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Negative affect, pain and sex: The role of endogenous opioids

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## Abstract

Opioid neurotransmission modulates pain and negative affect during psychological stress. To determine whether these effects differ between men and women, the opioid receptor antagonist naltrexone or placebo was administered double-blind to 21 men and 22 women before they completed 30 minutes of difficult mental arithmetic. To heighten negative affect, participants received seven moderately noxious electric shocks during the math task, which were believed to be contingent upon performance. Before and after the math task, participants rated pain intensity and unpleasantness while their left hand was immersed in 2°C water for up to 4 minutes. Anxiety, discouragement and anger were also rated before, during and after the math task. Tolerance of cold-induced pain was greater in men, whereas discouragement during the math task was greater in women. Opioid blockade did not influence ratings of negative affect, which increased in line with the intensity and unpleasantness of shock-induced pain. The intensity and unpleasantness of cold-induced pain increased after the math task only in women administered naltrexone. Within the naltrexone condition, pain ratings increased most in the most discouraged subjects. However, this relationship was absent in placebo recipients, implying that the hyperalgesic effect of psychological distress was tempered by opioid release. Greater stress-evoked discouragement in women than men may explain why cold-induced pain increased after the math task only in women administered naltrexone.

**Key words:** opioid neurotransmission; naltrexone; psychological stress; discouragement; sex effects

## Introduction

Uncontrollable aversive events evoke stress-induced analgesia (Amit and Galina, 1986; Fields and Basbaum, 1999) due, in part, to an increase in  $\mu$ -opioid receptor-mediated neurotransmission in cortical and subcortical pain control circuits (Ribeiro et al., 2005). Bandura et al. (1988) reported that an intense cognitive stressor triggered an opioid-mediated increase in tolerance of cold-induced pain in distressed subjects, whilst this response was absent in subjects who could cope with task demands. Similarly, intense negative emotions such as fear, that inhibit pain (Rhudy and Meagher, 2000; Rhudy and Meagher, 2001a), may do so via opioid mechanisms (e.g., parachute jumps by novices – Janssen and Arntz, 2001; combat movies shown to Vietnam veterans – Pitman et al., 1990).

Administration of opioids may blunt the affective component of pain without necessarily dulling the sensation itself (Gutstein and Akil, 2001). In particular, opioid release in cortical regions involved in emotional processing appears to suppress the emotive element of pain (Zubieta et al., 2001) and affective states such as sadness (Zubieta et al., 2003), whereas blocking  $\mu$ -opioid receptors with naloxone increases activity in these regions (Borras et al., 2004). Thus, activation of the endogenous opioid system during psychological stress could suppress the affective and sensory components of pain independently. The presence of opioid peptides and receptor sites in areas of the brain that modulate responses to psychological stress is consistent with this idea (Drolet et al., 2001).

In general, pain sensitivity is greater in women than men (Weisenfeld-Hallin, 2005). For example, women experience more severe post-operative pain and require

more morphine than men to achieve a similar degree of analgesia (Cepeda and Carr, 2003; Aubrun et al., 2005). This may be due, in part, to a decrease in  $\mu$ -opioid receptor availability and suppression of endogenous opioid responses to pain during low oestrogen states (Zubieta et al., 2002; Smith et al., 2006). On the other hand,  $\mu$ -opioid receptor binding is greater in various cortical and subcortical brain regions of women than men (Zubieta et al., 1999). Furthermore, placebo analgesia – thought to be mediated by endogenous opioid release – and naloxone-induced increases in the stress-hormone cortisol are greater in women than men (Pud et al., 2006; Uhart et al., 2006). Therefore, effects of  $\mu$ -opioid receptor blockade on pain and emotional distress may differ between the sexes.

In the present study, the opioid receptor antagonist naltrexone or placebo was administered before participants completed a painful cold pressor test and stressful mental arithmetic that incorporated painful electric shocks. We expected that the intensity of distress generated during mental arithmetic would depend on individual differences in the capacity to deal with task demands, and that opioid release would be greatest in the most distressed subjects (Bandura et al., 1988). To explore this possibility, changes in cold-induced pain after mental arithmetic were investigated in relation to the intensity of negative affect. It was hypothesized that naltrexone would alter the relationship between negative affect and pain. In addition, it was hypothesized that the effect of naltrexone would differ between men and women.

## **Method**

### **Subjects**

The sample consisted of 21 men (mean age  $20.9 \pm 3.2$  years) and 22 women (mean age  $20.4 \pm 4.8$  years) who reported that they were in good health. Exclusion

criteria included any previous/current injury to the non-dominant arm which was used for pain testing (all participants were right-handed), chronic pain conditions or headache, and medical or psychiatric conditions necessitating the use of any form of analgesic, antidepressant, anti-anxiety or antihypertensive medication. Subjects were recruited from undergraduate psychology classes and the general university population. They were asked to refrain from consuming alcoholic or caffeinated beverages for 12 hours before the experiment, and food or tobacco for two hours before the experiment. They provided informed consent for the procedures, which were approved by the Murdoch University Human Research Ethics Committee. Subjects received \$15 for their participation.

### Procedures

*Design overview.* The experiment was carried out in a temperature-controlled laboratory maintained at  $22 \pm 2^{\circ}\text{C}$ . Subjects were randomly assigned to the naltrexone (10 men and 10 women) or placebo condition (11 men and 12 women). A 50 mg naltrexone caplet or a sugar pill was encapsulated and administered double-blind. Preliminary analyses indicated that age and sex distributions were similar in each drug condition. The experimental timeline is presented in Figure 1. Subjects rated anger, discouragement, anxiety and filler items (confusion, sluggishness and liveliness) on separate 100 mm visual analogue scales ranging from “not at all” to “extremely” at various stages throughout the experiment. They completed a cold pressor test and mood ratings before taking the drug, 50-60 minutes later when the drug had been absorbed, and shortly after the math task had been completed. During the math task, subjects rated mood at intervals of 5-7 minutes starting 1.5 minutes into the task. They also rated the pain intensity and unpleasantness of seven electric shocks on 100 mm visual analogue

scales ranging from “no pain” or “not unpleasant at all” to “pain as bad as it could get” or “as unpleasant as it could get”.

*Cold pressor test.* Before the test, the left hand was immersed up to the wrist in a 37°C water bath for three minutes to standardise hand temperature. The hand was then immersed in a 2°C ice-water slurry until the subject felt that cold-induced pain was too unpleasant to continue, or until 4 minutes had elapsed. To prevent pockets of warm water developing around the hand, a small aquarium pump circulated the ice-water. The female experimenter remained in the presence of the subject during the cold pressor test and used a stopwatch to measure the duration of immersion. Subjects rated pain intensity and unpleasantness at 30-second intervals by moving a slide along a 100 mm visual analogue scale. A final rating was made when they withdrew their hand from the ice-water.

*Mental arithmetic.* The math task involved addition and subtraction which varied across five levels of difficulty: level 1 [e.g.,  $(1 + 3) - 2$ ], level 2 [e.g.,  $(56 + 4) - 6$ ], level 3 [e.g.,  $(77 + 19) - 2$ ], level 4 [e.g.,  $(245 + 63) - 4$ ], and level 5 [e.g.,  $(771 + 195) - 2$ ]. To ensure that the task was difficult, the time limit set for questions at each level was shorter than the mean time required to answer these questions in preliminary piloting. Subjects were initially presented with problems from Level 3, and the difficulty of the problems was automatically adjusted to ensure a 75% failure rate. At the outset of the task subjects were told that the number of shocks they would receive depended on their performance; that is, poor or slow performers were led to believe that they had a greater chance of being shocked. However, so that the number of shocks did not confound results, no such contingency existed and all subjects received an identical number of shocks at similar stages throughout the task. Subjects initially completed a set of practice trials for 2-3

minutes, during which no shocks were delivered. Subjects then rated their ability to avoid shocks during the subsequent math task on a 100 mm visual analogue scale delimited by “no ability to avoid shocks” and “complete ability to avoid shocks”. This rating averaged  $23.7 \pm 21.9$  mm (S.D.) after the practice trials and did not change greatly thereafter, indicating that the task was thought to be extremely difficult. Subjects initiated the rest of the task by a keystroke, and were reminded that shocks could be delivered after this point. Each math question appeared in yellow 2 cm high numbers in the middle of a black computer screen. When solving questions, subjects were instructed to use their left hand to type in their answers on the row of numbers at the top of a computer keyboard (and not the number-pad) to increase the difficulty of the task. When each problem was completed, feedback such as ‘CORRECT’ (green), ‘INCORRECT’ (red) or ‘TOO SLOW’ (purple) appeared on the computer screen, and either a pleasant 3-note jingle (correct response) or an aversive loud beep (too slow or incorrect response) sounded for one second.

*Electric shocks.* Seven shocks were delivered at irregular intervals to prevent subjects from anticipating their occurrence. When queried after the task, none of the subjects reported being aware of the contingency of shock delivery. The shock consisted of a 15 mA rectangular pulse of 25 milliseconds duration. Each pulse was delivered by an S88 Grass Square Pulse stimulator and constant current unit via 1 cm<sup>2</sup> silver/silver chloride surface electrodes. The electrodes were filled with water-soluble electrode gel and attached 2 cm apart over the right lateral sural nerve behind the lateral malleolus. The skin was slightly abraded with a pumice stone and degreased with an alcohol swab to achieve skin impedance lower than 10 Kohms. The intensity of pulses was monitored via



a custom-built digital current meter. The math task was suspended after each shock whilst subjects gave pain intensity and unpleasantness ratings. As with mood ratings, subjects were instructed to complete their ratings within 15 seconds or risk receiving an electric shock whilst making their rating. This ensured that subjects re-engaged with the math task quickly.

*Data reduction.* The number of subjects who endured the cold pressor test for the entire four minutes did not differ between groups before naltrexone or placebo were administered (20% placebo, 20% naltrexone:  $\chi^2(1) = 0.05$ ;  $p = .83$ ), after drug absorption (10% placebo, 8.7% naltrexone:  $\chi^2(1) = 0.02$ ;  $p = .88$ ), or after the math task (20% placebo, 13% naltrexone:  $\chi^2(1) = 0.38$ ;  $p = .54$ ). Thus, mean pain intensity and pain unpleasantness ratings were calculated for each cold pressor test by averaging ratings until the tolerance point was reached. Mean ratings of pain intensity and unpleasantness were also calculated for the seven electric shocks administered during the math task.

### Statistical approach

To decrease the likelihood of type 1 errors, sets of dependent variables were investigated together in multivariate analyses of variance. Significant multivariate effects were then explored in univariate analyses of variance, and Bonferroni adjustments were used to control the type 1 error rate when assessing the source of significant interactions. Data are reported as the mean  $\pm$  standard error.

The relationship between pain and negative affect was compared across the naltrexone and placebo conditions in hierarchical multiple linear regression analyses. In each regression model, the Drug condition (naltrexone or placebo) was dummy-coded and entered in the first step. Mood, averaged across the math task, was also entered in the

first step, and the interaction term (the product of Drug and Mood) was entered in the second step. This interaction tested whether modulation of pain ratings by mood differed between the naltrexone and placebo conditions (as might be expected if stress-evoked opioid release inhibits pain).

*Mood ratings.* To determine whether opioid receptor blockade increased negative affect, the effect of naltrexone on anxiety, discouragement and anger was investigated in a Drug (naltrexone, placebo) x Sex (male, female) x Time (before versus after drug administration) multivariate repeated measures analysis of variance. Changes in negative affect during and after the math task were investigated in an additional multivariate repeated measures analysis with factors of Drug, Sex and Time (before the task, the five measures during the task, and the post-task measure).

*Electrically-evoked pain.* It was hypothesized that opioid receptor blockade would increase pain ratings to the electric shocks, and that this would differ between men and women. These hypotheses were investigated in a Drug (naltrexone, placebo) x Sex (male, female) multivariate analysis of variance. The relationship between electrically-evoked pain and negative affect was then compared across the naltrexone and placebo conditions in hierarchical multiple linear regression analyses, to assess whether stress-evoked opioid release inhibited pain.

*Cold-induced pain.* We expected that opioid receptor blockade would increase cold-induced pain, particularly after psychological stress, and that this would differ between men and women. To test these hypotheses, the effect of naltrexone on pain intensity and pain unpleasantness was investigated in a Drug (naltrexone, placebo) x Sex (male, female) x Time (pre-drug, post-drug, post-math) multivariate repeated measures

analysis of variance. Main effects and interactions that involved Time were assessed with planned contrasts before and after drug administration (to determine whether changes in pain were moderated by naltrexone), and before and after mental arithmetic (to determine whether naltrexone moderated effects of psychological stress on pain). The effect of naltrexone on pain tolerance was investigated separately because preliminary analyses indicated that pain tolerance was unrelated to pain ratings at any stage of the experiment (Pearson's correlation coefficient ranged between -0.12 and 0.21 in the placebo and naltrexone groups over the course of the experiment, not significant). Finally, the relationship between cold-induced pain and negative affect was compared across the naltrexone and placebo conditions in hierarchical multiple linear regression analyses. Since the effect of the math task on mood and pain was of interest, changes in mood and pain were calculated by subtracting ratings before the math task from ratings after the math task. These analyses aimed to assess whether stress-evoked opioid release inhibited cold-induced pain.

## **Results**

### Effect of naltrexone on mood ratings

Negative affect decreased after drug administration [Pillai's trace = .723; multivariate  $F(3,37) = 3.23$ ,  $p < 0.05$ ] due to a decrease in anxiety that presumably reflected familiarization with the experimental setting [ $F(1,39) = 8.46$ ,  $p < 0.01$ ] (Figure 2A). Negative affect increased rapidly during the math task, and persisted after the task had finished [Pillai's trace = .898; multivariate  $F(18,21) = 10.3$ ,  $p < 0.001$ ]. In particular, anxiety [ $F(6,33) = 14.8$ ,  $p < 0.001$ ], discouragement [ $F(6,33) = 24.5$ ,  $p < 0.001$ ] and anger [ $F(6,33) = 9.2$ ,  $p < 0.001$ ] all increased during the task (Figure 2). By-and-large, increases in negative affect during math were similar in men and women, and naltrexone had no

consistent effect on mood (none of the multivariate tests of statistical significance for effects that included Sex or Drug was statistically significant). However, in light of the findings reported below, it is worth noting that discouragement was greater in women than men [ $F(1,38) = 4.53, p < 0.05$ ] (Figure 2B).

#### Effect of naltrexone on electrically-evoked pain during the math task

The electric shocks were regarded as moderately painful (mean rating  $56.2 \pm 3.4$ ) and unpleasant (mean rating  $54.4 \pm 3.6$ ). These ratings did not differ consistently between men or women, or between naltrexone and placebo recipients.

In general, the intensity and unpleasantness of shock-induced pain was greatest in subjects who reported most negative affect (Table 1). None of the Drug x Mood interactions in hierarchical multiple linear regression analyses achieved statistical significance, indicating that administration of naltrexone did not alter the relationship between shock-induced pain and negative affect.

#### Effect of naltrexone on cold-induced pain

Pain tolerance decreased after drug administration [from  $102 \pm 11$  s to  $79 \pm 11$  s,  $F(1,39)=9.41, p < 0.01$ ] (Figure 3A), irrespective of whether naltrexone or placebo was administered, but did not change further after the math task. On average, pain tolerance during the three cold pressor tests was greater in men than women [ $114 \pm 15$  s versus  $65 \pm 15$  s,  $F(1,39)=5.55, p < 0.05$ ] (Figure 3A), but no other effect of Sex or Drug on pain tolerance was identified at any stage of the experiment.

Most participants considered the cold pressor test to be moderately or extremely painful and unpleasant (Figures 3B and 3C). Naltrexone did not affect pain ratings before mental arithmetic, and pain intensity and unpleasantness were similar in men and women.

After the math task, pain ratings increased in female naltrexone recipients but not in any other group [interaction between Drug, Sex and Time: Pillai's trace = .252; multivariate  $F(2,38) = 6.41, p < 0.01$ ]; this applied both for pain intensity [ $F(1,39) = 6.58, p < 0.05$ ] (Figure 3B) and pain unpleasantness [ $F(1,39) = 9.55, p < 0.01$ ] (Figure 3C). Investigation of these interactions indicated that increases in pain intensity were greater in female naltrexone than placebo recipients ( $p < 0.05$  after Bonferroni correction for multiple contrasts among groups). In addition, increases in pain unpleasantness were greater in female naltrexone recipients than in any other group ( $p < 0.05$  after Bonferroni correction for multiple contrasts).

As noted above, pain tolerance was unrelated to pain ratings, and did not differ between the naltrexone and placebo groups. Nevertheless, it is possible that variation in duration of the cold pressor test contributed to differences in pain ratings between the drug conditions or between men and women. This issue was investigated by entering changes in pain tolerance as a covariate in analyses of covariance. The Drug x Sex x Time interactions remained statistically significant after the change in pain tolerance was entered as a covariate, both for pain intensity [ $F(1,38) = 6.10, p < 0.05$ ] and pain unpleasantness [ $F(1,38) = 8.13, p < 0.01$ ]. Thus, changes in pain tolerance did not appear to account for the increase in pain ratings in female naltrexone recipients after psychological stress.

As shown in Figure 4, changes in discouragement during the math task were associated with changes in pain afterwards in the naltrexone group but not in the placebo group [Drug x Discouragement interaction, for pain intensity  $t(39) = 2.91, p < 0.01$ ; for pain unpleasantness  $t(39) = 2.08, p < 0.05$ ]. The cell size ( $N = 10-12$ ) was too small to formally

investigate the association between pain and discouragement separately for men and women within the placebo and naltrexone conditions. Nonetheless, inspection of Figure 4 suggests that the slope of this relationship was similar for each sex within each Drug condition.

Changes in anxiety and anger during the math task were not associated with changes in cold-induced pain afterwards (Table 2).

### **Discussion**

The aim of this experiment was to determine whether naltrexone would alter the relationship between negative affect and pain in men and/or women. Consistent with previous findings of heightened sensitivity to pain in women (Fillingim and Maixner, 1995; Weisenfeld-Hallin, 2005), women were less tolerant of cold-induced pain than men. Of greater interest, cold-induced pain intensity and unpleasantness increased after the math task only in women administered naltrexone. Within the naltrexone condition, pain ratings increased most in the most discouraged subjects. In contrast, pain ratings were unrelated to discouragement in placebo recipients. Subcortical opioid neurotransmission may be diminished in women in low-oestrogen states (Smith et al., 2006), but this does not account for the present findings. Instead, the findings imply that a hyperalgesic effect of psychological distress was tempered by opioid release, particularly in women. The effect of naltrexone on cold-induced pain may have been stronger in women than men because women generally became more discouraged during psychological stress than men.

Frequent, intense electrical stimuli induce opioid-mediated analgesia (e.g., Hyson et al., 1982; Willer and Albe-Fessard, 1980; Willer, Dehen, and Cambier, 1981). In the

present study, however, pain induced by brief, intermittent shocks was unaffected by the opioid receptor antagonist naltrexone. Instead, the intensity and unpleasantness of shock-induced pain generally increased in proportion to ratings of anxiety, anger and discouragement, irrespective of opioid receptor blockade. According to Rhudy and Meagher (2001b), the negative affect and high levels of arousal resulting from intense stimulation activate the endogenous opioid system, leading to pain inhibition. Conversely, lower levels of negative affect facilitate pain in subjects who are exposed to aversive, uncontrollable events. Rhudy and Meagher (2001b) speculated that negative emotions of low to moderate intensity increase attention towards and amplify pain via neural circuits in the amygdala and periaqueductal grey that also modulate startle responses. Alternatively, an increase in the concentration of circulating catecholamines during psychological stress (Janssen et al., 1998), or selective attention or misattribution of arousal (Janssen, 2002), might heighten sensitivity to pain. Anger is generally associated with hyperalgesia (Bruehl et al., 2002; Janssen, Spinhoven, and Brosschot, 2001), possibly for similar reasons.

Opioid-mediated stress-induced analgesia appears to be a by-product of learned helplessness or ‘passive coping’, which is an adaptive emotional mode of coping with inescapable, threatening or stressful situations (Bandler et al., 2000). This response may follow a period of active but unsuccessful engagement with a source of stress, and is characterized by quiescence, hypotension, decreased responsiveness to the environment, and prolonged opioid-mediated analgesia (Grau et al., 1981; Keay and Bandler, 2001; Ribeiro et al., 2005). In the present study high levels of discouragement apparently evoked opioid release which, in turn, ‘capped’ painful sensations during the final cold

pressor test. In contrast, neither anger nor anxiety modulated cold-induced pain after the math task. These findings support the notion that passive resignation triggers opioid release more readily than emotions that motivate fight or flight (Keay and Bandler, 2001). This stress-induced opioid release may suppress hyperalgesia evoked by arousal and negative affect (Rhudy and Meagher, 2001b).

Although opioid receptor blockade affected the subjective experience of cold-induced pain in women after psychological stress, pain tolerance did not differ between naltrexone and placebo recipients and did not change after psychological stress. Pain tolerance appears to be influenced by contextual cues, emotions, memory, attention and negative expectations about the painful experience (Hirsch and Liebert, 1998; Zelman et al., 1991). These factors may explain why pain tolerance decreased in all groups when the cold pressor test was repeated after drug administration, and why opioid release did not increase pain tolerance in men or women after the math task. Pain tolerance was greater in men than women throughout the experiment, possibly because of differences in pain sensitivity or because men were aware of being watched by a female experimenter. This factor may also have influenced pain ratings in men.

Contrary to expectations, cold-induced pain did not change after the naltrexone administration, prior to psychological stress. The effects of  $\mu$ -opioid receptor blockade on experimental pain are inconsistent, with reports of pain increasing after naloxone administration (Buchsbaum et al., 1983; Borrás et al., 2004), not changing (El-Sobky et al., 1976; Grevert and Goldstein, 1978), or decreasing (Stacher et al., 1988; Al'Absi et al., 2004). This inconsistency may be due to individual differences in pain sensitivity (Buchsbaum et al., 1983) or could be dose-related. For example, whilst high doses of



naloxone enhance dental post-operative pain, low doses induce analgesia (Levine et al., 1979). The 50 mg dose of naltrexone used in the present study most likely was great enough to saturate opioid receptors, because this dose blocks the effects of intravenously-administered heroin in opiate-dependent individuals (Gonzalez and Brogden, 1988). Thus, the findings suggest that cold-induced pain triggered minimal opioid release before the math task. Since inescapable pain and stress appear to be potent triggers for endogenous opioid release (Keay and Bandler, 2001), perhaps naltrexone initially had little effect on cold-induced pain because subjects retained control over the duration of stimulation.

One limitation of the present study is that women were studied at all stages of the menstrual cycle, and use of oral contraceptives containing oestradiol was not controlled. Smith et al. (2006) reported that activation of endogenous opioid neurotransmission in the brain during sustained pain was similar in men and women in a high oestrogen state, but was greater in women in high than low oestrogen states. Despite this, fluctuations across the menstrual cycle are inconsistent and relatively minor for most forms of experimentally-induced pain, including cold-induced pain (Sherman and Le Resche, 2006; Kowalczyk et al., 2006). If anything, variation in opioid secretion associated with fluctuations in brain levels of oestrogen would have obscured sex differences in the present study; thus, the effects that were identified are likely to be strong.

A second methodological limitation is that the duration of the cold pressor test was under the participant's rather than the experimenter's control, thereby potentially influencing pain ratings. We could find no evidence of this in the present study – pain tolerance was unrelated to pain ratings throughout the experiment, and effects of

psychological stress on pain ratings persisted in female naltrexone recipients after variation in pain tolerance was controlled statistically. Nevertheless, to verify that the anti-nociceptive effects of opioid release are greater in women than men after psychological stress, the present findings need to be replicated in an independent sample.

In conclusion, stress-induced opioid modulation of cold-induced pain was detected in women but not men. This finding is novel and requires replication, but does not support the view that reduced opioid activity in the pain modulation pathways of women is solely responsible for sex differences in pain sensitivity. In fact, in some circumstances opioid analgesia may be greater in women than men because they are more likely to experience emotions linked with passive coping such as discouragement. The present findings suggest that opioid neurotransmission suppresses experimentally-induced pain in discouraged women following a period of psychological stress. Additional investigation of this effect in patients with chronic pain may be important. For example, it is possible to envisage the development of a vicious circle between pain, discouragement and opioid activation that promotes opioid tolerance and the persistence of pain (Bruehl et al., 1999).

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Table 1: Association between mood ratings and shock-induced pain intensity and unpleasantness during the math task

	<b>Placebo (N=23)</b>	<b>Naltrexone (N=20)</b>
<b>Pain Intensity</b>		
Anxiety	.40	.42
Discouragement	.47*	.61**
Anger	.31	.38
<b>Pain Unpleasantness</b>		
Anxiety	.53**	.47*
Discouragement	.34	.67***
Anger	.45*	.36

Pearson's correlation coefficient statistically significant: \*p<.05; \*\*p<.01; \*\*\*p<.001.



Table 2: Association between changes in cold-induced pain and mood after the math task

	<b>Placebo</b> (N=23)	<b>Naltrexone</b> (N=20)
<b>Change in Pain Tolerance with:</b>		
Change in Anxiety	-.04	.29
Change in Discouragement	-.02	-.20
Change in Anger	-.07	.02
<b>Change in Pain Intensity with:</b>		
Change in Anxiety	-.12	-.01
Change in Discouragement	-.28	.53*
Change in Anger	-.21	-.31
<b>Change in Pain Unpleasantness with:</b>		
Change in Anxiety	-.11	-.08
Change in Discouragement	-.05	.50*
Change in Anger	.02	-.12

Pearson's correlation coefficient statistically significant: \* p<0.05.

## Figure legends

Figure 1. Timeline of the experiment.

Figure 2. Mood ratings ( $\pm$  S.E.M.) before, during and after the math task. The five ratings during the math task were obtained at intervals of 5-7 minutes, starting 1.5 minutes into the task. Discouragement during and after the math task was greater in women than men ( $p < 0.05$ ), but anger and anxiety did not differ across the Sex or Drug conditions.

Figure 3. Cold-induced pain tolerance, pain intensity and unpleasantness ratings ( $\pm$  S.E.M.) before and after drug absorption, and after the math task. Pain tolerance was greater in men than women throughout the experiment ( $p < 0.05$ ), and decreased after drug administration ( $p < 0.05$ ). Pain intensity and unpleasantness increased in female naltrexone recipients after the math task ( $*p < 0.05$ ), but not in any other group.

Figure 4. Association between change in discouragement from before to after the math task, and change in the intensity and unpleasantness of cold-induced pain in men (filled circles) and women (open circles).







