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The role of heart rate variability in mindfulness-based pain relief

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Abstract

Mindfulness meditation is a self-regulatory practice premised on sustaining non-reactive awareness of arising sensory events that reliably reduces pain. Yet, the specific analgesic mechanisms supporting mindfulness have not been comprehensively disentangled from the potential non-specific factors supporting this technique. Increased parasympathetic nervous system (PNS) activity is associated with pain relief corresponding to a number of cognitive manipulations. However, the relationship between the PNS and mindfulness-based pain attenuation remains unknown. The primary objective of the present study was to determine the role of high frequency heart rate variability (HF HRV), a marker of PNS activity, during mindfulness-based pain relief as compared to a validated, sham-mindfulness meditation technique that served as a breathing-based control. Sixty-two healthy volunteers (31 females; 31 males) were randomized to a four-session (25 minutes/session) mindfulness or sham-mindfulness training regimen. Before and after each group's respective training, participants were administered noxious (49°C) and innocuous (35°C) heat to the right calf. HF HRV and respiration rate were recorded during thermal stimulation and pain intensity and unpleasantness ratings were collected after each stimulation series. The primary analysis revealed that during mindfulness meditation, higher HF HRV was more strongly

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associated with lower pain unpleasantness ratings when compared to sham-mindfulness meditation (B = −0.82, p = 0.04). This finding is in line with the prediction that mindfulness-based meditation engages distinct mechanisms from sham-mindfulness meditation to reduce pain. However, the same prediction was not confirmed for pain intensity ratings (B = −0.41). Secondary analyses determined that mindfulness and sham-mindfulness meditation similarly reduced pain ratings, decreased respiration rate, and increased HF HRV (between group *ps* < 0.05). More mechanistic work is needed to reliably determine the role of parasympathetic activation in mindfulness-based pain relief as compared to other meditative techniques.

Keywords

mindfulness meditation; heart rate variability; pain; placebo

INTRODUCTION

Non-pharmacological therapies, such as mindfulness-based regimens [61], are often characterized as safe[99] and effective approaches to treat clinical pain. Mindfulness meditation is a self-regulatory practice premised on sustaining non-reactive attention to arising sensory events that reproducibly reduces pain symptomology in response to clinical [16, 19, 38, 41, 64, 65, 80, 81] and experimentally induced pain [10, 33, 46, 47, 73, 90, 129, 131, 132, 136]. Yet, the corresponding mechanistic underpinnings of mindfulness-based practices remain poorly characterized [111]. In spite of the commonly held assumption that meditation engages mechanisms supporting placebo, placebo-controlled mindfulness studies have been limited. Benefits related to participating in mindfulness interventions may simply be associated with a spectrum of non-specific factors (conditioning, facilitator attention, social support, body posture, and/or demand characteristics). To better address this issue, we recently developed and validated a sham-mindfulness meditation comparison condition to control for these non-specific factors. [131, 135]. This breathing control condition did not include the specific cognitive stance supporting mindfulness. In brief (see Methods for more details), the sham-mindfulness meditation condition consists of a self-facilitated technique practiced by sitting with the eyes closed and taking deep breaths every few minutes. This practice significantly lowers pain, anxiety, and respiration rate [131, 135]. Preliminary evidence shows that mindfulness engages distinct mechanisms from this sham-mindfulness meditation condition to reduce pain [131]. As adapted in our laboratory, mindfulness meditation-based pain relief is associated with multiple neural mechanisms supporting the cognitive regulation of ascending nociceptive processing [↑ prefrontal (PFC) and ↑perigenual anterior cingulate cortex (pgACC); ↓thalamus] [136] and engages non-opioidergic endogenous systems [78, 129]. In contrast, this sham-mindfulness meditation comparison condition employs neural mechanisms reflecting lower cognitive control (↓ pgACC) and higher sensory processing (↑thalamus) during noxious heat [131]. Lower pain reports during sham-mindfulness meditation are associated with lower respiration rates [131], consistent with mechanisms involved in relaxation [5]. However, we have yet to determine if mindfulness-based pain relief engages physiological processes that are distinct from placebo-based pain reductions.

In particular, the mechanistic role of the autonomic nervous system (ANS) in mindfulness-based pain relief remains unknown. The ANS is critical for homeostatic control of heart rate, blood pressure, and body temperature, among other physiologic functions [25]. Heart rate variability (HRV), defined as the variability in the time between adjacent heartbeats, is an index of parasympathetic and sympathetic activity [9, 12, 23, 79] and autonomic flexibility [59]. Parasympathetic input to the heart is mediated by the vagus nerve, which exerts its effects on cardiac rhythm more rapidly than sympathetic fibers [9, 12, 23]. Thus, high frequency changes in heart rate [0.15 – 0.40 Hz; HF HRV] are largely driven by parasympathetic activation [9, 12, 23].

Importantly, lower HF HRV is a corollary marker of higher pain ratings during experimentally induced pain [121, 139] and clinical pain [7, 20, 44, 91, 121]. In contrast, slow, rhythmic breathing, a pain relieving practice associated with some meditative practices [8, 47], lowers pain and increases HF HRV [17, 77]. During normal breathing, changes in blood pressure activate the baroreceptor reflex, producing vagally mediated decreases in heart rate [11, 29, 54]. Progressive breathing reductions increase baroreceptor reflex sensitivity, resulting in higher HF HRV [29, 54]. Mindfulness meditation engages neural mechanisms supporting cortical control of vagal activity [3, 4, 6, 18, 100, 115] and increases HF HRV [2, 36, 71, 84, 112]. However, it is not known if heightened parasympathetic tone is related to the pain-relieving effects of mindfulness meditation.

Placebo-based pain reductions are not mediated by increased parasympathetic activity [62, 92, 120]. As adapted in our laboratory, the sham-mindfulness meditation comparison condition engages mechanisms supporting placebo [130, 138]. Thus, we postulated that increases in HF HRV would not be associated with sham-mindfulness meditation-induced pain relief after controlling for the influence of respiration rate on HF HRV. HF HRV is associated with higher cognitive control [86, 87], an outcome that is enhanced by mindfulness training [1, 37, 83, 134]. Thus, the primary hypothesis was explicitly powered to test if pain relief is more strongly associated with HF HRV during mindfulness meditation than during sham-mindfulness meditation (Hypothesis 1). Secondary analyses tested between-group differences in HF HRV, respiration rate, pain relief, and perceived meditative efficacy [130]. We predicted that the two meditation techniques would increase HF HRV (Hypothesis 2a) and lower respiration rate[130] (Hypothesis 3a) and there would be no between group differences on HRV (Hypothesis 2b) and respiration rate (Hypothesis 3b).

MATERIALS AND METHODS

Participants

Study exclusion criteria included individuals with mental illnesses, personality disorders, hypertension, chronic heart, lung, or ongoing pain condition, and those using psychotropic, pain, cardiac medications, or any nicotine products. Participants were instructed to refrain from caffeine and alcohol for 12 hours and exercise for 24 hours prior to participation in the pre-intervention and post-intervention sessions due to the influence of these variables on autonomic activity [12]. Two participants reported prior experience with meditation practices (1 mindfulness meditation group member; 1 sham-mindfulness meditation group member). Wake Forest School of Medicine's Institutional Review Board approved all study

procedures. All subjects provided written, informed consent recognizing that they would experience painful heat stimuli, that all methods were clearly explained, and that they were free to withdraw from the study at any time without prejudice. Outlier detection methods were conducted prior to data analyses to identify participants exhibiting extreme HF HRV values [122].

Sample size determination

To test the primary hypothesis, sample size determination (G*Power, 3.1.9.4; Test family: F tests; statistical test: Linear multiple regression, Fixed Model, R^2 increase; Effect size: Partial $R^2 = 0.13$; $f^2 = 0.15$; Alpha error probability: 0.05; power = 0.848; Number of tested predictors = 1; Total number of predictors = 8) was based on our previous studies' effect sizes assessing changes in respiration rate and pain during mindfulness meditation [129, 131, 136]. Sixty-two participants (n = 31/group) were estimated to provide 85% power ($p < 0.05$) to detect a medium effect size ($R^2 = 0.13$) to determine if mindfulness-based pain relief would be associated with greater HF HRV when compared to sham-mindfulness meditation.

We planned to recruit 70 participants to better account for statistical power due inter-individual HRV variability [98] but did not reach the target sample size due to the departure of key study personnel, necessitating the early closure of the study. Nevertheless, 66 participants successfully completed the study. Four participants completed the study but were subsequently removed from the final analysis due to HRV-related outliers (n = 3) and improper procedural adherence (n = 1) (See Participants for more details). Thus, there were a total of 62 participants analyzed in the present study.

Randomization procedure

All participants were recruited, screened, and randomized to one of the two mental training regimen groups by a study coordinator not involved in any data collection after the first study session. The randomization sequence was determined before study recruitment was initiated and all participants provided consent. The two arms (mindfulness meditation = A; sham-mindfulness meditation = B) were permuted with respect to treatment assignment and stratified across cohort-block sizes of 2, 4, and 6. Due to the influence of age on HF HRV [56, 72, 103], randomization was stratified, using an Excel based random number generator, by age (within five years) between the two groups employing their respective list of randomization codes. All participants were randomized into one of the two groups regardless of when they were screened and entered the study. After successful completion of the pre-intervention session (experimental session 1), the experimenter was informed of the respective participant's group assignment by study coordinator via an email and all participants were told that they had been randomly assigned to the mindfulness meditation intervention (regardless of group assignment). As such, the experimenter was not aware of the participant's group assignment until after completion of experimental session 1. If a participant was dismissed from the study (for whatever reason), we made a record of the reason and proceeded with the randomization procedure for the next cohort(s). Participants were debriefed as to the differences in sham-mindfulness vs. mindfulness meditation in an email after the conclusion of the study.

Stimuli

A TSA-II device (Medoc Inc.) was used to deliver all thermal stimuli using a 16mm^2 surface area thermal probe to the left arm (psychophysical training session) or back of the right leg (experimental sessions). This modest stimulus area allows a relatively wide range of noxious stimuli to be delivered. All stimulus temperatures were ≤ 49°C. Subjects placed the back of their right calf on the thermal probe and were free to lift their limb at any time. No stimuli produced any tissue damage. For the present study, innocuous stimulation was characterized by neutral series consisting of continual 35°C stimulation. Noxious stimulation were labeled heat series that included ten alternating, twelve second plateaus of 49°C interleaved with eight seconds of 35°C [129, 131, 136].

Psychophysical assessment of pain

Pain intensity and unpleasantness ratings were assessed separately using a 15 cm, 11-point plastic sliding visual analog scale (VAS) [95]. The minimum rating ("0") was designated as "no pain sensation" or "not at all unpleasant," whereas the maximum rating ("10") was labeled as "most intense pain imaginable" or "most unpleasant pain imaginable," respectively. Participants were instructed that, "the distinction between the two aspects of pain might be made clearer if you think of listening to a sound, such as a radio. The intensity of pain is like loudness; the unpleasantness of pain depends not only on intensity, but also on other factors which may affect you" [97]. These scales provide reliably separate assessments of pain intensity and unpleasantness, are internally consistent, and approximate ratio scale measurement accuracy [94].

Psychological measures

Perceived intervention effectiveness—As previously [131], "perceived meditative effectiveness" was assessed with an 11-point plastic sliding VAS ("0" = not effective at all; "10" = most effective imaginable) after the completion of each of the mental training sessions. Participants were asked to provide VAS responses to the following question: "How effectively did you meditate?" This measure served as a manipulation check of the sham-mindfulness meditation regimen by verifying that training led participants to believe they were practicing mindfulness meditation [131].

Physiological measures

Physiological acquisition—All participants were fitted with electrocardiography (ECG) sensors using a lead I configuration, where the positive electrode is placed on the left upper chest under the clavicle and the negative electrode is placed on the right upper chest directly under the clavicle [70]. Respiration was measured with a respiratory transducer belt that was placed around the participant's chest close to the diaphragm (Biopac MP100, AcqKnowledge; Biopac Systems, Goleta, CA). Subjects were fitted with these instruments before heat testing. All physiological activity was recorded at a rate of 1 kHz with an integrated software system (Biopac MP100, AcqKnowledge; Biopac Systems, Goleta, CA).

Physiological signal processing—All physiological data were processed using Autonomic Nervous System Laboratory software (ANSLab v2.51) [126]. The following

standardized procedures were employed to collect and analyze ECG data and HF HRV values [12]. First, cardiovascular data were visually inspected for artifacts and missing R-peaks. Missing R-peaks were determined based upon intervals between adjacent R-peaks that appeared too long or too short [12]. If an R-peak was missing, an R-peak was inserted at a time-point halfway between the two adjacent R-peaks (to preserve variability this insertion was not done more than once per minute). Fast Fourier Transformation was then performed on ECG data. HF HRV was calculated as the natural log of the high frequency power (0.15 – 0.40 Hz), a measurement shown to indicate vagal input to the heart [9, 12, 23]. Respiration rate was calculated as the average number of breaths per minute (min).

Study Design

Experimental sessions 1–6 were conducted on separate days (Figure 1).

Experimental session 1: pre-intervention session

7 minute physiological recording: After obtaining consent, all subjects were fitted with a respiratory transducer and ECG sensors. Participants then were instructed to "rest comfortably" in a supine position during physiological measurement recordings (7min 39s). The first three minutes of this time period were collected as an acclimation period to allow participants to adapt to the ECG sensors, respiration belt, and experimental setting [12]. The remaining time (4min 39s) was used to collect baseline respiration rate and HF HRV and matched the experimental procedures employed in the subsequent experimental sessions.

Psychophysical Training: All participants then underwent psychophysical training (PT), where they were familiarized with 32, five-second stimuli (35–49°C) and trained to use the VAS. During PT, stimuli were delivered to the ventral aspect of the left forearm. The thermal probe was moved to a new location after each stimulus to reduce habituation and/or sensitization. No physiological data were collected during PT.

Baseline heat testing (Rest + Heat): Two neutral and two heat series were administered in the following order (neutral-1, heat-1, neutral-2, heat-2; each series = 4min 39s) to all participants. VAS pain intensity and unpleasantness ratings were collected after each series. After each series, participants were instructed to "rate the feeling of pain (pain intensity and unpleasantness, respectively) for the overall experience" of each heat and neutral series. Physiological data were collected throughout each thermal stimulation series. The thermal probe was moved to a new location on the right calf after each series to reduce stimulus habituation and sensitization. Care was taken to place the thermal probe within the middle of the lower leg (i.e. on the calf muscle) as to avoid individual variability related to probe placement.

Intervention Training—Three trained mindfulness and sham-mindfulness interventionists facilitated the mindfulness and sham-mindfulness meditation interventions to better attenuate intervention variability[130, 135].

Experimental session 2–5: mindfulness meditation training—As previously [129, 131, 136], subjects in the mindfulness meditation group participated in four separate

sessions (25 min/session) of mindfulness-based mental training within seven days. Meditation training was introduced to subjects as a secular practice. While the majority of training sessions occurred in-group settings (2–5 people), three mindfulness meditators were trained in a one on one setting due to scheduling conflicts and/or participant drop-outs. Across all training sessions, subjects were trained to focus on the changing sensations of the breath and to non-reactively appraise arising sensations, thoughts, and feelings. Time spent providing guided meditation instructions were progressively reduced across meditation training days to allow subjects to meditate in silence [129, 131, 134–137].

As previously employed [129, 132, 134–137], participants were trained to focus on the breath sensations arising from the nose, chest, and abdomen in each training session. When their respective attention to breath sensations *drifted*, participants were taught to acknowledge arising thoughts, feelings, and/or emotions without reaction and to return "their attention to the sensations of the breath" in a repetitive fashion. Subjects were also taught that perceived sensory/affective events were "momentary" and "fleeting" and did not "require further evaluation". During meditation training sessions 1 and 2, participants were primarily instructed to focus on the breath sensations occurring "at the tip of the nose" and to expand their focus to the "full flow of the breath," including bodily sensations (e.g., rise and fall of the abdomen and chest). During meditation training sessions 3 and 4, subjects received minimal meditation instructions and meditated while in a supine position in order to better acclimate to the positioning in the postintervention session. Participants were not instructed to practice outside of training.

Experimental session 2–5: sham-mindfulness meditation training—The main purpose of the sham-mindfulness meditation intervention was to lead participants to believe they were practicing *mindfulness* meditation without providing the explicit instructions related to attending to the breath and engaging a non-reactive cognitive stance towards distractions [131, 135]. As previously described [131, 135], participants in the sham-mindfulness meditation group were told that they had been randomly assigned to the mindfulness meditation group. Most to all sessions were conducted in groups of two to 5 individuals. Six sham-mindfulness meditators were trained on a one on one basis due to their respective unforeseen scheduling conflicts and/or participant dropouts. The introduction to the practice was matched to the one described for the mindfulness meditation group (i.e., secular). In each of the four training sessions (within seven days; 25 min/session), subjects were instructed "to close their eyes and to take a deep breath" every 2–3 minutes "as we sit here in mindfulness meditation" [131, 135]. All other aspects of the sham-mindfulness meditation intervention (i.e., body position; intervention room; facilitator; eyes closed) matched the mindfulness meditation-training regimen. During meditation training sessions 3 and 4, participants *meditated* while in a supine position to better acclimate to the positioning in the post-intervention session. Subjects were not instructed to practice outside of training.

Experimental Session 6: post-intervention session

Rest + Stimulation: Similar to the pre-intervention session, participants were instructed to "rest comfortably" in a supine position and "to not meditate" during physiological recording (7 min 39 sec). The first three minutes of this time period was not analyzed because it was

used to allow participants to acclimate to the sensors and testing environment [12]. The remaining time was used to assess respiration rate and HF HRV after participation in the intervention sessions.

Subsequently, participants were fitted with the thermal probe on the right calf and were administered two neutral and two heat series in the following order (neutral-1, heat-1, neutral-2, heat-2). Participants provided VAS pain intensity and unpleasantness ratings after each series. The thermal probe was moved to a new location on the right calf after each series. Physiological data were collected during all thermal stimulation series in the post-intervention session.

Meditation: After the first four thermal stimulation series, participants in both groups were instructed to "begin meditating and continue meditating for the remainder of the experiment." They were provided ten minutes to meditate before the initiation of the noxious heat stimulation. Physiological data were collected continuously throughout "meditation."

Meditation + Stimulation: After ten minutes of mindfulness meditation or sham-mindfulness meditation, two neutral and two heat series (neutral-3, heat-3, neutral-4, heat-4) were administered. In order to not disturb participants' meditation practice, subjects were not informed that they would be administered a thermal stimulus immediately prior to neutral-3. The thermal probe was moved to a new location on the right calf after each series. Participants provided VAS ratings of pain intensity and pain unpleasantness after each thermal series.

Analysis of behavioral and physiological data

In all ANOVAs (SPSS 19.0 IBM, Armonk, New York), significant ($p < 0.05$) main effects and interactions were investigated with a priori simple effects tests. For all references pertaining to the post-intervention session and both groups, **1)** the delineation "rest" corresponds to data collected *before* subjects practiced mindfulness or sham-mindfulness meditation, and, **2)** the term "meditation" corresponds to data collected *during* mindfulness meditation and sham-mindfulness meditation. It is important to note that we were powered to explicitly test the primary analysis.

Primary Analysis—Is mindfulness-based pain relief associated with greater HF HRV when compared to sham-mindfulness meditation?

Two separate moderated analyses with pain intensity and pain unpleasantness ratings designated as the dependent variables, respectively, were conducted to test the primary hypothesis. Pain ratings during rest and heat series and meditation and heat series were averaged separately. Rest and meditation-related respiration rate and HF HRV were averaged across neutral and heat series values, respectively (i.e. Rest + Stimulation; Meditation + Stimulation). Group and HF HRV during meditation was multiplied to create the interaction term (group × meditation HF HRV) [55].

Age, rest-related pain ratings, respiration rate during rest, HF HRV during rest, respiration rate during meditation, "group", HF HRV during meditation, and group × meditation HF

HRV were entered in the analyses, respectively [21]. Significant interactions were investigated with a priori within group analyses to determine if the strength of the association between HRV and pain differed between mindfulness and sham-mindfulness meditation.

Secondary Analyses: Pre-Intervention Heart Rate Variability and Respiration Rate—For pre-intervention session analyses, two separate 2 (group: mindfulness vs. sham-mindfulness) × 2 (stimulation: heat vs. neutral) mixed ANOVAs were conducted on HF HRV and respiration rate across heat and neutral series, respectively. This was performed to verify that there were no group differences in HF HRV or respiration rate at baseline.

Secondary Analyses: Post-Intervention Heart Rate Variability & Respiration Rate—Two separate 2 (group: mindfulness vs. sham-mindfulness) × 2 (manipulation: rest vs. meditation) × 2 (stimulation: heat vs. neutral) mixed ANOVAs were performed on HF HRV and respiration rate, respectively, to determine if both groups would increase HF HRV (Hypothesis 2a) and lower respiration rate (Hypothesis 3a). We predicted that there would be no between group differences on these outcomes (Hypothesis 2b & 3b).

Secondary Analyses: Pain Ratings—Pain intensity and unpleasantness ratings were examined separately. A 2 (group: mindfulness vs. sham-mindfulness) × 2 (manipulation: rest vs. meditation) mixed ANOVA was conducted on post-intervention session pain ratings with "manipulation" as the within-subjects factor to assess if mindfulness and sham-mindfulness meditation lowered pain ratings. Pre-intervention pain intensity and unpleasantness ratings were entered as a covariate to control for pre-intervention pain ratings, respectively.

Secondary Analyses: Perceived Intervention Effectiveness—A 2 (group: mindfulness vs. sham-mindfulness) × 4 (session: meditation training sessions 1, 2, 3, and 4) mixed ANOVA was conducted on "perceived meditative effectiveness" scores with "group" designated as the between-subjects factor and "session" as the within-subjects factor. This was performed as a manipulation check of our sham-mindfulness meditation technique. However, in order to provide a more complete assessment of our observed data's support for the null hypothesis (i.e. no difference between groups) versus the alternative hypothesis (i.e. group differences on this outcome), we estimated Bayesian factors for the findings of interest. We used JASP software JASP Team[114] with Cauchy null distributions as priors. For the interaction terms, the ratio of the Bayesian factors for the model with and without the interaction term is presented ($BF_{F:R}$). To interpret the Bayesian factors, values below 1 support the null hypothesis, whereas values above 1 are considered stronger evidence for the alternative hypothesis. Values over 3 represent positive evidence for the alternative hypothesis [66]. In summary, this test helps to determine if groups are equivalent or different on perceived meditative effectiveness.

RESULTS

Participants

Seventy-five healthy, pain-free volunteers (age range: 18 – 55 years) provided informed consent in the present study. Nine subjects were dismissed from the study due to scheduling

conflicts (n=8) and a psychiatric disorder disclosure (Figure 2). Sixty-six participants successfully completed all study procedures (Figure 2).

Before we tested our hypotheses or analyzed any of our data, routine Tukey outlier hinges detection methods were conducted [122] to identify individuals exhibiting extreme HF HRV values. Subsequently, three individuals (1 female and 1 male sham-mindfulness meditation; 1 male mindfulness meditation group member) were identified as outliers and removed from the final analyses. Each of these three participants exhibited HF HRV values that were less than 1.5 times the interquartile range below the first quartile [122] and were 2.6 to 3 standard deviations (SD) below the mean for each HF HRV value measured in both physiological experimental sessions (i.e. pre/post-intervention sessions, across heat + neutral stimulation series). After all HF HRV values obtained were averaged across both experimental sessions, the three outliers exhibited a mean HF HRV value of 4.66 (SD = 0.16). In contrast, the other sixty-two participants (included in the final analysis) exhibited a mean HF HRV value of 8.11 (SD = 0.97). All analyses were also performed without excluding outliers (see Supplement A). Data from one participant (female mindfulness group member) was removed from the final analysis because the research technician inadvertently miscommunicated with the subject and was directed to and subsequently practiced meditation during the post-intervention session's Rest + Stimulation condition. Sixty-two participants [mean age (SD) = 31 ± 10 years; 41 = white, 18 = black, and 3 = Asian; 31 females; 31 males] (Table 1) were included in the final analyses. There were no significant differences between groups on age ($F_{(1, 60)} = 0.03$; $p = 0.86$, $\eta^2_p = 0.00$) or gender ($F_{(1, 60)} = 0.57$; $p = 0.45$, $\eta^2_p = 0.01$; Table 1).

Primary Analysis—Mindfulness-induced pain unpleasantness reductions were associated with higher HF HRV when compared to sham-mindfulness meditation

The significant group × HF HRV interaction, $B = -0.82$, $SE = 0.39$, $t(57) = -2.07$, $p = 0.04$; Table 3] demonstrated that mindfulness-based pain relief was associated with higher HF HRV when compared to the relationship between sham-mindfulness meditation-induced pain relief and lower HF HRV (Figure 3). Follow-up within group analyses revealed a trending to significance association ($\beta = -0.46$, $p = 0.07$; Figure 3a; Table 4) between mindfulness-induced pain relief and higher HF HRV. In contrast, there was not a significant relationship between sham-mindfulness-induced pain relief and lower HF HRV ($\beta = 0.42$, $p = 0.11$; Figure 3b; Table 5). There was no significant group × HF HRV interaction on pain intensity ratings during meditation, $t(57) = -1.45$, $p = 0.15$ (Table 2).

Secondary Analyses

Pre-Intervention Session *HF HRV*—There was a significant increase in HF HRV during noxious heat when compared to neutral series ($F_{(1, 59)} = 9.53$, $p = 0.003$, $\eta^2_p = 0.14$) (Table 1), and there were no significant between group differences ($F_{(1, 59)} = 1.01$, $p = 0.32$, $\eta^2_p = 0.02$) or a group × stimulation type interaction ($F_{(1, 59)} = 0.02$, $p = 0.88$, $\eta^2_p = 0.00$).

Pre-Intervention Session *Respiration Rate*—Respiration rate did not significantly vary by stimulation type (heat; neutral) ($F_{(1, 59)} = 3.34$, $p = 0.07$, $\eta^2_p = 0.05$) or by group

($F_{(1, 59)}$ = 0.73, p = 0.40, η^2_p = 0.01) and there was no significant group × stimulation interaction ($F_{(1, 59)}$ = 0.45, p = 0.51, η^2_p = 0.01; Table 1).

Post-Intervention Session *HF HRV*—There was a significant increase in HF HRV from rest to meditation across both groups ($F_{(1, 60)}$ = 27.96, p < 0.001, η^2_p = 0.32; Table 1). The significant manipulation × stimulation interaction ($F_{(1, 60)}$ = 7.64, p = 0.008, η^2_p = 0.11) revealed higher HF HRV values during heat and rest ($F_{(1, 60)}$ = 7.88; p = 0.007, η^2_p = 0.12) compared to neutral and rest ($F_{(1, 58)}$ = 0.35; p = 0.56, η^2_p = 0.01). There was no significant main effect of stimulation ($F_{(1, 60)}$ = 1.46, p = 0.23, η^2_p = 0.02) and no between group differences on HF HRV ($F_{(1, 60)}$ = 2.93, p = 0.09, η^2_p = 0.05).

Post-Intervention Session *Respiration Rate*—There was a significant reduction in respiration rate from rest to meditation across both groups (−29.5%, 95% CI [−26.7%, −32.1%]; $F_{(1, 60)}$ = 90.82, p < 0.001, η^2_p = 0.60; Table 1) and there was a significant manipulation × stimulation interaction ($F_{(1, 60)}$ = 22.09, p < 0.001, η^2_p = 0.27). Post-hoc analyses revealed that these respiration rate decreases were significantly greater during heat (−36.7%, 95% CI [−33.5%, −40.4%]; $F_{(1, 60)}$ = 106.69; p < 0.001, η^2_p = 0.64) when compared to neutral series (−22.3%, 95% CI [−20.3%, 24.5%]; $F_{(1, 60)}$ = 48.80; p < 0.001, η^2_p = 0.45). Respiration rate was significantly higher during neutral when compared to heat series ($F_{(1, 60)}$ = 68.40, p < 0.001, η^2_p = 0.53) and there was no significant between group differences ($F_{(1, 60)}$ = 1.38, p = 0.25, η^2_p = 0.02).

Pre/Post-Intervention Session: *Pain intensity*—Across both groups, pain intensity ratings significantly decreased (−21.9%), $F_{(1, 59)}$ = 5.92, p = 0.02, η^2_p = 0.09, 95% CI [−21.1%, −23.1%] (Figure 4a; Table 1) from rest to meditation. Pain intensity ratings were significantly higher during the pre-intervention session when compared to the post-intervention session ($F_{(1, 59)}$ = 89.24, p < 0.001, η^2_p = 0.60). There was no significant main effect of group ($F_{(1, 59)}$ = 0.03, p = 0.86, η^2_p = 0.00), group × manipulation interaction ($F_{(1, 59)}$ = 0.44, p = 0.51, η^2_p = 0.01), or between group differences in pre-intervention pain intensity ratings ($F_{(1, 60)}$ = 1.82, p = 0.18, η^2_p = 0.03).

Pre/Post-Intervention Session: *Pain unpleasantness*—Pain unpleasantness ratings significantly decreased by 35.6%, (95% CI [−33.2%, −38.7%]) across both groups during meditation when compared to rest ($F_{(1, 59)}$ = 10.88, p = 0.002, η^2_p = 0.16; Figure 4b; Table 1). Pre-intervention pain unpleasantness ratings were significantly higher than post-intervention pain ratings ($F_{(1, 59)}$ = 51.32, p < 0.001, η^2_p = 0.47). There were no significant group differences ($F_{(1, 59)}$ = 0.77, p = 0.39, η^2_p = 0.01), group × manipulation interaction ($F_{(1, 59)}$ = 0.30, p = 0.64, η^2_p = 0.00), or between group differences in pre-intervention pain unpleasantness ratings ($F_{(1, 60)}$ = 2.63, p = 0.11, η^2_p = 0.04).

Nine participants reported nonzero pain intensity and unpleasantness rating in response to neutral stimulation series (mean = 0.7 and 0.4, respectively). There were no group differences in pain intensity ($F_{(1, 60)}$ = 0.13; p = 0.72, η^2_p = 0.00) or pain unpleasantness ($F_{(1, 60)}$ = 0.03; p = 0.87, η^2_p = 0.00) in response to neutral series.

Perceived Intervention Effectiveness—Both groups reported significant increases in "perceived meditative effectiveness" across the four intervention sessions ($F_{(3, 58)} = 13.39$, $p < 0.001$ $\eta^2_p = 0.19$, $BF_{10} = 2.4 \times 10^5$; Table 1). There were no significant differences in perceived meditation effectiveness between groups ($F_{(1, 58)} = 1.46$, $p = 0.23$, $\eta^2_p = 0.03$, $BF_{10} = 0.61$) or a significant group × session interaction ($F_{(3, 58)} = 1.08$, $p = 0.36$, $\eta^2_p = 0.02$, $BF_{F:R} = 0.15$), demonstrating that the sham-mindfulness meditation regimen effectively led participants to believe they were practicing mindfulness meditation.

DISCUSSION

Primary Analysis

Mindfulness-induced pain unpleasantness reductions were associated with higher HF HRV when compared to sham-mindfulness meditation

The present study demonstrated that mindfulness-based pain unpleasantness relief was associated with a different parasympathetic pattern when compared to a robust, sham-mindfulness meditation condition. However, this relationship was not borne out with pain intensity ratings. Although, this difference was only shown when pain relief was measured by pain unpleasantness, and not when measured by pain intensity, visual inspection of the data reveals that in the case of pain unpleasantness, pain relief in the sham-mindfulness group was associated with lower, not higher HF HRV when compared to mindfulness meditation (Figure 3). This finding is consistent with converging lines of evidence demonstrating that placebo-based pain relief does not increase (and may reduce) parasympathetic nervous system activity [62, 92, 120]. Although mindfulness and sham-mindfulness meditation were designed to have procedural similarities, these mind-body techniques differed by a number of cognitive features that may explicate the observed (Figure 3) differential relationship between HF HRV and pain unpleasantness. Unlike sham-mindfulness meditation, mindfulness practitioners were trained to pay direct attention to the sensations of the breath and to reduce cognitive and affective evaluations of distracting thoughts and feelings. Mindfulness-based pain relief is associated with behavioral and neural correlates of interoception[30, 49, 68, 104] and when compared to sham-mindfulness meditation, mindfulness produced greater activation (right anterior insula; subgenual ACC)[130] in brain regions implicated in the so-called interoception network [15, 22, 24, 51, 60, 12769]. Mindfulness meditation reliably increases cognitive flexibility [1, 30, 74, 75, 108, 134] and affective resilience [49, 63, 88], factors that are also directly associated with higher heart rate variability [59, 109]. It is then fitting that mindfulness-based HF HRV increases were more aligned with modulating the affective (and not sensory) dimension of pain. Taken together, we stipulate that mindfulness-based cognitive reappraisal processes may uniquely regulate affective pain responses through executive level modulation and PNS processes, an integrative, multimodal process that may lead to improvements in pain and health outcomes. In that regard, affective regulation via cognitive reappraisal is associated with increases in HF HRV. Mindfulness-based relief of acute experimentally-induced pain is a non-opioidergic process associated with effortful, corticothalamocortical mediated regulation of ascending nociceptive information, a known neurophysiological correlate of higher HRV [32, 93, 118]. This reappraisal-based process engages supraspinal mechanisms presumably through the

recruitment of GABA-ergically mediated corticothalamocortical interactions[48, 129, 130, 136, 138].

In the present study, we showed that mindfulness and sham-mindfulness lowered pain and increased HF HRV. However, there was a significant difference between the sham-mindfulness meditation group and the mindfulness meditation group in how HF HRV was associated with pain relief. Although, this difference was only shown when pain relief was measured by pain unpleasantness, and not by pain intensity. Visual inspection of the data reveals that in the case of pain unpleasantness, pain relief in the sham-mindfulness group was associated with lower, not higher HF HRV when compared to mindfulness meditation (Figure 3), a finding consistent with converging lines of evidence demonstrating that placebo-based pain relief does not increase (and may reduce) parasympathetic nervous system activity (i.e. HF HRV).

Secondary Analyses

Pain Ratings—The sham-mindfulness meditation condition was employed to better characterize and disentangle the specific mechanisms supporting pain relief during mindfulness meditation. It is not particularly surprising that mindfulness and sham-mindfulness meditation produced pain intensity ($\eta^2_p = 0.09$) unpleasantness reductions ($\eta^2_p = 0.16$). However, there were no reliable between group differences on pain intensity ($\eta^2_p = 0.03$) or unpleasantness ($\eta^2_p = 0.01$) ratings.

Heart Rate Variability and Respiration Rate—We were not explicitly powered to test the secondary hypotheses relating to respiration rate and HF HRV. However, our results signified large effect sizes relating to HF HRV and respiration rate and revealed both meditative techniques increased HF HRV ($\eta^2_p = 0.32$) and decreased respiration rate ($\eta^2_p = 0.60$) and there were no between group differences on these outcomes ($\eta^2_p < 0.06$). Thus, if replicated, mindfulness and sham-mindfulness meditation may lower respiration rate and increase HF HRV.

Considerations for mindfulness-based pain relief

There are significant operational parallels between the two, slow-breathing practices. Recent work from our laboratory revealed that the cognitive state of mindfulness meditation and sham-mindfulness meditation exhibited significant overlapping activation in brain mechanisms supporting greater sensory evaluation (bilateral anterior insula) [110, 125], reward processing (putamen) [31, 85, 102, 128], attention to the breath (SI representation of the nose) [42, 89], and lower self-referential processing (deactivation of the default mode network) [26, 76, 106]. Yet, the mechanistic differences between these two conditions were borne out when the relationship between pain ratings and neural activation was disentangled. In contrast to the more active mindfulness meditation technique, sham-mindfulness meditation was associated with significant deactivation of the rostral ACC and the prefrontal cortex and significant thalamic activation, indicating a more-passive, perceived controllability of pain, a common mechanistic description supporting placebo-based pain relief [27, 28]. Similarly, this shows that mindfulness and sham-mindfulness produced comparable enhancements in pain relief, heart rate variability and respiration rate. Yet, here we demonstrate a preliminary step

in elucidating the analgesic effects of mindfulness meditation by demonstrating that increased parasympathetic tone (i.e., HF HRV) is associated with mindfulness-based reductions in affective pain.

The emotional augmentation of pain is a critical component supporting the cognitive modulation of pain [14, 105]. Pain accompanied by emotional distress (i.e. cancer pain) is rated as significantly more unpleasant than intense, whereas pain associated with positive experiences (i.e. childbirth) is characterized as more intense than unpleasant [96]. Thus, treatment approaches that "uncouple" noxious sensations from the cognitive evaluation of pain may enhance quality of life and well-being [64]. To this extent, mindfulness meditation lowers the affective dimension of pain (Figure 4) more than pain intensity [10, 33, 35, 46, 47, 73, 129, 131, 136]. Mindfulness alters one's relationship to a nociceptive stimulus in a way that lowers pain catastrophizing [38] and enhances pain-related coping [82] by increasing the capacity for non-reactive, acceptance-based appraisals of sensory events [39, 40]. We propose that mindfulness meditation may distinctively improve pain conditions that are associated with maladaptive coping strategies [19, 38, 45, 52, 101, 123]. Brief mindfulness-based training regimens, like the one employed in the current study, may be more clinically pragmatic since significant time commitments have been cited as barriers to the clinical utilization of mindfulness meditation [13]. Mindfulness is a nebulous construct that requires appropriate operational characterizations. Thus, the sham-mindfulness meditation condition in this experiment might be better described as a comparison mental training condition, especially in light of its similar analgesic effects to *genuine* mindfulness practice. Yet, sham-mindfulness meditation is an effective pain relieving technique and resembles other meditative techniques [58, 107]. Sham-mindfulness meditation is associated with significant deactivation of the rostral ACC and ventromedial PFC, suggesting[34, 46, 113] that *non-reactivity* is also a mechanism engaged by sham-mindfulness meditation. However, it is likely that sham-mindfulness based non-reactivity does not engage metacognitive states of awareness associated with mindfulness practices [1, 50, 67, 124, 129].

Consequently, it may not be appropriate to characterize this technique as a *placebo* manipulation, but rather an active, non-inert practice. Sham-mindfulness meditation has been reported to be easier to exercise than mindfulness meditation [131, 135] suggesting that this technique is clinically viable and pragmatic to treat pain [133]. Although we did not explicitly test this, pain conditions that exhibit comorbidities related to higher fatigue and cognitive deficits might then benefit from a less cognitively demanding practice (sham-mindfulness meditation).

The present findings are particularly generalizable to healthy, pain-free individuals and are not directly applicable to chronic pain patients. Chronic pain patients exhibit an array of comorbidities that can confound specific mechanisms of action supporting mindfulness. We employed healthy subjects, experimentally induced pain, and an event-related design to better identify the specific physiological processes supporting mindfulness-based pain attenuation. It is also difficult to explicitly ascertain that changes in heart rate variability were directly associated with noxious heat, due to the limitation that HRV measurements cannot be disentangled in an "on-off" block design[56, 72]. A third-arm, non-manipulation regimen may have provided a more suitable control for potential habituation/sensitization

effects, although our previous studies employing identical experimental paradigms [129, 131] show that non-manipulation controls exhibit significant pain increases (+16%) in response to noxious heat. We were only statistically powered to test the primary aim of the study (i.e., Hypothesis 1). Thus, we were not justified to determine if mindfulness-based analgesia is mediated by HRV. This analysis would also inform potential mechanistic differences between mindfulness and sham-mindfulness practices. We find that mindfulness, in this study, was not more effective than sham-mindfulness meditation in reducing pain. This suggests that mindfulness may not be more effective at reducing pain when compared to a robust and active sham-mindfulness meditative technique. It is also important to state that a technique labeled “mindfulness meditation” that is premised on lowering breathing rate could be an effective pain reliever. It would also be important to compare the mechanisms supporting mindfulness to other effective pain therapies, such as cognitive behavioral therapy (CBT). Mindfulness and CBT produce similar pain relieving effects and both techniques likely employ executive control processes to reduce pain, although CBT is premised on *changing thoughts about pain* whereas mindfulness is based on *accepting thoughts about pain*[19, 43, 53, 57].

Importantly, there were no significant differences in pain responses between the mindfulness and sham-mindfulness techniques. This could be due to the possibility that some participants had prior experience with mindfulness. That is, participants were not asked prior to participation in the study if they had any knowledge regarding the exact practices of mindfulness meditation based on their experiences or media exposure. As such, some participants may have recognized that sham-mindfulness meditation was not true mindfulness meditation. Nevertheless, we have solid evidence that the two interventions have the same effect on pain intensity and unpleasantness, and the present study provides some indication that there might be a difference in how parasympathetic responses relate to this analgesic effect. Yet, we were not statistically powered to state that both of these techniques are mediated by different mechanisms. More mechanistic work is needed to reliably determine the role of parasympathetic activation in mindfulness-based pain relief as compared to other meditative techniques.

It is also possible that the facilitators were more motivated to promote relief for the mindfulness training as compared to the sham-mindfulness technique. Further, while participants were not asked to meditate between intervention sessions, we did not explicitly ask if they had done so. It should also be noted that the experimenter was not blinded to participants’ group assignments (i.e. sham-mindfulness vs. mindfulness) during the post-intervention session, a factor that may have confounded our results. Of note, HF HRV was higher during heat when compared to neutral stimulation during the pre-intervention session and the “rest” condition of the postintervention session. HF HRV is a potential marker of the body’s ability to reestablish a homeostatic state [116, 117, 119] and may reflect a self-regulatory response during the experience of a painful stimulus. It should also be considered that we were primarily powered to test Hypothesis 1, the regression analysis examining the between groups difference in the relationship between HF HRV and pain ratings. Consequently, our secondary analyses should be interpreted with caution and primarily utilized as a tool to guide future studies. We have restricted our interpretation of analyses to the manipulation checks and primary analysis. The process of age matching may have introduced bias into the

study procedures and should be considered when interpreting the results. Specifically, if groups were unbalanced, it would be dictated that an individual of a certain age would be assigned to whichever group required matching. It is important to note that several fundamental principles are embedded in the treatment modality supporting mindfulness-based practices such as non-reactivity, attention regulation, meta-cognition, distraction, beliefs, conditioning, and other factors. Investment in demonstrating the clinical efficacy of a suite of these processes under the construct of mindfulness may hamper the comprehension and operationalization of mindfulness-based practices and the potential for therapeutic progress. Thus, future studies should be conducted to explicitly test the purported mechanisms and clinical efficacy supporting each of these factors across different patient populations to better tailor and target the use of these potential pain therapies. We also urge caution in using the term “sham-mindfulness meditation” in the clinical treatment of pain because there are likely active mechanisms that are shared by genuine and sham-mindfulness meditation that are therapeutic. Mindfulness-based regimens are premised on increasing one’s ability to self-regulate and accept maladaptive experiences. Growing evidence demonstrates that one’s ability to sustain non-reactive attention in the present moment (i.e., mindfulness) uniquely modulates the elaboration of maladaptive pain-related appraisals and improves parasympathetic processes, factors that may serve as a buffer for the exacerbation of clinical pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

DISCLOSURES

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HIGHLIGHTS

- Mindfulness and sham mindfulness meditation reduced pain during noxious heat
- Mindfulness and sham mindfulness meditation increased heart rate variability (HRV)
- Mindfulness-based pain relief was associated with higher HRV
- Higher HRV during sham mindfulness meditation was associated with higher pain

PERSPECTIVE

Mindfulness has been shown to engage multiple mechanisms to reduce pain. The present study extends on this work to show that higher heart rate variability is associated with mindfulness-induced reductions in pain unpleasantness, but not pain intensity ratings, when compared to sham-mindfulness meditation. These findings warrant further investigation into the mechanisms engaged by mindfulness as compared to placebo.

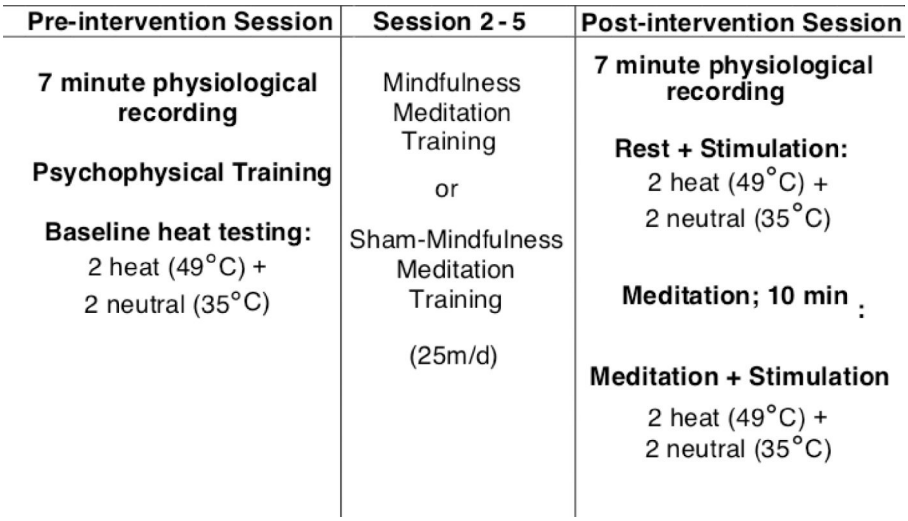

FIGURE 1. Overview of Experimental Design. First column, Pre-intervention session.
We collected baseline respiration rate and HF HRV while participants were asked to "rest quietly" in a supine position. Participants then underwent psychophysical training (PT) where they were familiarized with the Visual Analog Scales (VAS) and the range of thermal stimuli. All participants were administered two neutral and two heat thermal stimulation series in the order neutral, heat, neutral, heat. Pain intensity and pain unpleasantness ratings were collected after each thermal series. Participants were then randomly assigned to a mindfulness meditation or a sham-mindfulness meditation group after completion of the pre-intervention session. *Second column, Sessions 2–5.* Subjects participated in four sessions (25m/d) of mindfulness meditation or sham-mindfulness meditation training. *Third column, Post-intervention session.* Baseline measures of respiration rate and HF HRV were collected while participants were instructed to "rest quietly" in the supine position. VAS ratings of pain intensity and pain unpleasantness were collected after all thermal series. Two neutral and two heat series were administered in the order neutral, heat, neutral, heat while subjects were instructed to "rest comfortably" and "not to meditate" (i.e., **Rest + Stimulation**). Subjects in both groups were then instructed to "begin meditating and continue meditating for the remainder of the experiment." Participants were provided ten minutes to meditate (**Meditation).** Subsequently, all participants were administered two neutral and two heat series in the order neutral, heat, neutral, heat while they continued to meditate (**Meditation + Stimulation)**. Participants were provided two minutes to meditate in between each of the thermal series.

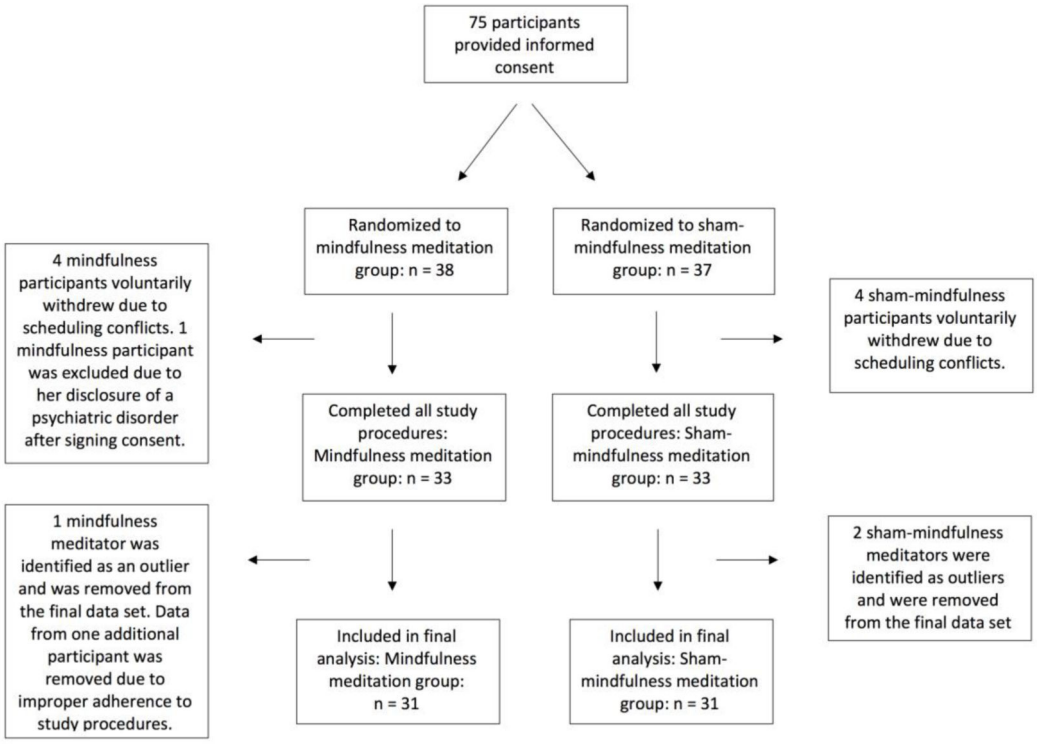

FIGURE 2.

Participant inclusion flow diagram. Seventy-five participants provided informed consent for the current study, and 38 individuals were randomized to the mindfulness meditation group whereas 37 participants were randomized to the sham-mindfulness meditation group. Eight participants (4 mindfulness; 4 sham-mindfulness) voluntarily withdrew after signing consent due to scheduling conflicts or unknown reasons and were replaced. One mindfulness meditator was excluded due to disclosure of a psychiatric illness after signing consent. Sixty-six participants (33 mindfulness; 33 sham-mindfulness) completed all study procedures. Data corresponding to 3 individuals (1 mindfulness; 2 sham-mindfulness) were removed from the data set due to significant outlier detection. One mindfulness meditator was removed due to a miscommunication between the participant and researcher leading to the participant meditating during the post-intervention session Rest + Stimulation condition. Consequently, sixty-two participants (31 mindfulness; 31 sham-mindfulness) are included in the final analyses.

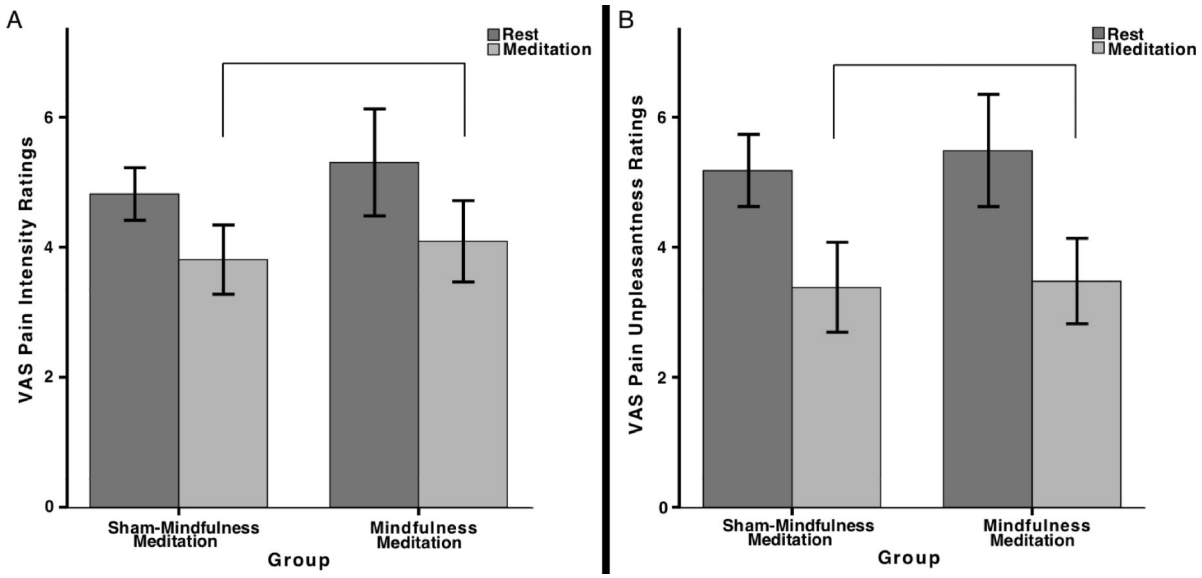

FIGURE 3. The relationship between HF HRV and pain unpleasantness ratings.

There was a significant ($p = 0.04$) group difference on the relationship between HF HRV and pain unpleasantness. **A)** Post-hoc analyses revealed that there was a marginally significant relationship between increased HF HRV and decreased pain unpleasantness ratings (r = −0.46; $p = 0.07$) for the mindfulness meditation group after controlling for age, pain ratings during rest, respiration rate, and HF HRV during rest. **B)** HF HRV was not significantly (r = 0.42; $p = 0.11$) associated with pain unpleasantness after accounting for age, pain ratings during rest, respiration rate, and HF HRV during rest in the sham-mindfulness meditation group.

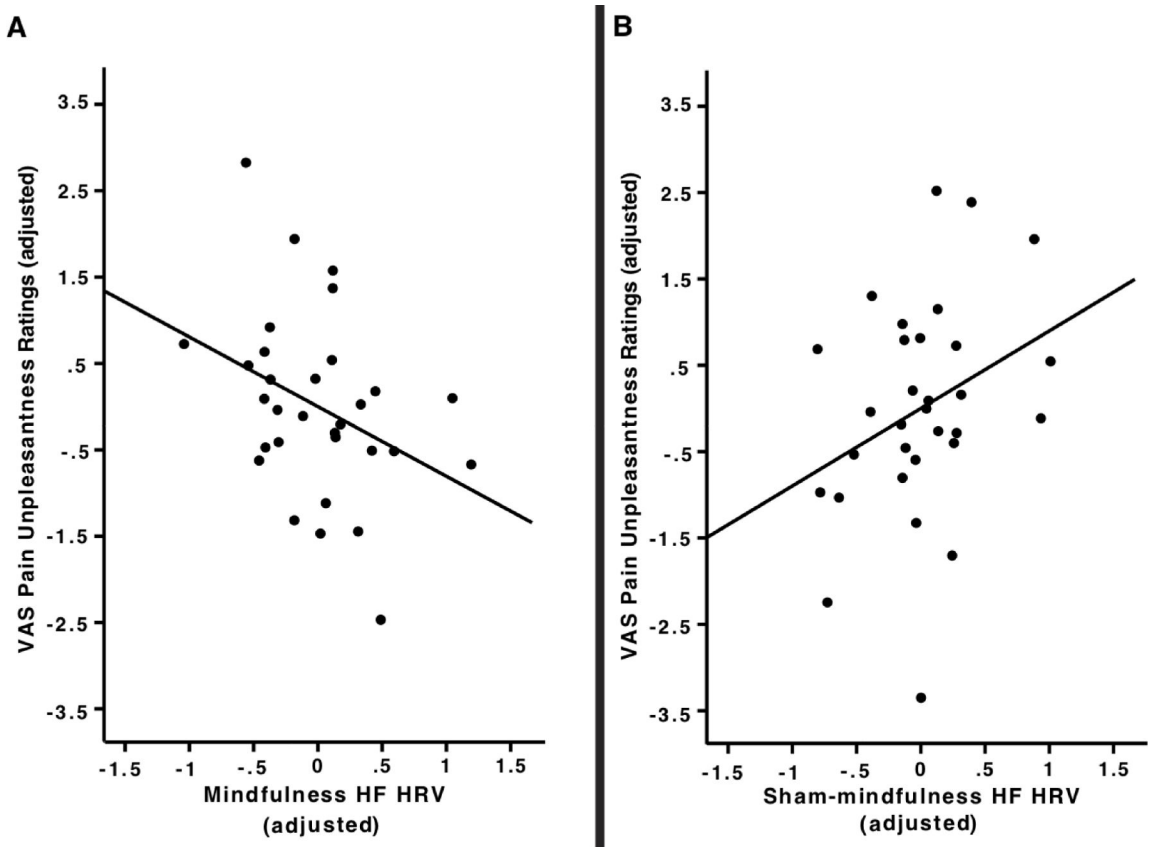

FIGURE 4. Post-intervention session psychophysical pain intensity (A) and pain unpleasantness (B) ratings (mean ± SEM).

Both groups significantly reduced pain intensity ($p = 0.02$; left) and unpleasantness ($p = 0.002$; right) ratings when compared to rest and when controlling for pre-intervention pain ratings. There was no significant group × manipulation interaction on pain intensity ($p = 0.51$) or unpleasantness ($p = 0.64$) ratings.

TABLE 1.

Participant demographic, VAS pain intensity and unpleasantness ratings, respiration rate (RR), high frequency heart rate variability (HF HRV), and perceived intervention effectiveness ratings (mean ±SEM).

Variable	Mindfulness Meditation	Sham-mindfulness	Combined
Age	30.77 (1.98)	30.29 (1.78)	30.53 (1.32)
Sex	M = 14; F = 17	M = 17; F = 14	M = 31; F = 31
Pre-intervention pain intensity	5.43 (0.40)	4.77 (0.29)	5.10 (0.25)
Pre-intervention pain unpleasantness	6.03 (0.45)	5.10 (0.37)	5.56 (0.29)
Post-intervention Rest pain intensity	5.31 (0.41)	4.82 (0.20)	5.06 (0.23)
Post-intervention Meditation pain intensity	4.09 (0.31)	3.81 (0.27)	3.95 (0.20)*
Post-intervention Rest pain unpleasantness	5.48 (0.43)	5.18 (0.28)	5.33 (0.26)
Post-intervention Meditation pain unpleasantness	3.48 (0.33)	3.38 (0.35)	3.43 (0.24)*
Pre-intervention heat RR	16.65 (0.85)	15.70 (0.63)	16.17 (0.53)
Pre-intervention neutral RR	17.14 (0.65)	16.54 (0.64)	16.83 (0.45)
Pre-intervention heat HF HRV	8.15 (0.20)	8.43 (0.23)	8.29 (0.15)*
Pre-intervention neutral HF HRV	7.96 (0.17)	8.25 (0.21)	8.11 (0.14)
Post-intervention Rest RR heat	17.31 (0.72)	15.89 (0.48)	16.60 (0.44)
Post-intervention Rest RR neutral	17.79 (0.74)	17.18 (0.49)	17.48 (0.44)
Post-intervention Meditation RR heat	11.04 (0.86)	9.96 (0.72)	10.50 (0.56)
Post-intervention Meditation RR neutral	13.83 (0.85)	13.34 (0.64)	13.58 (0.53)
Post-intervention Rest HF HRV heat	7.75 (0.20)	8.27 (0.18)	8.01 (0.14)
Post-intervention Rest HF HRV neutral	7.60 (0.21)	8.07 (0.18)	7.83 (0.14)
Post-intervention Meditation HF HRV heat	8.05 (0.21)	8.45 (0.17)	8.25 (0.13)
Post-intervention Meditation HF HRV neutral	8.14 (0.18)	8.45 (0.17)	8.29 (0.13)
TS 1 perceived meditative effectiveness	5.16 (0.36)	4.43 (0.32)	4.80 (0.24)
TS 2 perceived meditative effectiveness	5.47 (0.34)	4.87 (0.36)	5.17 (0.25)
TS 3 perceived meditative effectiveness	5.81 (0.44)	4.78 (0.41)	5.30 (0.30)
TS 4 perceived meditative effectiveness	6.23 (0.46)	6.07 (0.33)	6.15 (0.28)

* $p < 0.05$.

During session 6, both groups significantly (p <.05) reduced pain intensity (−22%) and pain unpleasantness ratings (−36%) when compared to rest when controlling for pain ratings at session 1. There were no between group differences on pain intensity or unpleasantness ratings ($ps > .05$). At session 1, HF HRV during heat was higher for both groups when compared to neutral stimulation ($p < .05$).

TABLE 2.

Moderated regression analysis on HF HRV and pain intensity ratings in the post-intervention session.

Variable	*B*	SE *B*	β	sr^2	Model R^2	*F*
					0.66	13.11 **
Age	0.01	0.02	0.06	0.00		
Rest pain intensity	0.70	0.08	0.78	0.52 **		
Rest RR	−0.03	0.05	−0.07	0.00		
Rest HF HRV	−0.07	0.26	−0.04	0.00		
Meditation RR	0.04	0.04	0.09	0.01		
Meditation HF HRV	0.80	0.51	0.49	0.02		
Group	3.35	2.35	1.05	0.01		
Group × Meditation HF HRV	−0.41	0.28	−1.07	0.01		

B, unstandardized beta coefficient; SE *B*, standard error of unstandardized beta coefficient; β, standardized beta coefficient; sr^2, semipartial coefficient squared; Rest pain intensity, averages of pain intensity ratings during the Rest + Stimulation condition; Rest RR, averages of heat and neutral respiration rate during the Rest + Stimulation condition; Rest HF HRV, averages of heat and neutral HF HRV during the Rest + Stimulation condition; Meditation RR, averages of heat and neutral respiration rate during the Meditation + Stimulation condition; Meditation HF HRV, average of heat and neutral HF HRV during the Meditation + Stimulation condition; Group, value depicting assignment to the sham-mindfulness or mindfulness meditation group; Group × HF HRV, interaction between Group values and Meditation HF HRV values.

** $p < 0.001$

TABLE 3.

Moderated regression analysis on HRV and pain unpleasantness ratings during the post-intervention session.

Variable	*B*	SE *B*	β	sr^2	Model R^2	*F*
					0.51	6.83 **
Age	0.03	0.02	0.15	0.02		
Rest pain unpleasantness	0.57	0.09	0.61	0.35 **		
Rest RR	0.01	0.07	0.02	0.00		
Rest HF HRV	−0.04	0.36	−0.02	0.00		
Meditation RR	0.07	0.05	0.16	0.02		
Meditation HF HRV	1.32	0.72	0.70	0.03		
Group	6.60	3.29	1.79	0.04		
Group × Meditation HF HRV	−0.82	0.39	−1.85	0.04 *		

B, unstandardized beta coefficient; SE *B*, standard error of unstandardized beta coefficient; β, standardized beta coefficient; sr^2, semipartial coefficient squared; Rest pain unpleasantness, averages of pain unpleasantness ratings during the Rest + Stimulation condition; Rest RR, averages of heat and neutral respiration rate during the Rest + Stimulation condition; Rest HF HRV, averages of heat and neutral HF HRV during the Rest + Stimulation condition; Meditation RR, averages of heat and neutral respiration rate during the Meditation + Stimulation condition; Meditation HF HRV, average of heat and neutral HF HRV during the Meditation + Stimulation condition; Group, value depicting assignment to the sham-mindfulness or mindfulness meditation group; Group × HF HRV, interaction between Group values and Meditation HF HRV values.

** $p < 0.001$

* $p = 0.04$

TABLE 4.

Regression analysis on HRV and pain unpleasantness ratings for the mindfulness meditation group.

Variable	*B*	SE *B*	β	sr^2	Model R^2	*F*
					0.70	9.53^{**}
Age	0.08	0.02	0.45	0.13^{*}		
Rest pain unpleasantness	0.34	0.10	0.45	0.16^{*}		
Rest RR	−0.01	0.06	−0.02	0.00		
Rest HF HRV	0.56	0.39	0.34	0.03		
Meditation RR	0.09	0.05	0.22	0.04		
Meditation HF HRV	−0.81	0.43	−0.46	$0.04^{\dagger}$		

B, unstandardized beta coefficient; SE *B*, standard error of unstandardized beta coefficient; β, standardized beta coefficient; sr^2, semipartial coefficient squared; Rest pain unpleasantness, averages of pain unpleasantness ratings during the Rest + Stimulation condition; Rest RR, averages of heat and neutral respiration rate during the Rest + Stimulation condition; Rest HF HRV, averages of heat and neutral HF HRV during the Rest + Stimulation condition; Meditation RR, averages of heat and neutral respiration rate during the Meditation + Stimulation condition; Meditation HF HRV, average of heat and neutral HF HRV during the Meditation + Stimulation condition.

$^{**}p < 0.001$

$^{*}p < 0.01$

$^{\dagger}p = 0.07$

TABLE 5.

Regression analysis on HRV and pain unpleasantness ratings for the sham-mindfulness meditation group.

Variable	*B*	SE *B*	β	sr^2	Model R^2	*F*
					0.62	6.49**
Age	−0.02	0.03	−0.10	0.01		
Rest pain unpleasantness	0.89	0.17	0.72	0.44**		
Rest RR	−0.02	0.12	−0.03	0.00		
Rest HF HRV	−0.94	0.53	−0.47	0.05		
Meditation RR	−0.03	0.09	−0.06	0.00		
Meditation HF HRV	0.90	0.54	0.42	0.04		

B, unstandardized beta coefficient; SE *B*, standard error of unstandardized beta coefficient; β, standardized beta coefficient; sr^2, semipartial coefficient squared; Rest pain unpleasantness, averages of pain unpleasantness ratings during the Rest + Stimulation condition; Rest RR, averages of heat and neutral respiration rate during the Rest + Stimulation condition; Rest HF HRV, averages of heat and neutral HF HRV during the Rest + Stimulation condition; Meditation RR, averages of heat and neutral respiration rate during the Meditation + Stimulation condition; Meditation HF HRV, average of heat and neutral HF HRV during the Meditation + Stimulation condition.

** $p < 0.001$