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Expectancy Effects on Conditioned Pain Modulation are not Influenced by Naloxone or Morphine

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Abstract

Background—Recent studies suggest that participant expectations influence pain ratings during conditioned pain modulation testing. The present study extends this work by examining expectancy effects among individuals with and without chronic back pain after administration of placebo, naloxone, or morphine.

Purpose—To identify the influence of individual differences in expectancy on changes in heat pain ratings obtained before, during, and after a forearm ischemic pain stimulus.

Methods—Participants with chronic low back pain (n=88) and healthy controls (n=100) rated heat pain experience (i.e., “test stimulus”) before, during, and after exposure to ischemic pain (i.e., “conditioning stimulus”). Prior to testing, participants indicated whether they anticipated that their heat pain would increase, decrease, or remain unchanged during ischemic pain.

Results—Analysis of the effects of Expectancy (pain increase, decrease, or no change), Drug (placebo, naloxone, or morphine), and Group (back pain, healthy) on changes in heat pain revealed a significant main effect of Expectancy ($p = 0.001$), but no other significant main effects or interactions. Follow-up analyses revealed that individuals who expected lower pain during ischemia reported significantly larger decreases in heat pain as compared to those who expected either no change ($p = 0.004$) or increased pain ($p = 0.001$).

Conclusions—The present findings confirm that expectancy is an important contributor to conditioned pain modulation effects, and therefore significant caution is needed when interpreting

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Authors’ Statement of Conflict of Interest

The authors (C.R. France, J.W. Burns, R.J. Gupta, A. Buvanendran, M. Chont, E. Schuster, D. Orlowska, and S. Bruehl) have no conflicts of interest to report.

Authors’ Statement of Adherence to Ethical Standards

All procedures, including the informed consent process, were conducted in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

findings that do not account for this individual difference. Opioid mechanisms do not appear to be involved in these expectancy effects.

Keywords

Conditioned Pain Modulation; Ischemic Pain; Heat Pain; Opioid

Introduction

Counter-irritation or “pain-inhibiting-pain” procedures, such as cupping, scarification, and cauterization, have been used for centuries to provide temporary relief from chronic and recurrent pain [1]. Although it is currently recommended that this phenomenon be labelled as conditioned pain modulation (CPM) [2], over the years a variety of terms have been used including diffuse noxious inhibitory controls and heterotopic noxious conditioning stimulation. Regardless of the label applied, these paradigms share a common notion that exposure to a noxious “conditioning stimulus” can reduce the experience of pain from a second “test stimulus” applied to an anatomically remote area of the body. Because CPM is believed to reflect pain-evoked activation of central pain inhibitory mechanisms, this paradigm is often employed in clinical pain studies to assess potential deficiencies in endogenous pain modulation [3].

Several studies have demonstrated that CPM analgesia is reduced following administration of opioid antagonists (e.g., naloxone, naltrexone) [4–6], suggesting that individual differences in CPM efficiency may be related to endogenous opioid activity. Other studies have reported that naloxone has no effect on CPM analgesia [7–9]. Whereas the lack of uniform findings may be attributable to a variety of factors (e.g., diverse conditioning and test stimuli; different opioid antagonists, doses, and routes of administration; small samples), individual differences in expectancy during CPM testing may also play a role [10–12]. For example, Goffaux and colleagues [10] conducted a CPM study in which participants were told to expect that immersion of their arm in cold water would either increase or decrease electrical pain during nociceptive flexion reflex (NFR) assessment. Although the hypoalgesia expectation was associated with reduced pain ratings and NFR activity, this was not the case for the hyperalgesia expectation group. Investigators from the same laboratory reported similar findings when participants were asked to report their own expectations for the degree of either hyperalgesia or hypoalgesia anticipated when a cold pressor conditioning stimulus was paired with a heat thermode test stimulus [11]. Although expectancy was not the primary focus of that study and therefore did not receive significant attention in the analyses, it was reported that participant expectations were positively correlated with CPM-related changes in heat pain threshold values ($r = 0.27$, $p = 0.057$). More recently, these design elements were combined in a CPM study that assigned participants to one of four groups: no-manipulation control, hypoalgesia expectation, hyperalgesia expectation, or self-reported expectation (wherein 80% anticipated a decrease in pain) [12]. Reductions in pain ratings and NFR activity were observed in all groups except the hyperalgesia expectation group, which showed increases in pain ratings ($p = 0.09$) and NFR activity ($p < 0.001$).

As a whole the findings summarized above suggest that participant expectations, which typically are not reported in CPM studies, may help to explain variability in prior studies of CPM effects. Further, given that placebo analgesia involves opioidergic mechanisms whereas nocebo hyperalgesia has been related to non-opioid mechanisms [13–15], variability in opioid-mediated modulation of CPM effects may reflect individual differences in hypoalgesic versus hyperalgesic expectations. We hypothesized that hypoalgesic CPM expectancies would be related to subsequent decreases in pain responses during a CPM protocol via opioid-related mechanisms, whereas effects of hyperalgesic CPM expectancies would demonstrate no opioid-related effects. To evaluate these hypotheses, we conducted a secondary analysis of previously unreported CPM data from a repeated measures, double-blind CPM design in which participants received either placebo, naloxone (an opioid antagonist), or morphine (an opioid analgesic). Results for the primary aim of this study, which was to examine the relationship between endogenous opioid function and analgesic responsiveness to morphine among individuals with and without chronic low back pain, have previously been published [16]. Because expectancy effects on CPM were anticipated to be greatest when participants were naïve to the pain testing procedures, we focused our analyses on their first experimental session.

Methods

Participants

The sample included 188 individuals (106 women, 82 men) with a mean age of 34.7 years (SD = 10.5), including 88 with chronic low back pain and 100 healthy controls. Participant self-reports of race included 58.5% White, 35.1% Black, 1.1% Asian, and the remaining 5.3% either reported no race or more than one race. The majority of the sample (94.7%) self-identified as Not Hispanic or Latino.

All participants were recruited either through on-line advertisements on the Vanderbilt e-mail recruitment system, the Rush Pain Clinic, advertisements in local print media, or posted flyers. General criteria for participation included age between 18–55; no self-reported history of cardiovascular disease, hypertension, liver or kidney disorders, posttraumatic stress disorder, bipolar disorder, psychotic disorder, diabetes, seizure disorder, or alcohol or drug dependence; no use of anti-hypertensive medications; and no daily use of opioid analgesics (with absence of recent use confirmed via urine opiate screen). As in our past opioid blockade studies [17–19], additional inclusion criteria for the back pain group were chronic daily low back pain of at least 3 months' duration with an average past month severity of at least 3 on a 0–10 verbal numeric pain intensity scale. Individuals with chronic pain related to malignancy, autoimmune disorders, or fibromyalgia were excluded. Potential participants who were pregnant (determined by urine pregnancy screens) were excluded to avoid unknown effects of naloxone on the fetus. Among those with low back pain, 13 (14.8%) reported occasional use of opioid analgesics including hydrocodone/acetaminophen and oxycodone; however, none reported any opioid use in the preceding 3 days. None of the healthy controls reported opioid analgesic use.

Procedure

Procedures and findings from the primary study, which was designed to examine the relationship between endogenous opioid function and analgesic responsiveness to morphine among individuals with and without chronic low back pain, have been published [16]. However, data from the CPM protocol, described below, have not previously been analyzed or reported.

Identical data collection procedures were conducted at Vanderbilt University Medical Center and Rush University Medical Center and were approved by the Institutional Review Boards at the respective institutions. Upon arrival for the testing session participants provided informed consent and then completed a packet of questionnaires, including information regarding demographics, pain, trait anxiety [20], pain catastrophizing [21], and depression [22]. Next, participants completed a 10-min seated rest period, after which an indwelling venous cannula was inserted into their dominant arm by a trained research nurse under physician supervision. This was followed by four phases that are described in detail below, including 1) drug administration, 2) assessment of forearm ischemic pain, 3) assessment of heat pain threshold and tolerance, and 4) assessment of conditioned pain modulation.

Drug administration—After a 30-min resting period to allow adaptation to the indwelling venous cannula, participants were randomly assigned to have one of three drugs (saline placebo, naloxone, or morphine) infused in the cannula over a 10 minute period. The investigational pharmacy at each institution prepared and provided the study drugs in blinded fashion to the study nurses. Blockade of opioid receptors was achieved by administration of naloxone, an opioid antagonist with a brief half-life (1.1 hours) [23]. As in past work [17–19], an 8 mg dose in 20 ml normal saline was infused intravenously over a 10-minute period through the intravenous cannula. At this dosage, naloxone provides effective blockade of all three major opioid receptor subtypes [24]. Peak naloxone activity is achieved within 5–10 minutes, and duration of action ranges from 30 minutes to 4 hours [25]. The opioid analgesic medication examined in this study was morphine sulfate, the prototypic mu opioid receptor agonist. As in similar laboratory acute pain studies with morphine [26], the current study employed a dosage of 0.08 mg/kg (in 20ml normal saline), which was infused in the same manner as naloxone. This dosage (approximately 7mg for an average sized male) was selected because it was judged to be sufficient to produce analgesia, but low enough to avoid ceiling effects that might obscure key individual differences in morphine responding. Peak morphine activity is achieved within approximately 15 minutes [27]. Fifteen minutes following drug infusion, participants then completed the forearm ischemic pain assessment.

Ischemic pain assessment—Participants underwent an ischemic pain task based on procedures described by Maurset and colleagues [28], similar to our past opioid blockade studies [17–19]. Participants first engaged in two minutes of dominant forearm muscle exercise using a hand dynamometer set at 50% of their maximal grip strength. Then they raised their dominant forearm over their head for 15 seconds and a blood pressure cuff applied to their dominant upper arm was inflated to 200 mmHg. Their arm was then lowered and the cuff remained inflated. Participants were asked to indicate “when you first start to

experience what you would call pain" and to continue "as long as possible until you have reached your maximum pain tolerance, at which point you need to tell me to stop". In addition, at 30 second intervals participants were asked to rate the level of pain experienced using a 0–100 verbal numeric rating scale, with anchors of 0 = "no pain" and 100 = "worst possible pain". Ischemic pain threshold was defined as the time elapsed from task onset to when the sensation was first described as "painful." Ischemic pain tolerance was defined as the time elapsed between onset of the pain task and participants' expressed desire to terminate the task. For safety, a pre-determined maximal exposure time was set to 8 minutes, but participants were not informed of this limit. If a participant failed to report pain prior to the 8 minute exposure limit then ischemic pain threshold was recorded as missing. An alternative strategy is to assign a maximum exposure value of 480 seconds for the 4.3% (8/188) of the sample where this occurred; however, doing so did not alter the results as ischemic pain thresholds still did not differ as a function of expectancy group.

Heat pain threshold and tolerance assessment—A Medoc TSAII NeuroSensory Analyzer (Medoc US., Minneapolis, MN) was used to assess heat pain threshold and tolerance using an ascending method of limits protocol [26, 29, 30]. Four trials each were conducted for heat pain threshold and tolerance, with each trial conducted sequentially at one of four different non-overlapping sites on the non-dominant ventral forearm. An interval of 30 sec between successive stimuli was employed. For pain threshold trials, the probe started at an adaptation temperature of 32°C, with the temperature increasing at a ramp rate of 0.5°C/sec until participants indicated that the stimulus had begun to feel "painful" by depressing a button on a computer mouse. For each tolerance trial, the probe started at an adaptation temperature of 40°C, with the temperature increasing at a ramp rate of 0.5°C/sec until participants indicated maximum tolerance had been reached. Means of the four thermal pain threshold and tolerance trials were separately derived for use in analyses. A maximum temperature of 51°C was used to ensure participant safety. At the beginning the testing session participants received a brief standardized exposure to the thermal stimulation procedures to familiarize them with the thermal stimulus device and the concepts of pain threshold and tolerance.

Conditioned pain modulation assessment—As illustrated in Figure 1, participants experienced repeated exposure to the test stimulus (heat pain applied to the non-dominant forearm) before, during, and after exposure to the conditioning stimulus (dominant arm ischemic pain). More specifically, the entire protocol included 1) a pre-conditioning phase involving 5 minutes of repeated heat pain ratings, using the 0–100 verbal numeric rating scale, when the test stimuli were delivered at 30 seconds intervals at an intensity of 1.2 times the mean heat pain threshold as determined in the four trials described above; 2) 2 minutes of dominant forearm muscle exercise, exsanguination, and inflation of a blood pressure cuff to 200mmHg on the dominant upper arm as described in the forearm ischemic pain procedure above, 3) a conditioning phase involving heat pain ratings every 30 seconds for 5 minutes while the blood pressure cuff remained inflated, and 4) a post-conditioning phase involving heat pain ratings every 30 seconds for 5 minutes after the blood pressure cuff was deflated. Prior to beginning the pre-conditioning phase of the CPM assessment, participants received an oral description of the procedure that was complemented by a visual aid. After

confirming that they understood the procedure and answering any questions that they may have had, participants were asked “What do you think that having the blood pressure cuff inflated on one arm will do to the heat pain that you feel on your other arm?” Possible responses included a) it will not change the pain, b) it will decrease the pain, or c) it will increase the pain. If participants chose either b or c, then they were asked to indicate what percentage change they expected on a scale of 0–100%. These data were then used to compute an expected change percentage value for each participant, where expected change equaled zero for the no change group, the percentage estimate times -1 for the expected decrease group, and the original percentage estimate for the expected increase group.

Following the CPM assessment participants remained in the laboratory under observation until 2 hours had elapsed after the peak drug activity point to allow possible drug effects to remit. They were then released to a responsible adult.

Statistical Analyses

Analyses were conducted using IBM SPSS for Windows Version 21 (SPSS Inc., Chicago, IL). Group differences in demographic characteristics were examined using ANOVAs for continuous measures and Chi-Square analyses for categorical variables. We examined CPM effects as a function of expectancy, drug, and presence of chronic back pain using a 3 Expectancy (no change in pain, pain increase, pain decrease) × 3 Drug (placebo, naloxone, morphine) × 2 Group (chronic low back pain, healthy) ANOVA of the change in mean heat pain ratings from pre-conditioning phase to the conditioning phase. Consistent with recommended guidelines [2, 31], changes during CPM were calculated so that pain reductions were represented as negative values (i.e., conditioning phase - pre-conditioning phase). In addition to the primary analysis, one-sample T-tests were conducted to determine whether change scores within each expectancy condition differed significantly from zero. A Pearson correlation analysis was also conducted to examine the relationship between individual estimates of expected change and the observed change. Finally, to examine persistence of expectancy effects into the post-conditioning phase, a 3 Phase (pre-conditioning, conditioning, post-conditioning) × 3 Expectancy (no change in pain, pain increase, pain decrease) ANOVA was conducted on mean heat pain ratings. The Drug and Group effects were dropped from this latter model given absence of main or interaction effects observed in the previous analysis above. Inclusion of study site (Rush or Vanderbilt) as a variable did not alter the overall results; hence, this factor was not included in the reported analyses. All analyses used the maximum number of available cases and a two-tailed probability value of $p \leq 0.05$ as the criterion for significance. All post-hoc analyses were conducted using Bonferroni adjusted p-values.

Results

Participant Characteristics

As shown in Table 1, comparison of participant characteristics across the expectancy conditions revealed only one significant difference between the groups: participants who expected pain to decrease during CPM procedures were approximately five years younger than participants in the other two groups. In contrast, there were no significant expectancy

group differences with respect the proportion of women, the proportion of participants with chronic low back pain, or mean body mass index, trait anxiety, pain catastrophizing, and depression levels. The groups also did not differ significantly in terms of their average ischemic pain and heat pain threshold and tolerance levels. Because age was not significantly correlated with the observed change in heat pain from pre-conditioning to conditioning for either the group as a whole or within specific expectancy subgroups, age was not included as a covariate in the following analyses (although it is noted that similar results were obtained when controlling for age).

Expectancy, Drug, and Chronic Pain Group Effects on Conditioned Pain Modulation

To examine the effects of expectancy, drug, and chronic back pain status on CPM, a 3 Expectancy × 3 Drug × 2 Group ANOVA was conducted on the conditioning - pre-conditioning changes in thermal pain ratings. Results of this analysis revealed a significant main effect of Expectancy, $F(2,170) = 6.87$, $p = 0.001$, $\eta_p^2 = .075$, but no other significant main effects or interactions. As illustrated in Figure 2, post-hoc comparisons of the expectancy effect revealed that individuals who expected lower pain during CPM reported significantly larger decreases in pain during CPM procedures as compared to those who expected either no change in pain ($p = 0.004$) or an increase in pain ($p = 0.001$). However, the observed change in pain ratings did not differ significantly between those who expected no change and those who expected an increase in pain. Figure 2 also illustrates the absence of significant Drug ($p = 0.82$) or Drug × Expectancy ($p = 0.61$) effects on the change in pain ratings during CPM procedures across the three expectancy groups, indicating that the association between CPM expectancies and actual CPM elicited did not differ as a function of prior placebo, naloxone, or morphine administration. Although not illustrated, the lack of a main effect or interactions involving Group indicated that the pattern of findings was consistent across those with and without a history of chronic low back pain.

A one sample T-test, conducted to determine whether the change in pain ratings in each expectancy condition differed from zero revealed significant decreases among those who expected a decrease, $t(81) = -6.24$, $p < 0.001$, but no significant change among those who expected either no change, $t(58) = -1.68$, $p = 0.10$, or an increase, $t(46) = -0.81$, $p = 0.41$.

Figure 3 illustrates that across the three drug conditions, participant expectations of the change in heat pain during CPM procedures were positively correlated with the observed change from the pre-conditioning to conditioning phase ($r = 0.26$, $p < 0.001$, two-tailed).

Persistence of Expectancy Effects on Conditioned Pain Modulation

To examine whether the CPM effect persisted into the post-conditioning phase, a 3 Phase × 3 Expectancy MANOVA was conducted on the pre-conditioning, conditioning, and post-conditioning heat pain ratings. Results of this repeated measures analysis revealed significant effects of Phase, $F(2,183) = 22.54$, $p < 0.001$, Pillai's Trace = .198, Expectancy, $F(2,184) = 2.92$, $p = 0.05$, $\eta_p^2 = .031$, and Phase × Expectancy, $F(4,368) = 4.66$, $p = 0.001$, Pillai's Trace = .097. No other significant main effects or interactions were observed. Figure 4 illustrates the Phase × Expectancy interaction effect, with post-hoc comparisons revealing that heat pain was significantly lower than the pre-conditioning phase: 1) during the

conditioning ($p < 0.001$) and post-conditioning ($p < 0.001$) phases among those who expected pain to decrease, and 2) during the post-conditioning phase among those who expected pain to increase ($p = 0.01$). For those who expected no change, the heat pain ratings did not differ significantly during the conditioning phase ($p = 0.35$) but were marginally lower during the post-conditioning phase after adjustment for multiple comparison ($p = 0.07$).

Discussion

The results of the present study support, strengthen, and extend prior findings on the relationship between expectancy and degree of conditioned pain modulation (CPM) elicited during experimental procedures. Specifically, our findings demonstrated that concomitant application of ischemic pain (the conditioning stimulus) was associated with decreases in heat pain (the test stimulus) only among those who expected their pain to decrease. Those who expected either no change or an increase in heat pain did not show a significant change in their heat pain ratings during concomitant application of the ischemic conditioning stimulus. These findings are consistent with those of Goffaux and colleagues who demonstrated that participants who were told to expect that a CPM paradigm would decrease their pain subsequently reported such a decrease, whereas those who were told to expect that it would increase their pain reported no significant change [10]. Similar results were obtained by Cormier and colleagues [12], although in their study the expectancy of hyperalgesia was associated with a marginal increase in pain ratings and a significant increase in NFR activity. Lastly, we observed a correlation between the change in heat pain that participants expected and their subsequent change in reported heat pain ratings that was almost identical to that reported by Larivière and colleagues (i.e., $r = 0.26$ and $r = 0.27$, respectively) [11]. Although we are reticent to draw firm conclusions based on only a few studies, as a whole the existing data indicate that expectancy plays a significant, and likely underappreciated, role in determining results of CPM testing. The data also indicate that individual differences in expectancy are more likely to be borne out among those who expect their pain to either decrease or stay the same as compared to those who expect it to increase. The absence of a consistent hyperalgesic expectancy effect is particularly noteworthy, as it suggests that participants are not merely reporting changes in pain ratings simply to appear faithful to their own a priori expectations (at least not among those who expect pain to increase).

The present study also extends the current literature in several important respects. First, in contrast to our hypothesis that the lack of uniform findings in prior CPM studies that evaluated opioid-related mechanisms may have been due in part to individual differences in CPM expectancies, our findings argue against this. Neither naloxone (an opioid antagonist) nor morphine (an opioid agonist) had a significant effect on associations between a priori CPM expectancies and subsequent CPM effects. Hence, in contrast to our hypothesis that hypoalgesic expectancy effects would be opioid-mediated whereas hyperalgesic expectancies would not, the absence of significant drug by expectancy interactions failed to support this notion. Thus, at least in our data, hypoalgesic expectancy effects do not appear to be mediated by the same opioid pathways that have been implicated in placebo analgesia [13, 14], despite the fact that they both share a common expectancy for pain relief. Because

other neurotransmitters such as serotonin have been implicated in laboratory animal studies of diffuse noxious inhibitory controls [32, 33], it is possible that hypoalgesia in the context of CPM expectancies may be mediated by different neurotransmitter systems than placebo analgesia.

The present findings also demonstrated that nearly one-third of all participants did not expect exposure to a conditioning stimulus to change their test pain ratings, an expectation borne out on subsequent CPM testing. When combined with the approximately 44% of participants who expected CPM to produce hypoalgesia, a full three-quarters of the sample were in groups for which the observed mean pain response during the CPM protocol was consistent with the group expectation. This has clear implications for future CPM testing in that participant expectations are likely to contribute to the variance in test pain ratings for a significant proportion of the sample; thus, at a minimum these expectations need to be assessed and considered in interpreting CPM effects.

A third contribution of the present study is the observation that hypoalgesia among those who expected pain to decrease persisted into the post-conditioning phase. This is important as the most recent recommendations on the practice of CPM testing highlight the benefit of having an interval of test stimulus exposure that follows the conditioning stimulus in order to demonstrate modulatory effects in the absence of distraction from a concurrent conditioning stimulus [31]. Interestingly, in the present sample both hypoalgesic and hyperalgesic expectations were associated with lower test stimulus pain ratings in the post-conditioning phase. Although the reductions in heat pain ratings relative to the pre-conditioning phase were smaller among those who expected pain to increase as compared to those who expected it to decrease, the presence of such a decrease in the hyperalgesic expectancy group may suggest a true CPM effect independent of participant expectancy. This conclusion must be tempered, however, by the fact that only marginal pre- to post-conditioning reductions were observed among those who expected no change. Given this discrepancy, future studies are needed to examine the change from conditioning to post-conditioning as a potential indicator of endogenous pain modulation over and above participant expectancy effects. It should also be noted that habituation to repeated testing is a potential alternative explanation for the gradual decrease in pain ratings observed across the conditioning and post-conditioning phases. This explanation does not appear to fully account for the relatively larger decreases observed among those who expected pain to decrease as compared to those who expected pain to increase or not change; nonetheless, future studies should include a non-conditioning control condition to help separate true CPM effects from simple habituation effects. Finally, it is worth highlighting that the present findings are based on a diverse sample that is more than three times the size of prior reports and includes participants with and without a history of chronic low back pain. In this respect our data provide reassurance that expectancy effects on CPM are robust and likely to generalize to both clinical and non-clinical samples.

As with any study, several limitations must be noted. One important limitation is that, unlike prior reports that have incorporated NFR assessments as part of the test stimulus to provide an objective measure of nociceptive responding [10, 12], the present findings are based on subjective reports of thermal pain. Hence, the observed change in test stimulus pain ratings

may reflect differences in the participants' experience of heat pain, differences in participant willingness to report pain, or some combination thereof. Although a simple reporting bias does not appear to be the case among participants who reported hyperalgesic expectancies (as they did not report higher pain ratings during the conditioning phase and did report lower pain during the post-conditioning phase), this does not rule out the possibility that such an effect is operating among the larger subgroup of participants who expected a pain decrease. Related to these issues, the present findings of significant expectancy effects on CPM do not imply that there is no concurrent objective physiological descending inhibitory effect on pain responses during CPM procedures. A second limitation relates to the use of between-subjects analyses to examine possible effects of administering an opioid antagonist and opioid agonist. Although this approach is necessitated by the fact that participant expectancies are likely to evolve with repeated exposure to the CPM paradigm, thereby confounding any assessment of within-subject drug effects, it leaves open the possibility that opioid modulation of CPM effects may exist within-subjects that are not observed in a between-subjects design. This concern is perhaps reduced, but certainly not eliminated, by the relatively large sample tested.

In sum, the results of the present study demonstrate that CPM effects can be influenced by individual differences in expectancy for pain to increase, decrease, or remain unchanged. These CPM expectancy effects do not appear dependent on opioid systems. As previously noted by Cormier and colleagues [12], caution should be exercised in interpreting CPM findings as an index of the efficiency of endogenous pain modulation without considering the potential role of participant or patient expectations.

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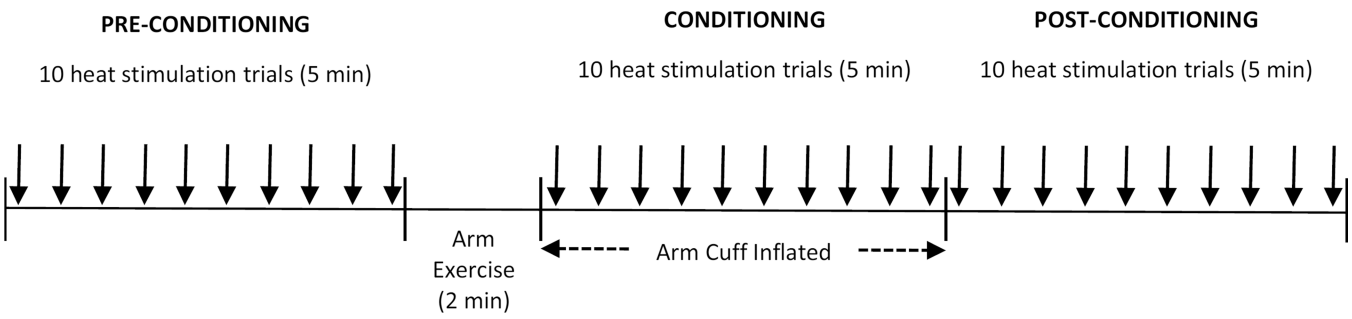

Figure 1.
Conditioned pain modulation protocol.

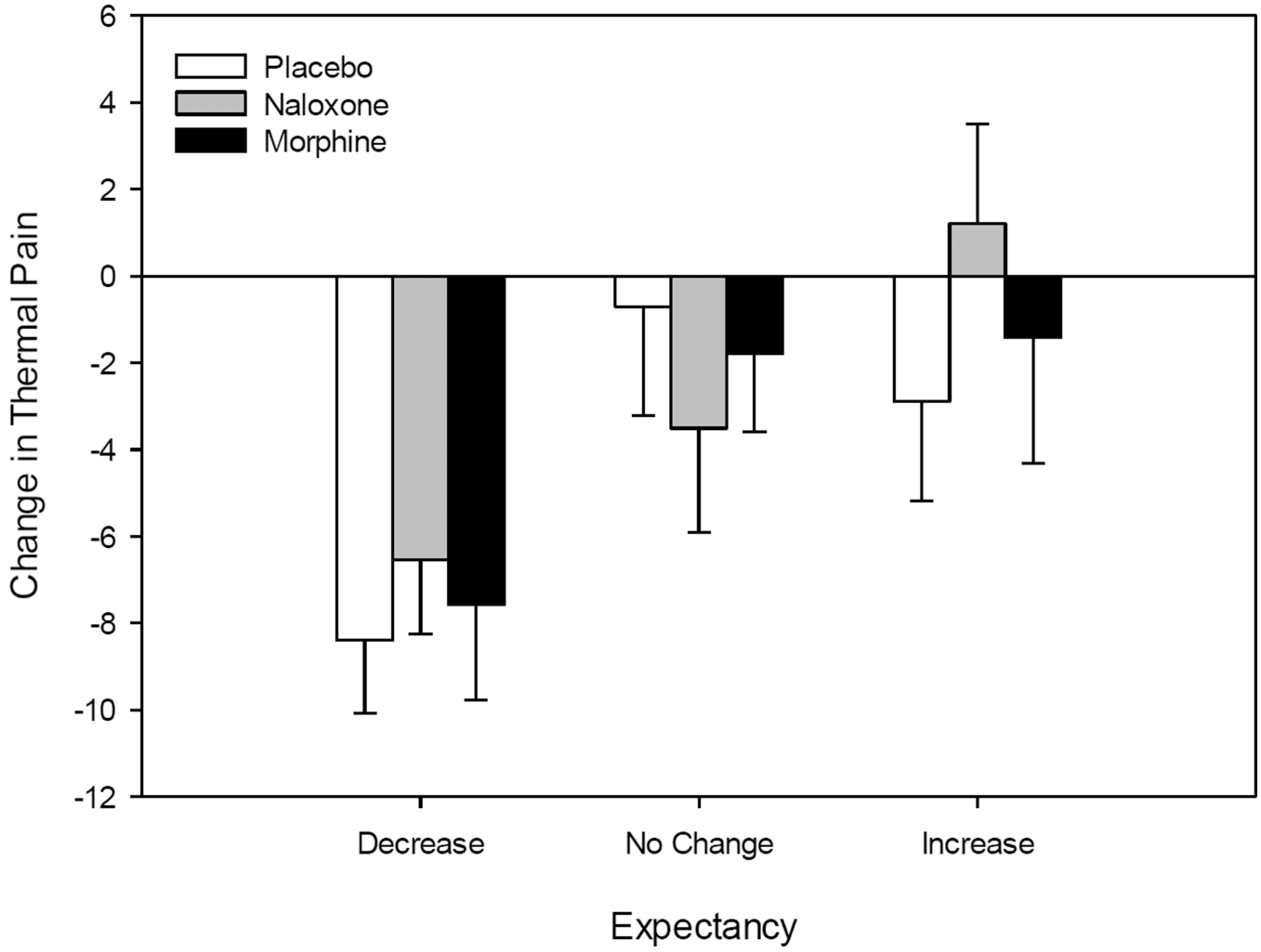

Figure 2.
Change in thermal pain from pre-conditioning to conditioning as a function of expectancy and drug administered.

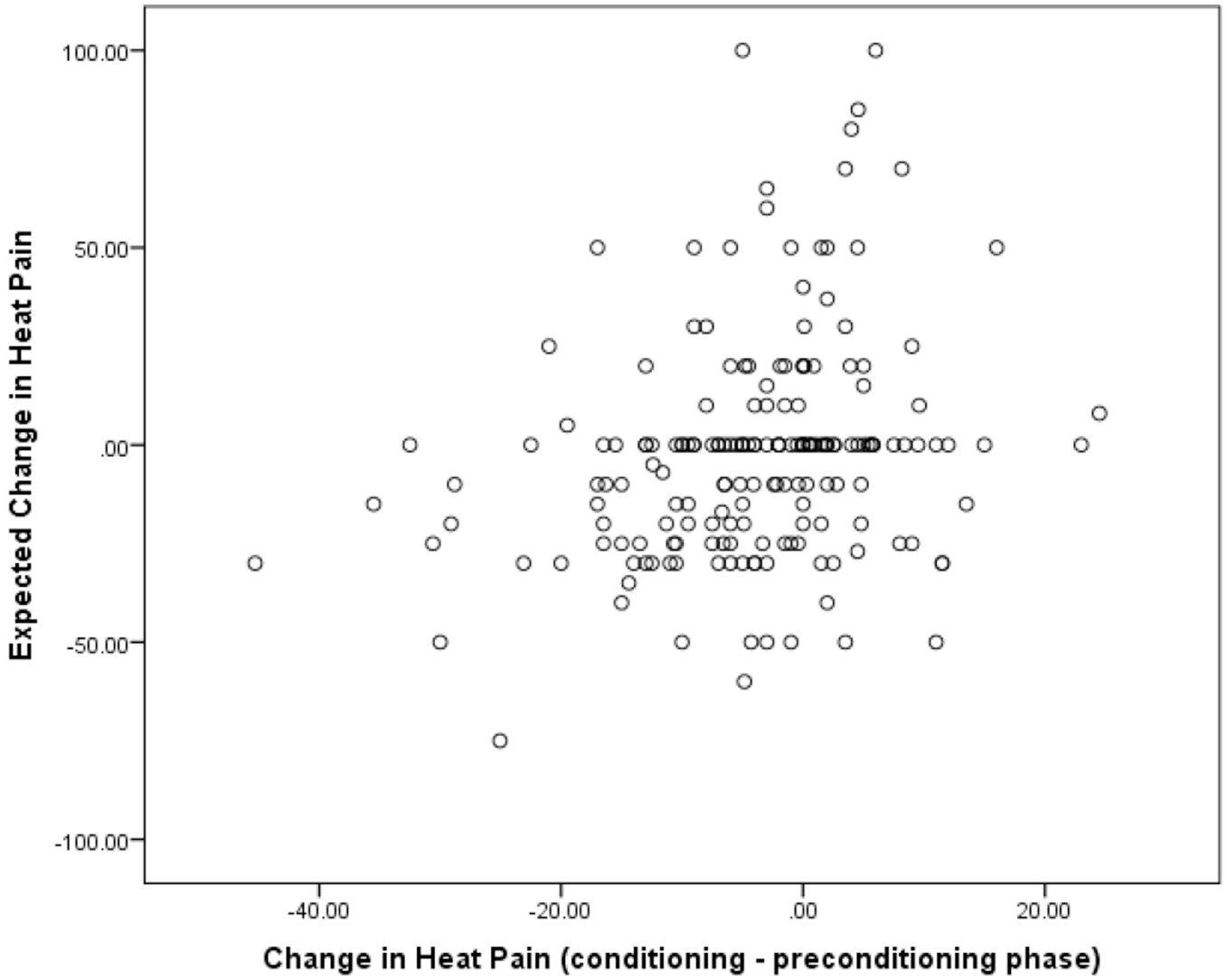

Figure 3.

A scatterplot of the relationship between participant expectations of the change in heat pain during conditioned pain modulation and the observed change from pre-conditioning to conditioning ($r = 0.26$, $p < 0.001$, two-tailed).

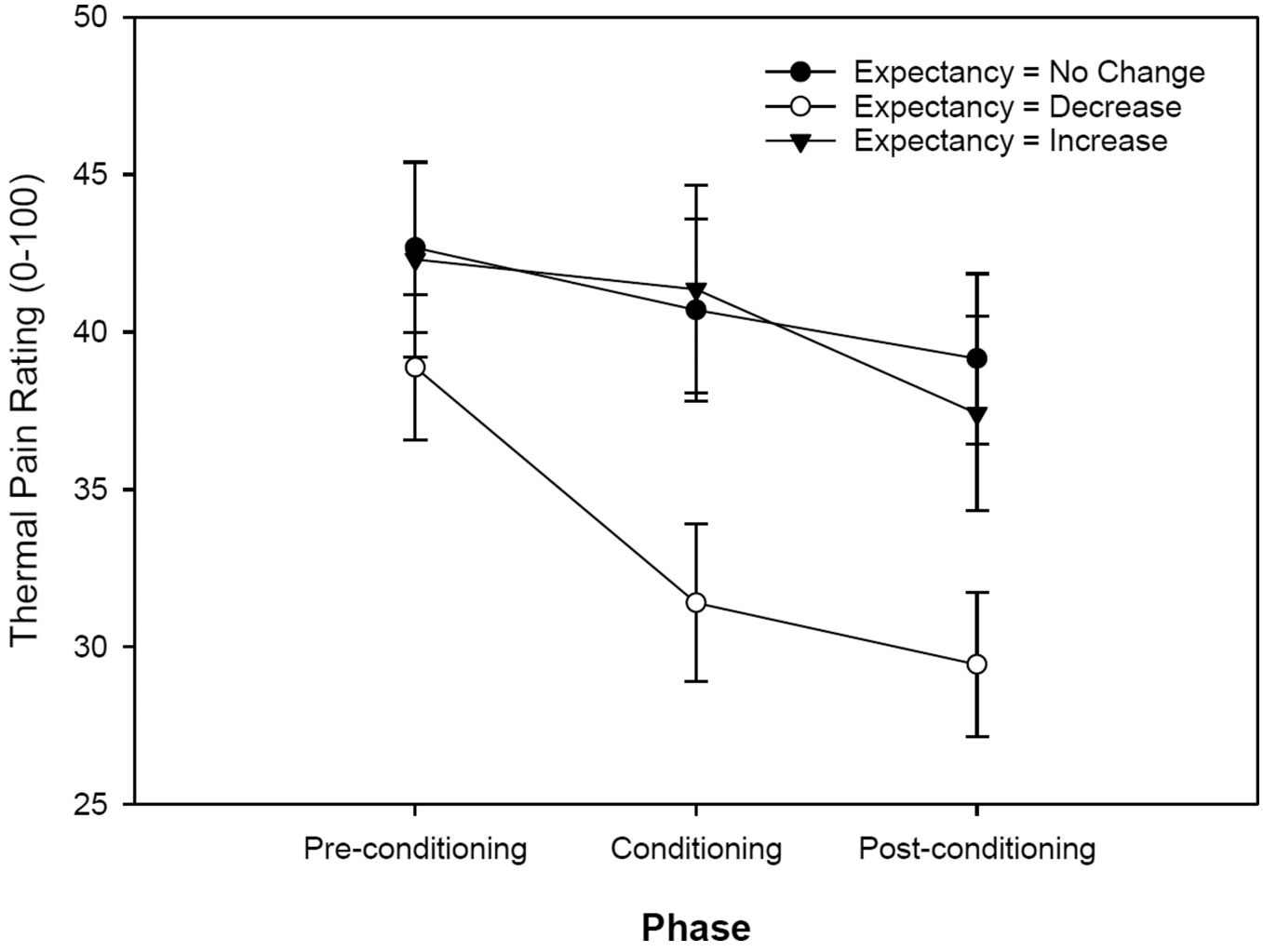

Figure 4.
Thermal pain ratings reported at pre-conditioning, conditioning, and post-conditioning phases as a function of expectancy.

Table 1

Participant characteristics, expressed in Means (SD) or percentages, as a function of conditioned pain modulation expectancy.

	Expectancy (N=188)		
Measure	**No Change (n = 59)**	**Pain Decrease (n = 82)**	**Pain Increase (n = 47)**
Age (years)	37.0 (10.1)[a]	31.9 (10.3)[b]	36.6 (10.3)[a]
Gender (% female)	49.2	59.8	59.6
Condition (% Chronic Low Back Pain)	45.8	47.6	46.8
Body Mass Index (kg/m^2)	28.3 (7.0)	27.5 (6.3)	27.8 (5.4)
Trait Anxiety Scale	34.1 (9.7)	34.1 (11.5)	35.5 (11.1)
Pain Catastrophizing Scale	9.1 (12.3)	8.4 (10.6)	10.8 (12.7)
Beck Depression Inventory	4.8 (7.3)	4.4 (6.5)	5.3 (6.3)
Ischemic Pain Threshold (seconds)	90.1 (131.7)	51.5 (99.3)	77.9 (116.8)
Ischemic Pain Tolerance (seconds)	341.9 (165.6)	317.2 (164.0)	281.2 (169.9)
Heat Pain Threshold (°C)	44.0 (3.0)	43.1 (3.1)	43.6 (3.9)
Heat Pain Tolerance (°C)	47.9 (1.5)	48.0 (1.4)	47.7 (1.7)

Note: Cells with different superscripts are significantly different at $p<.05$; Means ischemic pain threshold values exclude 8 participants (3 in No Change, 3 in Decrease, and 2 in Increase Expectancy groups) who did not reach pain threshold.