Affective Modulation of Pain in Substance-Dependent Veterans

Jamie L. Rhudy, PhD,† Patricia M. Dubbert, PhD,‡§ Jefferson D. Parker, PhD,†§ Randy S. Burke, PhD,†‡§ and Amy E. Williams, BS*

*The University of Tulsa, Tulsa, Oklahoma; †Veteran’s Affairs Medical Center (VAMC) VISN 16 Mental Illness Research, Education, and Clinical Centers (MIRECC), Jackson, Mississippi; ‡Veterans Affairs Medical Center, Jackson, Mississippi; §University of Mississippi School of Medicine, Jackson, Mississippi, USA

ABSTRACT

Objective. Prior work suggests that positive affect inhibits pain while negative affect facilitates it. The current study sought to determine whether: 1) affective modulation of pain extends to a patient population; 2) cocaine and alcohol dependence influences the pattern of modulation; and 3) affective modulation of pain is mediated by changes in arm temperature.

Design. Thirty-seven participants with and without substance dependence (14 alcohol, 13 cocaine, 10 none) attended three experimental sessions intended to induce emotions (negative, neutral, positive) by picture-viewing. Following emotion-induction, participants were asked to submerge their arm in 33°C water and keep it there until they reached tolerance. During submersion, pain ratings were made on a mechanical visual analog scale (M-VAS).

Outcome Measures. Latency from submersion to first movement of the M-VAS (pain threshold) and latency to arm removal (pain tolerance) were measured. Arm temperature and manipulation checks for emotion-induction (corrugator electromyogram, heart rate, skin conductance, self-report) were also recorded.

Results. Manipulation checks confirmed that targeted affective states were achieved. Pain threshold and tolerance were higher after viewing pleasant pictures than after unpleasant ones. Although arm temperature did vary based on the affect induced, analyses suggested that temperature did not influence pain outcomes.

Conclusions. Affect modulates pain perception in patients and does not appear to be mediated by changes in arm temperature. Additionally, pain modulation was not significantly influenced by cocaine or alcohol dependence. These data are encouraging, because they suggest that nonpharmacological methods of pain modulation may be effective in substance-dependent individuals.

Key Words. Emotion; Pain Threshold; Pain Tolerance; Pictures; Psychophysiology; Substance Use

Research suggests that emotion influences pain perception [1–7]. Positive valenced affect (e.g., happiness, euphoria) has been found to inhibit pain, whereas negative valenced affect (e.g., anxiety) generally facilitates it. Some evidence has suggested that negative affect can also inhibit pain, but this appears to be limited to intense negative emotions that are very arousing (e.g., extreme fear) [8,9]. In contrast, no known published research has found that positive affect can induce pain facilitation (for reviews, [10,11]). Therefore, under most conditions negative affect would be expected to increase pain and positive affect dampen it. The exact mechanisms of affective modulation of pain are not completely understood; however, it has been hypothesized that the neural circuitry associated with emotions might directly activate endogenous central nervous system (CNS) pain modulation circuitry that alters nociception in the spinal cord [8,10–12]. Indeed, a recent study from our laboratory sug-
gests that spinal nociception is modulated by emotion [13].

The most widely studied CNS mechanism of pain modulation includes the periaqueductal gray (PAG) and its connections to the rostroventral medulla (RVM) and the dorsolateral pons/tegmentum (DLPT) [14,15]. These regions participate in a descending circuit that modulates the nociceptive signal within the dorsal horn of the spinal cord. Opioid receptors are distributed throughout this circuit and endogenous and exogenous opiates activate it causing pain inhibition [14]. However, this circuit is not just responsible for inhibition. Evidence suggests that this same circuit is also involved with pain facilitation [14,15]. Therefore, pain inhibition and facilitation can result from a common neural mechanism. Although much of the research on supraspinal initiation of descending pain modulation has focused on the participation of midbrain and brainstem regions (RVM, PAG), multiple areas of the forebrain are known to play a role, such as the amygdala, hypothalamus, hippocampus, anterior cingulate cortex (ACC), and nucleus accumbens [12,14,16–20]. Indeed, the amygdala may play a critical role in this descending circuitry [12,18,19,21,22]. Interestingly, many of these forebrain regions are involved in the processing and experience of emotion, particularly the amygdala.

Emotion is believed associated with two biologically based motive systems that promote survival [23,24]. The defensive system is comprised of a network of brain regions that process threat information and includes the amygdala and its projections, the hippocampus, hypothalamus, and sensory and right prefrontal cortices [25–28]. This system is activated by harmful or potentially dangerous stimuli/contexts (e.g., predators, noxious events) and results in negative valenced affect. In contrast, the appetitive system is comprised of a network of brain regions that process reward information and includes areas of the dopaminergic system such as the ventral tegmental area, nucleus accumbens, and striatum, but also the amygdala [29,30]. In addition to dopamine, endogenous opioids are known to play an important role in the appetitive system. This system is activated by appetitive stimuli/contexts (e.g., food, sex) and results in positive valenced affect.

Thus, motivationally relevant stimuli that represent reward or threat (e.g., pictures depicting sex or an attack scene, respectively) activate these two motive systems leading to the experience of affect. The valence (negative/unpleasantness vs positive/pleasantness) of the affective experience is determined by the system that is activated (defensive vs appetitive). Self-report ratings (e.g., pleasure/valence) and psychophysiological (e.g., facial electromyogram [EMG], heart rate [HR]) indices are used to measure affective valence [23,31]. The level of activation of a particular system is thought to be reflected in the arousal level that accompanies the affective state. Therefore, self-report (e.g., subjective arousal) and psychophysiological (e.g., skin conductance [SC] response) indices of arousal are used to measure the level of activation of the systems. Together, measures of valence and arousal can be used to characterize the affective state and infer the activation level of the underlying motive systems.

Given the overlap in the neural systems responsible for affect and pain modulation, it seems plausible that emotion modulates pain via activation of the descending pain modulatory circuitry (see Figure 1). Indeed, some animal studies and neuroanatomical evidence support this notion [20,26,29,32,33]. The amygdala and PAG are likely involved in the affect–pain modulation mechanism, but also the dopaminergic reward system. Therefore, variables that alter these circuits, their receptors, or their associated neurochemicals (i.e., endogenous opioids, dopamine) are likely to alter affective modulation of pain, and perhaps pain modulation in general [18,19,21,29,34–38].

One potential confound to this CNS theory of affective pain modulation stems from the fact that much of the research examining the influence of emotion on pain has relied on noxious thermal stimuli (e.g., cold pressor task, radiant heat). It is possible that emotion-induced changes in skin temperature (via changes in peripheral vasculature) alter perceived sensations of the thermal stimuli without altering the nociceptive signal [39–41]. For example, negative affect can lead to vasoconstriction (threat-related response) and skin cooling that in turn might enhance the perception of noxious cold. Alternatively, positive affect can lead to vasodilation (pleasure response) and skin heating that in turn might reduce the perception of cold. However, if true, then affect would be expected to have the opposite effects when noxious heat was used. To date, only one human study is known to have examined this issue and found that skin temperature did not mediate affective modulation of radiant heat pain [42]. However, additional research is needed to clarify this issue.

Most research on the affective modulation of pain has studied healthy participants. Thus, it is
unclear whether findings extend to patient populations, such as chronic substance users [cf, 43,44]. This is an important area of exploration given the positive relationship between substance dependence and chronic pain [45]. Indeed, extensive drug use might alter or damage the mechanisms responsible for pain modulation and emotion [14,46]. Studies have shown that cocaine and alcohol use influence opioid and dopamine function [47–49]. As a result, chronic use of these substances may lead to dysfunction of the emotion and/or pain modulation systems; thus, interfering with the body’s natural ability to regulate pain. It is not clear what is the relationship between the duration of substance use and disruption of these systems; however, it is reasonable to assume that longer use is associated with greater damage/disruption [50]. Understanding the influence of substance use on psychological mechanisms of pain modulation may have direct clinical relevance given that nonpharmacological interventions for pain (e.g., emotion-induction/regulation techniques) may be particularly important in this population.

However, studying affective modulation of pain in patient populations can be challenging because
Rhudy et al.

a number of comorbid factors can influence affect, pain modulation, or pain perception. For example, affect/motive system function can be influenced by comorbid factors. Affective disorders such as anxiety and/or depression are common in patient populations and are associated with enhanced pain [28,51]; whereas older age is associated with reduced affective arousal [52,53]. Other factors may influence pain modulation system function. Some chronic pain and/or disability may reflect overactivity of facilitatory mechanisms and/or underactivity of inhibitory mechanisms [54]. Hypertension and cardiovascular problems are associated with decreased pain sensitivity [55], and older age is associated with increased pain sensitivity [56–58]. Other factors that are important to consider in patient populations are ethnicity and self-efficacy [59,60], because black ethnicity and lower self-efficacy are associated with higher pain sensitivity. Therefore, consideration of these patient characteristics is warranted.

The present study examined affective modulation of pain in male veterans with and without a primary diagnosis of substance dependence (alcohol, cocaine, controls). Each participant attended three experimental sessions in which emotion was experimentally induced by picture-viewing and then pain perception was assessed using the cold pressor task. Each session varied only by the valence of the emotion that was induced: negative (threat pictures), neutral (household objects, mushrooms), and positive (erotic pictures). Therefore, picture content (intended to manipulate affective valence) was a within-subject variable. In each experimental session, 24 pictures were presented for 4 minutes and then participants were asked to submerge their arm in 33°C water (cold pressor task) and keep it there until they could no longer tolerate it. During arm submersion, participants made pain ratings on a mechanical visual analog scale (M-VAS). Pain threshold was defined as the time (latency) from arm submersion to the first movement of the M-VAS and pain tolerance as the time (latency) to arm withdrawal from the water. Self-report and psychophysiological measures of valence and arousal were collected to verify that targeted affective states were achieved. Analyses were conducted to determine whether alcohol or cocaine dependence moderated the influence of affect on pain perception. Although affect may influence pain through central mechanisms [10], affect-related changes in arm temperature may also alter perceptions of thermal stimuli. Specifically, if positive emotions result in higher arm temperature, the latency to pain threshold and tolerance during exposure to noxious cold would be increased leading to the inference of hypoalgesia (pain reduction). In contrast, if negative emotions result in lower arm temperature, the latency to pain threshold and tolerance would be reduced leading to the inference of hyperalgesia (enhanced pain). To examine this issue, changes in arm temperature during emotional picture-viewing were recorded and analyses examined whether temperature covaried with the emotion induced. Several patient characteristics (age, ethnicity, hypertensive status, medications, depression, anxiety, history of pain/disability, self-efficacy) were assessed from medical charts, interviews, and questionnaires and controlled in analyses.

Hypotheses/Aims

- It was hypothesized that picture-viewing would significantly influence the affective state of the participant [23]. Pictures depicting threat were expected to induce negative valenced affect with moderate arousal. Neutral pictures were expected to induce neutral valenced affect and low arousal. Pictures depicting erotica were expected to induce positive valenced affect with moderate arousal.

- It was hypothesized that affect would modulate pain perception. Positive affect was expected to increase pain threshold and tolerance (reduced pain) and negative affect was expected to decrease threshold and tolerance (enhanced pain).

- It was hypothesized that chronic substance use would moderate the influence of affect on pain perception; therefore, an interaction of substance use group and affective valence (picture content) was expected. It was predicted that alcohol and cocaine use would be associated with less positive affect-induced pain inhibition and perhaps greater negative affect-induced pain facilitation.

- It was hypothesized that CNS mechanisms underlie affective modulation of pain; therefore, arm temperature was not expected to covary with the emotion induced (picture-viewing).

Methods

Participants

Participants were 37 male veterans recruited from a southeastern Veterans Affairs Medical Center using fliers and physician referrals. Substance-using participants were recruited from the Chemical Dependence Treatment Program and were
actively involved with treatment (inpatient or recently released to half-way house). Of those, 14 had a primary diagnosis of Alcohol Dependence and 13 had a primary diagnosis of Cocaine Dependence. Control participants (N = 10) were recruited from other hospital units and did not have a substance abuse/dependence diagnosis. Average age was 52.8 (SD = 9.8), with 54% being white, 43% African American, and 3% Hispanic. Most were married (41%) or divorced (39%) and 81% had a high school diploma or some college. Participants were excluded for: less than 2 weeks of sobriety, severe cognitive impairment, neurological problems, recent use of analgesic or sedative medication, numbness in hands/feet, history of psychotic disorder or post-traumatic stress disorder (PTSD), specific phobia of snakes or spiders, problems healing, and/or Raynaud’s disease. All diagnoses and medical histories were verified by medical records by the first author (J.L.R.). All participants provided informed consent.

**Stimulus Materials**
To manipulate affective state, 72 pictures were presented from the International Affective Picture System (IAPS) [61]. To elicit positive affect, 24 pictures were used that depicted attractive nude women and couples in sexual acts (erotic). To elicit negative affect, 24 pictures were used that depicted human and animal attack scenes (threat). To elicit neutral affect, 24 pictures were used that depicted household objects, mushrooms, and neutral faces (neutral). Erotic and threat picture contents were chosen because they have been shown to produce the greatest modulation of pain and acoustic startle reflex (ASR) [2,23]. Each image was presented for 10 seconds on a 17-inch flat panel monitor positioned approximately 0.5 meter from the participant in a dimmed room. The order of the pictures for each content was randomized but held constant across participants. To minimize the effects of distraction, pictures intended to evoke affective responses were presented before (not concurrent with) the cold pressor task.

**Apparatus and Psychophysiological Response Measurement**
All stimulus presentation and data acquisition were controlled using an IBM-compatible PC. Cold pressor timing and pain ratings (M-VAS voltages) were collected using a National Instruments A/D board (PCI-6036E) and LabVIEW software (Austin, TX, USA). Psychophysiological signals were collected and stored using a ProComp+ system and Biograph software (Thought Technology, Montreal, Canada) that was synchronized with LabVIEW. Blood volume pulse was collected using a photoplethysmograph attached to the palmer surface of the distal tip of the right index finger. Blood volume pulse was continuously converted to HR in beats per minute. SC was measured using Velcro sensors attached to the palmer surface of the second digit on the right index and middle fingers. Other than hand washing prior to each trial, no other skin preparation was used for these sensors as the ProComp+ system does not require isotonic paste for SC recording. A temperature probe was attached to the surface of the inner elbow on the left arm to measure cold pressor arm temperature (°F). This placement allowed the probe to be as close to the peripheral vasculature (and its temperature) as possible without being exposed to the water during the cold pressor task. Corrugator muscle EMG (frowning muscle) was measured using electrodes applied according to the placement recommendations of Fridlund and Cacioppo [62]. Facial EMG was filtered to provide an active range of 20–500 Hz and converted to root mean square (µV). Signals were sampled at 32 Hz and stored digitally. SC, HR, and corrugator EMG were used as psychophysiological manipulation checks to verify that targeted emotional states were achieved. Corrugator and HR have been shown to covary with affective valence. Corrugator increases with the unpleasantness of the affect and HR tends to be higher during positive affect and lower during negative affect. SC correlates with sympathetic nervous system activation; therefore, it was collected to measure affective arousal [23]. Arm temperature was recorded to determine whether changes in pain were mediated by changes in arm heating/cooling.

**Cold Pressor Device**
To induce pain, a cold pressor apparatus with water pump circulated ice water maintained at a constant temperature of 33°F. The device was

---

1 IAPS picture numbers are: Erotic: 2030, 4005, 4141, 4142, 4210, 4232, 4235, 4290, 4300, 4310, 4608, 4651, 4653, 4658, 4659, 4660, 4664, 4669, 4670, 4680, 4683, 4690, 4800, 4810. Threat: 1050, 1052, 1111, 1114, 1120, 1201, 1205, 1220, 1300, 1301, 1525, 1930, 2100, 3530, 4608, 4651, 5290, 5520, 5530, 5531, 5731, 5740, 7000, 7004, 7009, 7010, 7020, 7025, 7031, 7035, 7050, 7235.
constructed from an insulated cooler with an arm cradle where the lid was originally positioned. The cradle was constructed from PVC pipe and netting and was used to position the arm and hand in the cold pressor. It was attached to the cold pressor by hinges at one end and a pressure-released latch at the other. A small amount of pressure on the cradle unlatched and lowered the hand and forearm into the water. The participant was instructed to always keep their hand gripped to the handle of the cradle to ensure that each participant’s hand was submerged to the same depth. Water level was always kept constant and a screen kept the participant’s arm separate from the ice and pump. To measure pain tolerance, each participant was asked to keep their arm in the water for “as long as you can tolerate it.” The latency (second) from arm submersion to withdrawal was used as the measure of pain tolerance. A magnetic switch detected the downward/upward movement of the cradle that signaled the computer to begin and end timing of tolerance latency. A 5-minute cutoff was used to minimize stress.

M-VAS for Pain Intensity
During the cold pressor task, participants were asked to rate their pain on a M-VAS for pain intensity [63]. The M-VAS was constructed from a 10 cm linear sliding potentiometer that participants moved as their pain changed. At one end, the scale read, “no pain sensation” and the other end read, “the most intense pain imaginable.” Movements of the potentiometer sent a proportional voltage to the computer that allowed “real-time” continuous pain ratings. The latency (second) from arm submersion to withdrawal was used as the measure of pain tolerance. The M-VAS was attached to a clip board that was positioned in the participant’s lap during the cold pressor procedure.

Self-Report Measures
Background Measures/Patient Characteristics
Demographics/Health Status Questionnaire
Demographics/Health Status Questionnaire, a brief instrument, asked participants to respond to items regarding their demographics, physical health, medication and tobacco use, psychoactive drug history, phobias, and chronic medical problems. This questionnaire and a medical chart review were used to determine inclusion/exclusion status.

State-Trait Anxiety Inventory
The State-Trait Anxiety Inventory (STAI) was used to determine whether substance use groups differed in trait anxiety [64]. The trait subscale is a 20-item measure of dispositional anxiety symptoms. Respondents answered on a 4-point Likert scale indicating how they generally feel (1 = almost never, 3 = almost always). Trait anxiety was measured prior to any cold pressor trials. Scores range from 20 to 60 with higher scores indicating greater trait anxiety.

Beck Depression Inventory, Second Edition
The Beck Depression Inventory, Second Edition (BDI-2) is a 21-item measure of depression severity [65]. Questions tap affective, cognitive, somatic, and behavioral symptoms. Each item consisted of four self-evaluative statements asking respondents to rate their intensity from the last 2 weeks. Intensity ratings for each item range from 0 to 3 and are summed to achieve a total score ranging from 0 to 63 with higher scores indicating greater depressive symptomatology. This scale was used to ensure that substance use groups did not differ on depressive symptoms.

Medical Outcomes Study Short Form
The Medical Outcomes Study Short Form (SF-36) [66] was used to measure participants’ disability. This questionnaire measures several facets including: physical functioning, role limitations due to physical problems, role limitations due to emotional problems, social functioning, mental health, energy vitality, bodily pain, and general health perception. This questionnaire was used to determine whether differences in disability existed between substance use groups.

Self-Efficacy for Pain Reduction-Brief
The Self-Efficacy for Pain Reduction (SEPR) was used to measure the participants’ belief that they can influence their pain [8]. This measure was shortened to five items (SEPR-brief) and asked whether participants believed they could make reductions in different levels of pain (mild, discomforting, distressing, horrible, excruciating). Ratings were made on 11-point Likert scales ranging from 0 (uncertain) to 10 (certain). Items were summed to achieve a score ranging from 0 to 50 with higher scores indicating greater self-efficacy to reduce pain without using medications. The SEPR-brief was used to ensure substance use groups were equivalent on self-efficacy.
Manipulation Checks for Emotion-Induction

Self-Assessment Manikin
The Self-Assessment Manikin (SAM) [67] consists of two sets of five pictographs depicting affective valence and arousal. Participants place an “X” on or between any of the figures that best describes their affective reaction. This yields ratings between 1 and 9 for each dimension. Affective valence ranges from 1 = unpleasant to 5 = neutral to 9 = pleasant. Affective arousal ranges from 1 = calm to 9 = excited. Participants used the SAM to rate their affective reactions to each picture set (erotic, neutral, threat) at the end of each experimental session.

Emotion Descriptors
At the end of each session, participants also rated their emotional reactions to the picture set using several emotion words (angry, disgusted, fearful, happy, sexually aroused, sad, surprised, and neutral). For each word, participants used an 11-point Likert scale (0 = not at all to 10 = strongly) to rate their reaction. Participants used the Emotion Descriptors to rate their affective reactions to each picture set (erotic, neutral, threat) at the end of each experimental session.

Manipulation Check for Arm Withdrawal from the Cold Pressor

Post-Experiment VAS-Pain
At the end of each experimental session, participants were asked to think back to the cold pressor task and rate their pain intensity and unpleasantness on two 100 mm paper-and-pencil visual analog scales (VAS). For pain intensity, the anchors ranged from: “no pain sensation” to “the most intense pain sensation imaginable.” For unpleasantness, the anchors ranged from: “not at all unpleasant” to “the most unpleasant imaginable.” This measure of pain was used as a manipulation check to ensure that participants were removing their arms from the water at the same criterion point (i.e., pain tolerance). If pain intensity or unpleasantness varied between substance use groups or across picture contents (experimental sessions), then this would call into question the behavioral measure of pain tolerance (arm withdrawal) because it means that participants were using different subjective criteria for arm withdrawal.

Procedure
Prior to their inclusion in the study, the first author (J.L.R.) met with each potential participant to discuss the procedures and to briefly assess for exclusion factors. At that time, each participant provided informed consent, was provided the packet of background questionnaires (demographics/health status, BDI-2, STAI-trait, SF-36, SEPR-brief), and the first experimental session was scheduled. Between this meeting and the first session, a thorough medical chart review was conducted to verify inclusion/exclusion criteria and diagnoses.

At the beginning of each trial, participants were asked to wash and dry their hands, then HR, SC, temperature, and EMG sensors were applied and general instructions regarding the procedure were provided. The participant was seated comfortably in a chair in front of a small desk with the computer monitor positioned directly in front of them. The cold pressor device was positioned at their left and the M-VAS was attached to a clip board in their lap where it could be easily seen and adjusted with their right hand. When the participant was ready to begin, the lights were dimmed and the experimenter left the room. The computer then presented instructions for the participant to sit quietly and relax while 1 minute of baseline physiology was recorded. Next, the computer presented one set of 24 pictures of erotic, neutral, or threat content for 4 minutes to induce either positive, neutral, or negative affect, respectively. After picture-viewing, the computer instructed the participant to place their arm in the water and to keep it submerged for as long as they could tolerate it. To place their arm in the water, the participant pressed down on the arm cradle of the cold pressor that lowered their hand and forearm into the water. The downward movement of the cradle activated a magnetic switch that triggered the computer to begin timing. The computer also prompted the participant to rate their pain on the M-VAS while their arm was submerged. Pain threshold was defined as the time (latency) from arm submersion to the first movement of the M-VAS (in seconds). Pain tolerance was defined as the time (latency) from arm submersion to arm withdrawal (in seconds). After arm withdrawal, participants were instructed by the computer to dry their arm and sit quietly until the experimenter returned, which was always 5 minutes after the last picture (the maximum allowable time in the water). Participants then filled out the SAM and Emotion Descriptors questionnaires to rate their emotional reactions to the pictures they viewed in that session. Additionally, the Post-Experiment VAS-Pain questionnaire was administered to measure their pain intensity and unpleasantness during...
the cold pressor task. Participants were then scheduled for the next session (scheduled a minimum of 24 hours later). For each session, the same procedure was repeated except that pictures of a different content were presented (erotic, neutral, or threat). After each session, participants were provided a $25 honorarium in coupons for merchandise in the VAMC canteen store. Upon study completion, participants received an additional $25 in coupons. Order of picture contents across the three sessions was counterbalanced between-subjects using a Latin-Square design. All procedures were approved by the University of Mississippi Medical Center and VAMC human ethics review boards.

Analyses and Data Reduction

Initially, analyses (chi-square, one-way ANOVAs) were conducted to determine whether groups differed on background variables/patient characteristics.

Change scores for tonic corrugator EMG, SC, and HR were created by subtracting the mean baseline value (during 1 minute of rest) from the mean of the 4 minutes of picture-viewing. For arm temperature, two change scores were created. First, the mean baseline value was subtracted from the mean of the 4 minutes of picture-viewing. Second, the mean baseline value was subtracted from the mean of the temperature during arm immersion (cold pressor). All change scores and self-report measures of affective reactions (SAM, Emotion Descriptors) were analyzed using a mixed ANOVA with picture content entered as the within-subject variable and substance use group as the between-subject variable. Post-Experiment VAS-Pain scores were analyzed using a mixed ANOVA, with rating type (intensity, unpleasantness) and picture content (threat, neutral, erotic) as within-subject variables and substance use group (alcohol, cocaine, control) as a between-subject variable.

To examine the influence of affect on pain variables, mixed ANOVAs were conducted separately for pain threshold and tolerance. Picture content was entered as a within-subject variable and substance use group was a between-subject variable. When appropriate, covariates were entered to control between-group differences on background variables, but only variables found to be significant covariates were kept in the final models. To address whether duration of substance use influenced pain modulation, variables coding for the number of years of cocaine, alcohol, and marijuana use were entered as covariates into the pain analyses. None of these variables were significant covariates, suggesting that duration was unrelated to pain outcomes.

For all repeated measures analyses, multivariate tests (Wilks Lambda, $\lambda$) were interpreted to overcome problems with the violation of sphericity. Follow-up comparisons were made with Fisher’s Least Significant Difference tests and when appropriate linear or quadratic contrasts (trend analysis). To facilitate trend analyses, the levels of the within-subject variable (picture content) were ordered from lowest to highest in terms of affective valence/pleasure (i.e., threat, neutral, erotic). Partial $\eta^2$ are listed for effect sizes of $F$-tests and Cramer’s $V$ for chi-square. Cohen [68] recommends the following guidelines for interpreting $\eta^2$: small = 0.01, medium = 0.06, large = 0.14. It was expected that pain threshold, pain tolerance, corrugator EMG, and self-reported pleasure (valence) would show linear trends across picture contents. Conversely, self-reported arousal and SC should show quadratic trends across picture contents. Lang and colleagues [31] have found that HR assesses affective valence, although not always consistently—especially with the picture contents used in the present study [23]. Therefore, it was unclear whether HR would show a linear or quadratic trend.

Results

Participant Characteristics

Table 1 presents participant characteristics by substance use group. Groups differed in substance use diagnoses. But, the attempt to select substance-dependent patients without comorbid substance use diagnoses was unsuccessful. Of the alcohol group, 23% had a comorbid marijuana diagnosis, but no comorbid cocaine use. Of the cocaine group, 77% had a comorbid alcohol diagnosis and 8% had a marijuana diagnosis. Due to comorbidity, additional pain analyses were conducted in which the presence or absence of each substance-related diagnosis (cocaine abuse/dependence, alcohol abuse/dependence, marijuana abuse/dependence) was coded and entered as between-subject factors. The results of these analyses did not differ from those reported below.

Groups were found to significantly differ in age ($F(2,36) = 15.59$, $P < 0.001$, $\eta^2 = 0.48$), ethnicity ($\chi^2(N = 37) = 12.94$, $P = 0.01$, Cramer’s $V = 0.42$), antihypertensive medication use ($\chi^2(2, N = 36) = 7.56$, $P = 0.02$, Cramer’s $V = 0.46$), role limita-
Affective Modulation of Pain

Table 1  Participant characteristics by group

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Alcohol</th>
<th>Cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>63.60(^a)</td>
<td>50.21(^b)</td>
<td>47.31(^b)</td>
</tr>
<tr>
<td>(2.30)</td>
<td>(1.95)</td>
<td>(2.02)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>90.00</td>
<td>50.00</td>
<td>30.80</td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
<td>50.00</td>
<td>69.20</td>
</tr>
<tr>
<td>Hispanic</td>
<td>10.00</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Comorbid substance use (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine abuse/dependence*</td>
<td>0</td>
<td>0</td>
<td>100.00</td>
</tr>
<tr>
<td>Alcohol abuse/dependence*</td>
<td>100.00</td>
<td>76.92</td>
<td></td>
</tr>
<tr>
<td>Marijuana abuse/dependence</td>
<td>23.07</td>
<td>7.69</td>
<td></td>
</tr>
<tr>
<td>Tobacco use*</td>
<td>20.00</td>
<td>78.57</td>
<td>53.85</td>
</tr>
<tr>
<td>Medications (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>70.00</td>
<td>30.77</td>
<td>15.38</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>10.00</td>
<td>30.77</td>
<td>38.46</td>
</tr>
<tr>
<td>Disability/quality of life (mean)</td>
<td>10.00</td>
<td>23.07</td>
<td>46.15</td>
</tr>
<tr>
<td>Physical functioning scale</td>
<td>92.00(^a)</td>
<td>75.36(^a)</td>
<td>79.96(^a)</td>
</tr>
<tr>
<td>(5.28)</td>
<td>(4.45)</td>
<td>(4.61)</td>
<td></td>
</tr>
<tr>
<td>Role-physical scale*</td>
<td>92.50(^b)</td>
<td>51.79(^b)</td>
<td>80.77(^b)</td>
</tr>
<tr>
<td>(10.96)</td>
<td>(9.26)</td>
<td>(9.61)</td>
<td></td>
</tr>
<tr>
<td>Role-emotional scale*</td>
<td>96.67(^a)</td>
<td>71.43(^a)</td>
<td>74.36(^a)</td>
</tr>
<tr>
<td>(10.68)</td>
<td>(9.03)</td>
<td>(9.37)</td>
<td></td>
</tr>
<tr>
<td>Vitality scale*</td>
<td>76.00(^a)</td>
<td>56.91(^b)</td>
<td>61.92(^b)</td>
</tr>
<tr>
<td>(5.01)</td>
<td>(4.23)</td>
<td>(4.39)</td>
<td></td>
</tr>
<tr>
<td>Emotional well-being scale*</td>
<td>86.40(^a)</td>
<td>66.29(^a)</td>
<td>88.69(^b)</td>
</tr>
<tr>
<td>(6.00)</td>
<td>(5.07)</td>
<td>(5.27)</td>
<td></td>
</tr>
<tr>
<td>Social functioning scale*</td>
<td>95.00(^a)</td>
<td>63.30(^a)</td>
<td>67.31(^a)</td>
</tr>
<tr>
<td>(7.19)</td>
<td>(6.07)</td>
<td>(6.30)</td>
<td></td>
</tr>
<tr>
<td>Bodily pain scale</td>
<td>84.25(^a)</td>
<td>72.68(^a)</td>
<td>67.31(^a)</td>
</tr>
<tr>
<td>(8.76)</td>
<td>(7.47)</td>
<td>(7.69)</td>
<td></td>
</tr>
<tr>
<td>General health scale</td>
<td>76.00(^a)</td>
<td>61.16(^b)</td>
<td>59.62</td>
</tr>
<tr>
<td>(6.17)</td>
<td>(5.22)</td>
<td>(5.42)</td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms* (mean)</td>
<td>4.10(^a)</td>
<td>13.50(^b)</td>
<td>15.15(^b)</td>
</tr>
<tr>
<td>(3.18)</td>
<td>(2.69)</td>
<td>(2.78)</td>
<td></td>
</tr>
<tr>
<td>Trait anxiety* (mean)</td>
<td>19.40</td>
<td>33.86</td>
<td>36.23</td>
</tr>
<tr>
<td>(4.12)</td>
<td>(3.48)</td>
<td>(3.61)</td>
<td></td>
</tr>
<tr>
<td>Self-efficacy for pain reduction</td>
<td>21.10(^a)</td>
<td>26.21(^a)</td>
<td>19.39(^a)</td>
</tr>
<tr>
<td>(3.76)</td>
<td>(3.21)</td>
<td>(3.32)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Significant F or chi-square for group effect at \(P < 0.05\).
\(^b\) Means in the same row that share a superscript are not different at \(P < 0.05\).
SEM is listed below each mean in parentheses. SF-36 subscales are scored 0–100, with higher scores indicating better health in each area.

Table 2 reports means, standard errors, and results of LSD comparisons for all manipulation check variables.

Did Picture-Viewing Influence the Affective State of the Participant?

Affective Valence

Measures of affective valence were expected to demonstrate linear trends with unpleasant stimuli resulting in the lowest pleasure, neutral intermediate, and pleasant stimuli the highest pleasure. Supporting this, a significant main effect of picture content was found for pleasure/valence ratings (\(\lambda = 0.56, F(2,33) = 12.80, P < 0.001\), \(\eta^2 = 0.44\)) and corrugator EMG (\(\lambda = 0.76, F(2,33) = 5.32, P = 0.001, \eta^2 = 0.24\)), as well as respective linear trends (pleasure ratings: \(F(1,34) = 26.38, P < 0.001, \eta^2 = 0.44\); corrugator: \(F(1,34) = 10.62, P = 0.003, \eta^2 = 0.24\)). Threat pictures resulted in the lowest pleasure ratings (SAM valence), neutral pictures were intermediate, and erotic pictures were the highest (\(P < 0.005\)). For corrugator EMG, threatening pictures led to the greatest EMG activity, followed by neutral pictures, and then erotic pictures. But the comparison between neutral and erotic did not reach significance (\(P = 0.24\)). Figure 2 presents these data. Although threat pictures resulted in lower HR than neutral, no significant effect of HR was noted (\(\lambda = 0.96, F(2,33) = 0.62, P = 0.54, \eta^2 = 0.04\)). No effect of substance use group was found in any analyses. In sum, self-reported and psychophysiological measures of affective valence were influenced by picture content, an effect that did not vary by substance use group.

Arousal

Measures of affective arousal were expected to demonstrate quadratic trends with threat and erotic stimuli resulting in greater arousal relative to neutral. Supporting this, a significant main effect of picture content was found for arousal ratings (\(\lambda = 0.52, F(2,33) = 15.54, P < 0.001, \eta^2 = 0.49\)) due to physical problems (\(F(2,36) = 4.53, P = 0.02, \eta^2 = 0.21\)), vitality (\(F(2,36) = 4.39, P = 0.02, \eta^2 = 0.21\)), emotional well-being (\(F(2,36) = 4.50, P = 0.02, \eta^2 = 0.21\)), social functioning (\(F(2,36) = 6.34, P = 0.005, \eta^2 = 0.27\)), depressive symptoms (\(F(2,36) = 3.85, P = 0.03, \eta^2 = 0.19\)), and trait anxiety (\(F(2,36) = 5.35, P = 0.01, \eta^2 = 0.24\)). The control group was: older than other groups, more likely to be prescribed antihypertensive medications, reported higher quality of life, reported fewer symptoms of depression and anxious traits, and were more likely to be white. Groups did not differ on self-efficacy for pain reduction, antidepressant or anxiolytic use, physical functioning, role limitations due to emotional problems, bodily pain, or general health (\(P > 0.05\)). Variables that were found to differ between groups were entered into pain analyses as covariates; however, only age was found to be a significant covariate and only in the pain tolerance analysis. Given that some-group differences (e.g., hypertensive status) may influence pain perception, it was also decided to examine affective modulation of pain only in the two substance-dependent groups. Although these analyses lack a control group, they test whether emotion influences pain in substance-dependent individuals.

Manipulation Checks

Measures of affective valence were expected to demonstrate linear trends with unpleasant stimuli resulting in the lowest pleasure, neutral intermediate, and pleasant stimuli the highest pleasure. Supporting this, a significant main effect of picture content was found for pleasure/valence ratings (\(\lambda = 0.56, F(2,33) = 12.80, P < 0.001, \eta^2 = 0.44\)) and corrugator EMG (\(\lambda = 0.76, F(2,33) = 5.32, P = 0.001, \eta^2 = 0.24\)), as well as respective linear trends (pleasure ratings: \(F(1,34) = 26.38, P < 0.001, \eta^2 = 0.44\); corrugator: \(F(1,34) = 10.62, P = 0.003, \eta^2 = 0.24\)). Threat pictures resulted in the lowest pleasure ratings (SAM valence), neutral pictures were intermediate, and erotic pictures were the highest (\(P < 0.005\)). For corrugator EMG, threatening pictures led to the greatest EMG activity, followed by neutral pictures, and then erotic pictures. But the comparison between neutral and erotic did not reach significance (\(P = 0.24\)). Figure 2 presents these data. Although threat pictures resulted in lower HR than neutral, no significant effect of HR was noted (\(\lambda = 0.96, F(2,33) = 0.62, P = 0.54, \eta^2 = 0.04\)). No effect of substance use group was found in any analyses. In sum, self-reported and psychophysiological measures of affective valence were influenced by picture content, an effect that did not vary by substance use group.
Table 2: Means and standard errors for manipulation check data by picture content

<table>
<thead>
<tr>
<th>Picture Content</th>
<th>VAS-Pain</th>
<th>Psychophysiology</th>
<th>Self-Report Affect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Int</td>
<td>Unpl</td>
<td>∆Corr EMG (µV)</td>
</tr>
<tr>
<td>Threat</td>
<td>63.03a</td>
<td>60.88b</td>
<td>2.98a</td>
</tr>
<tr>
<td></td>
<td>(3.51)</td>
<td>(3.73)</td>
<td>(0.59)</td>
</tr>
<tr>
<td>Neutral</td>
<td>60.93a</td>
<td>62.96b</td>
<td>1.71a</td>
</tr>
<tr>
<td></td>
<td>(3.97)</td>
<td>(4.04)</td>
<td>(0.04)</td>
</tr>
<tr>
<td>Erotic</td>
<td>64.92a</td>
<td>62.16a</td>
<td>1.28a</td>
</tr>
<tr>
<td></td>
<td>(3.80)</td>
<td>(3.95)</td>
<td>(0.41)</td>
</tr>
</tbody>
</table>

SBM s are listed in parentheses below means. Means in the same column that share a superscript are not different at $P < 0.05$. Int = Post-Experiment VAS Pain Intensity; Unpl = Post-Experiment VAS Pain Unpleasantness; ∆Corr EMG = change in corrugator electromyogram (frowning) during picture-viewing; ∆SC = change in skin conductance (sympathetic arousal) during picture-viewing; ∆HR = change in heart rate during picture-viewing; ∆Temp-Picture = change in arm temperature during picture-viewing; ∆Temp-Cold = change in arm temperature during cold pressor; Self-reported affect are measures assessed following each experimental session in which participants rated their affective state induced by picture-viewing; SAM = Self-Assessment Manikin.
Affective Modulation of Pain

Figure 2 Manipulation checks for affective valence. Participants’ affective valence was effectively manipulated by picture-viewing. Threat pictures resulted in the lowest pleasure ratings (SAM valence), neutral pictures were intermediate, and erotic pictures were the highest ($P < 0.005$). Corrugator EMG (frowning) was higher during threat pictures compared with neutral ($P = 0.008$) and erotic ($P = 0.003$) pictures.

Figure 3 Manipulation checks for affective arousal. Participants’ affective arousal was effectively manipulated by picture-viewing. Significant quadratic trends were found for arousal ratings ($F(1,34) = 27.56$, $P < 0.001$, $\eta^2 = 0.45$) and skin conductance response ($F(1,34) = 4.00$, $P = 0.05$, $\eta^2 = 0.11$). This suggests that erotic and threatening pictures led to higher arousal ratings and skin conductance responses (sympathetic activation) relative to neutral pictures.

two participants’ tolerance latency (one alcohol, one control). Table 3 presents pain outcomes by substance abuse group and picture content. A significant main effect of picture content emerged for pain threshold ($\lambda = 0.78, F(2,25) = 3.51, P = 0.045, \eta^2 = 0.22$); however, the effect of picture content for pain tolerance was not statistically significant although the effect size was large ($\lambda = 0.86, F(2,31) = 2.50, P = 0.099, \eta^2 = 0.14$). For pain threshold, linear and quadratic trends did not reach significance, but LSD comparisons found that erotic pictures resulted in higher threshold relative to neutral ($P = 0.016$) and threat ($P = 0.08$). Threat and neutral did not differ ($P = 0.35$). For pain tolerance, a significant linear trend was found ($F(1,32) = 4.35, P = 0.045, \eta^2 = 0.12$). Pain tolerance was lower following threat pictures than erotic or control pictures. Figure 4 presents pain outcomes.

Pain Outcomes: Did Chronic Substance Use Moderate the Influence of Affect on Pain Perception?

The main effect and interaction of substance use group were not significant for pain threshold (main effect: $F(2,26) = 0.10, P = 0.90$, $\eta^2 = 0.008$; interaction: $\lambda = 0.94, F(4,50) = 0.37, P = 0.83$, $\eta^2 = 0.03$) or pain tolerance (main effect: $F(2,32) = 0.76, P = 0.479$, $\eta^2 = 0.05$; interaction: $\lambda = 0.87, F(4,62) = 1.14, P = 0.35, \eta^2 = 0.07$). Furthermore, in the analyses examining only the substance-dependent groups, there was a significant main effect of picture content for pain threshold ($\lambda = 0.71, F(2,18) = 3.60, P = 0.048, \eta^2 = 0.29$) and pain tolerance ($\lambda = 0.67, F(2,22) = 5.53, P = 0.01, \eta^2 = 0.34$). For pain threshold, the linear contrast eluded significance ($F(1,19) = 3.46, P = 0.078$, $\eta^2 = 0.17$).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Means and standard errors for pain outcomes by picture content and substance use group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picture Content</td>
<td>Pain Threshold</td>
</tr>
<tr>
<td></td>
<td>Latency (second)</td>
</tr>
<tr>
<td>Mean</td>
<td>SEM</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Threat</td>
<td>14.59</td>
</tr>
<tr>
<td>Neutral</td>
<td>11.86</td>
</tr>
<tr>
<td>Erotic</td>
<td>18.52</td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
</tr>
<tr>
<td>Threat</td>
<td>13.53</td>
</tr>
<tr>
<td>Neutral</td>
<td>12.36</td>
</tr>
<tr>
<td>Erotic</td>
<td>14.82</td>
</tr>
<tr>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Threat</td>
<td>14.72</td>
</tr>
<tr>
<td>Neutral</td>
<td>14.01</td>
</tr>
<tr>
<td>Erotic</td>
<td>17.13</td>
</tr>
</tbody>
</table>
\[ \eta^2 = 0.15 \], but LSD comparisons found that erotic pictures resulted in higher thresholds relative to neutral \((P = 0.02)\) and threat \((P = 0.08)\). For pain tolerance, a significant linear trend was found \((F(1,23) = 8.58, P = 0.008, \eta^2 = 0.27)\), but no LSD comparisons reached significance. Examination of the means suggests that pain tolerance was lower following threat pictures \((M = 81.12, SD = 89.20)\) than erotic \((M = 89.20, SD = 100.75)\) or neutral pictures \((M = 90.56, SD = 103.55)\). Substance use diagnosis did not influence pain outcomes \((Ps > 0.45)\). Together, these data suggest that pain was lower following the induction of positive emotion than following the induction of negative emotion. Substance use history did not appear to influence affective modulation of pain \((Ps > 0.35)\).

**Discussion**

The present study examined the influence of emotional states on pain perception using an experimental paradigm. On three experimental trials, participants with and without a substance use diagnosis (alcohol, cocaine, none) viewed emotionally evocative pictures prior to a cold pressor task. During each trial, pictures of a different content (erotic, threat, neutral) were presented that were intended to elicit different affective states. Results indicated that targeted emotional states were achieved. Erotic pictures increased self-reported positive affect (sexual arousal, happiness), pleasure, and arousal; and decreased corrugator EMG. Threatening pictures increased self-reported negative affect (anger, disgust, fear, sadness), arousal, and corrugator EMG; and decreased pleasure ratings. Moreover, results suggested that pain varied according to the emotional state elicited: pain threshold and tolerance were higher following erotic pictures than following threat pictures. These data are generally consistent with previous studies examining modulation of experimental pain that suggest positive affect inhibits pain, whereas negative affect enhances it [1–7].
However, the present data suggest that the influence of affective state may be specific to the pain measure. Positive affect led to reduced pain on the pain threshold measure, but not on the tolerance measure. Alternatively, negative affect enhanced pain on the pain tolerance measure, but not on the threshold measure. This may reflect differences in perception indexed by each pain measure. Our pain threshold measure was derived from a visual analog scale of pain intensity believed to tap the sensory-discriminative dimension of pain; whereas pain tolerance is thought to tap the affective-motivational dimension of pain [3,63]. Further, pain tolerance assessment is thought to be a better approximation of clinical pain states that simultaneously elicit anxiety and arousal [69]. It is possible that positive emotions have the greatest impact on early discrimination of the noxious signal, perhaps by distracting attention away from the stimulus. Tolerance assessment, though, requires longer exposure to the noxious stimulus and concomitant negative emotions are elicited that may cancel out the impact of the positive emotions. In contrast, the relatively subtle negative emotions induced by picture-viewing may not be intense enough to alter pain threshold (note a lack of physiological arousal elicited by threat pictures), but may enhance pain on the tolerance measure because of the additional negative emotion elicited by the noxious stimulus. This interpretation is consistent with a similar study that also found positive emotions did not modulate pain tolerance [2]. Although these results should be replicated with a larger sample, it suggests that minimizing negative emotions may be a better strategy for dealing with clinical pain, whereas increasing positive emotions may be a better strategy for dealing with brief, acute pain (e.g., venipuncture).

The present study suggests that affective modulation of pain can be observed in patient populations. Substance use was not found to influence pain modulation, because similar patterns of pain modulation were found in cocaine and alcohol groups. But the present study was limited by a small sample, limiting the ability to detect an effect of substance use. Indeed, the size of the substance use interaction (moderation) effect was quite small (less than 3% of the variance explained in pain outcomes). Moreover, the cocaine and alcohol groups in the present study were not “pure” representations of these disorders. Seventy-seven percent of the cocaine group had a comorbid alcohol diagnosis and several members of each group had a comorbid marijuana diagnosis. Clearly, these issues confound our ability to determine whether alcohol and cocaine groups differed in their pain modulation. Additionally, loss of pain threshold data in the alcohol group likely reduced power to determine whether a difference existed in this group. Despite these limitations, our results are still encouraging because they suggest that affective pain modulation can be observed in persons with substance dependence. Indeed, the pattern of means was consistent across all groups—pain threshold and tolerance were lower after viewing threatening pictures than erotic pictures.

Another issue stemming from small sample size was our inability to adequately address an important issue—the duration of substance use and its effect on pain modulation. Ostensibly, persons with longer histories of substance use should show greater dysfunction of emotion and/or pain modulation systems. Ideally, analyses would have examined this issue at the group and individual levels. We were only able to address this issue by entering duration of use as a covariate in the pain outcome analyses. Duration was not found to significantly covary with pain outcomes. Given its importance, however, future work should employ a larger sample to better address this issue. Additionally, it will be important to determine whether the present findings extend to women, because gender differences have been noted in affective modulation of pain [2,70–72]—perhaps due to differences in the processing or experience of emotion [73].

Arm temperature was found to covary with emotion, with warming found to erotic pictures relative to threat. Therefore, it is possible that emotion-induced changes in peripheral temperature may alter perceived sensations of thermal stimuli, thus contributing to the effect of affective modulation of pain. However, despite emotion-related changes in arm temperature, these changes did not appear to influence pain outcomes. Correlations were small and nonsignificant between emotion-induced changes in arm temperature and pain threshold and tolerance latencies. Therefore, arm temperature does not appear to mediate the influence of emotion on pain. Further, additional evidence (to be discussed below) suggests that if arm temperature does mediate affective modulation of pain, it is not the only mechanism.

In the present study, several group differences were found on background variables. Control participants were older, less ethnically diverse, more likely to be prescribed hypertensive medication,
and reported better physical and psychological health. To address this issue, differences among groups were controlled statistically. Only age was found to covary with pain outcomes—and specifically only with pain tolerance. Even after controlling for age, the expected pattern of modulation was found. Therefore, it would appear that affective modulation of pain is a general phenomenon that can be observed in diverse populations, even those with a history of chronic alcohol or cocaine use. This is encouraging given that nonpharmacological pain management strategies may be important for persons with a history of substance abuse/dependence. Future studies should address whether a history of chronic substance use influences affective modulation of pain in patients with chronic pain disorders. Additionally, given that chronic opiate use may decrease the effectiveness of endogenous opiates in pain inhibition [38], future studies should examine whether opiate dependence alters affective modulation of pain. It would be expected that opiate tolerance consequential to opiate dependence would result in a failure of positive emotions to elicit pain inhibition if endogenous opioids mediate positive emotion-induced pain reduction.

Group differences in antihypertensive medication use suggested that there were more participants with hypertension in the control group. Although controlling statistically for medication use may equilibrate groups on hypertension status, it remains possible that group differences may have influenced our results. Indeed, several researchers have noted that higher blood pressure is associated with decreased pain sensitivity [74–81]. This may explain why overall threshold and tolerance latencies tended to be slightly higher in this group than the alcohol and cocaine groups (threshold: 15.29, 14.99, 13.57, respectively; tolerance: 112.29, 106.61, 67.32, respectively). Of greater importance, the control group tended to have greater variability in threshold and tolerance. The effect of this variability would have meant greater error in the ANOVA models, potentially altering the conclusions. To address this issue, additional analyses were conducted without the control participants. These analyses replicated those that included controls, suggesting that positive emotions led to lower pain relative to negative emotions. No difference was noted between cocaine- and alcohol-dependent groups. Although these analyses lacked a control group, the effect sizes associated with the main effect of emotion on pain was large. Together, this strengthens the argument that affective modulation of pain can be observed in substance-dependent individuals.

To date, we are aware of only three experimental studies that have examined the impact of emotion on substance-dependent participants [43,44,82]. The present findings are consistent with this early work. These studies found that anxiety enhanced pain. However, the present study has several improvements over prior work. Of greatest significance is the fact that the present experiment tested a more comprehensive model of the affect and pain relationship. Both positive and negative affect were induced, whereas prior work focused exclusively on anxiety (negative affect). Thus, this previous literature did not clarify the effect of positive emotion on pain in substance-abusing individuals. Additionally, the present study used well-studied and normed stimuli to elicit emotion, whereas Kornetsky et al. used “formal” and “informal” personal interactions to induce anxiety and Malow et al. did not experimentally induce emotion. Moreover, the present study used more sophisticated manipulation checks to verify that emotion-induction was successful. Although skin resistance was collected in Kornetsky’s studies to measure arousal, neither self-report nor psychophysical indices of valence were assessed. And finally, the present study examined the effect of emotion on pain threshold and tolerance. Kornetsky’s work examined participants’ ability to discriminate noxious stimuli and Malow et al. examined threshold and stimulus discriminability.

It has been previously hypothesized that affect may modulate pain through central mechanisms [8]. Although the present study did not directly test this hypothesis, a linear trend was found for arm temperature suggesting that emotion-induction did influence peripheral temperature. Thus, emotion may influence the perception of thermal stimuli by altering skin temperature. This may occur through autonomic outflow and/or changes in the peripheral vasculature. While more research is needed to delineate the mechanisms of affective modulation of pain, evidence suggests that CNS mechanisms may be involved with emotion-related pain modulation. For example, viewing the IAPS pictures has been shown to activate central regions involved with pain modulation [83]. Moreover, the effects of picture-viewing on pain parallels the effects on the ASR [84]. This is important given that the neurophysiology of ASR modulation has received extensive study [85,86] and components critical to affective modulation of
Affective Modulation of Pain

the ASR are also involved with pain modulation—namely the amygdala and PAG [14,26,32,87]. Given this common neural substrate, it is possible that affect modulates pain through this same circuitry. Moreover, a recent study from our laboratory using similar methodology suggested that picture-viewing modulates the nociceptive flexion reflex (NFR), a measure of spinal nociception [13]. The NFR is elicited by electrically stimulating the sural nerve and recording the involuntary spinal withdrawal reflex in the biceps femoris muscle using EMG. The amplitude of the reflex has been shown to correlate with perceived pain intensity; therefore, it can be used as a physiological index of nociception in the spinal cord [88]. We found that NFR amplitude covaried with picture valence, with amplitude being the greatest during threat pictures and the smallest during erotic pictures. Given that this measure of nociception does not rely on thermal perception, changes in peripheral temperature should not account for its modulation. Despite this, future human pain studies using imaging technology may be necessary to directly test whether central mechanisms are involved in affective modulation of pain in humans.

It is argued that the participant’s emotional state is responsible for the changes in pain observed. While the present methodology was designed to minimize the effect of distraction (pictures shown before pain induction), it is possible that different picture contents altered participants’ attentional set. Indeed, threatening pictures may have increased attention to pain, thus enhancing its intensity. In contrast, erotic pictures may have directed attention away from pain sensations. It is our perspective that the experience of emotion is a manifestation of underlying motivational systems designed to promote survival. Thus, emotion is inextricably tied to the perceptual processing of harmful and survival-enhancing stimuli. As a result, emotion and attention are difficult to disentangle [cf, 89]. Interestingly, however, the effects of distraction on pain appear to be the strongest when the distractor is a pleasant event/stimulus and not simply when it consumes the most cognitive resources [4,90,91].

In sum, this study extends prior work by demonstrating that affect modulates pain perception in cocaine- and alcohol-dependent individuals. Positive affect led to higher pain threshold and tolerance than negative affect. Although future work is needed to determine the exact nature of the underlying mechanisms, changes in arm temperature may contribute to these effects. Moreover, chronic alcohol and cocaine use do not appear to influence the pattern of affective modulation of pain, because the effect of emotion was observed in participants with substance dependence. Although preliminary, these data may have clinical relevance, because they suggest that psychological mechanisms to regulate pain can be used in populations in which pharmacological interventions for pain control may pose difficulties. Specifically, mechanisms of pain inhibition and facilitation appear to function in these populations and emotions can activate them. Therefore, persons with a history of alcohol and cocaine dependence may benefit from therapeutic interventions that focus on increasing positive and decreasing negative emotions. Such interventions are likely to result in reduced pain in these populations.

Acknowledgment
This work was supported by a Veteran's Affairs Medical Center (VAMC) VISN 16 Mental Illness Research, Education, and Clinical Centers (MIRECC) pilot grant.

References
44 Kornetsky C. Effects of anxiety and morphine on the anticipation and perception of painful radiant
91 Leventhal H. I know distraction works even though it doesn't! Health Psychol 1992;11:208–9.