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The role of expectations and endogenous opioids in mindfulness-based relief of experimentally-induced acute pain

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Abstract

Objective—Expectations contribute to cognitive pain modulation through opioidergically-mediated descending inhibition. Mindfulness meditation reduces pain independent of endogenous opioids, engaging unique corticothalamo-cortical mechanisms. However, it remains unknown whether expectations for pain-relief predict mindfulness-induced analgesia and if these expectations are modified by endogenous opioids.

Methods—In this secondary analysis of previously published work, 78 pain-free participants (mean age 27 ± 7 years; 50% women) were randomized to a 4-session mindfulness meditation or book-listening regimen. Expectations for intervention-induced pain-relief were assessed before and after each intervention. Pain ratings were examined after meditation or rest (control group) during noxious heat (49°C) and intravenous administration of saline-placebo or the opioid antagonist naloxone (0.15 mg/kg bolus + 0.1 mg/kg/h infusion).

Results—Mindfulness significantly lowered pain during saline and naloxone infusion. Higher expected pain-relief from mindfulness predicted lower pain intensity, $r(40) = -.41$, $p = 0.009$. The relationship between meditation-related expectations and pain intensity reductions were exhibited during naloxone, $r(20) = -.76$, $p < .001$ but not saline, $r(20) = -.22$, $p = 0.36$. Expectations for book-listening based analgesia did not significantly predict pain changes during saline, $r(20) = -.37$, $p = .11$ or naloxone, $r(18) = 0.26$, $p = .30$ in the control group.

Conclusions—These novel findings demonstrate a significant role for expectations in mindfulness-based pain-relief. However, this role was minimal during saline and stronger during opioid blockade, despite similar pain reductions. This supports growing evidence that mindfulness engages multiple mechanisms to reduce pain, suggesting that mindfulness might be an effective pain-reducing technique even for individuals with low expectations for pain-relief.

Keywords

mindfulness; expectations; naloxone; opioidergic; pain relief; meditation; placebo

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Introduction

The experience of pain is modulated by a myriad of sensory, cognitive and affective factors. A wide spectrum of cognitive manipulations are postulated to reduce pain through a common final neurophysiological pathway (1). For example, analgesia produced by placebo (2–6), conditioned pain modulation (7), distraction (8), and hypnosis (9, 10) are driven by opioidergically mediated descending inhibition of pain through prefrontal (PFC) regulation of the periaqueductal gray matter. This system is characterized as the central pain modulatory physiological system (11–13).

Prior beliefs and expectations also alter behavioral and neural pain responses (14, 15). Expectations for lower pain corresponding to a frankly noxious stimulus elicit attenuated behavioral and neural pain response (i.e., the placebo effect) (16–21), while higher expectations of pain during innocuous stimulation produce higher pain responses (i.e., nocebo effects) (22–26). Manipulation of *expectations* modulates pain through endogenous opioidergic release (3, 4, 6, 20, 27, 28). In contrast, *conditioned* placebo responses on pain are not typically mediated by opioids (29). Interestingly, reappraisal-based manipulations are postulated to reduce pain independent of opioidergically-driven systems (30–33).

Mindfulness-based meditation, a cognitive practice premised on sustaining non-judgmental awareness of the present moment, a reappraisal technique, reliably reduces experimental and clinical pain (34–38). As adapted in our laboratory, mindfulness meditation participants are taught to focus their attention on their breath in a non-reactive manner. We have repeatedly demonstrated that mindfulness-based pain-relief is not mediated by endogenous opioids (33, 39, 40) and engages multiple neural mechanisms distinct from placebo analgesia to exert its pain-relieving effects (33, 41, 42). Mindfulness meditation reduces anticipation and corresponding negative pain appraisals (43). However, it remains unknown a) whether expectations play a role in mindfulness-based pain relief, and b) if endogenous opioids are involved in facilitating this postulated effect.

In the current study, a secondary analysis was conducted on our previously reported double-blinded study that demonstrated that mindfulness-based pain relief is not reversed by high-dose intravenous (IV) naloxone (39). In that study, mindfulness-based meditation during IV opioidergic antagonism (naloxone) and saline infusion produced significant reductions in pain when compared to baseline and the control groups (31, 44). Thus, it was discovered that mindfulness-based meditation does not engage endogenous opioids to reduce pain. Here, we investigated the role of expectations for mindfulness-induced pain relief during noxious heat. Further, we interrogated whether the potential relationship between expectations of mindfulness-based pain relief and actual pain relief is altered by opioid blockade.

We hypothesized that expectations would not be significantly associated with mindfulness-based pain relief. There are a number of reasons for this hypothesis. For one, mindfulness meditation is premised on sustaining non-reactive attention to the present moment and *detachment* from expectations (45); thus, the impact of prior expectations should be assuaged. Second, converging lines of evidence demonstrate that mindfulness-induced pain

relief is associated with attenuated neural activation leading up to noxious stimulation (43, 46), providing some neural evidence for our overarching hypothesis. We also predicted that opioid blockade would not alter the effect of expectations for mindfulness-based analgesia because endogenous opioids do not mediate mindfulness-based pain relief (32, 33, 39).

Methods

Participants:

Data were collected from March 3, 2015 to June 24th, 2015. Seventy-eight participants (75 right-handed; mean age = 27 years \pm 7 years; 39 males; 39 females) successfully completed all study procedures (57 were White, 8 were Asian, 7 were Black, 4 were Hispanic, 1 was Native American, and 1 self-identified as “mixed”). Study procedures were approved by the Wake Forest School of Medicine Institutional Review Board. All participants were told that the study would assess whether meditation was associated with “the release of naturally occurring opiates” and that they would “receive intravenous administration of saline or naloxone, a relatively safe drug that blocks the transmission of opioid activity.” Male and female participants were separately randomized without replacement to one of four groups (meditation + naloxone, control + naloxone, meditation + saline, or control + saline) in a double-blind manner.

Stimuli:

Medoc TSA-II (Medoc, Inc.) delivered all thermal stimuli employing a 16mm² surface area thermal probe. To reduce habituation, the thermal probe was moved to a new stimulation site after each experimental series. All stimulus temperatures were less than or equal to 49°C and participants were free to escape the stimulator at any time by lifting their limb from a custom-made probe holder.

Psychophysical assessment of pain:

Pain intensity and unpleasantness ratings were assessed with 15cm plastic sliding visual analog scales (VAS) (47). The minimum rating (“0”) was designated as “no pain sensation” and “not at all unpleasant” whereas the maximum (“10”) was labeled as “most intense pain sensation imaginable” or “most unpleasant sensation imaginable”, respectively.

Naloxone and saline administration:

A 0.15 mg/kg bolus dose of naloxone (Naloxone HCl, Amphastar Pharmaceuticals, Inc., Rancho Cucamonga, California) or saline in 25ml normal saline was administered over 10 minutes (min) via the IV line inserted into the antecubital vein of the non-dominant arm. To ensure that naloxone would antagonize opioid receptors for entirety of the experiment, we administered a supplementary IV infusion dose of 0.1mg/kg/hour naloxone or saline immediately after the bolus infusion ceased, until the end of the experiment (~12 min). Only the study physicians, research pharmacist, and research coordinator were aware of participant-drug assignment. Participants, research nurses, and all experimenters were blinded to drug assignment.

Experimental Design

Experimental Session 1 (psychophysical training): Participants were initially familiarized with 32, 5 second (s) duration stimuli (35 – 49°C; ventral aspect of the left forearm) and use of the VAS (48–50). Baseline (pre-intervention) psychophysical responses to noxious heat were probed by administering two heat series. Heat series [4 min and 24 s] included ten, alternating 12 s plateaus of 49°C and 35°C stimulation to the back of the right calf. VAS pain ratings were collected after each series. Prior to randomization into groups, participants were asked to rate their expectations for pain relief from each intervention: “how much do you expect that meditation will be effective in reducing your pain symptoms?” and “how much do you expect that listening to a book will be effective in reducing your pain symptoms?” using separate VAS scales (0= “not at all” – 10 = “most effective imaginable”).

After successful completion of sensory testing, participants were instructed of their respective group assignment (i.e., meditation; control). There were four groups in the present study. Participants were randomized to a mindfulness + saline, mindfulness + naloxone, book-listening control + saline, and a book-listening control + naloxone group.

Experimental session 2–5: Group intervention sessions: Participants assigned to the mindfulness meditation intervention completed four 20-min sessions of mindfulness-based mental training on separate days. Training was premised on sustaining non-reactive attention to the breath. Participants assigned to the control group listened to *The Natural History of Selborne* (51) during four 20-min sessions on separate days. Participants were prohibited from talking, sleeping, or using their phones during these sessions. See (39) for complete regimen details.

Experimental Session 6: Pharmacologic infusion session: After reporting to the Wake Forest Clinical Research Unit, participants were administered an opiate-focused urine drug screen to avoid opiate-related withdrawal symptoms. Weight, blood pressure, respiration rate and oxygen saturation were collected and monitored, respectively. Results are reported elsewhere (31). A research nurse then inserted the IV catheter into the non-dominant arm and participants placed their right calf on a custom-made thermal probe holder.

Participants were then asked to rate “how effectively do you expect mindfulness meditation and listening to a book would to reduce your pain?” using a VAS scale (0= “not at all” – 10 = “most effective imaginable”).

Rest: Two heat series were then administered and VAS pain intensity and unpleasantness ratings were collected after each series.

Naloxone/Saline Administration: After the first two heat series, a research nurse initiated the naloxone/placebo infusion. Participants in the meditation group were instructed to “begin meditating and continue meditating until the end of the experiment.” Control group participants were told to “close your eyes and relax until the end of the experiment.” Participants were given 10 minutes to meditate before administering the additional heat series.

Manipulation (Meditation/Control): Two more heat series were administered during meditation or rest (i.e., control condition) and VAS pain intensity and unpleasantness ratings were collected after each series.

Data Analysis—The present analyses [SPSS 25.0 (IBM, Armonk, New York, USA)] are secondary from our previous work (39). A univariate ANOVA examined if pre-intervention pain ratings significantly varied by group.

A 4 (group) \times 2 [pre (rest) vs. post (manipulation=rest/meditation)] \times 2 (pain intensity vs. pain unpleasantness ratings) repeated measures (RM) ANOVA was conducted to test for the effect of the intervention and drug on heat-induced pain ratings. Post hoc assessments were performed to interpret significant interactions and pairwise comparisons.

Ratings of expected pain relief for mindfulness versus book-listening in Session 1 and in Session 6 were compared between session and between interventions using paired t-tests. A one-way ANOVA was conducted to test for baseline differences in intervention expectations by subsequent group randomization. Pearson bivariate correlations were computed between ratings of expected pain relief from both Sessions 1 and 6 and the percent change in VAS pain intensity and unpleasantness ratings from before to during the naloxone or saline infusion in Session 6. Correlations were also computed between expectation ratings and pain reductions within each group's respective naloxone and saline conditions.

Results

Pre-intervention expectations for pain relief were higher for mindfulness than book-listening

Ratings of expected pain relief collected in Session 1 before randomization were higher for the mindfulness than for the book-listening group, $t(75) = 10.97, p < 0.001$; Figure 1). There were no significant group differences in Session 1 expectation ratings of pain relief corresponding to mindfulness, $F(3,72) = 1.57, p = 0.20$, or book-listening, $F(3, 73) = 2.02, p = 0.12$.

Book-listening based expectations for pain relief predicted higher pain in the controls

When both mindfulness meditation groups were combined, Session 1 expectations for mindfulness-based pain relief did not significantly predict mindfulness-based reductions in Session in pain intensity, $r(40) = -.296, p = 0.064$ or pain unpleasantness $r(40) = -.107, p = 0.51$. In the average response of the two book-listening control groups, higher expected book-listening pain relief was associated with *higher* pain intensity $r(37) = .470, p = 0.003$, and higher pain unpleasantness ratings, $r(37) = .399, p = 0.014$, in Session 6.

During opioid antagonism, pre-intervention expected pain relief predicted post-intervention mindfulness-based pain relief and book-listening associated pain increases

In the mindfulness meditation and naloxone group, specifically, higher Session 1 expectations for mindfulness-based analgesia significantly predicted mindfulness-meditation-induced reductions in pain intensity, $r(20) = -.644, p = 0.002$, and pain

unpleasantness, $r(20) = -.462, p = 0.040$. Of note, in this same group, Session 1 expectations about book-listening were also predictive of mindfulness-meditation-induced reductions in pain intensity ($r(20) = -.541, p = 0.014$) and unpleasantness (trend, $r(20) = -.401, p = 0.080$). In contrast, in the mindfulness-meditation-saline group, there was no significant correlation between Session 1 mindfulness-meditation expectations and reductions in pain intensity, $r(20) = 0.026, p = .91$, and pain unpleasantness, $r(20) = 0.217, p = .36$.

The book-listening groups showed similar correlations between Session 1 expectations and pain changes experienced in Session 6 between the groups that received naloxone (pain intensity $r(18) = 0.556, p = .017$, pain unpleasantness, $r(18) = 0.498, p = .036$) and saline (pain intensity, $r(20) = 0.408, p = .083$, pain unpleasantness, $r(20) = 0.309, p = .20$).

Post-intervention expectations for pain relief were higher for mindfulness than book-listening

After the respective study interventions, ratings of expected pain relief were significantly higher for meditation-based pain relief in the meditation group than for book-listening based pain relief in the book-listening group, $t(76) = 10.92, p < 0.001$ (Figure 1). Completion of the meditation interventions did not significantly change expectations for pain relief in the mindfulness-meditation group, $t(39) = 1.06, p = 0.30$ (Figure 1). Completion of the book-listening interventions did not significantly change expectations for pain relief in the book-listening group, $t(36) = 0.70, p = 0.49$. Expectations for pain relief were significantly correlated between Sessions 1 and 6 for mindfulness meditation, $r(40) = .588, p < 0.01$ but not for book-listening control groups, $r(37) = .209, p = .22$.

Post-intervention expectations predicted mindfulness-based pain relief during opioid antagonism

Expected mindfulness-induced pain relief ratings after the meditation interventions predicted mindfulness-based reductions in pain intensity, $r(40) = -.406, p = 0.009$ and pain unpleasantness, $r(40) = -.342, p = .031$ ratings across both groups. In contrast, expected pain relief for the book-listening control groups did not predict ratings of pain intensity, $r(38) = -.071, p = 0.67$ or pain unpleasantness, $r(38) = -.045, p = .79$.

In the meditation + naloxone group specifically, higher expected pain relief predicted greater mindfulness-induced reductions in ratings of pain intensity, $r(20) = -.76, p < .001$ and pain unpleasantness, $r(20) = -.55, p = .01$ (Figure 2). In the meditation + saline group, expected pain relief did not predict ratings of mindfulness-based pain intensity, $r(20) = -.22, p = 0.36$ or pain unpleasantness, $r(20) = -.23, p = .34$ (Figure 2). The correlation between expectations for analgesia and pain relief reported during naloxone was significantly ($p = 0.024$) greater than the association between expectations for pain relief and pain relief experienced during saline infusion.

Expectations of pain relief for the book-listening control groups did not predict pain reductions during either saline (pain intensity $r(20) = -.37, p = .11$; pain unpleasantness $r(20) = -.30, p = .20$) or naloxone (pain intensity $r(18) = 0.26, p = .30$; pain unpleasantness $r(20) = 0.14, p = 0.60$) infusion.

Mindfulness-induced pain relief is not associated with endogenous opioids

A significant group \times pre vs. post \times pain type interaction, $F(3, 74) = 7.01, p < .001, \eta^2_p = .22$ was revealed. To interpret the significant interaction, we performed a separate RM ANOVAs on pain intensity and pain unpleasantness ratings, respectively.

Pain Intensity—There was a significant pre vs. post, $F(1, 74) = 4.22, p = .04, \eta^2_p = .05$ and a pre vs. post \times group interaction on pain intensity ratings, $F(3, 74) = 12.86, p < .001, \eta^2_p = .34$. Follow-up post-hoc univariate ANOVAs and pairwise comparisons on pain intensity percent changes revealed no significant differences ($p = .72$) between mindfulness + naloxone (-24%) and mindfulness + saline (-21%) groups (Figure 3). The mindfulness + saline group produced significantly greater pain intensity reductions when compared to the control + saline ($+21\%$; $p = .001$) and control + naloxone ($+11\%$; $p < .001$). The mindfulness + naloxone group produced significantly greater pain intensity reductions than control + saline and control + naloxone (p values $< .001$) (Figure 3). The percent change in pain intensity ratings between the two control groups did not significantly differ ($p = .38$).

Pain Unpleasantness—There was a significant pre vs. post main effect, $F(1, 74) = 14.93, p < .001, \eta^2_p = .17$ and a pre vs. post \times group interaction on pain unpleasantness ratings, $F(3, 74) = 18.09, p < .001, \eta^2_p = .42$. Post-hoc univariate ANOVAs and pairwise comparisons on the percent change in pain unpleasantness revealed no significant differences ($p = .75$) between mindfulness + naloxone (-33%) and mindfulness + saline (-36%) groups (Figure 3). The mindfulness + saline group produced significantly greater pain unpleasantness reductions when compared to the control + saline ($+15\%$; $p < .001$) and control + naloxone ($+18\%$; $p < .001$). The mindfulness + naloxone group produced significantly greater pain unpleasantness reductions than control + saline and control + naloxone (p values $< .001$) (Figure 3). The percent change in pain unpleasantness ratings between the two control groups did not significantly differ ($p = .74$).

Discussion

The current study investigated whether expectations for pain relief predicted mindfulness-induced pain reductions. Secondly, we examined the role of endogenous opioids in the relationship between expectations and mindfulness-based pain relief. In contrast to our hypothesis, expectations for mindfulness meditation-induced pain relief did significantly predict pain reductions during mindfulness meditation. However, this correlation was significantly higher during opioid antagonism than during the control saline condition and was not statistically significant during the control saline condition alone (Figure 2). A similar pattern of correlations was found for expectations *before* the mindfulness meditation intervention and even for expectations of book-listening in the mindfulness group, suggesting that the role of expectations was a general role of optimism and was not based on experience with meditation.

The low and not significant correlation between expectations and mindfulness meditation-based pain relief during saline contrasts with the role of expectations in facilitating placebo (29, 52, 53) and hypnosis-induced (54, 55) analgesia. Indeed, we have previously shown that mindfulness meditation operates via distinct neural, autonomic nervous, and endogenous

pain modulatory mechanisms from placebo analgesia (33, 36, 39, 42). The current finding fits with the novel, non-opioidergic pain modulatory pathway proposed to underlie the pain-relieving effects of mindfulness meditation (56). We have proposed that mindfulness meditation-based pain relief is mediated by self-regulated attention-to-breath, which may engage a PFC-thalamo-cortical pathway (31, 33, 36, 50, 57). This pathway presumably activates the GABA-ergic thalamic reticular nuclei via prefrontal projections to reduce transmission of ascending thalamocortical projections to somatosensory areas (58–60).

The low association between mindfulness-based pain relief and expectations during saline is also consistent with previous demonstrations that mindfulness reduces anticipatory pain appraisals. Mindfulness reduces anterior insular activation during the pre-stimulus onset period (46) and mindfulness-based pain relief is directly associated with lower electrophysiological anticipatory markers in the medial cingulate cortex (43). These findings suggest that mindfulness meditation may reduce expectation-driven activations in anticipation of painful stimulation, decreasing the role of expectations in the processing of acute pain.

Surprisingly, expectations did predict mindfulness-based pain relief during opioidergic antagonism. Opioids are thought to be necessary for the maintenance of expectations and their role in placebo analgesia (26, 61–63). There is precedent for a role of expectations during opioid blockade from reports of expectation-driven placebo effects being maintained during opioid blockade (64) and being unaffected by administration of an opioid analgesic drug (65). However, our result suggests that expectations are *more* relevant to the experience of pain during opioid blockade.

Possible explanations for the role of expectations during mindfulness-induced pain relief and opioid antagonism may reflect the mechanistic relevance of the dopaminergic and GABAergic systems. A number of brain areas are implicated in the maintenance of expectations during placebo analgesia including parts of the dopamine-rich nucleus accumbens–ventral striatum (NAc-VS), areas associated with modulating affect and value (66). Expectation-driven placebo analgesia generally increases activity in the NAc-VS (67, 68). The dopamine system is also heavily driven by gamma-aminobutyric acid (GABA) (69), an inhibitory neurotransmitter that regulates the excitability of cortical networks (70). Importantly, the release of endogenous opioids inhibits GABAergic synaptic transmission and inversely, opioid blockade increases GABAergic synaptic transmission (71). GABAergic neurons in the ventral tegmental area (VTA) are postulated to encode the value of expected reward which is then utilized by dopaminergic neurons in the VTA to compute prediction errors (i.e., the discrepancy between expected and realized rewards) (72, 73). If opioid antagonism increases GABA, this might strengthen (or induce) GABAergically mediated encoding via dopamine of expected reward, in this case pain relief (30, 74, 75), preserving the encoding of expectations for pain-relief despite the presumable present-minded focus engaged during mindfulness meditation. Although we did not test for this, we postulate that the more a participant expected and perceived meditation as rewarding in the context of positive mood and pain relief (76–78), the greater the GABA-mediated encoding of expected reward.

Before experience with the book, expectations for pain relief induced by book-listening predicted pain *increases* in the final session. After experience with the book, this correlation was not significant. The lack of correlation for the book-listening group may be due to a floor effect since expectations for pain relief from book-listening were quite low. Although we did not directly test for this, we postulate further that this lack of covariance may be due to a violation of expectations for book-induced analgesia after subjects experienced the “boring” and “dry” story material. Indeed, expectations for book-listening related pain relief between Session 1 and Session 6 were not significantly correlated.

In sum, we demonstrate that expectations exhibit low correlation with mindfulness meditation-based relief of acute pain under *normal*, opioidergic circumstances. However, we find a novel effect of endogenous opioids in modulating the role of expectations in meditation-induced pain relief; in the present study, opioid blockade strengthened the relationship between expected and experienced mindfulness-based pain relief, even for expectations rated before meditation exposure. Mindfulness may thus operate through multiple mechanisms that are shifted by the activity of opioids, potentially altering GABAergic and dopaminergic pathways. From a clinical perspective, these findings suggest that mindfulness alleviates acute pain largely independent of expectations. This is important because it suggests that under normal conditions individuals with low expectations for pain relief from mindfulness may still experience mindfulness-induced pain attenuation, an important consideration for the millions of chronic pain patients seeking a robust and reliable self-regulated pain therapy. However, further work is needed to confirm whether this finding holds true for relief of chronic pain, recurrent acute pain, and/or in a broader range of ages including older adults. That is, effects presented here may not be realized in chronic pain patients and older adults. Further, these findings demonstrate further evidence that mindfulness is mechanistically distinct from other cognitive techniques and provides mechanistic insight into the recent surge of well-controlled clinical trials demonstrating the analgesic benefits of mindfulness training on a spectrum of pain conditions (34, 37, 79–84).

Conflicts of Interest and Source of Funding:

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Acronyms

VAS	visual analog scale
IV	intravenous
VTA	ventral tegmental area
NAc-VS	nucleus accumbens–ventral striatum
GABA	gamma-aminobutyric acid; prefrontal cortex (PFC)
S	second

Min	minute
RM ANOVA	repeated measures analysis of variance

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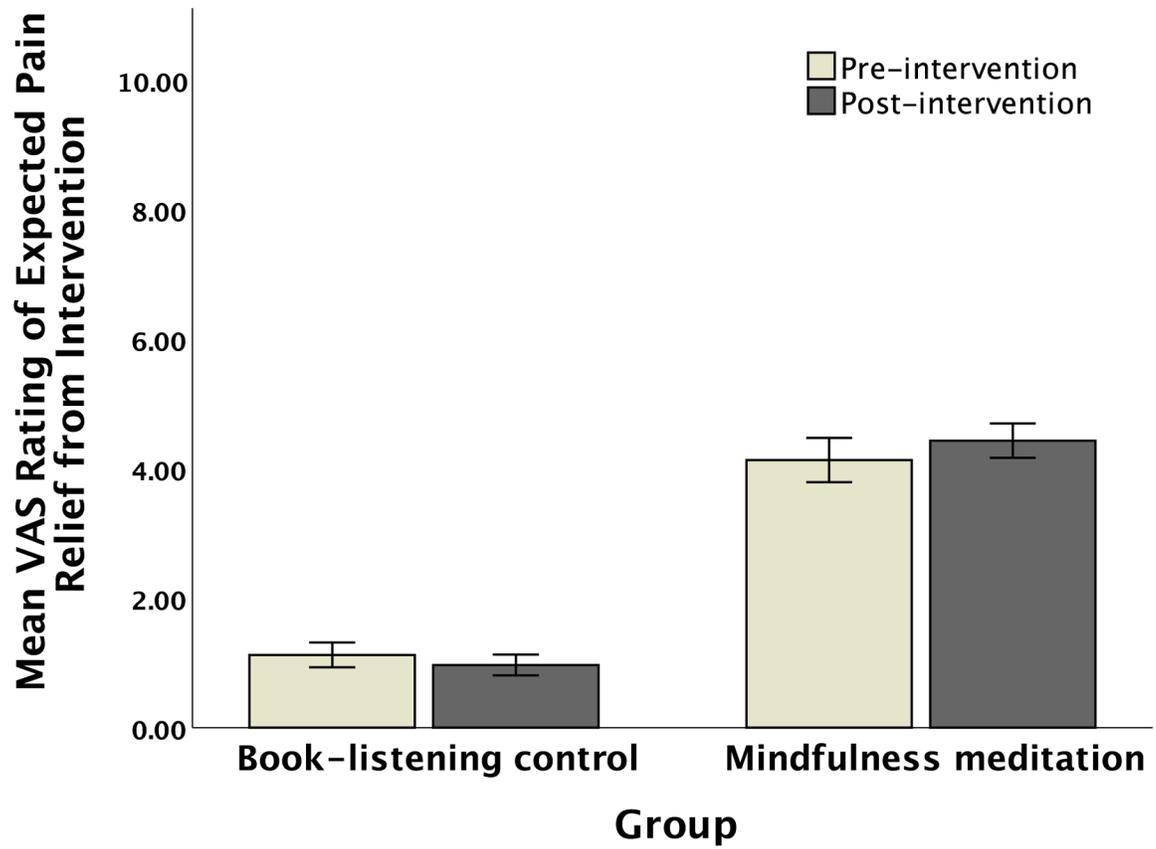


Figure 1. Naïve, pre-intervention (Session 1) and post-intervention (Session 6) ratings of expected pain relief from book-listening or mindfulness meditation, within each respective intervention group. Error bars depict SEM.

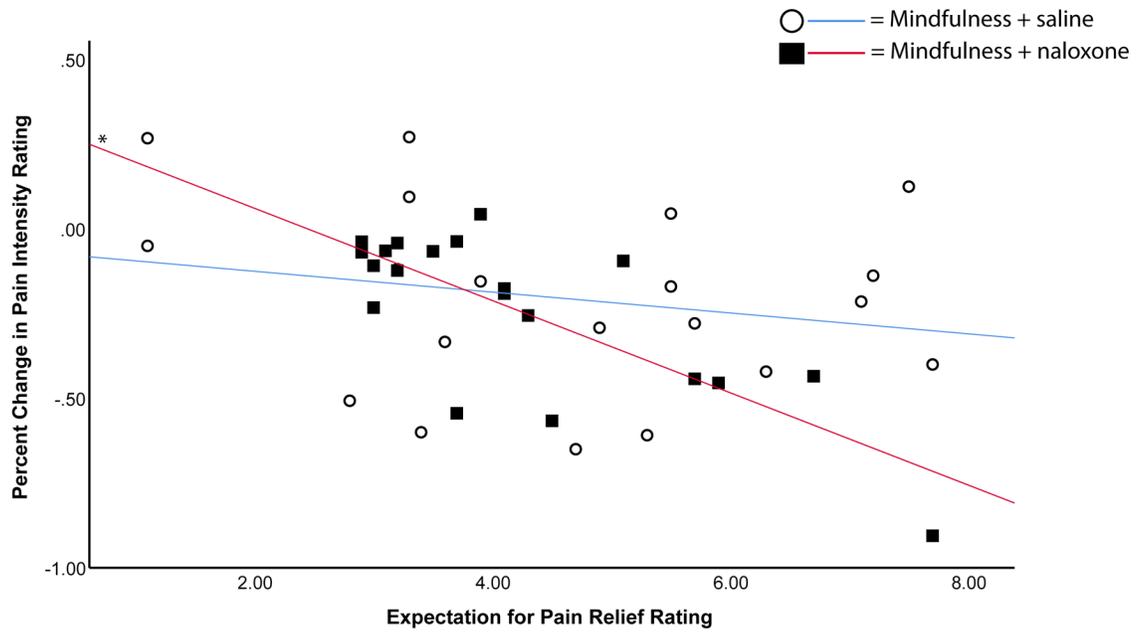


Figure 2. Correlations are displayed between ratings of expected pain relief due to mindfulness (“Expectation for Pain Relief Rating”) and percent changes in pain between baseline and intervention (“Percent Change in Pain Intensity Rating”). * = $p < 0.01$.

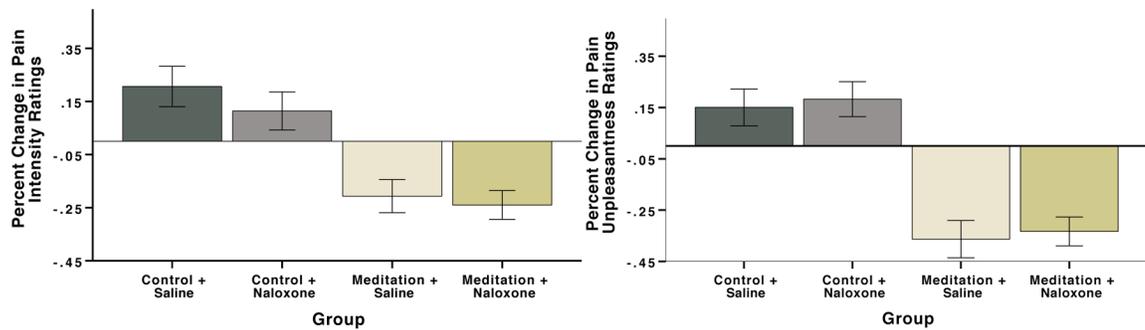


Figure 3.

Percent change in ratings of pain intensity (A) and pain unpleasantness (B) during meditation or control book-listening and naloxone or saline infusion, compared with rest. Error bars depict SEM. There were no significant differences between the mindfulness + naloxone and mindfulness + saline group (pain intensity $p = .72$; pain unpleasantness $p = .75$). The mindfulness + saline group produced significantly greater pain relief compared to the control + saline group (pain intensity $p = .001$; pain unpleasantness $p < .001$) or control + naloxone group (pain intensity and unpleasantness both $p < .001$). The mindfulness + naloxone group produced significantly greater pain relief than the control + saline group or control + naloxone group (all p values $< .001$).

Table 1.

Change in ratings (Mean and SD) of pain intensity and unpleasantness of heat administered before and during the infusion of naloxone or saline.

	Meditation + naloxone	Control + naloxone	Meditation + saline	Control + saline
Pain intensity before infusion (pre)	4.62 (1.45)	4.11 (1.63)	3.44 (1.78)	4.78 (2.51)
Pain intensity during infusion (post)	3.53 (1.58) <i>N</i> = 20 <i>p</i> = .000 *	4.40 (1.64) <i>N</i> = 18 <i>p</i> = .197	2.78 (1.64) <i>N</i> = 20 <i>p</i> = .003 *	5.33 (2.44) <i>N</i> = 20 <i>p</i> = .012 *
Pain unpleasantness before infusion (pre)	4.69 (1.64)	3.88 (1.59)	3.54 (2.11)	5.01 (2.57)
Pain unpleasantness during infusion (post)	3.11 (1.56) <i>N</i> = 20 <i>p</i> = .000 *	4.40 (1.62) <i>N</i> = 18 <i>p</i> = .073	2.05 (1.16) <i>N</i> = 20 <i>p</i> = .000 *	5.45 (2.54) <i>N</i> = 20 <i>p</i> = .107

* pairwise comparison between pre and post ratings, $p < 0.0125$ (Bonferroni correction for four groups)