THE IMPACT OF A NOISE STRESSOR ON CAPSAICIN-INDUCED PRIMARY AND SECONDARY HYPERALGESIA

A Thesis

by

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ABSTRACT

The Impact of a Noise Stressor on Capsaicin-Induced Primary and Secondary Hyperalgesia.

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In searching for new human pain models that more closely resemble clinical pain states, the capsaicin pain model has emerged as a viable model for both inflammatory and neuropathic pain states. A principal benefit of the capsaicin model is that it allows study of two different pain processes, primary and secondary hyperalgesia. Primary hyperalgesia is characterized by spontaneous pain and both heat and mechanical hyperalgesia. In addition, it is likely the result of activation and sensitization of both peripheral and central nociceptors. In contrast, secondary hyperalgesia is characterized by only mechanical hyperalgesia and is caused by the sensitization of central nociceptive neurons. Previous research utilizing the capsaicin pain model has primarily focused on the neural properties with little focus on the impact of affective states on capsaicin-related pain processes. The present study examined the impact of a noise stressor on both primary and secondary hyperalgesia. Results indicated that the effects of the noise stressor impacted secondary hyperalgesia, but not primary hyperalgesia.
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1. Means and Standard Deviations of Self-Report Data in Experiment 1 by Condition
2. Means and Standard Deviations of Self-Report Data in Experiment 2 by Condition
INTRODUCTION

Animal research has elucidated the neurobiological substrates and environmental determinants of pain modulation. Despite these advances, relatively little is known about how psychological processes activate pain modulatory systems. The present proposal examines the role of one psychological process, emotion. Emotional states are thought to play an important role in regulating pain sensitivity. Although animal research indicates that exposure to stress-inducing aversive stimuli can modulate pain, the outcome of hypoalgesia (Fanslow, 1984; Grau, 1984), versus hyperalgesia (Illich, King, & Grau, 1995; King, Joynes, Meagher, & Grau, 1996) depends on a variety of factors such as the severity of the aversive stimulus, its controllability, and how pain reactivity is measured. Indeed, the role of emotion in pain modulation remains a complex matter that is difficult to characterize even in a controlled environment. Moreover, it is unclear whether animal pain research generalizes to humans in either experimental or clinical settings.

In human studies, one determinant of whether hypoalgesia vs. hyperalgesia is reported is the affect of the subject. In general, fear induction results in hypoalgesia, or a decreased sensation to pain stimuli, (Janssen & Arntz, 1996; Johnson & Helmstetter, 1994; Rhudy & Meagher, 2000; Willer & Albe-Fessard, 1980; Willer, Dehen, & Cambier, 1981; Willer & Ernst, 1986) while anxiety induction results in hyperalgesia, or an increased sensation to painful stimuli (Chapman & Feather, 1973; Dellemijn &

This thesis follows the style and format of *Health Psychology*. 
Fields, 1994; Melzack, 1961; Rhudy & Meagher, 2000). However, most of this research primarily examines the role of affect in acute pain models, which may not generalize well to common clinical pain syndromes that are chronic or inflammatory in nature. To better generalize these experimental effects of pain modulation to clinical pain, new experimental models are needed. One model that has shown promise in replicating neuropathic and inflammatory clinical pain involves the use of capsaicin, which is an ingredient of hot peppers. In previous studies, capsaicin has been used to study spontaneous pain (i.e., Logan, Lutgendorf, Rainville, et al., 2001; Petersen & Rowbotham, 1999), hyperalgesia (i.e., Magerl, Wilk, & Treede, 1998; Raja, Campbell, & Meyer, 1984), and allodynia (i.e., Ali, Meyer, & Campbell, 1996; Fuchs, Campbell, & Meyer, 2000; Huang, Ali, Travison, et al., 2000), which is a phenomenon found in hyperalgesia where ordinary, non-painful stimuli are able to evoke pain.

A principal benefit of using a capsaicin pain model to study hyperalgesia is that it provides a means of studying both primary and secondary hyperalgesia, which are triggered by different neural mechanisms. Primary hyperalgesia is characterized by spontaneous pain and both heat and mechanical hyperalgesia (Dahl, Brennum, et al., 1993; Hardy, Wolff, & Goodell, 1950; Raja, Campbell, & Meyer, 1984). In addition, it is likely the result of activation and sensitization of both peripheral and central nociceptors (Koltzenburg, Lundberg, & Torebjork, 1992; Raja, Campbell, & Meyer, 1984; Torebjork, Lundberg, & LaMotte, 1992). In contrast, secondary hyperalgesia is characterized by only mechanical (static, dynamic, and punctate) hyperalgesia (Ali, Meyer, & Campbell, 1996; Fuchs, Campbell, & Meyer, 2000; Magerl, Wilk, & Treede, 1998; Raja, Campbell, & Meyer, 1984). Furthermore, secondary hyperalgesia is caused by the sensitization of central nociceptive neurons (Campbell, Khan, Meyer, & Raja, 1988; Hardy, Wolff, & Goodell, 1950; Torebjork, Lundberg, & LaMotte, 1992).
The central mediation of secondary hyperalgesia is supported by the finding that hyperalgesia can be evoked by stimulation of afferent fibers even after peripheral nociceptors have been anesthetized (Torebjork, Lundberg, & LaMotte, 1992). Although secondary hyperalgesia is normally triggered by a barrage of injury-related nociceptive afferent discharge, it can also be produced by the intense discharges of nociceptive C-fibers that are stimulated by topical capsaicin (LaMotte, Shain, Simone, & Tsai, 1991). The mechanical hyperalgesia in the region surrounding capsaicin application is the perceptual correlate of the sensitized dorsal horns pain transmission neurons to low-threshold mechanical stimuli. Since the enhanced responsiveness of dorsal horn neurons involves synapses other than those activated by the conditioning stimulus, heterosynaptic facilitation is involved.

Although most of the research using the capsaicin model has concentrated on deciphering the neural mechanisms of hyperalgesia, Lutgendorf, Logan, and colleagues (2000) examined the effects of relaxation and stress on capsaicin-induced inflammation. Relaxation training reduced flare size relative to control, but their experimental mental stress task (Stroop color-word test) did not. However, individual differences in sympathetic arousal (serum norepinephrine, heart rate, and systolic blood pressure) during the stressful experimental task predicted increased flare size, suggesting that stress-induced increases in sympathetic outflow modulated flare size. In a recent follow-up study, Logan and colleagues (2001) presented findings on capsaicin-related pain. Similar to their previous study, they examined the effects of relaxation and stress, finding that relaxation reduced ratings of spontaneous pain, whereas stress increased pain in women. Unfortunately, this study did not determine whether stress level altered primary or secondary hyperalgesia.
In addition, other studies have shown that pharmacological manipulations of the peripheral noradrenergic system alter capsaicin-induced thermal hyperalgesia, with agonists causing enhanced pain and antagonists reducing it. For example, Drummond (1995) has shown that pharmacological activation of peripheral noradrenergic receptors potentiates thermal hyperalgesia. However, this NE manipulation does not activate the sympathetic-adrenal medullary system, but rather is only a model for the NE release produced by stress-induced sympathetic-adrenal medullary excitation.

These findings suggest that stress and relaxation may affect the inflammatory flare and capsaicin pain responses by altering peripheral sympathetic outflow. Yet, one cannot determine whether NE is modulating pain at the level of the primary afferent nociceptor or whether it is altering pain modulatory circuits within the central nervous system (e.g., spinal cord dorsal horn). In addition, the NE manipulation can only be generalized to primary thermal hyperalgesia, which is peripherally and centrally mediated, and not secondary hyperalgesia, which is only centrally mediated.

Other studies implicate central pain modulatory mechanisms. Psychological interventions that modulate pain appear to be mediated, in part, by descending pathways that inhibit spinal nociceptive processes. This is supported by the finding that hypnotic analgesia inhibits the spinally mediated R-III nociceptive reflex, which is thought to reflect descending inhibition of spinal nociceptive processes (Kiernan, Dane, Phillips, & Price, 1995). Evidence for descending modulation of capsaicin pain comes from Witting and colleagues (1998) who reported that capsaicin-induced pain and allodynia are reduced by exposure to painful heterotopic stimulation (e.g., immersion of foot in cold water), an effect known as diffuse noxious inhibitory control (DNIC). DNIC appears to be mediated by the activation of a spinal-supraspinal-spinal feedback loop. In light of these findings, it seems plausible that emotion-induced activation
descending pain modulatory pathways could influence spinal processes of central sensitization or neurogenic inflammation.

The present experiments were conducted to test the impact of stress, using a noise stressor, on both the primary and secondary hyperalgesia associated with inflammation from a topical application of capsaicin on the forearm. The first experiment examined the effect of noise stress on capsaicin-induced secondary hyperalgesia by measuring pain to punctate mechanical stimuli. The second experiment examined the effect of the noise stressor on capsaicin-induced primary hyperalgesia by measuring pain to radiant heat stimuli.
GENERAL METHODS

Apparatus

Heart rate was measured using a Grass Instruments pulse transducer (Grass PPS) attached to the distal digit of the index finger of the non-dominant hand. All physiological data were collected using a Grass Instruments Model 7E Polygraph using Model 7DA driver amplifiers, preamplifiers were Model 7P8 and Model 7P1 for heart rate. Heart rate was sampled at 50 Hz. All stimulus control and data acquisition was computer controlled by LabVIEW software and an AT-MIO-16DL DAQ board (both by National Instruments).

The noise stressor consisted of bursts of white noise (105 db) against a background of white noise (60 db). The noises were generated using Cool Edit software (Syntrillium Software Corp, Phoenix, AZ). A computer controlled the noises by triggering a relay connecting the signal from a cassette deck to the subject’s headphones. Six noises were presented at pseudorandom intervals (3 sec to 1 min) and durations (0.75 to 10 sec) over a 2 min period.

Measures

Manipulation Checks

Self-report

To assess the emotional impact of the treatment condition (noise stress or no stress), participants filled out two questionnaires at the end of the experiment. The Self-Assessment Manikin (SAM; Lang, 1980) is a measure with two pictogram scales indicating various levels of valence (ranging from “happy” to “unhappy”) and arousal
(ranging from “excited” to “calm”). Participants were asked to place an “X” on or between any of the figures to indicate their emotional response to their treatment condition: the unpredictable bursts of noise (Stress) or being told that they would not receive unpredictable shocks (No Stress). Participants also rated their emotional reaction on 5 point Likert scales that ranged from “not at all” to “strongly” for ten affective descriptors (angry, disgusted, fearful, happy, sad, surprised, neutral, anxious, bored, and relaxed).

Because we are interested in the effects of stress on pain reactivity, it is necessary to assess any preexisting emotional distress that may contribute to unwanted group differences. To do so, the Center for Epidemiological Studies-Depression Scale (CES-D; Radloff, 1977), a brief, 20 item questionnaire that taps into depression and anxiety symptoms was filled out prior to the experiment. Subjects were instructed to read each item and rate the extent to which they felt that way at sometime during the past week.

There is evidence that self-efficacy can influence pain reactivity (Bandura, O’Leary, Taylor, Gauthier, & Gossard, 1987; Lackner, Carosella, & Fueurstein, 1996). To ensure that test results are not best accounted for by group differences in self-efficacy, a 15 item self-efficacy scale for pain reduction (SES) was created using guidelines proposed by Bandura, O’Leary, Taylor, Gauthier, and Gossard (1987). Here, participants indicated “yes” or “no” to questions that asked them if they believed that they could make reductions of varying degrees (small, medium, or large) in varying intensities of pain (mild, discomforting, distressing, horrible, and excruciating). For all questions they marked “yes,” they were asked to rate their certainty of this belief on
scales ranging from 0 = “uncertain” to 10 = “certain”. The sum of the scales’ ratings was used as an indicator of self-efficacy.

To evaluate whether subjects were aware of our hypothesis, subjects were given an exit questionnaire asking them what they believed the experiment to be studying. Those that gave answers indicating that they understood the hypothesis and purpose of the study were excluded. In addition, the exit questionnaire consisted of a number of open-ended questions regarding their feelings toward the experiment, noise stressor, and the spontaneous pain from the topical capsaicin.

**Physiological indicators**

To assess the impact of the psychophysiological effects of our affective manipulation, heart rate (HR) was recorded. It was sampled for 1 min prior to each pain test, as well as during the stress period. Changes in HR were examined by comparing baseline functioning to treatment and post-treatment periods. In addition, attempts were taken to collect galvanic skin response, but this data was not interpretable due to an equipment malfunction.
EXPERIMENT 1

To determine the impact of stress on secondary hyperalgesia, Experiment 1 examined the effect of a noise stress manipulation on capsaicin-induced secondary hyperalgesia. Heart rate and self-report measures were used to ensure the affect manipulation was stressful. To quantify secondary hyperalgesia, measures of allodynic pain to punctate mechanical stimuli and area of secondary hyperalgesia were employed.

Methods

Participants

Participants were 28 male and 23 female undergraduate psychology students who received course credit for their participation. Of those, 88.2% were Caucasian, 4% Hispanic, 4% Asian, 2% African-American, and 2% other. Mean age was 18.9 years (SD=0.87). Persons were excluded for: circulatory, cardiovascular, or neurological problems; chronic pain; or tobacco, analgesic, anti-histamine, anti-depressant, or recent drug/alcohol use.

Procedure

After filling out the informed consent, demographics, a health status questionnaire, SES, and CES-D, participants were seated upright in a comfortable chair. Heart Rate sensors were applied to their fingers. Subjects were then instructed on how to rate their pain using a mechanical VAS device with the anchors of “No Pain Sensation” and “The Most Intense Pain Imaginable”. Subjects practiced using the VAS device by rating changes in perceived pressure being applied to their arm via a blood pressure cuff. The cuff was inflated to 100, then 200, then back to 100, and finally the
pressure was brought back to 0. The goal of the practice was to ensure that subjects understood the VAS rating scale and would rate changes in perceived pressure consistently. Once the subjects demonstrated proficiency in this task, a grid with eight spokes radiating from the center was drawn in the center of both forearms. Each spoke consisted of ten pain application sites (see Fig. 1). Subjects then underwent a baseline pain test in which a large diameter von Frey hair (6.65 g) was applied to their dominant arm. Experimenters began on the wrist spoke, where all ten sites on each spoke were stimulated working from the outside in. After each spoke, the VAS device was brought back down to zero and the next clockwise spoke was stimulated. The subject was asked to rate changes in pain perception on the VAS device. All pain tests were conducted in the same manner. Figure 2 notes the details of the experimental procedure.

Following the baseline pain test, 300 µl of a 6.0% capsaicin solution was topically applied to the dominant volar forearm via a 1.5 cm x 1.5 cm gauze pad (Culp, Ochoa, et al., 1989; Simone, Baumann, & LaMotte, 1989). To impede evaporation, the site of application was covered with a dressing (Baron, Wasner, et al., 1999). The pad and dressing was left on the arm for a period of 30 min. During the 30 min capsaicin application subjects were asked to rate their affect using a SAM and a set of affective descriptors at 5 min intervals. Subjects were also asked to rate their pain at these 5 min intervals using a paper and pencil VAS, which contained both an “intensity” and an “unpleasantness” component. Since variability in skin temperature has been shown to
Site of Testing

Figure 1: Site of Testing in Experiment 1. Testing began outside the area of secondary hyperalgesia and worked inwards toward the primary injury site. Testing began at the wrist and was completed in a clockwise fashion.
introduce variance in studies using a capsaicin manipulation, skin temperature was recorded throughout the experiment (Liu, Max, et al., 1998).

After the 30 min application, the capsaicin was removed from the forearm and subjects underwent three pain trials, two trials on the arm with capsaicin (CAP) and one trial on the arm without capsaicin (CON). Subjects were then randomly assigned to a treatment condition (Stress or No Stress). During the Stress condition subjects were told “they may or may not be presented with brief, loud, surprising bursts of noise” and presented with pseudorandom bursts of white noise (105 db) against a background of 60 db white noise, which took place over a two minute period. Those in the No Stress condition were told, “they would not receive the brief, loud bursts of noise”. After the affect manipulation, subjects then underwent three retest pain trials consisting of two trials on the CAP arm and one on the CON arm.

Subjects were then asked to rate their emotional reactions to either the bursts of noise or being told that they would not receive the noise. Finally, subjects were given an exit questionnaire and debriefed.
Figure 2. Experimental Procedure for Experiment 1. Bars above the matrix indicate times that physiological data were recorded. Physiological data were recorded 1 min prior to every trial, as well as during the affect manipulation. The trials labeled CAP are pain trials conducted on the arm with capsaicin. The trials labeled CON are pain trials conducted on the arm which did not have capsaicin applied. There were two affective conditions a Stress and a No Stress condition.
Results

Manipulation Checks

Self-Efficacy and Distress

Table 1 lists all means and standard deviations for self-efficacy (SES) and CES-D. SES scores were analyzed using a one-way ANOVA with condition as a between-group variable. No significant group differences were found for either SES [F(1,47) = 2.15, MSE = 1582.61, p > 0.05] or CES-D scores [F(1, 49) = 0.07, MSE = 3.06, p > 0.05]. These results suggest that both conditions were homogeneous on these variables and any between-group differences resulting from the affective manipulation cannot be attributed to pre-existing differences in self-efficacy or distress.

Affective Manipulation

Self-report

To assess the impact of the affective manipulation, 2 x 2 ANOVAs were conducted on SAM valence and arousal scores entering gender and condition as between-subject variables. Table 1 illustrates means and standard deviations for self-reported affect to the affective manipulation. For valence, there was a significant main effect for condition, [F(1, 46) = 13.66, MSE = 73.76, p < 0.001]. This effect indicates that subjects in the Stress condition experienced the affective manipulation as more unpleasant than subjects in the No Stress condition. Analysis of arousal ratings indicates a significant main effect for condition [F(1,46) = 23.28, MSE = 147.94, p < 0.001].
This finding implies that the subjects in the Stress condition experienced the affective manipulation as more arousing than those in the No Stress condition. No gender differences were found for either measure.

A series of 2 x 2 ANOVAs were conducted on each of the verbal affective descriptors using gender and condition as between-group variables. Significant main effects for condition were found for: fear \( F(1, 46) = 28.89, \text{MSE} = 19.10, p < 0.001 \), surprise \( F(1,47) = 16.34, \text{MSE} = 34.51, p < 0.001 \), anxious \( F(1, 46) = 8.59, \text{MSE} = 13.89, p < 0.01 \), happy \( F(1, 46) = 8.95, \text{MSE} = 12.51, p < 0.01 \), and relaxed \( F(1, 47) = 14.48, \text{MSE} = 21.65, p < 0.001 \). Subjects in the Stress condition reported feeling more fearful, surprised, and anxious, and less happy and relaxed, than those in the No Stress condition. No gender differences were found in any of the analyses. Together, the affective descriptors and SAM valence and arousal results suggest that subjects experienced the affective manipulation as stressful.
Table 1  
Means and Standard Deviations of Self-Report Data in Experiment 1 by Condition

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>CES-D 0-60</th>
<th>SES 0-150</th>
<th>VALENCE 1-9</th>
<th>AROUSAL 1-9</th>
<th>FEAR 0-4</th>
<th>SURPRS 0-4</th>
<th>ANX 0-4</th>
<th>HAP 0-4</th>
<th>RELAX 0-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRESS</td>
<td>M</td>
<td>10.42</td>
<td>a 61.50</td>
<td>a 5.92</td>
<td>a 4.96</td>
<td>a 1.25</td>
<td>2.83</td>
<td>1.88</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>6.70</td>
<td>30.22</td>
<td>2.57</td>
<td>3.03</td>
<td>1.19</td>
<td>1.55</td>
<td>1.45</td>
<td>1.18</td>
</tr>
<tr>
<td>NO STRESS</td>
<td>M</td>
<td>9.93</td>
<td>a 50.07</td>
<td>a 3.58</td>
<td>b 1.54</td>
<td>b 0.38</td>
<td>b 1.19</td>
<td>b 0.85</td>
<td>b 2.00</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>6.45</td>
<td>24.39</td>
<td>2.06</td>
<td>1.86</td>
<td>0.20</td>
<td>1.30</td>
<td>1.05</td>
<td>1.17</td>
</tr>
</tbody>
</table>

Note. Below each scale is the range of potential scores. CES-D is the Center for Epidemiological Study-Depression scale, SES is the Self-Efficacy for Pain Reduction scale, valence and arousal are from the Self-Assessment Manikin, and the others are affective verbal descriptors. Means are in each column, below them are standard deviations. Means in the same column that do not share the same subscript differ at \( p < 0.01 \).
Heart rate was sampled in two ways, one by examining change from baseline and the other by analyzing heart rate during the affect manipulation. To begin, heart rate was recorded for 1 min prior to each set of pain tests and during the affect manipulation. These samples were represented as beats-per-min (BPM) scores and analyzed using a mixed ANOVA. Figure 3 depicts the heart rate data expressed as change scores. Change from baseline scores were created by taking the difference of the 2 min stress period, the first retest on the experimental arm, the retest on the control arm, and the second retest on the experimental arm from the subject’s baseline heart rate. Trial was entered as a within-subject variable while gender and condition were included as between-subject variables. After a Greenhouse-Geisser correction was made ($\varepsilon = 0.853$), there was a significant Trial x Condition interaction [$F(4, 148) = 5.19$, $\text{MSE} = 123.82$, $p < 0.001$]. Mean comparisons revealed that this interaction was attributed to a significant deceleration of heart rate observed in the Stress condition during noise presentation which was followed by a significant acceleration 2 min after the presentation of the stressor. In contrast, those in the No Stress condition did not show any significant fluctuations in heart rate.
Figure 3: Change in Heart Rate for Experiment 1. Change scores were created by taking the difference of each post-stress time point from baseline heart rate. The significance of the interaction results from those in the stress condition showing a significant deceleration of heart rate during the noise stressor followed by a significant acceleration peaking at 2 min after the presentation of the stressor.
The second analysis consisted of breaking the 2 min affect manipulation period into 5 sec blocks and examining the effect of the stressor on immediate heart rate. Figure 4 depicts this heart rate during the affect manipulation. Samples were analyzed using a mixed ANOVA, with the twenty-four 5 sec blocks being entered as a repeated measures variable (time) while condition and gender were entered as between-subjects variables. After a Greenhouse-Geisser correction was made ($\varepsilon = 0.475$), there was a significant Time x Condition interaction [$F(23, 851) = 3.70, \text{MSE} = 1.75, p < 0.001$]. Mean comparisons revealed that this interaction was attributed to subjects in the Stress condition demonstrating an initial acceleration followed by a significant deceleration of heart rate after the presentation of the first set of stressors. In contrast, those in the No Stress condition did not show any significant fluctuations in heart rate.

Pain Reactivity and Secondary Hyperalgesia

Spontaneous Pain

Figure 5 depicts the VAS scores for the six 5 min rating periods during the 30 min period following capsaicin application, but before affect induction. VAS intensity and unpleasantness scores were analyzed using mixed ANOVAs with all six ratings used
Figure 4: Mean Heart Rate (BPM) During the Presentation of the Stressor for Experiment 1. Subjects in the Stress condition showed an acceleration followed by a deceleration after the presentation of the first set of stressors, whereas subjects in the No Stress condition did not show any fluctuations in heart rate.
as a within-subject variable (time) and gender as a between-subject variable. Because
the assumption of sphericity was not met, the Greenhouse-Geisser correction was used
for both intensity ($\varepsilon = 0.367$) and unpleasantness ($\varepsilon = 0.369$). A significant effect was
found for time in both intensity [$F(5, 245) = 12.84, \text{MSE} = 1749.05, p < 0.001$] and
unpleasantness [$F(5, 245) = 11.90, \text{MSE} = 1685.34, p < 0.001$]. Pairwise comparisons
indicated that reports of spontaneous pain during the first time period were significantly
lower than the other time points ($p < .05$). Furthermore, the second time period was
significantly different to the time periods three, four, and five, but not the last time period ($p <
.05$). This suggests that during the last time period, subjects began to decrease their
spontaneous pain ratings. A significant effect was also found for gender in both VAS
ratings of intensity [$F(5,245) = 3.71, \text{MSE} = 505.20, p < 0.05$] and unpleasantness [$F(5,
245) = 4.39, \text{MSE} = 621.30, p < 0.05$], suggesting that females rated the capsaicin as
significantly more intense and unpleasantness than male.

**Secondary Hyperalgesic Pain**

Before examining the impact of the affective manipulation on secondary
hyperalgesic pain, the area of secondary hyperalgesia needed to be recorded for each
subject. To document this area, each spoke along the grid was examined beginning from
the center and radiating outward. The boundaries of secondary hyperalgesia were
decided using previously published methodology (Huang, et al., 2000). Specifically, a
boundary was defined as a 50% reduction in pain ratings for a given site relative to the
previous site on the spoke. Once the area of secondary hyperalgesia was documented,
Figure 5: Spontaneous Pain Ratings During the 30 Minute Capsaicin Period for Experiment 1. A significant effect was found for gender, suggesting that females rated their spontaneous pain from capsaicin as significantly more intense and unpleasant than males.
the average pain rating along each spoke within the secondary hyperalgesic zone was calculated.

To examine the impact of the affective manipulation on secondary hyperalgesic pain, change from pre-stress scores were calculated along each spoke. Figure 6 depicts changes in Post-stress VAS ratings from Pre-stress VAS ratings along the R3 spoke (see Fig. 1 for specific site of testing). Change scores were analyzed using a mixed ANOVA. The change scores for post-stress pain tests 1 and 2 were entered in as a repeated measures variable (trial) while condition and gender were entered in as between-subjects variables. A significant gender x condition effect emerged along the R3 spoke \( F(1,47) = 12.62, \text{MSE} = 126.74, p < 0.001 \). Pairwise comparisons indicate that pain ratings from females in the Stress condition significantly differed from females in the No Stress condition \( (p < .05) \). There was no effect by condition in male subjects. Furthermore, it appears that males and females significantly differ in how they perceive the tactile stimuli after the affect manipulation \( (p < .05) \). These results indicate that capsaicin induces allodynia which decays over time in those subjects in the No Stress condition, with females showing greater decay compared to males. However, when exposed to a stressor, allodynia is prolonged in females whereas males experience greater decay.
Figure 6: Post-Prestress Pain Ratings Along the R3 Spoke. Females in the Stress condition significantly differed from females in the No Stress condition ($p < .05$). Males and females significantly differ in how they perceive this allodynia after affect manipulation ($p < .05$). However, because all subjects reported a decrease in pain ratings, the results suggest that the affect manipulation impacted the decay of capsaicin's effects.
There was no effect by trial and no other significant effects emerged when the other spokes were analyzed in the same manner.

**Area of Secondary Hyperalgesia**

Figure 7 illustrates the impact of the affective manipulation on the area of the secondary hyperalgesic zone. Change scores were calculated by subtracting post-stress area scores from pre-stress area scores. A mixed ANOVA was used to analyze the area of secondary hyperalgesia. The change scores for post-treatment area at trial 1 and 2 were entered in as a repeated measures variable (trial) while condition and gender were entered in as between-subjects variables. A significant gender x condition effect emerged \( F(1, 47) = 4.22, \text{MSE} = 28421.82, p < 0.05 \). Pairwise comparisons indicated that males in the Stress condition demonstrated a significantly greater area of secondary hyperalgesia than the males in the No Stress condition \( (p < .05) \). No such effect was viewed in the female subjects. However, males and females in the Stress condition were shown to significantly differ from one another, where males demonstrated a significantly greater area of secondary hyperalgesia than females \( (p < .05) \). There was no effect by trial and no other significant effects emerged when the other spokes were analyzed in the same manner.
Figure 7: Post-Prestress Area Scores of Secondary Hyperalgesia. Males in the Stress condition demonstrate a significantly greater area of secondary hyperalgesia than males in the No Stress condition (p < .05). Males show a significantly greater area of secondary hyperalgesia than females after the presentation of the noise stressor (p < .05).
EXPERIMENT 2

To determine the impact of stress on primary hyperalgesia, Experiment 2 examined the effect of a noise stress manipulation on capsaicin-induced primary hyperalgesia to thermal stimuli. Heart rate and self-report measures were used to ensure the affect manipulation was stressful. To quantify primary hyperalgesia, measures of pain to thermal stimuli were employed.

Methods

Apparatus

Radiant heat was used as the pain stimulus in Experiment 2. A radiant heat device was constructed using a 300-W projector bulb focused on the participants’ volar forearm by means of a condenser lens positioned approximately 2 cm from the light source. A small square was drawn on the surface of both volar forearms and was blackened with a marker to reduce differences in light absorption by the skin. The radiant heat light source illuminated approximately 1.5 cm x 1.5 cm of the participants’ forearm, and was controlled by an AC potentiometer. The participant’s forearm was placed on a platform made from PVC tubing that was mounted on the side of the radiant heat device. Near the platform were photocells. Participants terminated the radiant heat by removing their forearm from the platform. By uncovering the photo cells, light was allowed to hit them triggering a relay that turned off the lamp. The latency from lamp onset to finger withdrawal was used as an indicator of pain threshold. To eliminate the risk of tissue damage, a 20-s cut off was used.
To reduce the likelihood of avoidance responding, participants were asked to look away from the device so they would not be cued by the light’s onset. All participants wore headphones to reduce auditory cues from the lamp and so the experimenter could communicate with them from the control room.

Participants

Participants were 28 male and 22 female undergraduate psychology students who received course credit for their participation. Of those, 80% were Caucasian, 14% Hispanic, 4% African-American, and 2% Middle Eastern. Mean age was 19.8 years (SD=1.66). Persons were excluded for: circulatory, cardiovascular, or neurological problems; chronic pain; or tobacco, analgesic, anti-histamine, anti-depressant, or recent drug/alcohol use.

Procedure

After filling out the informed consent, demographics, a health status questionnaire, SES, and CES-D, participants were seated upright in a comfortable chair. Heart Rate sensors were applied to their fingers. Subjects were then instructed on how to rate their pain using a mechanical VAS device with the anchors of “No Pain Sensation” and “The Most Intense Pain Imaginable”. Subjects practiced using the VAS device by rating changes in perceived pressure being applied to their arm via a blood pressure cuff. The cuff was inflated to 100, then 200, then back to 100, and finally the pressure was brought back to 0. The goal of the practice was to ensure that subjects would rate changes in perceived pressure consistently. Once the subjects demonstrated proficiency in this task, a small square was drawn on the center of both volar forearms.
Subjects then underwent a baseline pain test in which they placed the small square drawn on their forearm over a radiant heat source. Subjects are instructed to remove their arm when they reach pain threshold. After each radiant heat pain test, subjects rated their pain on the VAS device. Figure 8 notes the details of the experimental procedure.

Following the baseline pain test, 300 µl of a 6.0% capsaicin solution was topically applied to the dominant volar forearm via a 1.5 cm x 1.5 cm gauze pad (Culp, Ochoa, et al., 1989; Simone, Baumann, & LaMotte, 1989). To impede evaporation, the site of application was covered with a dressing (Baron, Wasner, et al., 1999). The pad and dressing was left on the arm for a period of 30 min. During the 30 min capsaicin application subjects were asked to rate their affect using a SAM and a set of affective descriptors at 5 min intervals. Subjects were also asked to rate their pain at these 5 min intervals using a paper and pencil VAS, which contained both an “intensity” and an “unpleasantness” component. Since variability in skin temperature has been shown to introduce variance in studies using a capsaicin manipulation, skin temperature was recorded throughout the experiment (Liu, Max, et al., 1998).

After the 30 min application, the capsaicin was removed from the forearm and subjects underwent four pain threshold trials at the site of capsaicin application, two trials on the arm with capsaicin (CAP) and two trials on the arm without capsaicin (CON). There was a 5 min wait between each pain test, to limit the amount of sensitization caused by the radiant heat. After the four pain threshold trials, average heat duration was calculated for each arm using the subject’s earlier pain latencies. After the
calculation, subjects underwent another four trials, two on the CAP arm and two on the CON arm using the calculated pain durations. However, for these pain tests, subjects were told to not remove their arm once they felt pain and to await a cue from the experimenter before removing their arm. Once the radiant heat reached the predetermined latency, subjects were then asked to rate their pain on the VAS device.

Subjects were then randomly assigned to a treatment condition (Stress or No Stress). During the Stress condition subjects were told “they may or may not be presented with brief, loud, surprising bursts of noise” and presented with pseudorandom bursts of white noise (105 db) against a background of 60 db white noise, which took place over a 2 min period. Those in the No Stress condition were told, “they would not receive the brief, loud bursts of noise”. After the affect manipulation, subjects then underwent four retest pain trials consisting of two trials on the CAP arm and two trials on the CON arm using the same calculated pain durations.

Subjects were then asked to rate their emotional reactions to either the bursts of noise or being told that they would not receive the noise. Finally, subjects were given an exit questionnaire and debriefed.
Figure 8. Experimental Procedure for Experiment 2. Bars above the matrix indicate times that physiological data were recorded. Physiological data were recorded 1 min prior to every trial, as well as during the affect manipulation. The trials labeled CAP are pain trials conducted on the arm with capsaicin. The trials labeled CON are pain trials conducted on the arm which did not have capsaicin applied. There were two affective conditions a Stress and a No Stress condition.
Results

Manipulation Checks

Self-Efficacy and Distress

Table 2 lists all means and standard deviations for self-efficacy (SES) and CES-D. SES and CES-D scores were analyzed using 2x2 ANOVAs with condition and gender as between-group variables. A significant effect for gender was found, $F(1,46) = 4.56, MSE = 6009.28, p < 0.05$. This finding suggests that males reported significantly greater self-efficacy to make a reduction in pain than females. However, no significant differences were found [$F(1,46) = 1.29, MSE = 1701.62, p > 0.05$] for condition, suggesting that both conditions were homogeneous in terms of self-efficacy for pain reduction. In contrast, CES-D scores resulted in a significant finding [$F(1, 44) = 5.24, MSE = 104.75, p < 0.05$] for condition, suggesting that those in the Stress condition came into the study with significantly greater pre-existing distress than those in the No Stress condition. However, the mean CES-D score for subjects in the Stress condition was 9.65 (SD = 4.78) and 6.86 (SD = 4.10) for those in the No Stress condition, neither of which are in clinical range for emotional distress. The CES-D did not significantly differ by gender.

Affective Manipulation

Self-report

To assess the impact of the affective manipulation, 2 x 2 ANOVAs were conducted on SAM valence and arousal scores entering gender and condition as between-subject variables. Table 2 illustrates means and standard deviations for self-reported
affect to the affective manipulation. For valence, there was a significant main effect for condition, \( F(1, 46) = 16.54, \text{MSE} = 59.61, p < 0.001 \). This effect indicates that the Stress condition experienced the affective manipulation significantly more unpleasant than the No Stress condition. Analysis of arousal ratings indicates a significant main effect for condition \( F(1,46) = 61.48, \text{MSE} = 254.54, p < 0.001 \). This finding implies that the noise stress elicited elevation in arousal relative to the No Stress condition. No gender differences were found for either measure.

A series of 2 x 2 ANOVAs were conducted on each of the verbal affective descriptors using gender and condition as between-group variables. Significant main effects for condition were found for: fear \( F(1, 46) = 14.08, \text{MSE} = 18.19, p < 0.001 \), surprise \( F(1,45) = 30.78, \text{MSE} = 49.41, p < 0.001 \), anxious \( F(1, 46) = 24.82, \text{MSE} = 32.95, p < 0.001 \), angry \( F(1, 46) = 7.86, \text{MSE} = 5.95, p < 0.01 \), neutral \( F(1, 46) = 8.42, \text{MSE} = 13.98, p < 0.01 \), bored \( F(1, 46) = 5.11, \text{MSE} = 11.10, p < 0.05 \), and relaxed \( F(1, 46) = 19.27, \text{MSE} = 31.72, p < 0.001 \). Subjects in the Stress condition reported feeling more fearful, surprised, anxious, and angry and less neutral, bored, and relaxed than the No Stress condition. Together, the findings from the list of affective descriptors and SAM valence and arousal suggest that subjects experienced the affective manipulation as stressful. In addition, a significant gender difference was found for anger \( F(1, 46) = 5.63, \text{MSE} = 4.23, p < 0.05 \), suggesting that males were significantly more likely to report feeling angry than females. A significant gender x condition interaction was also found for feeling bored \( F(1, 46) = 3.93, \text{MSE} = 8.54, p < 0.05 \). Pairwise
Table 2
Means and Standard Deviations of Self-Report Data in Experiment 2 by Condition

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>CES-D 0-60</th>
<th>SES 0-150</th>
<th>VALENCE 1-9</th>
<th>AROUSAL 1-9</th>
<th>FEAR 0-4</th>
<th>SURPRS 0-4</th>
<th>ANX 0-4</th>
<th>ANG 0-4</th>
<th>NEUT 0-4</th>
<th>BORED 0-4</th>
<th>RELAX 0-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRESS</td>
<td>M</td>
<td>9.65\textsubscript{a}</td>
<td>63.18\textsubscript{a}</td>
<td>6.65\textsubscript{a}</td>
<td>6.62\textsubscript{a}</td>
<td>1.42\textsubscript{a}</td>
<td>2.92\textsubscript{a}</td>
<td>2.39\textsubscript{a}</td>
<td>0.81\textsubscript{a}</td>
<td>1.08\textsubscript{a}</td>
<td>1.19\textsubscript{a}</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>4.78</td>
<td>40.36</td>
<td>1.79</td>
<td>2.45</td>
<td>1.47</td>
<td>1.44</td>
<td>1.27</td>
<td>1.16</td>
<td>1.42</td>
<td>1.13</td>
</tr>
<tr>
<td>NO STRESS</td>
<td>M</td>
<td>6.86\textsubscript{b}</td>
<td>40.55\textsubscript{a}</td>
<td>4.46\textsubscript{b}</td>
<td>2.04\textsubscript{b}</td>
<td>0.21\textsubscript{b}</td>
<td>0.88\textsubscript{b}</td>
<td>0.79\textsubscript{b}</td>
<td>0.08\textsubscript{b}</td>
<td>2.17\textsubscript{b}</td>
<td>2.25\textsubscript{b}</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>4.10</td>
<td>29.66</td>
<td>1.93</td>
<td>1.43</td>
<td>0.51</td>
<td>0.99</td>
<td>1.02</td>
<td>0.06</td>
<td>1.37</td>
<td>1.60</td>
</tr>
</tbody>
</table>

Note. Below each scale is the range of potential scores. CES-D is the Center for Epidemiological Study-Depression scale, SES is the Self-Efficacy for Pain Reduction scale, valence and arousal are from the Self-Assessment Manikin, and the others are affective verbal descriptors. Means are in each column, below them are standard deviations. Means in the same column that do not share the same subscript differ at $p < 0.05$. 

comparisons indicated that males in the No Stress condition were more likely to report feeling bored than males in the Stress condition.

**Heart rate**

Heart rate was sampled in two ways, one by examining change from baseline and the other by analyzing heart rate during the affect manipulation. To begin, heart rate was recorded for one minute prior to each set of pain tests and during the affect manipulation. These samples are represented as beats-per-minute (BPM) scores and analyzed using a mixed ANOVA. Figure 9 depicts heart rate expressed as a change from baseline. Change scores were created by taking the difference of the 2 minute stress period, the first retest on the experimental arm, first retest on the control arm, second retest on the experimental arm, and second retest on the control arm from the subject’s baseline heart rate. Trial was entered in as the within-subject variable while gender and condition were included as between-subject variables. After a Greenhouse-Geisser correction was made ($\varepsilon = 0.700$), there was a significant Trial x Condition interaction [$F(5, 80) = 3.31$, $\text{MSE} = 35.93$, $p < 0.05$]. Mean comparisons indicated that the interaction was attributable to the significant deceleration of heart rate observed in the Stress condition during the noise stressor followed by a significant acceleration. In contrast, those in the No Stress condition did not show any significant fluctuations in heart rate.
Figure 9: Change in Heart Rate for Experiment 2. Change scores were created by taking the difference of each post-stress time point from baseline heart rate. The significance of the interaction results from those in the stress condition showing a significant deceleration of heart rate during the noise stressor followed by a significant acceleration.
The second analysis consisted of breaking the 2 min affect manipulation period into 5 sec blocks and examining the effect of the stressor on immediate heart rate. Figure 10 depicts this heart rate during the affect manipulation. Samples were analyzed using a mixed ANOVA, with the twenty-four 5 sec blocks being entered as a repeated measures variable (time) while condition and gender were entered as between-subjects variables. After a Huynh-Feldt correction was made ($\varepsilon = 0.838$), there was a significant Time x Condition interaction [$F(23, 575) = 1.81$, $\text{MSE} = 0.65$, $p < 0.05$]. Mean comparisons revealed that this interaction was attributed to subjects in the Stress condition demonstrating a deceleration of heart rate after the presentation of the second set of stressors. In contrast, those in the No Stress condition did not show any significant fluctuations in heart rate.

**Pain Reactivity and Primary Hyperalgesia**

**Spontaneous Pain**

VAS intensity and unpleasantness scores for the six 5 min periods during the 30 min capsaicin period were analyzed using mixed ANOVAs with all six ratings used as a within-subject variable (time) and gender as a between-subject variable. Figure 11
Figure 10: Mean Heart Rate (BPM) During the Presentation of the Stressor for Experiment 2. Subjects in the Stress condition showed a deceleration after the presentation of the second set of stressors, whereas subjects in the No Stress condition did not show any fluctuations in heart rate.
illustrates the effects by trials. Because the assumption of sphericity was not met, the
Greenhouse-Geisser correction was used for both intensity ($\varepsilon = 0.526$) and
unpleasantness ($\varepsilon = 0.473$). A significant effect was found for trial in both VAS ratings
of intensity [$F(5, 230) = 14.14, \text{MSE} = 2370.28, p < 0.001$] and unpleasantness [$F(5, 230) = 16.50, \text{MSE} = 2878.53, p < 0.001$]. Pairwise comparisons indicated that reports
of spontaneous pain during the first two time periods were significantly lower than the
other time points ($p < .05$). Furthermore, the last two time periods were significantly
greater than the third time period ($p < .05$), suggesting that subjects were reporting an
increase in spontaneous pain over the 30 min capsaicin period.

**Primary Hyperalgesic Pain**

To examine the impact of the affective manipulation on primary hyperalgesic
pain, the data was examined in two ways. To begin, change scores (post-stress trials –
average pre-stress trials) were calculated. Change scores were analyzed using a mixed
ANOVA. The change scores for post-stress pain tests 1 and 2 were entered in as a
repeated measures variable (trial) while condition and gender were entered in as
between-subjects variables. No significant differences were found.
Figure 11: Spontaneous Pain Ratings During the 30 Minute Capsaicin Period for Experiment 2. Reports of spontaneous pain during the first two time periods were significantly lower than the other time points (p < .05). The last two time periods were significantly greater than the third time period (p < .05), suggesting that subjects were reporting an increase in spontaneous pain over the 30 min capsaicin period.
A second mixed ANOVA was performed with the pain ratings for each pain test (trial) along both the CAP and CON arm (site) being entered in as repeated measures variables. Gender and condition were entered in as between-subjects variables. Figure 12 illustrates the impact of the affective manipulation on both the CAP and CON arm. Because the assumption of sphericity was not met, the Greenhouse-Geisser correction was used for site ($\varepsilon = 1.000$), trial ($\varepsilon = 0.628$), and site x trial ($\varepsilon = 0.837$). A significant effect was found for site [$F(1, 46) = 13.62, \text{MSE} = 63.52, p < 0.001$], indicating that there were significantly higher pain ratings for the CAP arm compared to the CON arm. Furthermore, a significant 3 way interaction was found for site x condition x gender [$F(1, 46) = 7.92, \text{MSE} = 36.96, p < 0.01$]. Males in the Stress condition showed no significant difference in pain ratings on the CAP arm compared to the CON arm, while males in the No Stress condition rated the CAP arm as significantly more painful than the CON arm ($p < 0.05$). In contrast, females in the Stress condition rated their CAP arm as significantly more painful than the CON arm, while females in the No Stress condition showed no significant difference in pain ratings on the CAP arm compared to the CON arm ($p < 0.05$).
Figure 12: Pain Ratings for the Capsaicin and Control Arms for Experiment 2. Males in the Stress condition showed no significant difference in pain ratings on the CAP arm compared to the CON arm, while males in the No Stress condition rated the CAP arm as significantly more painful than the CON arm (p < .05). Females in the Stress condition rated the CAP arm as significantly more painful than the CON arm, while females in the No Stress condition showed no significant difference in pain ratings on the CAP arm compared to the CON arm (p < .05).
A significant effect for trial was also found $[F(5, 230) = 3.85, \text{MSE} = 7.24, p < 0.01]$. Pairwise comparisons indicated that regardless of condition or gender, that the two post-stress trials were significantly less painful than the two pre-stress trials ($p < 0.05$). Moreover, a significant interaction was found for site x trial $[F(5, 230) = 6.51, \text{MSE} = 7.75, p < 0.001]$. Figure 13 depicts the mean pain ratings for trial by both CAP and CON arm. Pairwise comparisons indicate that there were significantly higher pain ratings along the CAP arm compared to CON arm for the four pre-stress trials ($p < 0.05$). However, the two post-stress trials for both the CON and CAP arms did not significantly differ from one another.
Figure 13: Mean Pain Ratings over Time for Experiment 2. Subjects reported significantly greater pain for the CAP arm compared to the CON arm for the four pre-stress trials ($p < .05$). The two post-stress trials for both the CON and CAP arms did not significantly differ from one another.
GENERAL DISCUSSION

The present experiments were conducted to test the impact of stress, using a noise stressor, on both the primary and secondary hyperalgesia associated with inflammation from a topical application of capsaicin on the forearm. Previous studies have examined the impact of stress on capsaicin-related spontaneous pain and inflammation (Lutgendorf, et al., 2000; Logan et al., 2001); however, no studies have examined the impact of stress on primary and/or secondary hyperalgesia.

Affect Manipulation

The affect manipulation in these experiments was a noise stressor which has been shown in previous research to elicit a stress response (Rhudy & Meagher, 2001). In the present studies, subjects in both experiments elicited a stress response to the presentation of the noise stressor. Indeed, subjects in Experiment 1 reported feeling significantly more unpleasant, excited, fearful, surprised, and anxious after being presented with the noise stressor and significantly more happy and relaxed when told they would not receive the stressor. Similarly in Experiment 2, subjects reported feeling significantly more unpleasant, excited, fearful, surprised, anxious, and angry after being presented with the noise stressor and significantly more neutral, bored, and relaxed when told they would not receive the stressor.

In addition to self-report data, heart rate was also collected throughout the experiments to evaluate whether the affect manipulation altered sympathetic arousal. In both experiments, a significant deceleration of heart rate occurred during the stress period followed by an acceleration of heart rate after the stress period. Subjects who
were not presented with the stressor did not demonstrate this heart rate response. This deceleration-acceleration pattern has been observed in previous studies examining the impact of both noise and electrical shock stressors (Rhudy & Meagher, 2001; Rhudy & Meagher, 2000; Grimes, Creech, & Meagher, 2002). According to Lacey and Lacey’s (1979) intake-rejection hypothesis, heart rate deceleration is a response to the organism becoming more hypervigilant (intake) to its surroundings while the heart rate acceleration is a response to the organism rejecting the stimulus as threatening. Hence, the presentation of the stressor created a hypervigilance with the subjects orienting their attention to more possible stressors. Once the subjects had not received a stressor for a period of time their hypervigilance subsided and attention diverted which caused their heart rate to begin to accelerate back to baseline.

In contrast to the findings of Rhudy and Meagher (2001), who found a gender difference in how males and females reacted to the presentation of noise stressor, the present study found very few differences by gender. To begin, Rhudy and Meagher (2001) found that females rated the noise stressor as more fearful and males rated the stressor as more surprising, the current study found gender differences only for anger and boredom with males reporting feeling significantly more angry after the stressor and significantly more boredom in the absence of the stressor. Likewise, Rhudy and Meagher (2001) found that males exhibited a heart rate deceleration after the presentation of the noise stressor while females did not, leading the authors to suggest that males attended to the noise while women did not. In the present study, no gender effects were found for heart rate suggesting that all subjects attended to the noise stressor
alike. A possibility in why these results diverge is that although the presentations of the noise stressor were similar, the intensity of the stressor differed with the Rhudy and Meagher (2001) study using a 90 db noise and the present study using a 105 db noise.

Based on both the heart rate and self-report data, these findings suggest that the affect manipulation was successful. Although it is difficult to identify the exact emotion induced (i.e., fear or anxiety), it is clear that the presentation of the noise stressor induced a negative, stressful emotional state while the absence of the noise stressor induced a more positive, relaxed emotional state.

Pain Reactivity

Spontaneous Pain

Spontaneous pain VAS ratings for both intensity and unpleasantness were taken during the 30 min capsaicin application. In both experiments, subjects rated their spontaneous pain as increasingly more intense and unpleasant over the 30 min period, followed by a small decline. Suggesting that the capsaicin did induce a primary hyperalgesia. However, in Experiment 1, a gender effect was found with females rating their pain as significantly more intense and unpleasant than males. In Experiment 2, no such effect was found. A reason for these inconsistent findings is not clear, however, a post-hoc examination of the procedures may assist in an explanation. Specifically, in both experiments steps were taken to ensure that subjects did not visually attend to the capsaicin arm during the application period. In Experiment 1, the capsaicin arm was on the other side of a screen while in Experiment 2, the capsaicin arm was hidden from view by placing it in the radiant heat enclosure. When the screen was in use, the
subject's line of sight consisted only of the screen because of its positioning. In contrast, when the radiant heat device was used, the subjects’ view was not blocked and although they were instructed to look ahead, peripherally they could scan their environment. This difference in procedure may have led the subjects in Experiment 2 to engage in some alternative form of distraction that was not available for those participants in Experiment 1. Although post-hoc, it is a possibility that these slight changes in procedures were enough to impact the subjects’ experience of the capsaicin-related spontaneous pain.

**Primary and Secondary Hyperalgesia**

To examine the impact of stress on hyperalgesia the present study conducted two experiments, one examining secondary hyperalgesia induced by the mechanical stimulation of a firm von Frey hair and one examining primary hyperalgesia induced by thermal stimulation. In both experiments, the presentation of a stressor impacted subject’s reported pain and hyperalgesia compared to controls.

In examining mean pain ratings by arm, divergent effects by gender were found. Females reported significantly lower pain ratings on the control arm than the experimental arm when they were in the Stress condition, but those in the No Stress condition did not report any difference in pain ratings between the two arms. In contrast, males reported significantly lower pain ratings on the control arm than the capsaicin arm when they were in the No Stress condition, but those in the Stress condition did not report any difference in pain ratings between the two arms. These results suggest that
the stressful event produced a hypoalgesia in females and a hyperalgesia in males along the control arm, but not the capsaicin arm.

Although the findings on the control arm are similar to previous results examining the impact of a noise stress on thermal pain (Rhudy & Meagher, 2001), the lack of an effect on the capsaicin arm demands alternative explanations. For example, cross-sensitization between capsaicin and heat stimulation may produce a ceiling effect, suggesting that affective pain modulation may only occur when at relatively low pain intensity levels. To resolve this issue, future parametric studies are needed to evaluate whether affective pain modulation occurs when low intensity thermal stimuli are presented to the capsaicin treated arm. This an important issue because it may suggest that there are limits to affective pain modulation in clinical settings as well. It will also be important to evaluate whether noise stress alters spontaneous pain ratings in the same way that it is altered by other stressors (Logan et al., 2001). Furthermore, studies should also be conducted to examine the impact of positive, calming affective manipulations on primary and secondary hyperalgesia.

Furthermore, in examining the impact of the stressor on primary hyperalgesia across time, VAS ratings for the two post-stress pain trials were significantly lower than the pre-stress trials, regardless of condition. An interpretation suggests that this pattern is possibly a decay function in which the effects of capsaicin began to diminish over time, leading to the inability to see a post – pre-stress change in primary hyperalgesia. This decay function may be similar to the findings of recent studies showing parallel activation of descending inhibitory and ascending facilitatory pain pathways in
inflammatory and neuropathic pain states (Ren & Dubner, 2002). Indeed, the use of naloxone after topical application of capsaicin has been shown to reactivate spontaneous pain, suggesting that the inhibition of capsaicin-related pain is suppressed by endogenous opioids along inhibitory pain modulatory pathways (Anderson, Sheth et al., 2002). Therefore, the inflammation of capsaicin activates ascending pathways, producing a sensitization that heightens the perception of pain. Following this facilitation produced by capsaicin, it is plausible that there would also be an activation of descending inhibitory pathways.

Future attempts to examine the impact of a stressor on the capsaicin-related pain should take into consideration this possible inhibitory effect by timing the noise stressor relative to the curve of capsaicin’s effects. It is possible that with presenting the stressor earlier in the procedure, capsaicin–related pain may show the same pattern of results as seen in previous noise stress studies (Rhudy & Meagher, 2001) or as seen along the control arm in Experiment 2.

In examining the impact of the stressor on secondary hyperalgesia, two measures were examined, change in VAS ratings and calculated area of secondary hyperalgesia. Reported pain for secondary hyperalgesia was decreased regardless of the presentation of the stressor indicating that the effects of capsaicin decayed over the course of the experiment. This inhibition was most apparent in subjects that were not presented with the stressor, with females showing greater inhibition compared to males. However, when exposed to a stressor, allodynia is prolonged in females whereas males experience
greater inhibition. This prolonged allodynia found in females suggests that the noise stressor was able to disrupt the descending inhibition activated by capsaicin.

The opposite effect emerged in examining the area of secondary hyperalgesia, with males in the Stress condition demonstrating significantly greater area of secondary hyperalgesia than females. Furthermore, males in the Stress condition show greater area of secondary hyperalgesia than males in the No Stress condition. These results suggest that the stressful event produced an expansion of the area of secondary hyperalgesia in males while contracting the area of secondary hyperalgesia in females. Conflicting findings were also found in that while there was evidence for inhibition in pain ratings for primary and secondary hyperalgesia, evidence for inhibitory mechanisms at work were not found in the results for area of secondary hyperalgesia with the subjects in the No Stress condition reporting increased area of secondary hyperalgesia.

Although it is unclear why divergent effects were found for pain ratings vs. area of secondary hyperalgesia, there is evidence that area of allodynia and spontaneous pain are the two most robust or less variable measures of capsaicin’s effects (Hughes, Macleod, et al., 2002). Indeed, when looking at the present data, pain ratings for secondary hyperalgesia were taken along eight spokes (see figure 1) and out of those eight, one spoke emerged as having significant effects.
SUMMARY

In conclusion, the bulk of the present study’s results are comparable to other previous published findings that examine the impact of a noise stressor on human pain. Males and females both perceived the noise stressor as unpleasant and stressful. The noise stressor significantly altered secondary hyperalgesia by increasing the area of allodynia in men and slowing the inhibition of capsaicin-induced tactile pain in women. Although noise stress was found to alter thermal pain ratings in the control arm, primary thermal hyperalgesia was not affected by stress. However, this may reflect a ceiling effect due to cross-sensitization between capsaicin and the radiant heat stimulus, suggesting that affective pain modulation may only occur at low pain intensities. This result may have important implications for clinical pain management in that affective pain modulatory strategies may be limited to less intense pain states.
REFERENCES


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Presentations

