The role of emotion in pain modulation
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Although most agree that emotion can alter pain, little well-controlled research has been conducted to examine this issue. The present review provides psychological and physiological rationales for considering the influence of emotion on pain, followed by an overview of recent work in this area. We conclude that the pain-modulating effects of emotion are best characterized by an interaction between valence and arousal. Positive emotions lead to pain reduction as long as a minimal threshold of arousal is attained. However, negative emotions only lead to pain inhibition when they are highly arousing. Negative emotions coupled with low-to-moderate arousal facilitate pain. Curr Opin Psychiatry 14:241–245, © 2001 Lippincott Williams & Wilkins.

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Abbreviations
IAPS International Affective Picture System
PAG periaqueductal gray

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Introduction
Pain was once considered a sensory experience that mirrored the intensity of noxious stimulation. However, this conceptualization has proved inadequate, because the same stimulus can be experienced as painful at one time and innocuous at another. To address the variability in pain perception, Melzack and Wall [1] proposed a hypothetical gate within the spinal cord dorsal horn (i.e., gate-control theory) that could regulate the flow of nociceptive information from periphery to brain. Their theory included a mechanism by which psychological processes (central controls) emanating from higher brain centers could functionally 'close the gate' through descending pathways, thus modulating pain.

Research during the past 40 years has added much to our understanding of the physiology of ascending (transmission) and descending (modulation) pain pathways. Despite these advances, little is known about how psychological processes can activate pain modulatory mechanisms. The present review examines the role of one psychological process that can modulate pain, namely emotion. In doing so, we highlight three themes. First, pain and emotion are part of a larger motivational system that promotes survival. Second, the neurocircuits that are associated with emotion and pain overlap significantly, suggesting possible reciprocal influences. Third, emotional modulation of pain can be described by an interaction of the two dimensions of emotion: valence and arousal.

Pain, emotion, and motivation
Survival requires the recognition/discrimination of dangerous and health-enhancing stimuli. Over time, highly adaptive, but complex, motivational systems have evolved that serve this purpose. The appetitive/approach system guides us toward survival-enhancing stimuli (e.g., food, water, mates) and the aversive/defensive system guides us away from that which is harmful (e.g., predators) [2]. Activation of these motivational systems is related to the psychological experience of emotion.

In attempts to describe and define emotion, researchers have identified two orthogonal dimensions that capture most of the variance in self-reported emotion: valence (pleasantness-unpleasantness) and arousal (calm-excited) [3]. Emotions with positive valence are believed to result from activation of the appetitive system, whereas negatively valenced emotions result from activation of the defensive system. Arousal refers to the degree of activation of these systems, with self-
reported arousal correlating with physiologic indices such as galvanic skin response, heart rate, blood pressure, and electrical brain activity (as measured by electroencephalography) [4*].

Although pain was once considered a special case of sensation, recent accounts conceptualize pain as a multidimensional experience that is comprised of emotional, sensory, and cognitive components. Therefore, emotion is inherently part of pain. Noxious stimulation activates the defensive system, producing the psychological experience we call pain; this motivates us to engage in strategies to avoid such stimuli. In doing so, pain provides us with feedback regarding stimulation that is (actually or potentially) damaging.

The neurocircuitry of emotion and pain

Theoretically, emotions are linked to two motivational systems: appetitive and aversive. Recent work has suggested that these systems are grounded in biology by showing that activation of distinct neural structures results in subjective reports of affect, affect-related behavior, and autonomic nervous system correlates, whereas damage to these structures results in affective deficits [5*,6**]. The appetitive/defensive system is associated with a network of regions in the cortex (e.g., sensory and right prefrontal cortices), subcortex (e.g., amygdala, bed nucleus of the stria terminalis, sensory thalamus, hippocampus, hypothalamus), and midbrain [e.g. nucleus reticularis pontis caudalis, periaqueductal gray (PAG)] [7,8]. The appetitive/approach system is also a network, primarily involving dopaminergic neurons [9-11] and endogenous opioids [12,13]. The ventral tegmental area and the nucleus accumbens are essential to this system, but other areas that are potentially involved are the amygdala, lateral septum, left prefrontal cortex, and caudate/putamen.

In the ascending pain pathway, peripheral receptors that respond maximally to noxious stimulation (nociceptors) synapse onto neurons in the spinal cord where nociceptive (pain-related) information is transmitted to brain regions via several tracts. These tracts terminate in different brain structures and appear to process different aspects of the pain message [14**]. The spinohypothalamic tract, which carries signals from the spinal cord through the lateral nuclei of the thalamus to the somatosensory cortices, encodes the sensory quality of pain [15]. Other projections, to the anterior cingulate cortex and amygdala, are associated with the emotional experience of pain. Pathways to the hypothalamus and reticular formation are responsible for autonomic arousal. Therefore, ascending pain pathways can directly activate areas related to emotion. Given this anatomical relationship, emotion could influence pain by altering the processing of nociceptive signals within the brain. Supporting this, recent work indicates that both chemical and electrical activation of the anterior cingulate cortex enhances nociception in rats [16*].

Emotion could also influence pain perception through descending pain modulatory pathways. The descending system described by Fields and Basbaum [17**,18**] emphasizes the role of the PAG, its projections to the serotoninergic neurons of the rostroventral medulla and the noradrenergic neurons of the dorsolateral pons/tegmentum, and their subsequent inhibitory effects on neurons in the dorsal horn of the spinal cord. However, recent work [19*,20] suggests that the amygdala may be required to activate these descending controls. As noted earlier, the amygdala is critical in emotional processing, and therefore emotion may directly inhibit pain through this mechanism. Indeed, animal studies [19*,21,22] have demonstrated that threatening stimuli can activate fear circuits in the amygdala, causing pain reduction.

In addition to inhibitory controls, recent research [17**,18**] suggests that descending pain facilitatory pathways are also present. Fields and coworkers [17**,18**] have identified cells (on-cells) in the brainstem that show increased firing immediately before a pain-related response (e.g., tail-flick response to radiant heat). Furthermore, these cells are inhibited after administration of morphine. This research suggests that on-cells may be responsible for facilitating nociceptive transmission in the spinal cord. Interestingly, our laboratory [23*,24,25*,26] has shown that emotion-inducing stimuli can either facilitate or inhibit pain in animals. For example, exposure to mild shock enhances subsequent pain sensitivity, whereas severe shock attenuates pain. Moreover, systems that sensitize pain processing, and those that inhibit it, may be concurrently activated. Indeed, we found that lesions of the dorsolateral funiculus of the spinal cord, which eliminates descending inhibition from the brain, unveils an underlying sensitization [27]. It is not known whether this facilitatory pathway is the same as that described by Fields and coworkers; however, the path activated by mild shock does appear to depend on an intact forebrain [28*], dorsolateral PAG [29*], and central nucleus of the amygdala [19*] — structures that are implicated in emotion.

Taken together, these data suggest that emotion modulates pain through several physiologic mechanisms. Pathways exist by which emotion-related activation of the amygdala can inhibit or facilitate nociceptive signals at the level of the spinal cord before the brain can interpret the signal as pain. In addition, emotion may influence nociceptive signals at the level of the brain through activation of neural structures shared by the emotion and pain circuits.
Emotional modulation of pain

Clearly, psychological and physiological evidence suggests that emotion may influence pain. However, these data do not indicate when emotion may cause pain inhibition versus facilitation. To resolve this issue, it may be useful to consider a recent theory of motivational priming [30,31]. This theory suggests that prior activation of the appetitive or aversive motivational systems will modulate defensive behaviors. In support of this, Greenwald et al. [32] showed that priming the aversive system, by viewing negatively valenced pictures, anticipation of shock, or exposure to shock, augments the startle response (a defensive behavior). Conversely, priming the appetitive system by viewing positively valenced pictures results in startle inhibition. Interestingly, the same neural circuit that mediates emotional modulation of startle has been implicated in pain modulation, namely the amygdala and PAG [33,34]. Given this common neural substrate, we predicted that positive emotions should inhibit pain, whereas negative emotions should enhance it.

To test this prediction, we used the same visual stimuli used to manipulate emotion in startle modulation studies: the International Affective Picture System (IAPS), reported by Lang et al. [35]. In two studies, participants viewed a set of slides that evoked a specific emotion [36**]. Following slide presentation, participants immersed their hand in 2°C water (cold pressor test) while rating the unpleasantness and intensity of the pain on two mechanical visual analog scales. Participants were instructed to remove their hand from the water as soon as it became intolerable. This procedure allowed us to assess separately pain threshold (defined as the first movement of each mechanical visual analog scales) and pain tolerance.

In the first study, negative effect was studied by having participants view slides that evoked fear (e.g. attack scenes, snakes), disgust (e.g. mutilated bodies, injuries), or neutral (e.g. dustpan, broom) emotions. Using normative ratings, each set was chosen to evoke varying levels of self-reported valence (negative: disgust > fear > neutral) and arousal (disgust > fear > neutral). We found that the fear and disgust slides reduced pain unpleasantness and intensity thresholds as compared with neutral, but only fear slides reduced pain tolerance [36**]. In the second study, positive effect was studied by having participants view slides that evoked erotic (e.g. nudes, sex scenes), nurturant (e.g. babies, kittens), or neutral emotions. Again, sets varied in valence (positive: erotic > nurturant > neutral) and arousal (erotic > nurturant > neutral). We found that viewing erotic slides increased pain intensity and unpleasantness thresholds, but only in men, whereas tolerance was unchanged [36**].

These data, along with other work [37-40], provide preliminary support for the motivational priming hypothesis, because negative emotions augmented pain and positive emotions inhibited it. Additionally, arousal contributed because erotic slides inhibited pain whereas nurturant slides did not. Furthermore, the fear slides elicited greater autonomic arousal than did disgust, as indicated by skin conductance, possibly accounting for the divergent effects on pain tolerance. At first glance, the lack of an effect due to erotic slides in women appears to run counter to the motivational priming theory. However, manipulation checks revealed that women rated these pictures as sexually arousing and disgusting, therefore activating both appetitive and aversive systems, and canceling out any priming effects.

In a similar study, de Wied and Verbaten [41**] examined the effects of positive and negative emotion using the IAPS slides and cold pressor test. Participants were instructed to withdraw their hand 'when it began to hurt'. Those investigators also found support for the motivational priming hypothesis, with positively valenced slides leading to longer thresholds than the negatively valenced slides. Unfortunately, de Wied and Verbaten did not vary the levels of arousal in order to determine its relative contribution. However, they noted that slides with lower arousal did not lead to statistically significant pain modulation in a pilot study.

The use of visual stimuli to induce emotion, such as the IAPS, is convenient and reliable. Indeed, the development of these stimuli represents a huge step forward in emotion research. Although viewing slides produces differential levels of physiologic arousal that vary as a function of rated valence and arousal, they are not able to elicit intense, highly arousing emotional states [32]. To overcome this limitation, we used a stimulus that is commonly employed in animal paradigms to induce fear and anxiety [42**]: shock. In that study, pain threshold was measured using finger withdrawal to radiant heat before and after participants were exposed to one of three emotion conditions: in the fear group (negative valence, high arousal), participants were exposed to three, moderately painful shocks; in the anxiety group (negative valence, moderate arousal), participants were threatened with shock, but never received it; and in a neutral group (neutral valence, low arousal), participants were told that the shock would not be administered. Consistent with a motivational priming approach, the anxiety manipulation led to decreased pain thresholds (enhanced pain). Conversely, fear led to an increase in pain thresholds, suggesting that pain was inhibited. Although this finding appears to conflict with the pain enhancement observed after exposure to fear slides, it is consistent with studies that suggested that the dimensions of valence and arousal may interact to produce
different outcomes, depending on their product (e.g. low products yield hyperalgesia and high products yield analgesia) [23,24,25]. Indeed, prior human studies that involve intense fear (e.g. shock, parachute jump, trauma) have reported pain inhibition [43-46]. However, because we employed a noxious emotion-inducing stimulus, it is possible that descending pain modulatory pathways in the brainstem were directly activated by the ascending nociceptive signal produced by shock [47]. To address this issue, we conducted a follow-up study using startling nonnoxious bursts of white noise to induce fear [48]. The results confirmed our previous findings. Fear induced by surprising noises led to increased pain thresholds.

In subsequent studies we examined whether the modulatory effects of emotion are observed when pain is measured in other ways. This was done because animal studies [23,24,49,50] suggest that behavioral measures of pain vary in their sensitivity to emotion modulation, depending on the level of the neural axis that mediates the response. In the studies previously described [42,48], we measured finger withdrawal to radiant heat – a human analogue of the rodent tail-flick test. The tail-flick, and ostensibly the finger-flick, involve a spinally mediated nociceptive reflex, rather than a brain-mediated, evaluative response. To examine the effects of emotion on evaluative responses, we conducted two studies. In the first study [51], our radiant heat device was altered so that the heat took longer to reach painful levels. Thus, the participants had time to evaluate the stimulus, rather than respond in a reflexive manner. In another study [52], we used self-reported pain ratings in response to a constant intensity heat stimulus. Both studies found that fear led to pain reduction, suggesting that highly arousing negative effect inhibits pain across different measures of pain sensitivity.

Conclusion
The data presented here suggest that valence and arousal may interact, with positively valenced emotions leading to pain inhibition as long as a certain threshold of arousal is reached, because emotional stimuli that fail to arouse are also motivationally unimportant. Alternatively, emotions with negative valence and low arousal result in pain facilitation, whereas highly arousing negative emotions cause pain inhibition. From an evolutionary perspective, this makes adaptive sense. Stimuli that elicit negative emotions with high arousal are likely to pose an immediate threat, and therefore the probability of survival would be increased if pain perception was dampened during the times when pain-related behavior might interfere with fight or flight. Alternatively, during times of low threat, the chance of survival is increased if pain is enhanced so that behavioral responses can occur to minimize tissue damage.

The present review suggests that research can and should examine the relationship between emotional processes and pain at psychological and physiological levels of analysis. In order to determine the nature of this relationship, future work should employ designs that manipulate valence and arousal, using stimuli that evoke a wide range of emotional responses, and test pain using a variety of outcome measures.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
** of special interest
** of outstanding interest

7. This is another excellent review of the circuitry associated with emotion. This paper emphasizes the role of the amygdala in emotion, especially fear.
16. This paper reviews the neural pathways that are related to noiception and pain. The authors provide a good overview of the circuitry that processes sensory, emotional, and cognitive aspects of pain.
19. This recent study demonstrates that activation of the anterior cingulate cortex can cause changes in pain perception in the rat.
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