Gender Differences in Pain: Do Emotions Play a Role?

Jamie L. Rhudy, PhD; and Amy E. Williams, BS

Department of Psychology, University of Tulsa, Tulsa, Oklahoma

ABSTRACT

Background: Research suggests that the influence of gender on the processing and experience of pain is a result of several mechanisms. One mediating variable is emotion, which may modulate pain through an interaction of valence (pleasant–unpleasant) and arousal (calm–excited).

Objective: This review examines whether gender differences in the experience and processing of emotion contribute to differences in the modulation and perception of pain.

Methods: An English-language search of MEDLINE and PsycINFO was conducted from 1887 to May 2005. Additional literature was obtained from reference lists of articles retained in the initial search.

Results: Emotion appears to influence pain through a valence-by-arousal interaction. Specifically, negatively valenced emotions with low to moderate arousal (e.g., anxiety) enhance pain, whereas negatively valenced emotions with high arousal (e.g., fear) reduce pain. In contrast, positively valenced emotions always reduce pain, as long as minimal arousal is achieved. Some evidence suggests that women are more sensitive than men to threat-related stimuli and thus experience more negative affect than men. This would generally lead to enhanced pain perception in women. It is also possible that women are more likely than men to experience negative affect with high arousal (intense fear) and thus pain inhibition. However, the relatively lower base rate of intense negative emotions is not likely to contribute much to gender differences in pain. Evidence also suggests that men may be more sensitive to positive events, particularly sexual/erotic stimuli, which may lead to more positive emotion-induced pain reduction in men, relative to women.

Conclusions: This review suggests that gender differences in the experience of pain may arise from differences in the experience and processing of emotion that, in turn, differentially alter pain processing. Specifically, the system associated with negative affect may be more attuned to threatening stimuli in women, and the system associated with positive affect may be more attuned to pleasurable stimuli in men. However, there is a paucity of research directly addressing this issue; much of the research on this topic has failed to test a comprehensive model of emotion, failed to use adequate manipulation checks, or failed to use within-subject experimental designs that control for intra- and interindividual differences. Therefore, it is concluded that additional research is warranted. (Gend Med. 2005;2:208–226) Copyright © 2005 Excerpta Medica, Inc.

Key words: pain modulation, motivation, defensive system, appetitive system, emotion, gender.
INTRODUCTION

Sex differences in pain are well established. For example, women report clinical pain more frequently, with longer duration and greater severity, than do men. Additionally, gender exerts a moderate to large effect on experimental pain, with women exhibiting lower pain thresholds and tolerance. Interestingly, the differences in experimental pain are more pronounced when the noxious stimulus evokes a strong affective reaction (i.e., mechanical pressure, electrical stimulation) compared with stimuli that primarily evoke sensory pain (e.g., thermal stimulation). Although it seems clear that sex/gender influences pain, the reasons for these differences are not well understood. In her review, Berkley noted a number of potential mechanisms, including experiential (e.g., learning about pain), biological (e.g., hormones, contact with pathological agents), and psychological mechanisms (e.g., attitudes toward pain).

Experiential mechanisms include socialization, learning, and identification with gender roles. Men and women may react differently to pain in response to societal views governing their behavior. However, there is evidence that gender differences in pain stem from more than just socialization and learning. For example, differences between the sexes have been reported in objective measures of pain, such as the measurement of nociceptive reflexes. Biological factors may also influence sex differences in pain. In their reviews, Fillingim and Maixner and Fillingim and Ness outlined a comprehensive model illustrating several potential mechanisms. First, males and females may differ in the physiology and responsiveness of primary afferents, some of which may be mediated by gonadal hormones. Indeed, hormones can sensitize primary afferents or recruit afferents that are normally “silent” to noxious stimulation. Second, the central nervous system of males and females may process nociceptive information differently. For example, sex hormones can alter the levels of neurotransmitters known to play a role in pain modulation (and some involved in the modulation of affect), such as substance P, γ-aminobutyric acid, glutamate, dopamine, serotonin, and norepinephrine. Also, the activation of central pain inhibitory mechanisms by stress causes greater hypoalgesia in male animals than in females, an effect that appears to result from developmental and hormonal differences between the sexes. Further, exogenously administered opiates, which act on central pain modulatory circuits, affect men and women differently.

Of the few studies that have examined this issue, data suggest that women are more sensitive to the effects of μ- and κ-opiate receptor agonists. These differences may stem from hormonally mediated alterations in receptor affinity. Zubieta et al found that supraspinal systems involving μ-opiate receptors are less active in response to pain in women during the follicular phase than in men. Also, increases in estradiol decrease μ-opiate receptor binding in the hypothalamus and amygdala, structures that are important in central pain modulation and affective processing. Additionally, luteinizing hormone appears to desensitize opioid receptors, leading to decreased effectiveness of endogenous and exogenous opiates. Together, these studies suggest that there are a number of biological mechanisms that may contribute to sex differences in pain. Some of these mechanisms reflect differences in the underlying structure and physiology of neural systems, whereas others reflect the effects of phasic changes, such as fluctuations in the hormonal milieu.

In addition to the experiential and biological mechanisms, it is possible that men and women have fundamental differences in psychological mechanisms that activate pain modulation circuitry. For example, some of the gender differences may be explained by variations in the way emotion modulates pain.

The goal of this review is to examine the potential contribution of emotion in gender differences in pain. To do so, several points will be addressed. First, pain and emotion will be defined within a larger motivational framework that describes their relationships to systems that govern appetitive and defensive responses. Second, studies will be reviewed that have examined...
emotional modulation of pain and another defensive response—the acoustic startle reflex—that is modulated by circuitry similar to pain modulation circuitry. It will be argued that the influence of emotion on pain can be described by an interaction of affective valence and arousal. Third, the potential biological circuitry for emotional modulation of pain will be described. Fourth, research examining gender differences in affective modulation of pain will be discussed. Last, a summary of a model for understanding how emotion may contribute to gender differences in pain will be given, followed by suggestions for future research in this area.

**EMOTION AND PAIN: RELATIONS TO MOTIVATION**

Emotion and pain can be understood within a larger motivational context. The neurocircuitry associated with motivation is thought to comprise 2 adaptive, complex systems that promote survival by providing feedback about harmful or health-enhancing stimuli. The defensive system is associated with a network of brain regions that process potentially dangerous stimuli and generate fight, flight, or freezing behaviors. The amygdala appears to play a critical role in this system; other areas involved are the sensory and right prefrontal cortices, bed nucleus of the stria terminalis, sensory thalamus, hippocampus, hypothalamus, nucleus reticularis pontis caudalis, and periaqueductal gray.

The appetitive system also consists of a network of brain regions that involve dopaminergic neurons and endogenous opioids. Research suggests that the ventral tegmental area and the nucleus accumbens are essential to the appetitive system; other areas implicated are the amygdala, lateral septum, left prefrontal cortex, caudate, and putamen.

Linking these systems to emotion, it has been shown that activation of these 2 motivational systems results in subjective reports of emotion, emotion-related behavior, and autonomic nervous system correlates, whereas damage to these structures results in emotional deficits. Positive emotion is associated with activation of the appetitive system, and negative emotion is associated with activation of the defensive system. Additionally, the level of activation of each of these systems is thought to manifest itself in subjective and physiological arousal. Thus, emotion is typically defined by the orthogonal dimensions of valence (pleasant–unpleasant) and arousal (calm–excited). Valence provides an indicator of the motivational system activated, and arousal indicates the level of activation of the system. Phenomenologically, valence is associated with the tone and arousal with the intensity of the emotion.

This dimensional quality of emotion has important implications for studies that measure emotions and their effects. First, it is important to include indices of valence (pleasant–unpleasant) and arousal (calm–excited) when measuring emotion. Valence and arousal may have independent effects or they may interact (this issue will be addressed in greater detail later). Second, some emotions may have similar valence but may differ in arousal (intensity) level. For example, fear and anxiety are both negative in valence. Fear, however, results from a present environmental threat that leads to intense activation of the defensive system (high arousal). Alternatively, anxiety is a future-oriented emotion that does not involve a present environmental threat; therefore, the defensive system is less activated (low to moderate arousal). Third, studies that focus on one emotion (e.g., anxiety) will not capture variability in valence and arousal; rather, variation in that emotion will likely reflect changes in activation (arousal) of that particular motive system. Thus, studies that only measure anxiety levels may be tapping into changes in activation of the defensive system (i.e., arousal) to the exclusion of valence effects, which therefore cannot be assessed in these designs. Last, given the subjective nature of self-reported emotion and individual differences in the use of self-report measures and baseline physiology, studies attempting to understand the influence of emotion must test the same person under different emotional conditions (i.e., use repeated-measures designs). Thus, within-subject manipulations are preferable to between-subject,
emotion-induction procedures because these designs allow the experimenter to examine intra- and interindividual variability.

The experience of pain can also be conceptualized in a motivational context. Pain is a dynamic psychological experience that is characterized by sensory, affective, and to a lesser degree, cognitive components. The neurocircuitry associated with pain transmission (nociception) and perception is part of the defensive system and helps organisms avoid actual or potential tissue damage.

In the periphery, there are sensory receptors (nociceptors) that respond maximally to noxious stimulation. These nociceptors synapse onto neurons in the spinal cord, where nociceptive information is conveyed to the brain by several spinal tracts. These tracts terminate in different brain regions that process different aspects of the nociceptive message. The spinothalamic tract carries the signal from the spinal cord through the lateral nuclei of the thalamus to the somatosensory cortices and encodes the sensory quality of pain. Other projections to the anterior cingulate cortex (ACC) and amygdala are associated with the affective component of pain. Additionally, pathways to the hypothalamus and reticular formation elicit neuroendocrine and autonomic responses, respectively. Ascending nociceptive pathways can therefore directly activate areas related to emotion. Given this anatomic relationship, emotion may influence pain by altering the processing of nociceptive signals at the level of the brain. For example, animal research suggests that chemical and electrical activation of the ACC enhances nociception. Similarly, human imaging studies have implicated the ACC in pain modulation.

**Emotional Modulation of Pain**

Pain is not simply determined by the intensity or amount of noxious stimulation that activates the nociceptive system. Indeed, the same stimulus can be experienced as painful at one time and innocuous at another. In an effort to understand these changes, several theories have sought to characterize the mechanisms that modulate pain and the factors that activate them. It is not surprising that even early theorists considered the role of emotion. An understanding of the influence of emotion on gender differences in pain first requires an understanding of how emotion influences pain modulation.

**Evidence for Emotional Modulation of Pain**

Greenwald et al, Lang, and Lang et al proposed a theory of motivational priming that suggests emotion differentially modulates defensive behaviors. Whether the defensive behavior/response is inhibited or facilitated is determined by the motivational system (appetitive or defensive) that is activated, and thus, the valence of the affective state. Briefly, the motivational priming theory suggests that negatively valenced emotion (ie, activation of the defensive system) enhances/primes defensive responses (eg, escape, attack) while inhibiting appetitive responses (eg, eating, reproduction). Alternatively, positively valenced emotion (ie, activation of the appetitive system) enhances/primes approach behaviors and inhibits defensive responses. Support for this theory comes from studies examining emotional modulation of the acoustic startle response (a defensive reflex). This paradigm examines the magnitude of an eye blink reflex (in humans) or whole body reflexive movements (in animals) in response to a burst of surprising noise. In accord with the motivational priming hypothesis, stimuli that elicited positive emotion resulted in decreased startle magnitude (inhibited defensive response), whereas stimuli that elicited negative emotion caused enhanced startle magnitude (augmented defensive response).

Evidence from the startle literature may provide a basis for understanding the influence of emotion on pain, because there are similarities in the neurobiology of startle modulation and pain modulation. Recent work has expanded Lang's theory to the domain of pain perception. Using emotion-induction methodology similar to that used by Lang and others, independent laboratories have shown that negative emotion (induced by picture viewing) enhanced pain, and positive emotion inhibited pain. Further, Lang's theory can explain many of the
findings from human pain studies that have examined the influence of emotion. For example, the following ways of inducing positive emotions have been shown to reduce pain: (1) experimental induction of positive mood; (2) sexual excitation; and (3) relaxation. Conversely, the following relationships between negative emotions and increased pain have been shown: (1) state (situational) anxiety results in greater sensitivity to experimental pain; (2) higher anxiety before a medical procedure leads to increased post-procedural pain; (3) drugs that lower anxiety (eg, morphine, anxiolytics) decrease pain perception; and (4) trait-anxious persons demonstrate enhanced pain on experimental measures. Thus, motivational priming theory is consistent with most studies in humans on emotional modulation of pain, with the exception of some reports that negative affect inhibited pain.

The idea that negative affect could enhance or inhibit pain initially led to some confusion in the literature. However, drawing from the animal literature and a review of the extant literature on emotion and pain modulation in humans, Rhudy and Meagher have attempted to resolve this confusion. Experimental manipulations eliciting negative emotions were operationally defined and categorized. Rhudy and Meagher noted that emotion manipulations presenting an imminent threat in the immediate environment (leading to intense, highly arousing negative affect) resulted in pain inhibition. In contrast, manipulations presenting a potential threat not immediately present (leading to moderately arousing negative affect) resulted in pain enhancement. They proposed an extension to the motivational priming hypothesis to include manipulations that elicit active defense. Methods of emotion induction used to develop the motivational priming hypothesis involved procedures that limited the amount of arousal elicited. Viewing pictures or imagining emotional scenes cannot produce the same emotional intensity as being faced with the threat of a predator and/or potential death—stimuli that result in strong activation of the defensive system. After considering manipulations that produce active defense, the authors posited that a valence-by-arousal interaction explained the influence of emotion on pain. Specifically, negatively valenced emotions with low to moderate arousal (eg, anxiety) enhanced pain, whereas negatively valenced emotions with high arousal (eg, fear) inhibit pain. Alternatively, pain is always inhibited by positively valenced emotions, as long as a minimal threshold of arousal is attained (Figure 1).

This valence-by-arousal model was developed from studies examining the effect of transient emotions on pain modulation in healthy human participants. However, it is unclear whether the model will explain the effects of emotion on pathological pain states in which normal pain transmission or pain modulation has been altered. Similarly, the model may not predict pain outcomes when clinically significant emotion (anxiety or mood disorder) is present. These disorders may represent pathology of emotion neurocircuitry. But consistent with the model, evidence suggests there is a positive relationship between these disorders and pain.

In contrast, other clinically relevant emotions appear inconsistent with the model. For example, fear of pain and pain-related anger, emotions associated with increased arousal, are known to enhance pain. However, fear of pain and pain-related anger may represent different constructs than fear and anger elicited in the laboratory. Experimental manipulations to elicit fear and anger result in brief, intense activation of the defensive system that leads to very high arousal and a high probability of active defense (fight or flight). In clinical settings, fear and anger tend to be persistent, trait-like, negative states. Given the body’s affinity for homeostasis, the level of arousal observed in the laboratory is not normally sustainable. Therefore, fear and anger measured in clinical settings probably reflect moderately arousing negative emotions with a lower probability of active defense. Assuming that these clinically relevant emotions do not reflect intense activation of the defensive system, the model does predict their effect on pain. However, research is needed to test this hypothesis.
Biology of Emotional Modulation of Pain

Although a complete review is beyond the scope of this paper, it is important to provide a brief overview of the biological mechanisms by which emotion might influence pain. Central pain modulation involves a descending circuit that inhibits nociception at the level of the spinal cord. This circuit comprises the periaqueductal gray and its projections to the serotonergic neurons of the rostral ventromedial medulla and the noradrenergic neurons of the pontomesencephalic tegmentum and the descending path through the dorsolateral funiculus. These neurons synapse onto sensory neurons in the dorsal horn of the spinal cord, thereby inhibiting nociception. Interestingly, recent work has suggested that the amygdala can activate this descending circuit.

As previously noted, the amygdala plays a critical role in emotional processing; therefore, emotion may influence pain via amygdalar activation of the pain inhibition circuit. Supporting this, animal studies have shown that environmental stimuli (eg, predators, threat, cues that predict threat) that elicit fear-related behaviors can activate the amygdala and cause antinociception. Moreover, a recent human study using functional neuroimaging found that a valence-by-arousal interaction characterized amygdalar response to emotional stimuli. Stimuli that elicited positive emotion (regardless of arousal level) or negative emotion with high arousal caused amygdalar activation. However, stimuli that elicited negative emotion with low arousal did not cause significant activation. Also noted previously, negative emotion with high arousal and positive emotion lead to pain reduction, but negative emotion with low arousal leads to pain enhancement. Together, these data suggest that the amygdala may play a critical role in emotion-related pain inhibition.

Evidence suggests that the circuitry associated with the appetitive system can also inhibit pain. Animal studies propose that activation of the nucleus accumbens can cause antinociception with dopamine playing an important role. Although less is known about this mechanism of pain control, some evidence indicates that it may also be present in humans. Thus, this circuit may provide an additional mechanism for positive emotion-induced pain reduction.

What biological mechanisms are involved in pain enhancement? Research has implied that regions of the brain involved in descending pain inhibition may also participate in pain facilitation. Electrophysiological studies have

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**Figure 1.** A hypothetical depiction of the valence-by-arousal interaction characterizing the influence of emotion on pain.
identified cells (called on-cells) in the brainstem that show increased firing immediately before a pain-related response (eg, tail-flick response to radiant heat). The same cells also show inhibition following administration of morphine. These findings suggest that these brainstem cells are involved in facilitating nociceptive transmission in the spinal cord.

How might negative emotion (with low arousal) activate this facilitatory system? Animal studies have shown that exposure to mild shock (a stimulus that is likely to evoke negative emotion with low to moderate arousal in humans) can induce hyperalgesia. This shock-induced hyperalgesia depends on an intact forebrain, dorsolateral periaqueductal gray, and central nucleus of the amygdala, all structures that are implicated in emotion. Therefore, the amygdala may be critical for pain inhibition and facilitation. Currently, it is unclear whether these neural structures are part of the pain facilitatory circuit described by Fields and Basbaum or whether they represent a parallel system. However, it does appear that mechanisms exist by which emotion can enhance pain.

In sum, these findings support the assertion that emotion may modulate pain through descending controls emanating from the brain. Neurologic circuitry exists by which negative emotion-related activation of the amygdala can inhibit or facilitate nociceptive signals in the spinal cord before the signal reaches the brain. Furthermore, the nucleus accumbens may participate in a pain-control circuit, providing a means of positive emotion-induced pain inhibition. Supporting the idea that emotion may activate descending modulatory circuitry, recent data from our laboratory have shown that positive and negative emotions of moderate intensity have opposite effects on a spinal measure of nociception. Additionally, emotion may modify nociceptive signals once they reach the brain by activation of cortico-cortical circuits shared by emotion and pain. Figure 2 depicts the relationship between motivational systems and pain modulation.

**CAN EMOTION CONTRIBUTE TO GENDER DIFFERENCES IN PAIN?**

The experience of pain results from at least 4 factors that act in parallel: (1) the extent of noxious stimulation/tissue damage; (2) nociceptive transmission; (3) pain inhibitory processes; and (4) pain facilitatory processes (Figure 3). There-
fore, altering any variable can influence pain perception. A potential cause of gender differences in pain is sexually dimorphic pain modulation systems or factors that activate these systems. This section will highlight the potential influence of one factor—emotion. Gender differences in pain perception may occur due to increased sensitivity to negative stimuli in women and positive stimuli in men.

**Women Have Increased Sensitivity to Negative Stimuli/Events**

Women and men differ in their perception, experience, expression of, and reaction to emotional stimuli. In general, women tend to be more reactive to negative stimuli, particularly those involving threat. This is true even in girls as young as 7 to 10 years of age.

In a thorough analysis, Bradley et al. presented visual stimuli with varied motivational content to 45 men and 50 women and measured their reactions across multiple response systems (emotional judgments of valence and arousal, facial electromyography [EMG], skin conductance response, heart rate, startle reflex). Compared with men, women rated negatively valenced pictures as more arousing \((P = 0.007)\) and more unpleasant \((P < 0.001)\), showed greater corrugator EMG activity (frowning) \((P = 0.001)\), and greater bradycardia (heart rate deceleration) \((P < 0.05)\). Furthermore, women reported greater arousal during the negative stimuli than during the positive stimuli \((P < 0.05)\). In addition, women’s unpleasantness and arousal ratings of negative stimuli had a stronger correlation \((r = 0.77)\) than did men’s ratings of negative stimuli \((r = 0.55; z = 2.34; P < 0.05)\) or women’s ratings of positive stimuli \((r = -0.20; \text{this contrast not tested for significance})\). These findings suggest that pictures representing greater perceived threat led to greater unpleasantness and arousal in women—an effect that was smaller in men. Moreover, women’s startle reflex was facilitated by unpleasant stimuli to a greater extent than was men’s \((P = 0.007)\) and was enhanced by a wider array of negative picture content (contamination, mutilation, animal attack, human attack) and arousal levels, whereas men’s startle reflex was only enhanced by pictures representing the greatest threat (attack scenes). A study with 30 children (15 boys, 15 girls) also found that startle was enhanced by negative stimuli to a greater degree in young girls than in young boys \((P < 0.05)\). These findings suggest that compared with men, women may have a greater propensity for defensive activation.

Although social mechanisms probably contribute to women’s greater reaction to negative stimuli, the data previously discussed suggest that biological mechanisms also contribute. Specifically, sex differences were observed in young girls and in adults within systems less susceptible to voluntary control (heart rate, skin conductance response, reflex modulation). Moreover, functional imaging studies have shown sex differences in brain activation during experimentally induced negative emotion. In a study of 10 men and 10 women, sadness produced regional cerebral blood flow changes in women across several limbic and paralimbic areas (right medial frontal gyrus, left dorsolateral prefrontal cortex, bilateral cingulate gyrus, caudate, putamen, thalamus, fornix, left insula, and left midline cerebellum), suggesting that these areas were activated differently in women than in men (all comparisons, \(P < 0.05)\). Therefore, negative stimuli may activate different neurocircuitry in men and women, result-
ing in divergent emotional experiences and, perhaps, in differences in pain modulation.

How might women’s relatively greater sensitivity to negative stimuli influence pain perception and gender differences in pain sensitivity? **Figure 1** suggests that the same negative stimulus would lead to greater defensive activation (result in greater arousal) in women than in men. This would mean that the same stimulus could result in greater pain facilitation in women than in men. However, our model also makes another counterintuitive prediction. The same negative stimulus could lead to pain facilitation in men, but pain inhibition in women. Because women’s defensive system appears to be more attuned to threatening stimuli, a threatening stimulus could lead to high arousal in women but to low to moderate arousal in men. The result would be hyperalgesia in men but hypoalgesia in women.

To determine whether the literature supports these ideas, English-language searches were conducted in MEDLINE and PsycINFO electronic databases, from 1887 to May 2005, using combinations of the key words pain, pain modulation, gender, mood, emotion, anxiety, fear, and anger. Studies noting a sex/gender difference in pain that examined the role of emotion were retained. Other studies meeting these criteria were obtained from the reference lists of relevant articles.

In general, studies supported the idea that women’s greater tendency to experience negative emotion leads to increased activation of the pain facilitation system and enhanced pain. For example, Logan et al\(^{127}\) studied the effects of stress (as evidenced by increases in heart rate, diastolic and systolic blood pressure, and scores on the relaxation inventory) induced by a Stroop test (examinees must name the color of ink in which a color word is printed, for example the word red printed in blue ink) on capsaicin-induced pain. They found that compared with subjects in a relaxation group (10 men, 9 women), of the individuals undergoing stress (9 men, 7 women), only women reported increased pain after injection of capsaicin (all comparisons, \(P < 0.05\)). In a study of 28 men and 20 women by Logan and Gedney,\(^{128}\) pain was tested by cold pressor on 2 separate occasions 9 months apart. No gender differences were found with the first test. However, at the second test, women had greater negative expectations about the pain task than did men (\(P = 0.02\)). Moreover, women also had an increase in reported pain at the second test relative to the first test (\(P < 0.01\)), but men did not.

Dougher et al\(^{129}\) examined the influence of procedure-specific anxiety on pressure pain in 80 participants (40 men, 40 women). This resulted in greater anxiety and lowered pain threshold (\(P < 0.05\)) and tolerance (enhanced pain) (\(P < 0.05\)) in women but not in men. Similarly, in a study of 50 participants (34 men, 16 women), Robin et al\(^{130}\) found that women reported higher anxiety (although not significantly different from men) about their pain-induction method (electrical stimulation) and showed lower pain threshold (\(P < 0.05\)) and tolerance (\(P < 0.02\)). Interestingly, the anxiety scores showed a significant negative association to pain tolerance (\(r = -0.30; P < 0.02\)), suggesting that women’s reduced tolerance may have resulted from anxiety; however, this hypothesis was not directly tested. In 67 participants (30 men, 37 women), Robinson et al\(^{131}\) observed that temporal summation (series of 5 heat stimuli applied to the right hand) led to greater pain in women than in men (\(P < 0.05\)). Furthermore, when anxiety was entered as a variable in a regression model predicting change in pain (resulting from temporal summation), gender was no longer a significant predictor, suggesting that anxiety mediated the gender difference. In 2 samples of 40 participants (20 men and 20 women per sample), Buchanan and Midgley\(^{132}\) found that procedure-induced anxiety led to decreased pressure pain thresholds in women only (\(P < 0.05\)). The authors did not measure the emotional reactions of the participants to determine whether gender differences in the experience of anxiety mediated their effect. As noted earlier, a meta-analysis found that gender differences in experimental pain are more pronounced when the noxious stimulus evokes a strong emotional reaction.\(^{3}\) Ostensibly, this
arises because the noxious stimulus elicits a stronger negative emotion in women, a finding that is consistent with the notion that women’s defensive system is more attuned to negative stimuli.

Women’s increased sensitivity to negative stimuli, however, may not always result in enhanced pain. As previously noted, highly arousing negative emotion leads to pain reduction.\(^9^7\) Therefore, it is also possible that women may be more likely to experience highly arousing negative emotion, and in these instances, pain reduction. Unfortunately, it is difficult to elicit intense, highly arousing negative emotions experimentally (for obvious ethical reasons). Despite this, a few studies support this proposition. Westcott and Horan\(^6^8\) experimentally induced anger in 80 participants (40 men, 40 women) and found an increase in pain tolerance (decreased pain) in women but not in men \((P < 0.01)\). Rhudy and Meagher\(^8^8\) induced fear in 20 men and 20 women by presenting loud bursts of surprising white noise. They found that women reported fear but men did not \((P < 0.05)\). Moreover, only women exhibited increased heat pain thresholds (pain reduction) \((P = 0.01)\). Conversely, men reported moderate negative affect and arousal and became hyperalgesic relative to control \((P < 0.05)\). Also, in a study of 78 participants (36 men, 42 women), Jones et al\(^1^3^3\) found an interaction of gender and anxiety manipulation for pain threshold \((P = 0.08)\), suggesting that women’s pain threshold was increased by anxiety induction, but men’s threshold was decreased. Thus, preliminary evidence suggests that greater sensitivity to negative stimuli may lead to hypoalgesia in women.

Recent evidence appears to contradict our model for understanding how emotion may contribute to gender differences in pain. Jones, Zachariae, and colleagues have argued that anxiety leads to enhanced pain, but only in men. For example, Jones and Zachariae\(^1^3^4\) categorized 40 men and 40 women as either high or low in state anxiety based on sex-specific median splits. They found that men with high state anxiety had lower pain tolerance than did men with lower state anxiety \((P < 0.01)\), an effect that was not present in women. Additionally, these authors found a negative correlation between anxiety and tolerance \((\rho = -0.309; P < 0.01)\), the magnitude of which was greater for men \((\rho = -0.448; P < 0.01)\) than for women \((\rho = -0.100; P > 0.05)\). Despite this, there are reasons to believe that the findings are not inconsistent with our model. First, creating groups based on a median split is potentially problematic given our argument. As noted, negative emotions may enhance or inhibit pain. Therefore, forming groups based on an arbitrary cut point may not adequately define distinct groups. Specifically, the high-anxiety group may contain some persons who became hyperalgesic and others who were hypoalgesic. The result would appear to be no effect of pain modulation (zero net effect). This arbitrary grouping could potentially be more problematic for women, who appear more sensitive to defensive activation. The second problem with their interpretation of the data stems from their use of the linear correlation. The authors’ claim that anxiety was more correlated with pain in men than in women is unfounded. When compared statistically, although the magnitude was lower for women, the correlations were not significantly different between men and women. More importantly, the relationship between negative emotions and pain modulation is not a linear one. Thus, analytic procedures that assume a linear relationship (eg, Pearson’s \(r\), Spearman’s \(\rho\), linear regression) would not be appropriate. If women are more sensitive to defensive activation, then moderately aroused women could be expected to become hyperalgesic, whereas those who were highly aroused could be expected to become hypoalgesic. This would attenuate the correlation coefficient that assumes a linear relationship. Therefore, it is unclear whether anxiety truly led to enhanced pain in men only.

Jones et al\(^1^3^3\) induced anxiety using a multi-component intervention. They told participants the pain induction procedure (cold pressor) was very painful and dangerous, locked their arm into the cold-pressor device, and told them there would be a stressful interview following the procedure. Combined, these manip-
ulations represented a clear, present, environmental threat potentially resulting in active defense and fear. Interestingly, these authors found that women’s pain threshold was higher than men’s ($P = 0.08$), suggesting that women experienced more intense, highly arousing negative affect than did men. Supporting this, women’s heart rate in the anxiety condition was positively correlated with their length of time in the cold water ($\rho = 0.531; P < 0.05$) (pain reduction). Of importance, tachycardia is associated with sympathetic activation (arousal) and the propensity for active defense. In light of this interpretation, these data are not inconsistent with the model we present—women had a stronger reaction to negative stimuli than men had, causing them to experience pain reduction. In contrast, defensive activation was moderate in men, causing them to experience pain enhancement.

In another study, Jones et al\textsuperscript{135} investigated the relationship between trait anxiety and heat and cold pain in 144 participants (69 men, 75 women). Although men’s heat pain tolerance was greater than women’s, this relationship was associated with trait anxiety. However, pain during a cold-pressor task was related to anxiety levels. Men, but not women, with high trait anxiety reported increased pain intensity and unpleasantness and decreased pain tolerance compared with same-sex participants with low trait anxiety (all, $P < 0.05$). But correlational analyses did not find a gender difference between the relationship of trait anxiety and any pain outcome. Similar to previous research by Jones et al, it is difficult to draw conclusions from these data and, unfortunately, measures of state anxiety were not presented in this study. Trait anxiety (a personality disposition) may not reflect changes in the underlying motivational systems that we argue are responsible for emotional modulation of pain. Moreover, the correlational analyses may be invalid because of their assumption of a linear relationship between negative affect and pain. To determine whether studies support or refute the proposed model, research is needed that measures valence and arousal via convergent operations.

It should be noted that some studies have failed to find a gender difference in pain when examining the influence of negative affect.\textsuperscript{72,92} For example, Rhudy and Meagher\textsuperscript{72} found that anxiety and fear modulated pain threshold in 60 participants (30 men, 30 women), but gender did not have an effect. Willer and Albe-Fessard\textsuperscript{92} found that stress increased the nociceptive reflex threshold, but gender did not moderate this relationship. However, this latter study was likely too statistically underpowered to detect a gender effect (4 men, 2 women).

Nonetheless, evidence suggests that women may have greater reactions to negative stimuli, thus potentially contributing to gender differences in pain via differential activation of pain modulation systems. Interestingly, data suggest that women may be more likely to experience highly arousing negative emotion and pain reduction. This appears counterintuitive to the general notion that women are more sensitive to pain than are men. However, the relatively greater base rate of negative emotion with low to moderate arousal (eg, anxiety) is likely to contribute more to gender differences in pain sensitivity than do highly arousing negative emotions.

**Men Have Increased Sensitivity to Positive Stimuli/Events**

Some evidence suggests that, compared with women, men may be more responsive to positive events, particularly sexual/erotic stimuli. In a meta-analysis of 46 studies, Murnen and Stockton\textsuperscript{136} found that men tend to respond more than women to sexual stimuli ($d = 0.31; z = 13.72; P < 0.001$). In a thorough analysis of several reactions to different categories of positive visual stimuli (eg, nature, families, food, sports, adventure, erotic couples), Bradley et al\textsuperscript{120} found that men generally rated the stimuli as more pleasant and arousing than did women (all comparisons, $P < 0.08$). For the most appetitive stimuli (erotic), men’s pleasure and arousal ratings were clearly much higher than women’s (all comparisons, $P < 0.01$). Moreover, positive stimuli led to greater skin conductance response in men ($P = 0.07$), indicating greater sympathetic arousal—an effect that was even greater for
erotic (P < 0.02). Subjectively, men’s pleasantness and arousal ratings of positive stimuli showed a stronger correlation (r = 0.68) than men’s ratings of negative stimuli (r = −0.55, this contrast not tested for significance) or women’s ratings of positive stimuli (r = 0.20; z = 3.66; P < 0.01). This suggests that pictures representing appetitive stimuli led to greater pleasure and arousal for men than for women. Together, these data may indicate that men have a greater propensity for appetitive activation. However, men may be less likely to display their reactions through facial expressions because they were less likely than were women to smile in reaction to the positive stimuli, as evidenced by facial EMG (all comparisons, P < 0.05).

If men are more reactive to positive stimuli, this could contribute to gender differences in pain. Specifically, men may be more likely to experience positive emotion–induced pain reduction than may women. To determine whether empirical evidence supports this idea, we conducted an English-language search of MEDLINE and PsycINFO from 1887 through May 2005 using combinations of the following key words: gender, male, men, pain, sexual arousal, positive emotion, positive mood, positive affect, humor, happiness, and pleasure. Other studies meeting these criteria were obtained from the reference lists of relevant articles. Consistent with our hypothesis, Weaver and Zillmann56 examined the influence of humor on discomfort thresholds in 36 men and 36 women and found that only men exhibited significantly higher thresholds or reduced pain (all comparisons, P < 0.05). Unfortunately, no manipulation checks were collected in this study to determine if differences in emotional responses were present.

Meagher et al51 examined the influence of positive emotion on cold-pressor pain in 70 participants (36 men, 34 women) and found that sexually arousing slides increased pain intensity threshold in men (P < 0.005) but not in women. Manipulation checks indicated that men rated the sexual slides to be more pleasant than did women (P < 0.05), whereas women were more likely to react with mixed emotions to the slides (ie, with both sexual arousal and disgust) (P < 0.05). Thus, it appears that women reacted with a dual motivational state, potentially canceling out the effect on pain. Perhaps this occurred as a result of women’s greater propensity toward defensive activation. Additionally, Fillingim et al137 used correlational analyses to predict baseline pain perception in 39 men and 49 women. These results suggested that positive affect predicted lower pain in several pain measures (heat pain threshold, heat pain tolerance, heat pain rating, ischemic pain tolerance) in men (all comparisons, P < 0.05) but not in women. Moreover, regression analysis found that positive affect accounted for 17.3% of the variance in pain outcomes in men. Interestingly, women’s pain responses were best predicted by negative affect (all comparisons, P < 0.05).

Other studies have examined the effects of genital stimulation and orgasm in women, finding profound reductions in pain (for a review, see Komisaruk and Whipple63). Pleasurable vaginal stimulation and orgasm have been shown to increase pain tolerance up to 55% and 75%, respectively (all comparisons, P < 0.05). These effects did not appear to be due to distraction and were larger (P < 0.05) than pain reduction caused by nonpleasurable vaginal stimulation. Unfortunately, studies have not been conducted to examine whether gender differences in this effect are present.

Limited data currently support the notion that men have a greater sensitivity to positive stimuli that may contribute to greater pain reduction. Indeed, sometimes positive emotions have been found to reduce pain only in women. For example, Marchand and Arsenault138 induced positive emotions in 40 participants (20 men, 20 women) by olfactory stimuli and found that pain intensity and unpleasantness were reduced in women (P = 0.01) but not in men. Other studies have failed to find a gender difference in pain when inducing positive emotions.55,58,61,66 However, most research examining the influence of emotion on pain has tended to focus on negative emotions. Additional work is needed to determine the relationship between gender, positive emotions, and pain.
DISCUSSION
The role of gender in the experience of pain is not simply explained by a single mechanism. Several factors appear to mediate this relationship, including experiential, biological, and psychological mechanisms. In the present study, we focused on one understudied mechanism—the experience and processing of emotion. To do so, a comprehensive model of the impact of emotion on pain and pain modulation was first discussed, and potential gender differences in the emotional modulation of pain were reviewed.

We propose that emotion influences pain through a valence-by-arousal interaction. Specifically, negatively valenced emotions (defensive activation) can enhance or inhibit pain, depending on the level of arousal that accompanies the emotion (ie, how intensely the negative emotion is experienced). Pain is enhanced with negative emotions that range from low to moderate arousal, but it is inhibited at higher arousal levels (Figure 1). Alternatively, positive emotions always inhibit pain, as long as minimal arousal is obtained. Moreover, evidence suggests that highly arousing positive emotions (ie, orgasmic bliss) profoundly attenuate pain.

Working from this model, we propose that gender differences in the experience of pain may arise from differences in the experience and processing of emotion that, in turn, differentially alter the processing of pain. Specifically, the defensive system may be more attuned to threatening stimuli in women. As a result, women are more reactive to negatively valenced stimuli than are men. On the other hand, the appetitive system may be more attuned to pleasurable stimuli in men than in women, the result being that men are more reactive to positively valenced stimuli (at least for visual stimuli depicting sexual targets). This difference may cause women to experience more negative emotion across a wider array of stimuli/situations than do men, leading to enhanced pain. In contrast, men may have a greater tendency to experience positive emotion, leading to reduced pain.

The model predicts that a given negative stimulus will result in greater defensive activation and arousal for women, placing them to the right of men on the curve depicting defensive activation/negative emotion (Figure 1). Therefore, some negative stimuli can cause women to be more hyperalgesic. However, for highly threatening stimuli, men may become hyperalgesic at the same time that women become hypoalgesic. This highlights the importance of including self-report and physiological measures of valence and arousal in studies examining the influence of emotion, because variations in these components of emotion can lead to diverse pain outcomes. Furthermore, using statistics that assume a linear relationship between negative emotions and pain is inappropriate. The model predicts a nonmonotonic relationship between negative emotions and pain, consistent with animal research.139

Some positive stimuli are expected to elicit greater arousal in men. This would place them to the right of women on the curve depicting positively valenced emotions. Therefore, for some positive stimuli, men may become hypoalgesic, whereas no pain modulation is observed in women. With stimuli that provoke greater activation, however, this model predicts that men will show greater hypoalgesia relative to women.

Evidence suggests that emotion modulates pain through descending circuitry that alters the afferent nociceptive signal at the level of the spinal cord. But what physiological mechanisms are responsible for gender differences in motivational circuit sensitivity? One probable mechanism involves the effect of hormones. Research has shown that differences in estrogen levels influence positive emotions, with higher estrogen levels leading to more positive ratings of picture stimuli.140 Additionally, when postmenopausal women receive estrogen replacement therapies, they report more positive moods than do women who are not taking estrogen.141 Therefore, the influence of hormones on emotional state could mediate the impact of emotion on pain.

CONCLUSIONS
Until recently, most studies that have examined the role of emotion in pain modulation have
generally failed to consider sex/gender. This review suggests there are gender differences in the experience and processing of emotion that, in turn, differentially alter the processing of pain. Of the few studies that did include gender as an independent variable, most did not use adequate manipulation checks to test the proposed model and the characteristics of emotion that may contribute to gender differences in pain. It is recommended that future studies include self-report and physiological measures of emotional valence and arousal. Furthermore, it is important that studies test a comprehensive model of emotion that systematically manipulates valence and arousal level. These suggestions will allow researchers to examine the independent effects of each variable. It is also recommended that within-subject designs be used to induce emotion. This allows for the examination of intra- and interindividual differences in baseline, emotional reactivity, and self-report tendencies.

In sum, it is likely that multiple mechanisms are responsible for gender differences in pain sensitivity. The present review suggests that gender differences in emotion and emotion physiology may be an area worthy of further study.

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Address correspondence to: Jamie L. Rhudy, PhD, University of Tulsa, 600 South College Avenue, Tulsa, OK 74104. E-mail: jamie-rhudy@utulsa.edu