MENSTRUAL CYCLE EFFECTS ON PAIN MODULATION AND AUTONOMIC

AROUSAL

A Dissertation

by

JEFFREY SCOTT GRIMES

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

August 2006

Major Subject: Psychology

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ABSTRACT

Menstrual Cycle Effects on Pain Modulation and

Autonomic Arousal. (August 2006)

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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. One

psychological process that is thought to play an important role in regulating pain

sensitivity is emotion. In addition, previous research into the human menstrual cycle and

the animal estrous cycle have determined that either the presence of certain gonadal

hormones or the fluctuations of these hormones may lead to changes in how females

perceive pain, regulate emotion, and modulate pain. The present study examines both

the role of emotion and the human menstrual cycle in pain modulation. Participants

were 39 female undergraduate students with a mean age of 18.7 years ($\underline{SD}$=1.46).

Results are consistent with prior studies indicating that progesterone has anti-

inflammatory effects. Specifically, significant effects were observed primarily in the

luteal phase. Subjects in the luteal phase demonstrated less sympathetic arousal during

the experiment but greater autonomic arousal during the noise stressor. Participants in

the luteal phase also demonstrated an analgesic/anti-inflammatory response evidenced

by an observed decrease in secondary hyperalgesia for those that did not receive the noise stressor. No such changes in pain perception were discovered in the ovulation and follicular phases. Finally, in response to the noise stressor, an inhibition of the analgesic/anti-inflammatory effects was observed in the luteal phase. No such evidence of stress-induced pain modulation was discovered in the ovulation and follicular phases. Although the specific mechanisms of this action still remain unclear, prior evidence points to the role of centrally-mediated pain modulation. It is likely that the stressor worked to inhibit the anti-inflammatory effects commonly observed in the luteal phase to persistent inflammatory pain through centrally-mediated pain modulatory mechanisms. It is hypothesized that hormone-mediated effects at the level of the amygdala influenced the impact of affective pain modulation.

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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. One psychological process that is thought to play an important role in regulating pain sensitivity is emotion. In addition, previous research into the human menstrual cycle and the animal estrous cycle have determined that either the presence of certain gonadal hormones or the fluctuations of these hormones may lead to changes in how females perceive pain, regulate emotion, and modulate pain. Hence, the present study hopes to examine both the role of emotion and the human menstrual cycle in pain modulation.

Sex Hormones in Pain

Previous animal research has demonstrated increased variability in the pain perception of females when compared to males with most studies demonstrating that females are more sensitive to pain than males (Romero & Bodnar, 1986; Romero et al., 1988). It is assumed that much of the sex difference is due to the modulatory influence of gonadal hormones. In fact, many studies have demonstrated that when ovariectomized rats are administered estrogen they display increased pain sensitivity, but when both progesterone and estrogen are administered, analgesia is observed (Drury & Gold, 1978; Martinez-Gomez et al., 1994; Ratka & Simpkins, 1991; Ryan & Maier, 1988). Researchers have also documented that pain sensitivity varies along the estrous

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This dissertation follows the style of Pain.

cycle with most studies finding increased pain sensitivity during periods in the estrous cycle when estrogen peaks compared to periods where estrogen decreases and progesterone increases (e.g., Cason, Samuelson, Berkley, 2003; Kayser et al., 1996; Sapsed-Byrne et al., 1996). Taken together, it appears that for the most part, estrogen has demonstrated a pro-nociceptive effect, but when progesterone is introduced greater analgesia is observed.

As in the animal research, human studies have described differences in how the two genders perceive and respond to pain. In general, most experimental human pain studies have demonstrated that women show greater pain sensitivity (Fillingim, 2003; Fillingim, Maixner, Kincaid, & Silva, 1998; Riley et al., 1999). However, mixed findings have been reported in clinical pain studies with most studies reporting greater pain sensitivity in specific chronic pain syndromes, such as fibromyalgia, arthritis pain, and multiple sclerosis (e.g., Anderberg et al., 1999; Affleck et al., 1999; Keefe et al., 2000, Warnell, 1991), while others report minimal gender differences in other chronic pain populations, such as cancer-related pain (Turk & Okifuji, 1999).

Researchers have proposed several psychosocial, evolutionary, and biological hypotheses to help explain the observed gender difference in human pain. Biologically, the focus of much of the research has been on the impact of gonadal hormones and/or the menstrual cycle on pain perception, however, much of the human research has not focused on the assessment of sex hormone levels in the body, but rather patient report of menstrual cycle (e.g., Amodei & Nelson-Gray, 1989; Hapidou & Rollman, 1998). This methodology is problematic in that approximately 20% of cycles can be anmenstrual

(Girdler et al., 1993) and self-report relies solely on the presumption that cycles are not variable in length. These studies have produced inconsistent findings when viewed on an individual basis, but when a meta-analytic procedure is utilized to correct for the problem of small sample size, effects by menstrual cycle emerge with menstrual and luteal phases producing greater pain sensitivity than follicular phases (Riley et al., 1999).

Although much of the research has focused on the use of self-report, there have been some studies that quantify sex hormone levels using either ovulation predicting devices and/or plasma hormone levels. Fillingim and colleagues (1997; 2000) have shown that women demonstrate decreased pain tolerance to ischemic pain in their luteal phases versus follicular phases. In examining thermal pain sensitivity, the researchers did not find any effects by menstrual cycle. However, they did find that regardless of menstrual cycle phase, periods of higher estrogen levels predicted higher thermal pain sensitivity. In addition, to assessing the level of hormone, studies have also examined the use of estrogen-replacement therapies and pain response. In general, the research has demonstrated that the use of exogenous estrogen is correlated with increased risk of specific pain disorders and associated symptoms, such as temporomandibular disorders (LeResche et al., 1997) and back pain (Musgrave, Vogt, Nevitt, & Cauley, 2001). Oral contraception use has also been examined with typical findings purporting that oral contraception leads to a decrease of the menstrual cycle effects found in pain perception (Hapidou & Rollman, 1998; Thompson et al., 1997).

Sex Hormones in Inflammation

Studies examining the role of sex hormones in inflammatory responses to tonic pain models (i.e., carageenan, formalin) have found progesterone to attenuate inflammatory responses (Ren et al., 2000; Ji et al., 2005, Nakagawa et al., 1979, Uchida et al., 2003, Kuba et al., 2006). For example, Ren and colleagues (2000) found that during lactation, female rats demonstrate an inhibition to persistent inflammatory hyperalgesia. Because lactation is a period where progesterone levels are high and estradiol levels are low, it was concluded that progesterone produced the anti-inflammatory/anti-nociceptive effect. Furthermore, studies have also demonstrated that injected progesterone attenuates the pro-nocicieptive activity of estradiol in ovariectomized animals; however, progesterone alone does not (Ji et al., 2005, Kuba et al., 2006). These finding suggest that although progesterone may have anti-nociceptive and anti-inflammatory effects, it does not produce these effects in isolation but rather through the interaction between either the simple presence or levels of estradiol and progesterone.

In contrast, older studies examining the effects of sex hormones on the inflammatory process in wound healing have found that administration of estradiol to ovariectomized animals inhibits the inflammatory response associated with the first phase of wound healing (Taubenhaus & Amromin, 1949; Rigdon & Chrisman, 1941). More recently, Josefsson and colleagues (1992) also have observed that exogenous estradiol appears to have anti-inflammatory effects because it reduces foot swelling in ovariectomized animals. Although not specific to the inflammatory phase of wound

healing, other studies have similarly demonstrated possible anti-inflammatory effects of estrogen in finding that estradiol reduces the concentration of polymorphonuclear leucocytes in humans (PMNLs; Ito et al., 1995; Miyagi et al., 1992). This reduction in PMNLs has been shown to promote healing in the initial inflammatory phase.

As in other areas of sex hormone research, definitive conclusions regarding the role of sex hormones in inflammation remain elusive. Similar to other hormonal studies, a primary problem in understanding this research is that it utilizes the induction of excessive amounts of exogenous hormones into damaged animals. One might ask, does simply the presence of estradiol inhibit the inflammatory response or does the sharp increase in level of estradiol produce inhibition? It is difficult then, to understand the role of natural variations in sex hormones in the inflammatory response.

Sex Hormones in Emotion

Similar to pain research, gender differences have long been observed in the presentation and regulation of emotion. Clinically, researchers have documented that women are twice more likely than men to experience a mood disorder and women will experience longer and more severe episodes of mood disruption than men (Nolen-Hoeksma, 1987). The reasons for this gender difference, however, remain unclear. In examining the biological mechanisms for this difference, most research has focused on the presence and fluctuation of gonadal hormones (Shors & Leuner, 2003). In fact, Sonnenberg and colleagues (2000) found that after menopause, when the fluctuation and presence of gonadal hormones are significantly decreased, gender differences in mood disruption tend to lessen.

In general, most of the evidence regarding mood disturbance and gonadal hormones is derived from clinical observation and epidemiological studies. For instance, postpartum periods, menopause, premenstrual syndrome, and premenstrual dysphoric disorder are all highly correlated with increased levels of negative affect (Bloch, et al., 2000; Rubinow, 1992). During these periods, women experience low levels of gonadal hormones and/or precipitous fluctuations in the level of these hormones. It is thought that these hormones, especially estrogen, work to facilitate serotonergic systems and, in the absence of estrogen, women are more likely to develop mood disturbance (Belthea, et al., 1999). Clinically, some studies have demonstrated the antidepressant effect of estrogen and/or the combination of estrogen and progesterone (Derman et al., 1995; Klaiber et al., 1996) while others have found that other factors, such as history of depression, were better predictors of mood disturbance then the use of exogenous estrogen (Bloch et al., 2000).

Learned helplessness paradigms have also been employed to examine the impact of gonadal hormones on aversive conditioning. Although most studies have demonstrated that females do not demonstrate learned helplessness in the traditional paradigms (Kirk & Balmpied, 1985; Steenberben et al., 1990), Shors (1998; 2000), utilizing an eye-blink conditioning paradigm, has found a gender difference in associative learning after presentation of various stressors. Specifically, males show facilitation in associative learning after presentation of stress while females show inhibition. This effect is reversed with ovariectomy and exogenous presentation of estrogen antagonists (Woods & Shors, 1998). Hence, this evidence suggests that the

presence of female sex hormones produces difficulty in the rat's ability to learn avoidance strategies to aversive stimuli, which in humans could potentiate and maintain negative affective states. And although it appears that the presence of estrogen impairs aversive learning during the presence of stress, it is unclear whether it is simply the presence of estrogen or swift changes in estrogen that produce the impairment in learning.

Sex Hormones in Pain Modulation

Although much of the earlier animal research examining the circuitry of pain modulation focused primarily on males, more recent studies have begun to examine the role of pain modulation in females and how the presence and fluctuation of gonadal hormones can influence pain modulation. Although the research remains unclear on the direction of pain modulation with some studies demonstrating that the presence of gonadal hormones increases (Banerjee et al., 1983), decreases (Kepler, et al., 1989; Krzanowska & Bodnar, 1999), or does not affect (Cicero et al., 1996; Kepler et al., 1991) anti-nociception, as a whole, most animal studies demonstrate that periods in which estrogen is elevated either alone through exogenous hormone introduction or accompanied by corresponding elevations in progesterone either endogenously or exogenously are characterized by diminished analgesia (Fillingim & Ness 2000).

It has been shown that pharmacological manipulations in which exogenous substances that either mimic the presence of estrogen or promote its release diminish the analgesic effect of morphine (Berglund et al., 1988; Berkley, 1997; Ratka & Simpkins, 1991). In addition, prenatal de-feminization and orchidectomy eliminate sex differences

in opioid analgesia (Cicero et al., 2002; Krzanowska et al., 2002). Stress-induced

hypoalgesia paradigms have demonstrated that female rats show both significantly less

analgesia than male rats, as well as differences in the neural substrates that modulate this

hypoalgesia (Kavaliers & Choleris, 1997; Kepler et al., 1989; Mogil & Belknap, 1997;

Mogil et al., 1993). These findings have led researchers to examine the role of estrogen

in this form of pain modulation. These studies, however, have not always found

consistent results with some studies finding no effect by estrous cycle (Romero &

Bodnar, 1986) and others showing reduced opioid-mediated stress-induced hypoalgesia

during phases of the estrous cycle that estrogen dominate (Ryan, & Maier, 1988).

Furthermore, when ovariectomy is performed, females begin to demonstrate similar

forms and levels of analgesia that males display. This analgesia can later be eliminated

via estrogen replacement therapy (Mogil et al., 1993).

Although there is a history in the animal literature of examining gender

differences in pain modulation, human research has not clearly demonstrated a

consistent gender effect in pain modulation. While some studies have found women to

demonstrate greater analgesia to mu and kappa opioid agonists on tonic pain models

when compared to men (Fillingim, 2002; Zacny, 2002), others demonstrate a lesser

involvement of mu opioid receptor systems in women during low hormonal phases of

the menstrual cycle compared to men (Zubieta et al., 2002).   It should be noted that

although this latter study suggests greater activation of endogenous opioids in men, the

authors did find greater mu opioid receptor availability in women. Gender differences in

affective pain modulation have also been observed with anger (Westcott & Horan, 1977)

and noise stress (Rhudy & Meagher, 2001) producing hypoalgesic pain responses in women when compared to men and anxiety manipulations (Dougher et al., 1987) producing hyperalgesic pain responses when compared to men.

Pain Modulation in an Inflammatory Pain Model

Previous human research has been instrumental in determining the role of emotion in pain modulation using acute pain models (Janssen & Arntz, 1996; Johnson & Helmstetter, 1994; Rhudy & Meagher, 2000; Willer & Albe-Fessard, 1980; Willer, Dehen, & Cambier, 1981; Willer & Ernst, 1986). Unfortunately, acute pain models may not generalize well to common clinical pain syndromes that are chronic or inflammatory in nature and to better generalize these experimental effects of pain modulation to clinical pain, new experimental models are needed. The use of capsaicin, which is an ingredient of hot peppers, has shown promise in modeling neuropathic and inflammatory clinical pain (i.e., Ali, Meyer, & Campbell, 1996; Fuchs, Campbell, & Meyer, 2000; Magerl, Wilk, & Treede, 1998; Raja, Campbell, & Meyer, 1984). 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 (Raja, Campbell, & Meyer, 1984). In addition, it is likely the result of activation and sensitization of both peripheral and central nociceptors (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; 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 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.

Other studies implicate central pain modulatory mechanisms in the capsaicin pain model. 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 of descending pain modulatory pathways could influence spinal processes of central sensitization or neurogenic inflammation.

Previously, our laboratory (Grimes et al., 2003; 2004) set out to further study the role of affective pain modulation on capsaicin-induced pain by examining the impact of noise stress on both primary and secondary hyperalgesia. Men and women 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 in women. Although the noise stressor did show a significantly greater pain modulatory effect (hyperalgesia) in stressed men than unstressed men, women in the stress condition did not show any significant pain modulatory effect when compared to women in the no

stress condition, but did show a slowing of the inhibition of capsaicin-induced tactile pain. A gender effect for spontaneous pain emerged with women experiencing the capsaicin as much more intense and unpleasant than men.

The present study further examines the modulatory impact of stress on inflammatory pain in women by controlling for the role of sex hormones. In controlling for the menstrual cycle we hope to provide evidence that, similar to previous animal research, the sex hormones are integral in both female pain perception and affective pain modulation. This is an extremely important question clinically in that there are numerous pain disorders that are significantly more prevalent in women than in men (Riley et al., 1999; Fillingim & Ness, 2000) and much of the treatment for these disorders do not take into account the possibility of alternate female-dependent pain modulatory pathways, such as an estrogen-dependent pain modulatory pathway. Furthermore, this study is unique in that we are examining the role of endogenous, normally fluctuating sex hormones in pain modulation. It is hypothesized that natural fluctuations in hormones, especially phases that are characterized by greater fluctuations in hormones (ovulation and luteal), will influence both pain perception as well as pain modulation. According to the literature, it is thought that women in the ovulation phase will demonstrate greater pain sensitivity, and less pain modulation. Given the propensity of sensitivity to negative affect, it is thought that the luteal phase will demonstrate the greatest degree of affective pain modulation.

METHODS

Participants

Participants were 106 female undergraduate psychology students who received course credit for their participation. Of these 106 subjects, 58 failed to schedule DAY 2 pain testing. Of the remaining 48 subjects, 2 subjects withdrew from the study during DAY 2 experimentation and 4 subjects were dismissed during DAY 2 testing because of equipment malfunction. In addition, 3 subjects were removed from the analyses because they reported not experiencing any pain to the tactile pain tests. Final analyses included 39 subjects, 87% were Caucasian, 5% Hispanic, 3% African-American, and 5% other. Mean age was 18.7 years (SD=1.46). Persons were excluded for: circulatory, cardiovascular, or neurological problems; chronic pain; or tobacco, analgesic, anti-histamine, anti-depressant, anti-inflammatory, hormonal birth control, or recent drug/alcohol use.

Apparatus

To assess the participants' menstrual phase, an OvuLens (Craig Medical Distribution) saliva fertility prediction microscope was used. Participants were instructed on the proper use of the device, which consists of placing a saliva sample on the internal slide and focusing the microscope on the slide. When the estrogen level increases near the participants' ovulation period, the dried electrolyte crystals in the saliva form a fern-like pattern. When this fern-like pattern appeared, participants scheduled an appointment to complete Day 2 of the experiment. The appointment time was dependent on their placement in an menstrual phase (ovulation, luteal). Participants

in the follicular phase were scheduled appointments based on report that they completed their menstruation.

Skin conductance (SCL) was recorded via 2 velcro sensors (Grass F-EGSR) attached to the palmar surface of the middle digits on the index and middle fingers of the non-dominant hand. Heart rate (HR) 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 both skin conductance and heart rate. Skin conductance and heart rate were sampled at 50 Hz. All stimulus control and data acquisition was computer regulated by LabVIEW software and an AT-MIO-16DL DAQ board (both by National Instruments).

A mechanical visual analog scale was used to measure pain reactivity. The device consists of a sliding potentiometer, which is an electronic component that allows a user to adjust the resistance (i.e., similar to a volume knob). Labels were affixed to the device with the anchors "No Pain" and "The Most Intense Pain Imaginable". Because there is a nonlinear relationship between voltage output and position of the potentiometer slide, all recorded voltages were later transformed from nonlinear to linear scales with the use of a mathematically derived logarithmic function. This logarithmic transformation creates a linear visual analog scale with points ranging from 0 "No Pain" to 10 "The Most Intense Pain Imaginable".

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.

<div align="center">**Measures**</div>

Self-Report

To examine the presence of any medical problem or the use of medication/substance that may impact pain perception and inflammation, a health status questionnaire was presented to participants. The questionnaire inquired about demographic information, their current use of any medications, including hormonal birth control, and the presence of any medical abnormality/illness that may potentially impact pain perception or inflammation. Furthermore, 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.

To assess the emotional impact of the noise stressor, 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).

To evaluate whether subjects were aware of our hypothesis, subjects were given an exit questionnaire asking them what they believed the experiment was designed to investigate. Subjects 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) and skin conductance level (SCL) were recorded. It was sampled for 1-min prior to each pain test, as well as 1-min prior to capsaicin induction and for the entirety of the 2-min noise stress period. Examinations of skin conductance were performed with tonic levels of skin conductance during the recording periods. Heart rate was examined in 5-sec blocks of time and represent beats per minute (BPM).

Procedure

On DAY 1, all subjects met in the experiment room where an experimenter read aloud the requirements, details, and instructions of the experiment. Subjects filled out the informed consent, demographics, a health status questionnaire, and CES-D. The experimenter then presented the subjects with the OvuLens device and instructed them on its use. No pain testing occurred on DAY 1. Contact information was exchanged. Subjects were told to contact the laboratory both when they viewed a positive fern pattern on the OvuLens device and after they completed their menstruation. During DAY 1, subjects were placed in either the Stress or No Stress condition and it was decided during which phase (Ovulation, Luteal, Follicular) the subject would be asked to return for DAY 2 pain testing. For those in the Ovulation phase, subjects were asked to return to the lab for DAY 2 pain testing 1-to-3 days after observing a positive fern pattern; subjects in the Luteal phase were asked to return 5-to-10 days after observing a positive fern pattern; and subjects in the follicular phase were asked to return within 10 days after finishing their menstruation.

On DAY 2, subjects brought the OvuLens device to the laboratory to ensure that the positive fern pattern was read correctly. If read correctly, the participant's informed consent, health status, and pre-existing level of distress were again reviewed. Subjects were then presented with procedural information and instructed on the required experimental tasks (i.e., rating their emotional reactions and pain reactivity). To ensure that subjects were able to rate changes in pain consistently, a cross-modality practice trial was employed where subjects were asked to practice rating changes in perceived

pressure being applied to their arm via a blood pressure cuff using the VAS device. The cuff was inflated to 100, then 200, then back to 100, and finally the pressure was brought back to 0. Proficiency in this task suggests that the subject will be likely to generate consistent pain ratings over time. After the practice, heart rate and skin conductance sensors were applied to their fingers. A grid with eight spokes radiating from the center was drawn in the center of their dominant volar forearm (Figure 1) with each spoke consisting of ten pain application sites. The subject was then given final instructions and questions regarding the procedures were fielded. A curtain is drawn and the subject's dominant forearm is placed on the experimenter's side of the curtain. The curtain is required to ensure that the participants are not receiving visual clues of inflammatory status or level of pain reactivity from the von Frey hair, which could impact pain ratings.

Site of Testing

ELBOW

SECONDARY
SITE

PRIMARY
SITE

**8 radial
pathways were
used to assess the
size of the
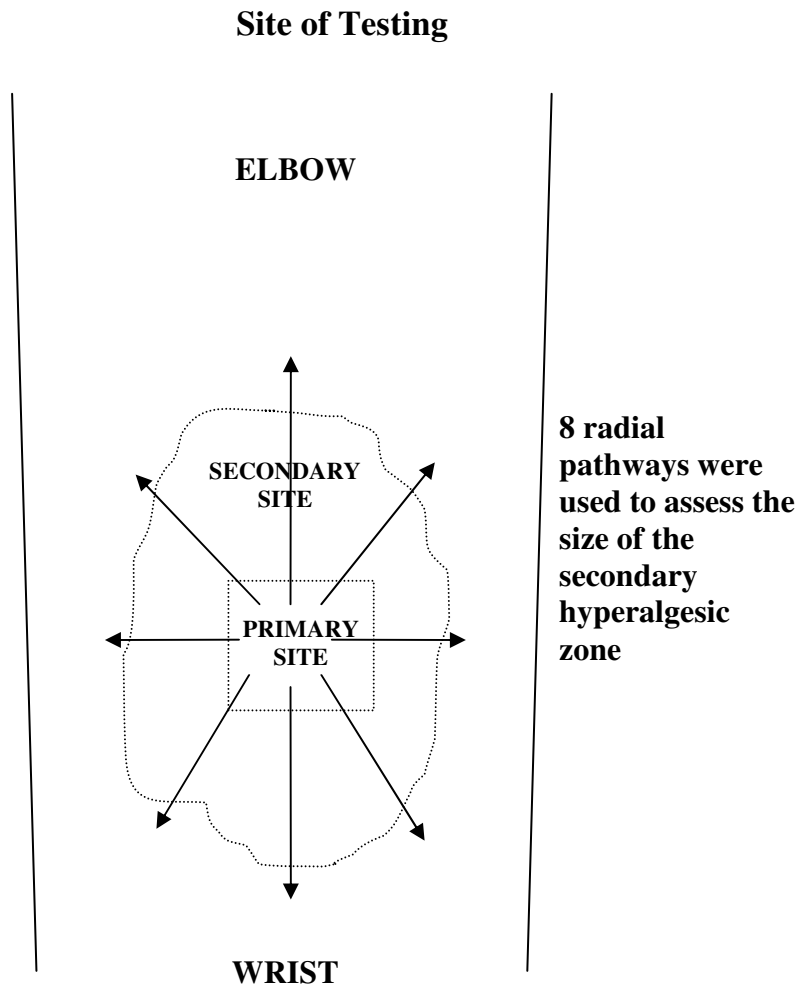secondary
hyperalgesic
zone**

WRIST

Figure 1: Site of Testing. Testing began outside the area of secondary
hyperalgesia and worked inwards toward the primary inflammatory site.
Testing began at the wrist and was completed in a clockwise fashion.

Figure 2 illustrates the experimental procedure, specifically when pain tests, capsaicin, and noise stressors were presented as well as when psychophysiological data were recorded. To begin, subjects underwent a practice pain test in which a large diameter von Frey hair (6.65 g) was applied to each pain site along the spokes. The experimenter 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. All pain tests were conducted in the same manner. Following the practice 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 et al., 1989; Simone, Baumann, & LaMotte, 1989). To impede evaporation, the site of application was covered with a dressing (Baron et al., 1999). The pad and dressing was left on the arm for a period of 25-min. During this time, subjects were asked to rate their emotion 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 VAS, which contain both an "intensity" and an "unpleasantness" component.

DAY 2
Experimental Procedure

PHYSIOLOGICAL RECORDING:

[--------]   [-------]   [--------]   [---------------------]

1 MIN	PRAC ALLOD YNIC PAIN TEST	4 MIN WAIT	1 MIN	CAP APP 25-min	1 MIN	ALLO DYNIC PAIN TEST	2 MIN WAIT	NOISE STRESS 2-min	1 MIN	ALLODY NIC PAIN TEST

Figure 2: Experimental procedure for Day 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 noise stress manipulation.

Since variability in skin temperature has been shown to introduce variance in studies using a capsaicin manipulation, skin temperature was regulated throughout the experiment to ensure that temperature at the inflammatory site remained 36 degrees Celsius (Liu et al., 1998).

After capsaicin induction, the capsaicin was removed from the forearm and subjects underwent a pain trial, as described earlier. Subjects were then randomly placed into a stress condition (Stress or No Stress). During the Stress conditions 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. The affect manipulation 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 phase, subjects then underwent a retest pain trial. At the conclusion of the Day's experiment, subjects were 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 also given an exit questionnaire and were debriefed.

RESULTS

Manipulation Checks

Pre-existing Distress

To examine the presence of any pre-existing levels of emotional distress, CES-D scores were analyzed using a one-way ANOVA with Phase as a between-group variable. No significant group differences were found for CES-D scores [$F(2, 37) = .95$, $MSE = 37.42$, $p > 0.05$]. This result suggests that regardless of menstrual phase, subjects were homogeneous in their level of pre-existing emotional distress and any between-group differences resulting from the affective manipulation cannot be attributed to pre-existing differences distress.

Affective Manipulation

Self-Report

To assess the impact of the noise stressor, 2 x 3 ANOVAs were conducted on SAM valence and arousal scores entering Phase (Ovulation, Luteal, Follicular) and Stress (Stress, No Stress) as between-subject variables. Figure 3 illustrates emotional Valence and Arousal scores to the presentation of the noise stressor. For valence, there was a significant main effect for Stress, [$F(1, 34) = 30.47$, $MSE = 98.74$, $p < 0.001$]. This effect indicates that subjects in the Stress condition experienced the affective manipulation as more unpleasant than subjects in the No Stress condition. Although there was not a significant Stress x Phase interaction [$F(2, 34) = 17.55$, $MSE = 8.78$, $p = 0.08$], an exploratory pairwise comparison indicated that subjects in the Luteal phase who did not receive the noise stressor experienced the experiment as more unpleasant
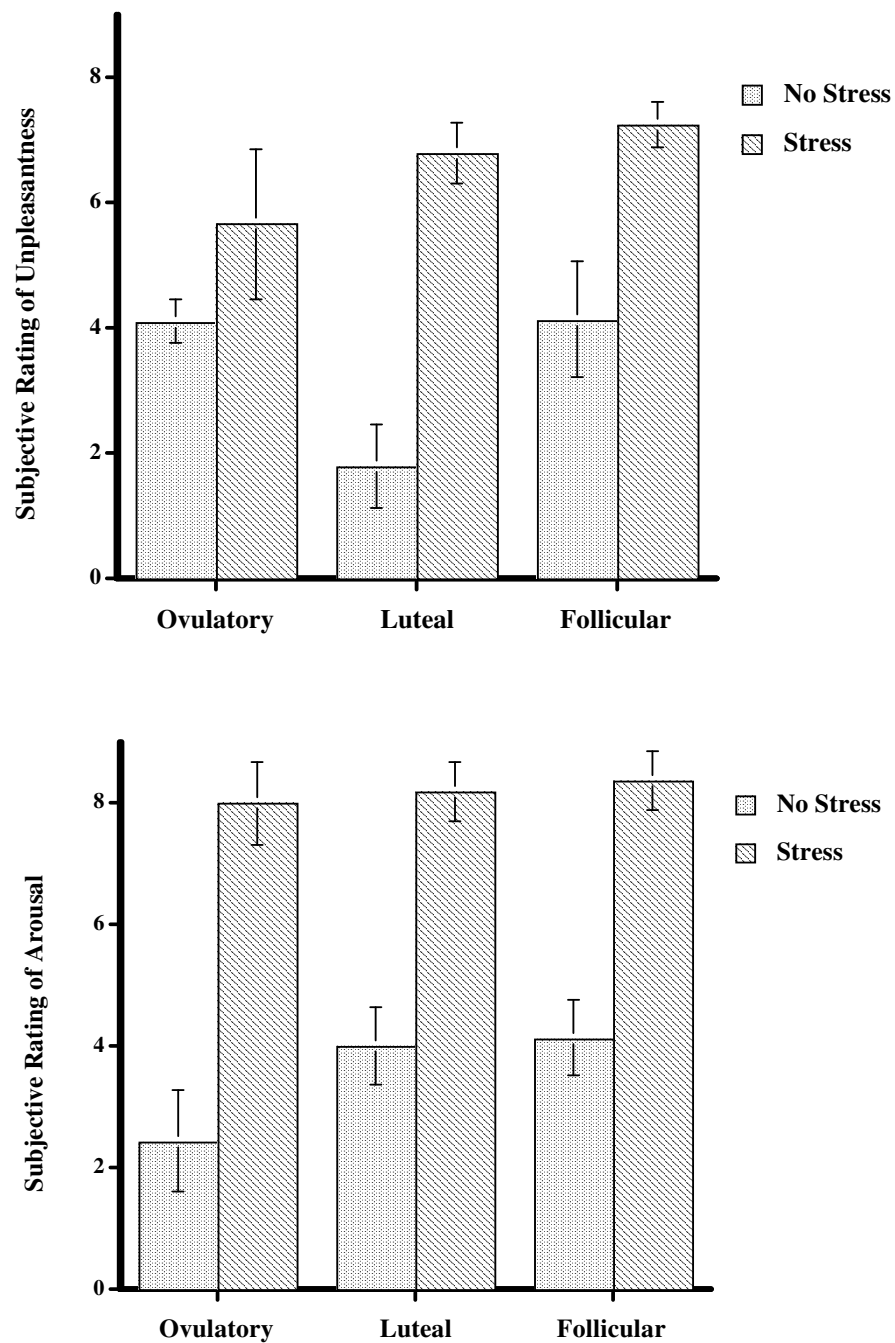
Figure 3: Self-Reported SAM Valence and Arousal Ratings of Stress. A significant main effect for stress was found for both valence and arousal in SAM ratings. Subjects rated the noise stressor as significantly more unpleasant and arousing than those subjects who did not receive the noise stressor ($p < 0.001$). There were no significant findings by phase.

than subjects in either the Ovulation or Follicular who also did not receive the noise

stressor ($ps < 0.05$).   Analysis of arousal ratings indicates a significant main effect for

Stress, [$F(1, 34) = 65.29$, MSE $= 206.90$, $p < 0.001$]. This finding implies that the

subjects in the Stress condition experienced the noise stressor as more arousing than

those in the No Stress condition. Neither Phase differences nor interactions between

Stress and Phase were found for either measure.

A series of 2 x 3 ANOVAs were conducted on each of the verbal affective

descriptors using Phase (Ovulation, Luteal, Follicular) and Stress (Stress, No Stress) as

between-group variables. Table 1 illustrates means and standard deviations for self-

reported affect to the noise stressor. Significant main effects for condition were found

for: fear [$F(1, 32) = 27.21$, MSE $= 29.81$, $p < 0.001$], surprise [$F(1, 33) = 43.07$, MSE $=$

49.29, $p < 0.001$], anxious [$F(1, 33) = 13.19$, MSE $= 18.53$, $p < 0.001$], happy [$F(1, 33)$

$= 7.51$, MSE $= 9.33$, $p < 0.01$], relaxed [$F(1, 33) = 8.64$, MSE $= 10.79$, $p < 0.01$],

disgusted [$F(1, 33) = 4.43$, MSE $= 4.43$, $p < 0.01$], and anger [$F(1, 33) = 15.63$, MSE $=$

13.20, $p < 0.001$]. No significant findings for the affective descriptors, bored, neutral,

and sad, were discovered. Subjects in the Stress condition reported feeling more fearful,

surprised, anxious, angry, disgusted, and less happy and relaxed, than those in the No

Stress condition. Although no significant interactions were found, a significant main

effect for Phase was found for the anxiety descriptor, [$F(2, 33) = 4.18$, MSE $= 5.87$, $p <$

0.05]. This finding suggests that those in the Follicular phase felt greater levels of

anxiety when compared with those in other menstrual phases regardless of whether or

Table 1

Means and Standard Deviations of Self-Reported Affective Response to the Noise Stressor

Condition		Fear 1 - 5	Surprise 1 - 5	Anx 1 - 5	Hap 1 - 5	Relax 1 - 5	Disgust 1 - 5	Anger 1 - 5	Bored 1 - 5	Neutrl 1 - 5	Sad 1 - 5
Stress	**M**	2.28**	3.47**	2.84**	0.79*	0.68*	0.74*	1.26**	0.79	0.68	0.47
	SD	1.36	1.07	1.21	0.79	1.11	1.10	1.28	1.13	0.82	0.84
No Stress	**M**	0.35**	0.90**	1.45**	1.70*	1.80*	0.00*	0.00**	1.45	1.55	0.05
	SD	0.75	1.17	1.40	1.34	1.20	0.00	0.00	1.47	1.32	0.22

Note. Below each scale is the range of potential scores. Means are in each column and below them are standard deviations. Superscript ** specifies that means in the same column differ at $p < 0.001$. Superscript * specifies that means in the same column differ at $p < 0.01$.

not they were presented with the noise stressor.   There were no other significant

findings by Phase. Together, the affective descriptors and SAM valence and arousal

results suggest that subjects experienced the noise stressor as stressful.

Heart Rate

Heart rate data were sampled in two ways, one by examining changes in heart

rate over the length of the experiment and the other by analyzing heart rate during the

noise stressor. To begin, heart rate was recorded for a 1-min period prior to each set of

pain tests and during the 2-min presentation of the noise stressor. These samples were

represented as beats-per-min (BPM) scores and analyzed using a mixed ANCOVA. The

1-min block of time prior to the noise stressor was entered in as a covariate. The 2-min

stress period pain and the 1-min block of time after the stressor were entered in as a

repeated measures variable (Time), while Stress and Phase were entered in as between-

subjects variables. After a Greenhouse-Geisser correction was made ($\varepsilon = 0.84$), there

was a significant Time x Stress interaction [$\underline{F}(2, 40) = 7.79$, $\underline{MSE} = 109.06$, $\underline{p} < 0.01$].

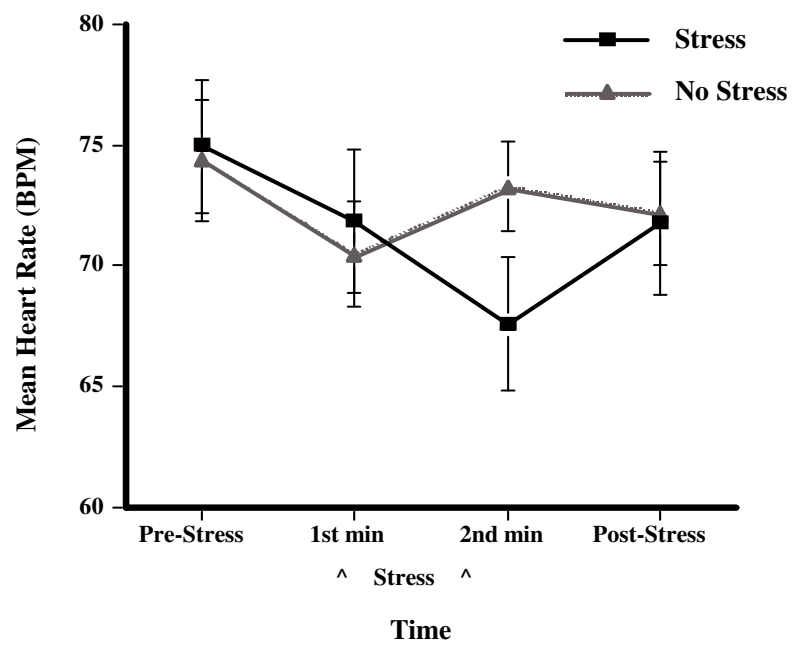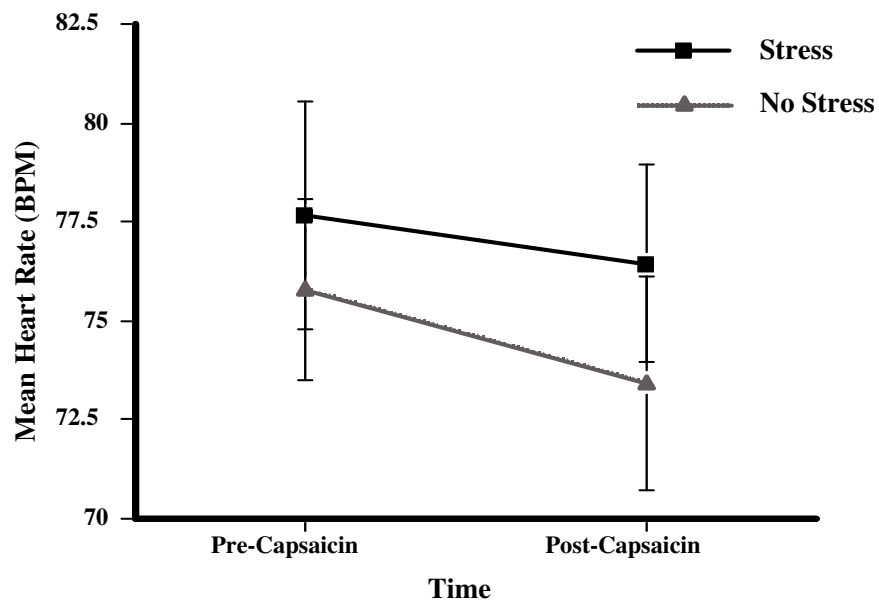Figure 4 depicts the impact of the stressor on heart rate.

Figure 4: The Impact of the Stressor on Mean Heart Rate. Subjects in the Stress condition demonstrate a significant decrease in their mean heart rate during the 2nd minute of the noise stressor ($p < 0.05$). There are no differences in mean heart rate for subjects in the No Stress condition.

Mean comparisons revealed that this interaction was attributed to a deceleration of heart rate observed in the Stress condition during noise presentation. In contrast, those in the No Stress condition did not show any significant fluctuations in heart rate.

In addition to examining the impact of the stressor across the length of the experiment, there was a significant Stress x Phase interaction [F(2, 95) = 5.71, MSE = 2141.94, $p < 0.01$]. Figure 5 depicts mean heart rate across the experiment. Pairwise comparisons revealed that subjects in the Ovulation phase who were presented with the noise stressor had an overall lower mean heart rate during the length of the experiment, while subjects in the Luteal phase who were presented with the noise stressor had an overall higher heart rate during the length of the experiment ($ps < 0.05$). Furthermore, subjects in the Luteal phase who did not experience the stressor demonstrated a lower mean heart rate when compared to those in either the Ovulation or Follicular phases who also did not experience the noise stressor ($ps < 0.05$). Subjects in the Follicular phase demonstrated no differences in their mean heart rate.
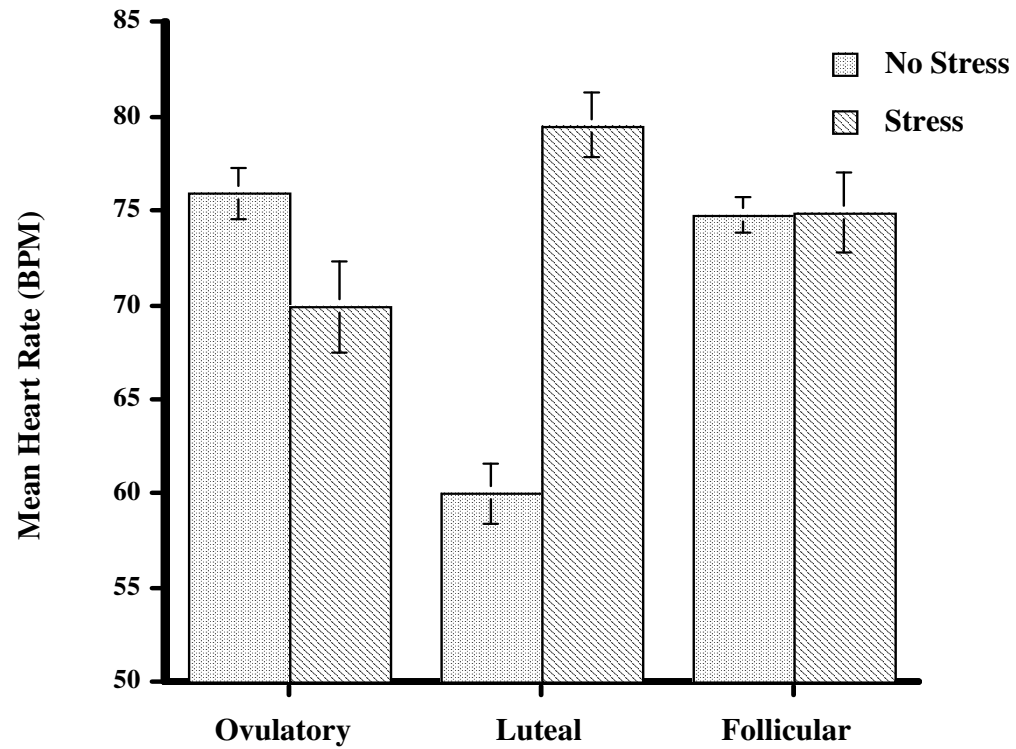
Figure 5: Mean Heart Rate (BPM) over the Length of the Experiment. There was a significant interaction between Stress and Phase. Subjects in Luteal phase who were presented the noise stressor demonstrate a significantly higher mean heart rate compared to those who did not receive the stressor ($p < 0.05$). Subjects in the Ovulatory phase who received the stressor demonstrated significantly lower mean heart rate when compared to those who did not receive the stressor as well as subjects in the Luteal phase who received the stressor ($p < 0.05$). There were no effects found in the Follicular phase.

To examine the direct effects of the noise stressor on heart rate, a second analysis was conducted that consisted of breaking the 2-min noise stress period into 5-sec blocks and examining the effect of the stressor on immediate heart rate. Samples were analyzed using a mixed ANOVA, with the twenty-four 5-sec blocks being entered as a repeated measures variable (Time) while Stress and Phase were entered as between-subjects variables. After a Greenhouse-Geisser correction was made ($\varepsilon = 0.37$), there was a significant Time x Stress interaction [$\underline{F}(23, 575) = 2.93$, $\underline{MSE} = 1.50$, $\underline{p} < 0.001$]. Figure 6 depicts this heart rate during the presentation of the noise stressor. Mean comparisons revealed that this interaction was attributed to subjects in the Stress condition demonstrating significant fluctuations in heart rate during the presentations of noise stress. In contrast, those in the No Stress condition did not show significant fluctuations in heart rate.
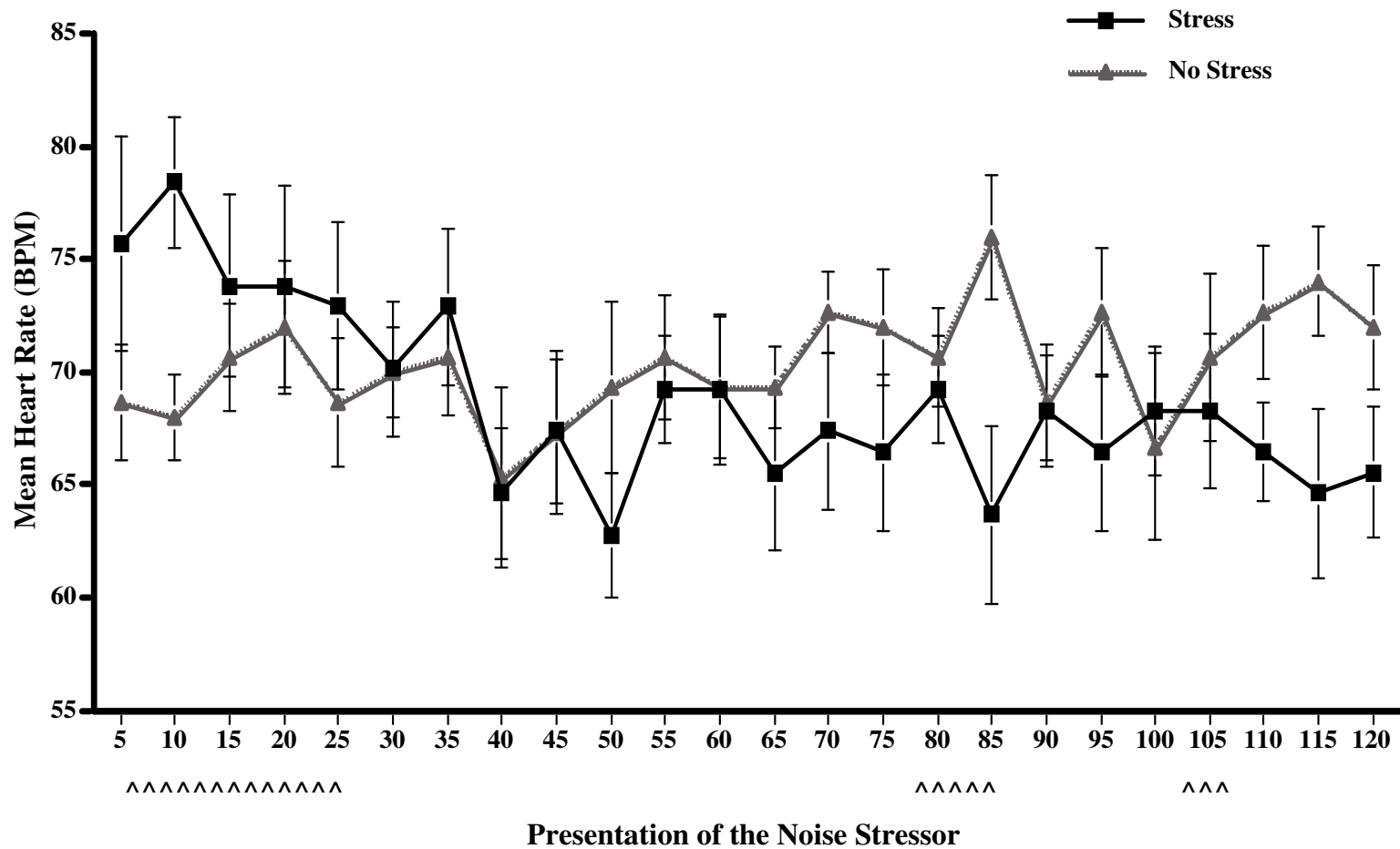
Figure 6: Mean Heart Rate (BPM) across the Presentation of the Noise Stressor. Subjects in the Stress condition demonstrate significant decreases in mean heart rate after presentations of the noise stressor ($p < 0.05$).

In addition to examining the fluctuations of heart rate during the length of the 2-min presentation of noise stress, there was also a significant Stress x Phase cross-over interaction [$\underline{F}$(2, 575) = 5.92, $\underline{MSE}$ = 57.66, $\underline{p} < 0.01$]. Figure 7 depicts mean heart rate during the 2-min presentation of noise. Pairwise comparisons revealed that subjects in the Ovulation phase who were presented with the noise stressor had an overall lower mean heart rate during the 2-min presentation of noise, while those in the Luteal phase who were presented with the noise stressor had an overall higher heart rate during 2-min presentation of noise ($\underline{ps} < 0.05$). This finding is similar to the significant interaction found when examining heart rate during the length of the experiment. Together, both findings suggest that noise stress produces divergent autonomic effects across the menstrual cycle specifically between the Ovulation and Luteal phase. In addition, this cross-over interaction demonstrates that those in the Luteal phase who did not receive the stressor had an overall lower mean heart rate during the 2-min affect manipulation compared to those in the Ovulation phase who did not receive the stressor who had an overall higher mean heart rate ($\underline{ps} < 0.05$). Those in the Follicular phase demonstrated no differences in their mean heart rate and there were no significant interactions between those in the Follicular phase and the other two phases.
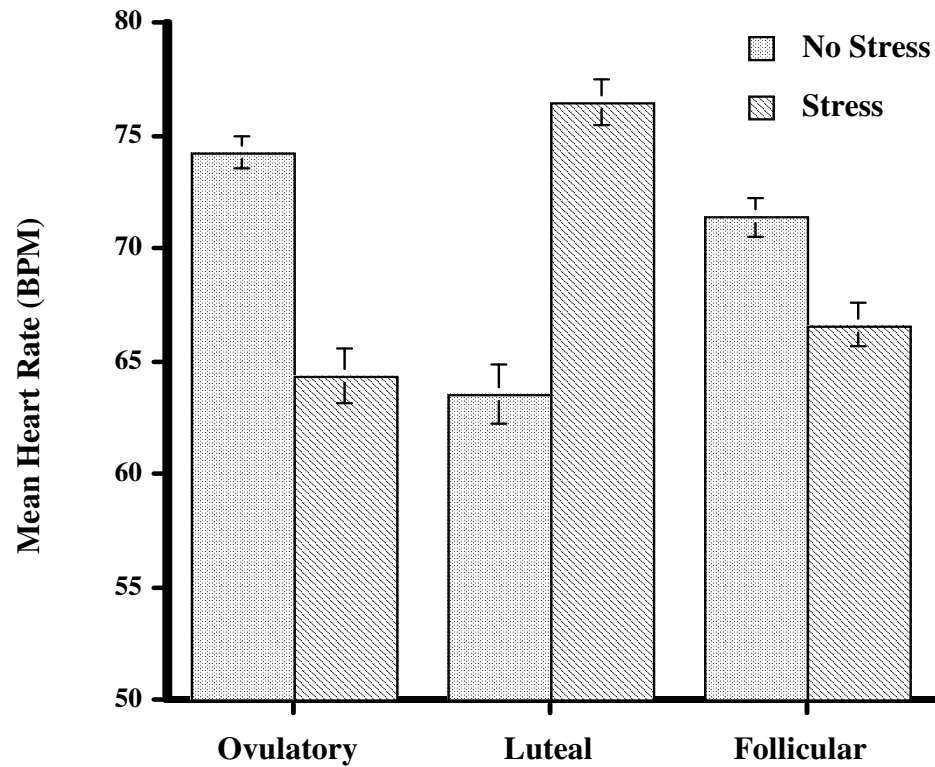
Figure 7: Mean Heart Rate (BPM) during the Presentation of the Noise Stressor. There was a significant interaction between Stress and Phase. Subjects in the Luteal phase demonstrated a significantly lower mean heart rate in the No Stress condition ($p < 0.05$). Both the Ovulatory and Follicular phase demonstrated significantly decreased mean heart rate during the noise stressor ($p < 0.05$). However, the Luteal phase demonstrated a significant increase in mean heart rate ($p < 0.05$).

Skin Conductance Level

Tonic skin conductance was sampled as a mean skin response level in 1-min blocks prior to the pain tests as well as during the 2-min presentation of noise stress. These tonic samples were analyzed using a mixed ANOVA with the blocks of time being entered into the analysis as a repeated measures variable (Time), while Stress and Phase were entered in as between-subjects variables. After a Greenhouse-Geisser correction was made ($\varepsilon = 0.59$), there was a significant Time x Stress interaction [$\underline{F}(4, 88) = 4.45$, $\underline{MSE} = 2.84$, $\underline{p} < 0.01$]. Figure 8 depicts the skin conductance data over the length of the experiment. Mean comparisons revealed that subjects presented with the noise stressor demonstrated significant increases in skin conductance, which suggests that the noise stress was autonomically stressful. In contrast, those in the No Stress condition did not show any significant fluctuations in their level of skin conductance. There were neither any significant menstrual phase differences nor interactions found.

Pain Reactivity and Secondary Hyperalgesia

Spontaneous Pain

VAS intensity and unpleasantness scores were analyzed using mixed ANOVAs with all five ratings used as a within-subject variable (Time) and Phase as a between-subject variable. Because the assumption of sphericity was not met, the Greenhouse-Geisser correction was used for both intensity ($\varepsilon = 0.45$) and unpleasantness ($\varepsilon = 0.39$). A significant effect was found for time in both intensity [$\underline{F}(4, 136) = 38.52$, $\underline{MSE} = 6740.20$, $\underline{p} < 0.001$] and unpleasantness [$\underline{F}(4, 136) = 29.19$, $\underline{MSE} = 6102.03$, $\underline{p} < 0.001$].
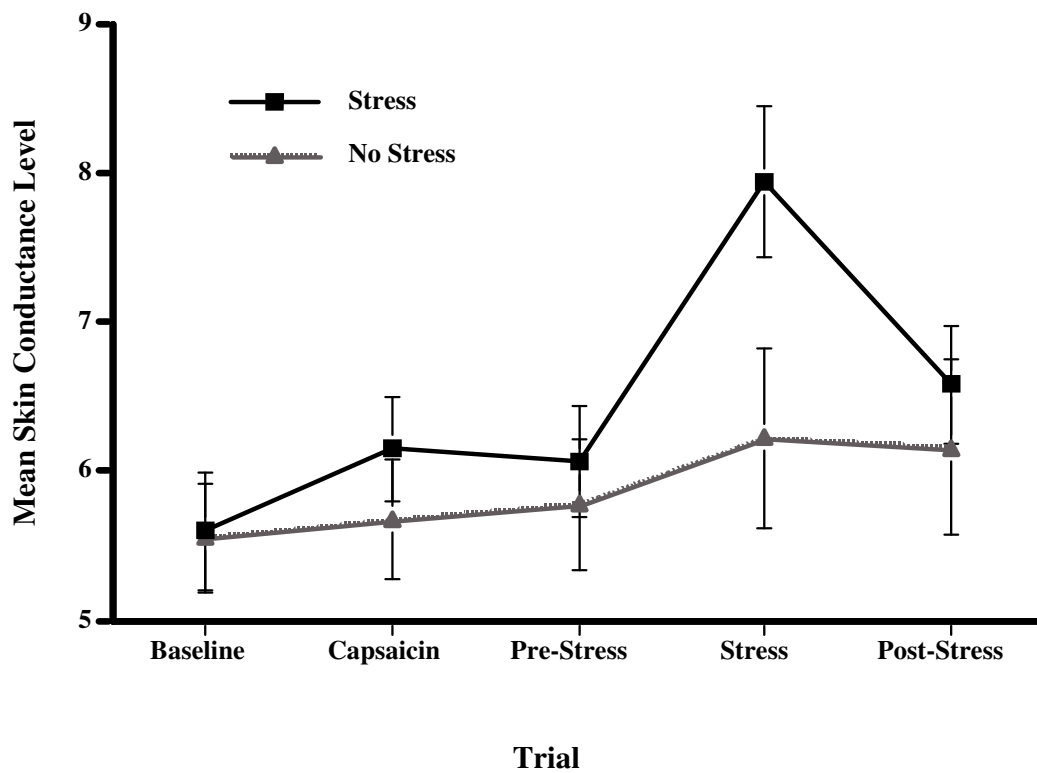
Figure 8: Mean Skin Conductance Level across the Experiment. Subjects in the Stress condition demonstrated a significant increase in their mean skin conductance level during the noise stressor ($p < 0.05$). There were no differences in mean skin conductance for subjects in the No Stress condition.

Figure 9 depicts the VAS scores for the five 5-min rating periods during the 25-min period following capsaicin application, but before the noise stress manipulation. 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 time periods three, four, and five ($p < .05$). No significant differences were found for Phase. This finding suggests that the capsaicin manipulation produced a significant spontaneous pain response that indicates the presence of secondary hyperalgesia. Two additional simple ANOVAs were conducted in hope of examining the role of Phase in spontaneous pain. The first ANOVA examined the impact of Phase on mean VAS ratings for intensity [$F(2, 34) = 0.06$, $MSE = 31.58$, $p = 0.94$] and unpleasantness [$F(2, 34) = 0.30$, $MSE = 192.90$, $p = 0.74$], but they were not significant. The second ANOVA examined the impact of Phase on the slopes of VAS ratings for intensity [$F(2, 34) = 0.50$, $MSE = 12.56$, $p = 0.61$] and unpleasantness [$F(2, 34) = 1.12$, $MSE = 37.67$, $p = 0.34$], but again no significant findings were discovered.

Ovulation Phase

Mean VAS Pain Ratings vs. Time during Capsaicin Application (5-min to 25-min). Intensity and Unpleasantness curves.

Luteal Phase

Mean VAS Pain Ratings vs. Time during Capsaicin Application (5-min to 25-min). Intensity and Unpleasantness curves.

Follicular Phase

Mean VAS Pain Ratings vs. Time during Capsaicin Application (5-min to 25-min). Intensity and Unpleasantness curves.
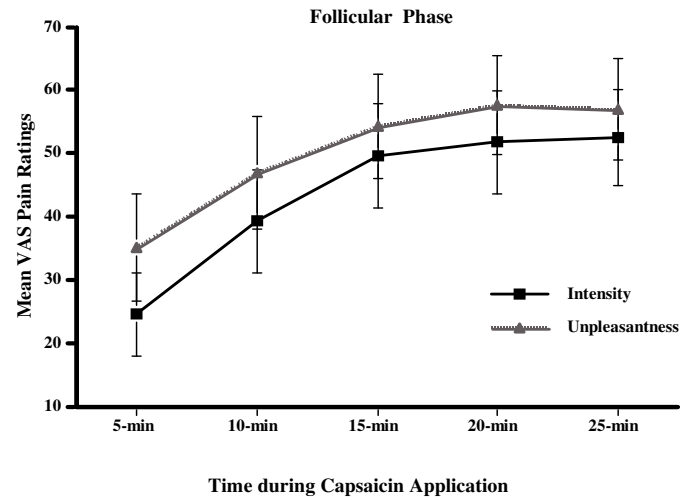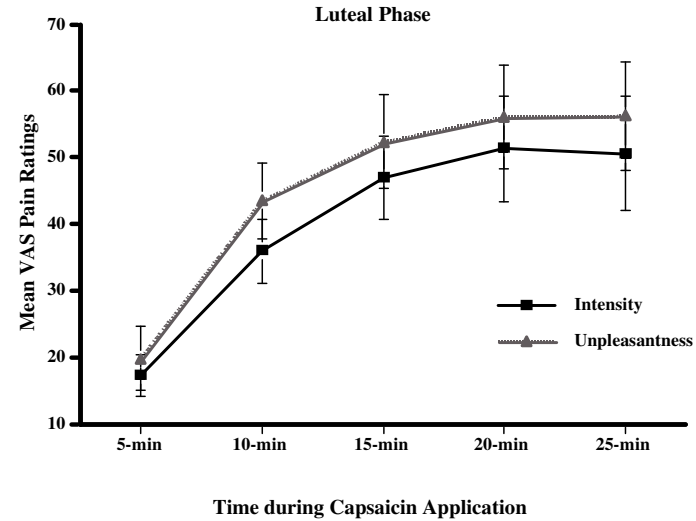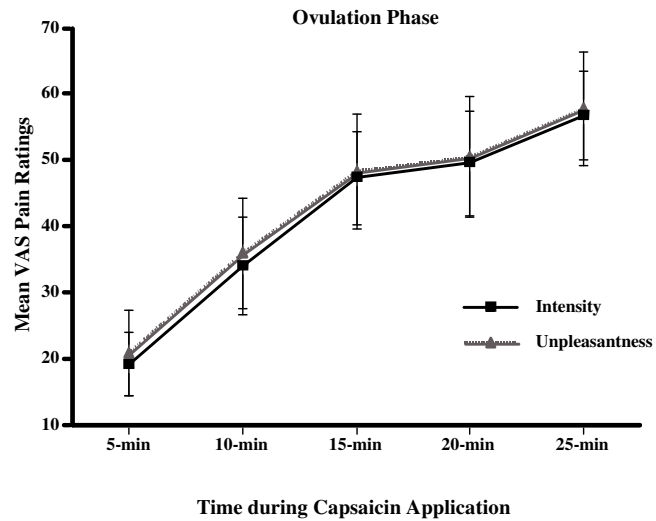
Figure 9: VAS Pain Ratings during Capsaicin Application. There was a significant time effect for both the pain dimensions of Intensity and Unpleasantness ($p < 0.001$). There were no interactions or main effects for Phase.

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, 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 10 depicts changes in post-stress VAS ratings from pre-stress VAS ratings. Change scores were analyzed using a 2 x 3 ANOVA with Stress and Phase being entered in as between-subjects variables. Although the Stress x Phase interaction was not significant [$\underline{F}$(2, 31) = 2.69, $\underline{MSE}$ = 0.33, $\underline{p}$ = 0.08], an exploratory pairwise comparison indicated that only subjects in the Luteal phase demonstrated affective pain modulation ($\underline{p} < 0.05$), specifically greater hyperalgesia. There were no other effects by either Phase or Stress. However, there is a non-significant trend where subjects in the Luteal phase who did not experience the noise stressor demonstrated greater decay of allodynia over the experiment. This is evidenced by these subjects' lower pain ratings to the allodynia
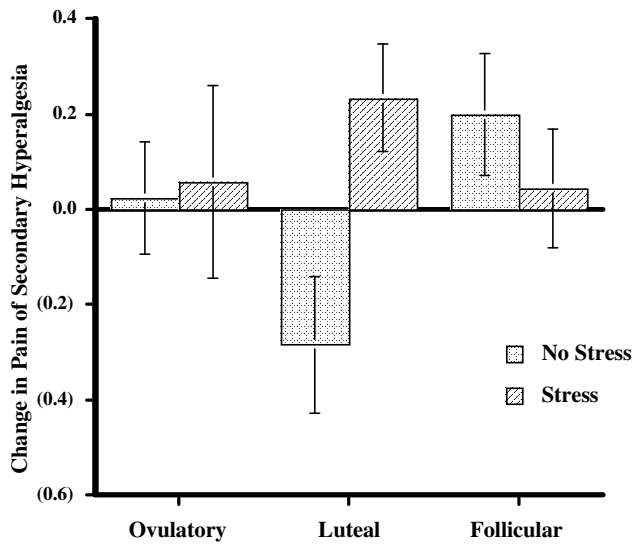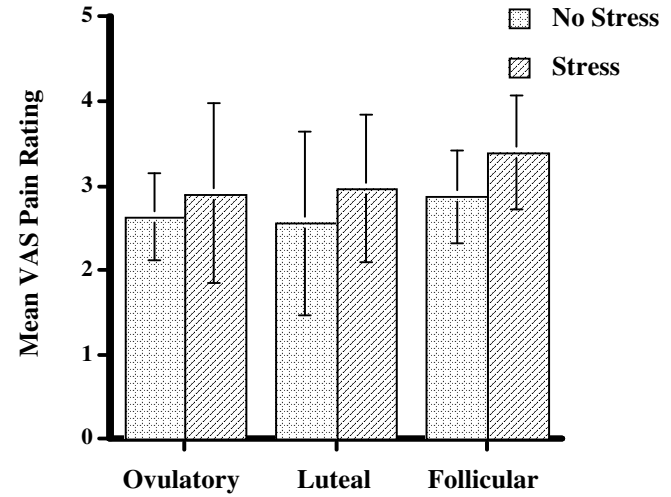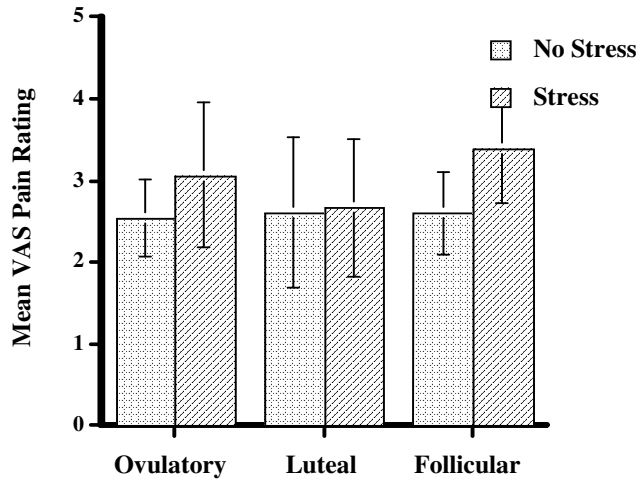
Figure 10: Change in Mean Pain Ratings of Secondary Hyperalgesia. Although there were no significant findings in pain ratings by phase or stress, an exploratory Pairwise comparison of the Luteal phase demonstrates greater hyperalgesia ($p < 0.05$). No other significant exploratory Pairwise comparisons were found.

during the post-stress pain test when compared to the means of subjects in the Ovulation and Follicular phases who also did not experience the noise stressor.

Area of Secondary Hyperalgesia

First, to examine the impact of menstrual phase on area of secondary hyperalgesia an analysis was conducted with the pre-stress pain test. An ANOVA was used with Phase being entered in as a between-subject variable. No significant Phase effects on pre-stress secondary hyperalgesia were found, [$F(2, 37) = 0.32$, $\underline{MSE} = 2632.95$, $\underline{p} = 0.73$]. Figure 11 illustrates the impact of the noise stress on the area of the secondary hyperalgesic zone. A change score was calculated by subtracting the post-stress area score from the pre-stress area score. A 2 x 3 ANOVA was used to analyze the area of secondary hyperalgesia, with Stress and Phase being entered in as between-subjects variables. A significant Stress x Phase interaction emerged [$\underline{F}(1, 31) = 3.47$, $\underline{MSE} = 4482.70$, $\underline{p} < 0.05$]. Pairwise comparisons indicated that subjects in the Luteal phase demonstrated significantly greater secondary hyperalgesia after the presentation of the noise stressor ($\underline{p} < 0.01$). Subjects in both the Menstrual and Follicular phase failed to demonstrate any significant changes in area of hyperalgesia. Furthermore, pairwise comparisons also demonstrated that subjects in the Luteal phase also demonstrated significantly greater decay of secondary hyperalgesia over the course of the experiment ($\underline{p}s < 0.05$). Specifically, subjects in the Luteal phase who did not experience the noise stressor demonstrated significantly greater decreases in the area of secondary hyperalgesia when compared to those subjects in the Menstrual and Follicular phases who also did not experience the noise stressor.
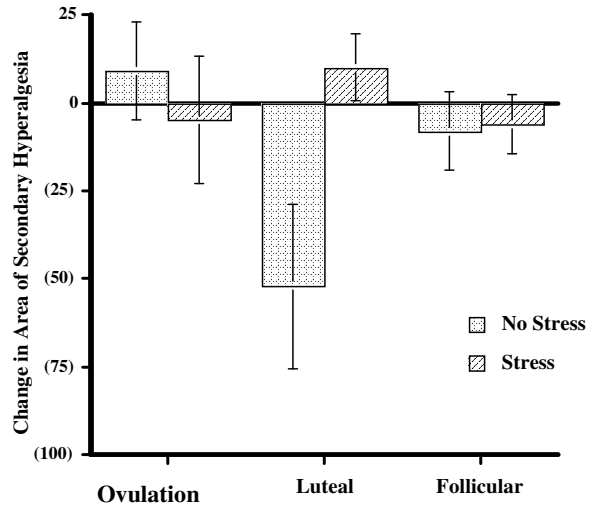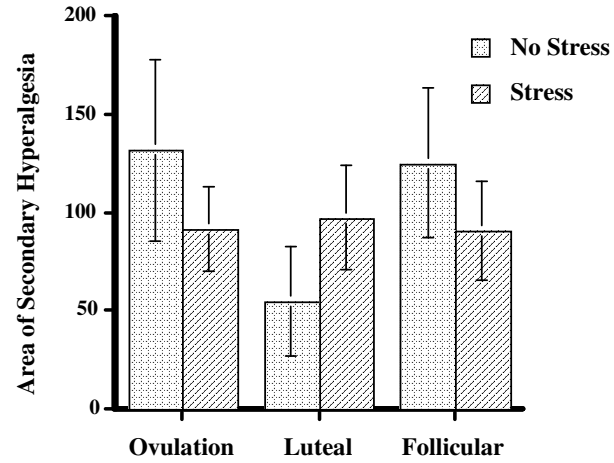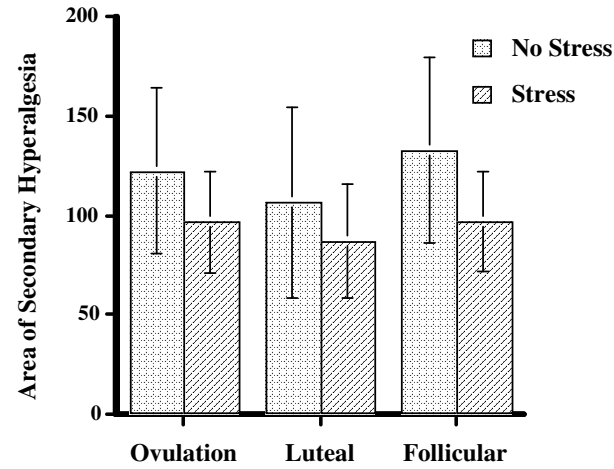
Figure 11: Change in Area of Secondary Hyperalgesia. Subjects in the Luteal phase demonstrated a significantly greater area of secondary hyperalgesia after the presentation of the noise stressor ($p < 0.05$). Subjects in the Luteal phase who did not experience the stressor demonstrated greater decay of secondary hyperalgesia than those in the Ovulatory and Follicular phases ($p < 0.05$). There were no significant findings in either the Ovulatory or Follicular phases.

GENERAL DISCUSSION AND SUMMARY

The present experiment was conducted to test the impact of both noise stress and the menstrual cycle on 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 secondary hyperalgesia. Furthermore, no study to date has either examined the role of the human menstrual cycle on inflammatory pain perception or the role of the human menstrual cycle on models of affective pain modulation.

To summarize the findings of the current study, significant effects were observed primarily in the luteal phase. To begin, those in the luteal phase who did not receive the noise stressor reported that the experiment was more unpleasant than those in the other phases. Furthermore, they demonstrated less sympathetic arousal during the experiment but greater autonomic arousal during the noise stressor. Participants in the luteal phase also demonstrated an analgesic/anti-inflammatory response evidenced by an observed decrease in secondary hyperalgesia for those that did not receive the noise stressor. No such changes in pain perception were discovered in the ovulation and follicular phases. Finally, in response to the noise stressor, an inhibition of the analgesic/anti-inflammatory effects was observed in the luteal phase. No such evidence of stress-induced pain modulation was discovered in the ovulation and follicular phases. The relation of these findings to previous studies will be discussed. Potential hypotheses regarding the nature, mechanisms of action, and relevance will be discussed as well.

Affect Manipulation

The affect manipulation in these experiments was a noise stressor which has been shown in previous research to elicit a stress response (Grimes et al., 2004; Rhudy & Meagher, 2001). In the present study, subjects exhibited a stress response to the presentation of the noise stressor. Specifically, subjects reported feeling significantly more unpleasant, excited, fearful, surprised, anxious, disgusted, and angry after being presented with the noise stressor and significantly more happy and relaxed when told they would not receive the stressor. In terms of self-report, the only effect that emerged by phase suggested that those in the luteal phase viewed the prospect of receiving the noise stressor as significantly more unpleasant than the other phases, evidenced by higher unpleasantness ratings in those in the luteal phase that did not received the noise stressor.

Heart rate was also monitored and recorded at specific times throughout the experiment to evaluate whether the affect manipulation altered sympathetic arousal. 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 et al., 2003; Grimes et al., 2004). 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.

A cross-over effect was discovered between the luteal and ovulation phases in that they displayed divergent effects in their mean heart rate during the presentation of noise. Specifically, the luteal phase demonstrated a high heart rate during the stressor and a low heart rate in the absence of the stressor, while the ovulation phase demonstrated a low heart rate during the stressor and a high heart rate in the absence of the stressor. This finding for those receiving the stressor is consistent with other literature examining menstrual cycle effects on autonomic arousal where those in a pre-menstrual group (analogous to the luteal phase) were observed to have lower heart rate than those in an inter-menstrual group (inclusive of both the follicular and ovulation phases) (Kuczmierczyk & Adams, 1986).

The manner in which subjects responded to the noise stressor was dependent on the specific menstrual phase in which they were tested. Both those in the ovulation and follicular phase produced lower mean heart rates during the stressor compared to those in the luteal phase who produced a higher mean heart rate during the stressor. This pattern of results suggests that those in the luteal phase were significantly more autonomically aroused at the prospect of a negative stressor. And although subjects in different menstrual phases did not report the stressor as significantly more or less

stressful, the luteal phase is typically highly correlated with increased level of negative affect (Bloch, et al., 2000; Rubinow, 1992) suggesting that during this phase women are more likely to perceive stressful events as more negative.

In addition to heart rate, skin conductance levels were also collected throughout the experiment to evaluate whether the affect manipulation altered sympathetic arousal. A significant increase in skin conductance was observed during the presentation of the noise stressor. Subjects who were not presented with the stressor did not demonstrate any change in their level of skin conductance. Based on heart rate, skin conductance and self-report data, these findings suggest that the affect manipulation was successful with the greatest autonomic response to the stressor generated by those in the luteal phase.. 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 25-min capsaicin application. Subjects rated their spontaneous pain as increasingly more intense and unpleasant over the 25-min period, which suggests that the capsaicin produced an inflammation of the forearm. We hypothesized that ratings to spontaneous pain would be dependent on the subject's menstrual phase, however, no such effects were observed. One possible explanation for this null finding is that the

concentrations of varying inflammatory agents (i.e., formalin, carrageenan) employ different pain pathways, with low concentrations producing central sensitization and high concentrations producing both central and peripheral sensitization (Kuba et al., 2006; Yashpal & Coderre, 1998). In comparison to other studies that utilize a capsaicin model, the current study's 6% topical capsaicin application would best be considered a low concentration in that most other human studies utilize a 6-10% capsaicin that is intradermally injected into skin (Fillingim & Ness, 2000). Therefore, it is a possibility that the lower intensity capsaicin model used in this study relies more on central than peripheral sensitization pathways, which may have lessened the immediate impact of hormones on increasing inflammation and spontaneous pain. Approximately 11-min after removal of the topical capsaicin, changes in pain perception begin to occur in the luteal group without the impact of any affective manipulation. Given these observations, it seems likely that there is the potential to discover phase-specific effects to spontaneous pain if measurements are taken for a longer duration. In addition, perhaps if either a higher concentration capsaicin or an alternative delivery method of the capsaicin was incorporated, then an attenuation of spontaneous pain in the luteal phase would be observed, which would be similar to the findings in other studies examining the role of sex hormones in inflammatory response to tonic pain models in animals (Ji et al., 2005; Kuba et al., 2006; Ren et al., 2000).

Secondary Hyperalgesia

To examine the impact of stress and menstrual phase on secondary hyperalgesia, the present study induced secondary hyperalgesia by the mechanical stimulation of a

firm von Frey hair on inflamed skin associated with the application of a topical capsaicin. Effects on secondary hyperalgesia and modulation of this hyperalgesia were observed only in the luteal phase. No significant findings were discovered in the ovulation and follicular phase.

In examining secondary hyperalgesia, two measures were examined, change in VAS ratings and change in the calculated area of secondary hyperalgesia. Subjects in the luteal phase who did not experience the stressor demonstrated significant decay of secondary hyperalgesia over the length of the experiment when compared to both the ovulation and follicular phases. Furthermore, those in the luteal phase demonstrated significantly greater secondary hyperalgesia after the presentation of the noise stressor. Specifically, it is likely that the stressor worked to inhibit the anti-inflammatory effects of progesterone to persistent inflammation, which is consistent with previous studies (Ren et al., 2000; Ji et al., 2005; Kuba et al., 2006). As stated earlier, subjects in the luteal phase were significantly more sympathetically aroused to the noise stressor when compared to those in the ovulation and follicular phase, suggesting that they experienced the noise as more stressful. This possible heightened susceptibility to negative affect during the luteal phase may explain why it was the only phase that demonstrated any pain modulatory effects.

Given that the luteal phase is characterized by decreasing levels of estrogen and increases in progesterone, it is likely that progesterone-mediated effects are underlying the observed alterations in anti-nociception observed in the study. Although progesterone appears to have the potential to alter both central and peripheral pain

transmission and modulatory systems (Fillingim & Ness 2000), it is unclear how progesterone may be modulating pain in the present study. Peripherally, a potential hypothesis may be related to hormone-mediated effects at the level of the primary nociceptor and/or observed differences in autonomic arousal between menstrual phases. For example, sex hormones have been observed to impact pain modulation at the level of the primary nociceptor in that both chronically administered progesterone (Datta et al., 1989) and pregnancy (Kaneko et al., 1994) have been observed to enhance the analgesic effects of local anesthetics in rats. Furthermore, consistent with a previous study (Kuczmierczyk & Adams, 1985), subjects in the luteal phase who did not receive the stressor demonstrated lower mean heart rate than those in the ovulation and follicular phase. And since previous studies have demonstrated the role of the noradrenergic system in potentiating capsaicin-induced hyperalgesia (Drummond, 1995; Chen & Levine, 2005) it is plausible that this overall lower sympathetic arousal in those that did not receive the stressor may have diminished secondary hyperalgesia while the higher sympathetic arousal in those that experienced the stressor may have maintained secondary hyperalgesia.

Although this finding in the luteal phase may be related to peripheral sensitization and modulation, the attenuation of secondary hyperalgesia is also similar to the findings of other laboratories that progesterone has an anti-inflammatory/anti-nociceptive effect in persistent inflammation models that appears to be centrally-mediated (Ren et al., 2000; Ji et al., 2005; Kuba et al., 2006). Multiple studies have described the impact of sex hormones on a variety of central pain transmission and

modulatory pathways (Fillingim & Ness, 2000). For example, gonadal hormones appear

to influence spinal NMDA receptors (Ren et al., 2000) as well as GABA receptors and

levels of enkephalin in the periaqueductal gray (Smith et al., 1994), all of which play a

significant role in centrally-mediated nociceptive processing.

Hormonal effects have also been demonstrated in limbic regions, particularly the

amygdala. Walf and Frye (2003) demonstrated that intra-amygdala administration of

estrogen and progesterone produces analgesia in rats, which suggests that the amygdala

may be involved in hormone-mediated modulation of pain. In relation to inflammatory

pain, 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 et al., 2002). This evidence together with a large body of research that

demonstrates the significant role of the amygdala in affective processing and stress-

induced analgesia (e.g., Helmstetter, 1992; Helmstetter & Bellgowan, 1993), suggests

that gonadal hormones have the propensity to produce centrally-mediated influences on

affect and its modulation of pain.

To further examine the hypothesis that sex hormones play a role in affective pain

modulation, future studies should also be conducted to examine the impact of positive,

calming affective manipulations on secondary hyperalgesia. Perhaps a calming or

positive affective manipulation may either enhance the analgesic effects of the luteal

phase or even possibly impact the ovulation phase. The potential to observe pain

modulatory effects in the ovulation phase is particularly intriguing in that positive mood

states appear to be facilitated through estrogen-dependent serotonergic systems (Belthea et al., 1999; Derman et al., 1995).

Summary

In conclusion, although investigations into the role of sex hormones in pain, inflammation, emotion, and pain modulation have not always reported consistent findings along multiple lines of research, the results of the current study are consistent with past research that specifically examines the role of sex hormones in inflammation produced through tonic pain models. Specifically, our results are consistent with prior studies indicating that progesterone has anti-inflammatory effects. Although the specific mechanisms of this action still remain unclear, prior evidence points to the role of centrally-mediated pain modulation. Women in the luteal phase demonstrated greater sympathetic arousal during the stressor followed by a decrease in anti-nociception. It is likely that the stressor worked to inhibit the anti-inflammatory effects commonly observed in the luteal phase to persistent inflammatory pain through centrally-mediated pain modulatory mechanisms. It is hypothesized that hormone-mediated effects at the level of the amygdala influenced the impact of affective pain modulation.

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