomic reactions were smaller during pleasant pictures relative to neutral and unpleasant pictures ($p$ values $<.01$, $d$ values $>.66$); however, the comparison between unpleasant and neutral was not significant ($p>.05$, $d=.11$). Although the Response-Type × Picture Valence interaction was not significant, the simple effect of picture valence was examined for each autonomic reaction to determine the variance explained by picture-viewing. The simple effect was significant for both reactions and explained 15% of the variance in skin conductance response and 37% in HR acceleration.

### 4. Discussion

This study examined the influence of affective picture-viewing on autonomic reactions to noxious electric stimulation. Consistent with the motivational priming theory (Lang et al., 1990), autonomic reactions were smaller during pleasant pictures than unpleasant pictures. However, unpleasant pictures did not lead to significant facilitation relative to neutral pictures. Although the reason for the lack of facilitation by negative emotions is currently unknown, there are at least two possible reasons. First, is that autonomic baseline activity could be elevated during testing (perhaps due to shock exposure), thus placing an upper limit on how much autonomic facilitation is possible (i.e., the law of initial values). However, examination of resting autonomic activity does not support this. Tonic skin conductance level was 5.65 $\mu$S (S.D. = 3.71 $\mu$S) and heart rate was 71.62 bpm (S.D. = 13.38 bpm). A second explanation, albeit not independent, is related to the emotional context during testing. Electric shock is known to elicit negative emotions (e.g., Rhudy and Meagher, 2000). So, a background of negative emotion is generated by shock upon which picture-evoked emotional reactions are superimposed. Therefore, the impact of picture-evoked negative emotion may be limited by a ceiling effect. Indeed, we also find the influence of unpleasant pictures on pain ratings and the noxious flexion reflex is smaller than the influence of pleasant pictures (Rhudy et al., 2005, in press). In contrast, studies of acoustic startle reflex modulation (in which noise probes are not likely to elicit a background of negative emotion) find the opposite – the influence of unpleasant pictures on the acoustic startle reflex is larger than the influence of pleasant pictures (e.g., Schupp et al., 1997; Vrana et al., 1988). Whatever the reason for the lack of facilitation during unpleasant pictures, it does not appear to be due to a failure of unpleasant pictures to induce negative affect. Both sexes reported that unpleasant pictures evoked displeasure and subjective arousal despite sex differences in subjective pleasure evoked by erotic pictures. In spite of the lack of significant facilitation by negative emotion, these data are generally consistent with the modulation of other noxious reactions, such as subjective pain and the noxious flexion reflex (Rhudy et al., 2005). Results suggest that affective valence exerts a consistent effect on reactions to aversive/noxious stimulation. Indeed, 26% of the variance in the multivariate combination of skin conductance response and heart rate acceleration was explained by the valence linear trend.

What is more, we recently analyzed the autonomic reactions from the present study together with the subjective pain ratings and NFR magnitude data that have been reported elsewhere (Rhudy et al., 2005, in press). A MANOVA was conducted with
picture valence (unpleasant, neutral, pleasant) and reaction-type (SCR, HR acceleration, pain report, NFR magnitude) as within-subject variables. Only a significant main effect of picture valence emerged from this analysis (reaction-type main effect and Picture Valence × Reaction-Type interaction, \( p \) values > .05) and the valence linear trend explained 52% of the variance in the multivariate combination of the four nociceptive reactions (McCabe et al., 2006). This suggests that emotion exerts a strong, coordinating effect on spinal (NFR), supraspinal (SCR, HR acceleration), and subjective (pain ratings) reactions to nociception. The effect of emotion on autonomic reactions was not as strong as the effect on pain and the NFR, however. As noted in the present study, picture valence explained 15% and 37% of the variance in skin conductance and heart rate acceleration, respectively. Whereas analyses conducted on pain ratings and NFR reported elsewhere suggested that picture valence explained 44% of the variance in each of these measures (McCabe et al., 2006).

While autonomic reactions to noxious stimulation are likely controlled by the same central mechanisms as pain and spinal nociception (i.e., amygdala and periaqueductal gray) (Fields and Basbaum, 1999; LeDoux, 2000), additional central and/or peripheral influences (e.g., parasympathetic controls) may add variability to autonomic outcomes. Alternatively, smaller effect sizes could be due to greater measurement error (lower reliability) associated with autonomic reactions. If true, increasing the number of shock trials could improve reliability and increase effect sizes. A study that will examine this issue is currently underway.

One limitation of this study was the relatively short post-stimulation epoch of data available for analysis. This precluded an examination of long-latency (~35 s post-stimulus) cardiac defense responses that might show greater modulation by emotion (e.g., Turpin, 1986). Nonetheless, short-latency heart rate acceleration and SCR were moderated by affective valence in the present study, implying that motivational priming theory does extend to nociceptive reactions (Lang et al., 1990). These results suggest that SCR and HR acceleration are outcomes that can be assessed together with NFR and pain report during picture-viewing to study affective modulation of spinal (NFR), supraspinal (SCR, HR acceleration), and subjective (pain report) nociceptive reactions. Together, these procedures could be used as a unique tool for studying individual differences in nociception modulation.

References