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Citation for published version (APA):

Vencatachellum, S., van der Meulen, M., Van Ryckeghem, D. M. L., Van Damme, S., & Vogege, C. (2021). Brief mindfulness training can mitigate the influence of prior expectations on pain perception. *European Journal of Pain*, 25(9), 2007-2019. <https://doi.org/10.1002/ejp.1817>

Document status and date:

Published: 01/10/2021

DOI:

[10.1002/ejp.1817](https://doi.org/10.1002/ejp.1817)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

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Brief mindfulness training can mitigate the influence of prior expectations on pain perception

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Funding information

The University of Luxembourg and the Fonds National de la Recherche Luxembourg (FNR; <https://www.fnr.lu/>) funded this research (AFR PhD grant awarded to S. Vencatachellum, Project ID: 11274510).

Abstract

Background: Recent neuroimaging evidence suggests that mindfulness practice may mitigate the biasing influence of prior cognitive and emotional expectations on pain perception. The current study tested this hypothesis using a pain-cueing paradigm, which has reliably been shown to elicit conditioned hypoalgesic and hyperalgesic effects. Specifically, we aimed to investigate whether the instructed use of a mindfulness compared to a suppression strategy differentially modulates the magnitudes of conditioned hypoalgesia and hyperalgesia.

Methods: Sixty-two healthy non-meditators were assigned to listen to either brief mindfulness or suppression instructions, in between the conditioning and testing phases of a pain-cueing task. Participants provided ratings of anticipatory anxiety, pain intensity and pain unpleasantness throughout the task. They also completed trait and state self-report measures of mindfulness and pain catastrophizing.

Results: Results indicated that the paradigm was successful in inducing conditioned hyperalgesic and hypoalgesic effects. Importantly, while we found evidence of cue-induced hyperalgesia in both groups, only the suppression group reported cue-induced hypoalgesia. No group differences in pain ratings were found for unconditioned (novel-cued) stimuli.

Conclusions: These findings provide partial support for recently proposed predictive processing models, which posit that mindfulness may lead to a prioritization of current sensory information over previous expectations. We explore potential explanations for the asymmetrical group differences in conditioned hypoalgesia versus conditioned hyperalgesia, and discuss our results in light of recent neuroimaging insights into the neuropsychological mechanisms of mindfulness and expectancy-driven pain modulation.

Significance: The current study provides novel insights into the working mechanisms of mindfulness-driven pain modulation. Our data suggest that brief mindfulness training may reduce the influence of prior beliefs and expectations on pain perception. This finding adds to growing evidence suggesting that mindfulness may alleviate pain via neuropsychological mechanisms opposite to those typically observed in conditioning/placebo procedures and other cognitive manipulations. These unique mechanisms underline the potential of mindfulness as an alternative to traditional cognitive pain regulatory strategies.

1 | INTRODUCTION

An extensive body of literature has linked mindfulness-based interventions to increased pain tolerance, lower pain unpleasantness and improved pain symptomology across a wide range of chronic pain conditions (Hilton et al., 2016; Lakhan & Schofield, 2013; Veehof et al., 2011, 2016). Yet, despite this surge of interest in its clinical effects, little is known as to how mindfulness conveys these benefits.

Successful cognitive modulation of pain (e.g. via distraction, suppression, placebo and reappraisal) is typically accompanied by reduced activation of brain regions commonly associated with pain processing (Atlas & Wager, 2012; Jensen et al., 2016; Knudsen et al., 2011). Recent neuroimaging evidence, however, suggests that mindfulness-driven pain relief may instead elicit a contrasting neural pattern, involving increased activation of areas associated with the sensory-discriminatory processing of painful stimuli and reduced activation of putatively cognitive-evaluative regions (Gard et al., 2011; Grant et al., 2011; Lutz et al., 2013; Zeidan et al., 2011, 2015). While these findings may appear counter-intuitive, they are nevertheless in line with traditional conceptualizations of mindfulness as a non-judgmental, non-elaborative and non-conceptual (i.e. abatement of evaluative and memory-related processes) form of awareness towards the ongoing flux of present moment experience (i.e. enhanced sensory processing activity). In light of these observations, recently formulated predictive processing accounts posit that mindfulness may, via the reallocation of attention to current experience, lead to an amplification of afferent sensory signals and a concomitant attenuation of the relative weight ascribed to a priori expectations (Farb et al., 2015; Pagnoni & Porro, 2014). This assumption raises the possibility that mindfulness may reduce susceptibility to the well-documented biasing influence of prior cognitive and emotional expectations on pain experience (Atlas & Wager, 2012). While this interpretation has so far relied largely on reverse referencing, preliminary evidence from Taylor et al., (2018), showing that experienced meditators exhibit reduced hyperalgesic effects relative to controls following a fear conditioning procedure, provides initial support for this notion. Given the same overarching hypothesis that mindfulness mitigates the influence of priors on perception, we would expect to find similar evidence for mindfulness-induced reductions in conditioned hypoalgesia. Moreover, how these modulatory effects of mindfulness compare with other top-down regulatory strategies remains an open question.

In the current study, we used a classical pain-cueing paradigm to assess whether the instructed use of a mindfulness or a suppression strategy differentially modulates conditioned hypoalgesia and hyperalgesia. Contrary to mindfulness, suppression strategies encourage the inhibition, rather than acceptance, of unwanted emotional and physical experience.

Pain-cueing paradigms provide an ideal testing ground for the current hypothesis, given the elicited mismatch between incoming sensory information and conditioned expectations. Previous research has shown that heat stimuli of equivalent temperature are rated as more painful if preceded by a conditioned high-pain cue and less painful if preceded by a conditioned low-pain cue (Madden et al., 2015). We hypothesized that participants assigned to the mindfulness condition would report reduced cue-induced hypoalgesia and hyperalgesia, relative to the suppression group.

2 | METHODS

2.1 | Design

The study used a 3×2 mixed factorial design, with Cue Type (low vs. novel vs. high pain cues) as the within-subject factor and Group (mindfulness vs. suppression) as the between-subject factor. The dependent variables consisted of self-reported anticipatory anxiety, pain intensity and pain unpleasantness ratings.

2.2 | Participants

Participants were recruited via flyers and the University's webpage for study opportunities. Participants were invited to take part in a study investigating the psychological processes behind the coping strategies people commonly use when dealing with pain and anxiety. The flyers did not include any mention of conditioning, expectancy manipulation, mindfulness or suppression in order to rule out potential placebo or demand effects unrelated to our experimental manipulation. Ninety-two individuals initially expressed interest in the study. A screening procedure was conducted prior to the study to ensure that participants did not have any acute or chronic pain, skin conditions, mental disorders or neurological diagnoses (anxiety, depression, post-traumatic stress disorder, schizophrenia, substance abuse, dementia, epilepsy, stroke or Parkinson's), and were not taking any medication with potential hypo/hyperalgesic effects. Sixty-eight healthy volunteers (50% female), with a mean age of 26.85 ($SD = 7.35$) met the inclusion criteria to take part in the study. None of the participants had prior experience with mindfulness practices. Participants provided written informed consent prior to participation and were remunerated via course credit or gift vouchers at the end of the session. The experiment was conducted in either English ($N = 60$), French ($N = 3$) or German ($N = 5$), according to the participant's preference. Questionnaires were also available in each language. The protocol was approved by the ethics committee of the University of Luxembourg (ref: ERP 17–036).

2.3 | Pain-cueing paradigm

The pain-cueing task was divided into an acquisition (conditioning) and a testing phase. Two visual stimuli (a purple and a green fixation target) served as cues during the acquisition phase. The fixation targets were in the shape of a combined bullseye and cross hair (based on Thaler et al., 2013). One of the cues (high pain cue) was systematically followed by a high pain stimulus while the other (low pain cue) always preceded a low pain stimulus (see Figure 1a). Cue colour-stimulus pairings were counterbalanced across participants. The visual cue was initially presented for 4 s. The cue then disappeared from the screen and was followed by an anticipatory phase ranging between 4 and 6 s. The heat stimulus was then delivered for a duration of 12 s (see below). After each trial, participants indicated on VAS scales the levels of anticipatory anxiety (i.e. ‘how anxious were you prior to the stimulus’), ‘pain intensity’ and ‘pain unpleasantness’ they experienced during the trial (see VAS ratings section below). There was a 10-s interval between trials. The acquisition phase consisted of two blocks of eight trials each (i.e. four low pain-cued stimuli and four high pain-cued stimuli per block), with a self-timed break between each block. Presentation order of the low and high pain stimuli was randomized within each block.

The testing phase (see Figure 1b) consisted of three blocks of 12 test trials each and followed a trial timeline similar to the acquisition phase (see Figure 1c). The heat stimuli were preceded by either the low pain cue, the high pain cue or a novel unconditioned (brown) cue. In contrast to the acquisition phase, the stimulation temperature was identical across all 36

test trials (i.e. the medium pain intensity derived from the calibration procedure described below). Each testing block consisted of four stimuli of each condition (i.e. low cue, high cue and novel cue) presented in a randomized order. Six reminder trials (i.e. with the same cue-stimulus pairing as in the acquisition phase) were presented at the beginning of Block 1, to reduce any suspicion that the cue-stimulus relationship had been altered following the mindfulness/suppression induction. Four additional reminder trials were randomly interspersed within each of Block 2 and 3 to reduce the likelihood of premature extinction. There was an equal number of low-cued and high-cued reminder trials in each block.

2.4 | Thermal pain stimulation

Heat stimuli were administered via a contact thermal stimulator (Somedic AB, Sweden), which was attached to the volar surface of the participant's left forearm. An individual pain calibration procedure was conducted prior to the pain cueing task. Participants received a pseudorandomized series of 20 heat stimuli (ranging from 43°C to 49.5°C) and were asked to indicate, via a mouse click, the level of pain experienced for each stimulus on a VAS scale (0 = ‘No pain’ to 100 = ‘Unbearable pain’). An overall stimulus-response (i.e. temperature-VAS rating) curve was produced for each participant using a linear regression fitting process (Mischkowsky et al., 2018), to derive individual temperatures that reliably elicit ratings of 40 (low pain), 60 (medium pain) and 80 (high pain). Heat stimulus delivery lasted 12 s (ramp up - 1.5 s, plateau - 9 s, ramp down - 1.5 s), with a baseline temperature of 35°C.

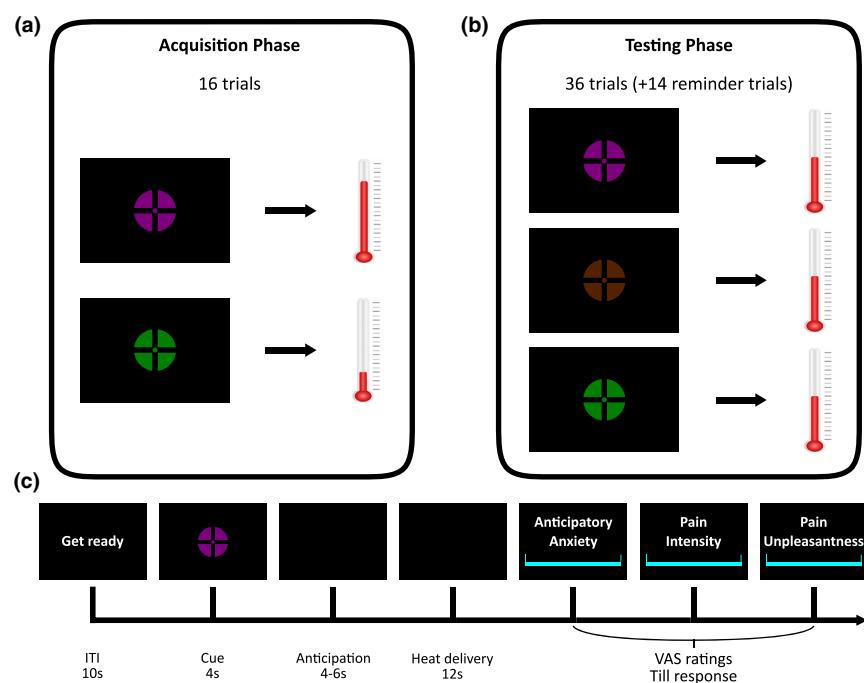


FIGURE 1 Schematic representation of acquisition and testing blocks and trial timeline. (a) During the acquisition phase, one visual cue (e.g. purple) preceded the high pain stimuli while another cue (e.g. green) preceded the low pain stimuli (cue colour-stimulus contingency counterbalanced across participants). (b) During the testing phase, the high pain cue, the low pain cue and a novel cue (e.g. brown) were all followed by identical medium pain stimuli. (c) Depiction of the time-course for a typical trial

2.5 | Pain Coping Instructions

We used a similar approach to that employed by Hooper et al., (2011) and Prins et al., (2014) for our mindfulness and suppression induction procedures. Participants were fitted with headphones and were randomly assigned to listen to a 10-min audio recording of either mindfulness or suppression instructions, in between the acquisition and testing phases of the pain-cueing paradigm. The instructions were adapted from scripts previously used by Garland et al., (2015). Participants, assigned to the mindfulness condition, were encouraged to “openly monitor any arising sensations, thoughts and emotions... in a non-judgmental, non-evaluative manner... without seeking to modify, suppress or avoid them”. For the suppression condition, participants were instructed to “focus on mentally blocking out any arising sensations, thoughts and emotions...and concealing any external manifestation of what (they) are currently experiencing”. The experiential avoidance stance inherent to suppression provides a sharp contrast to the non-judgmental form of awareness encouraged by mindfulness, whilst allowing us to match both conditions in terms of instructions delivery format and length. All audio instructions were delivered by the same female narrator. The narrator was fluent in English, French and German. To encourage participants to make use of the audio instructions during the testing phase of the study, they were also provided with additional on-screen text instructions more directly applicable to the pain procedures (audio and text instructions in all languages are included as Appendix S1). The text instructions were presented at the start of the testing phase. Participants were instructed to press the space bar once they finished reading the on-screen instructions. They were then presented with the following multiple choice comprehension check item: “During the next pain stimulation session, you should aim to (A: accept” / “B: inhibit”) incoming sensations, emotions and thoughts”. The text instructions were repeated if the participant failed to respond correctly to the comprehension check.

2.6 | Self-report measures

2.6.1 | Five facet mindfulness questionnaire

The Five Facet Mindfulness Questionnaire (FFMQ; Baer et al., 2006) was used to assess participants’ dispositional mindfulness levels. The questionnaire comprises 39 items (e.g. “I watch my feelings without getting lost in them”) tapping into five dimensions of mindfulness: observing, describing, acting with awareness, non-judging of inner experience and non-reactivity to inner experience. Each item is rated on a 1 (never or very rarely true) to 5 (always true) Likert scale with higher scores indicative of higher

mindfulness levels. The items were averaged to compute a mean trait mindfulness score (Cronbach’s α for the current sample = 0.83). Validated German (Michalak et al., 2016) and French (Heeren et al., 2011) adaptations of the FFMQ were also available.

2.6.2 | Pain catastrophizing scale

The 13-item Pain Catastrophizing Scale (PCS; Sullivan et al., 1995) is a widely used pain measure, which assesses an individual’s tendency to engage in catastrophic thinking about actual or anticipated pain. Items (e.g. “I worry all the time about whether the pain will end”) are rated on a scale of 0 (not at all) to 4 (all the time). An overall pain catastrophizing score was computed, ranging from 0 to 52 (Cronbach’s α = 0.89), with higher scores indicative of higher catastrophizing levels. Validated German (Meyer et al., 2008) and French (Sullivan et al., 1995) adaptations of the questionnaire were also made available to participants.

2.6.3 | Toronto mindfulness scale

The Toronto Mindfulness Scale (TMS; Lau et al., 2006) was used to assess state mindfulness levels. The 13-item questionnaire measures two factors, that is, decentering (e.g. “I was aware of my thoughts and feelings without over-identifying with them”) and curiosity (e.g. “I remained curious about the nature of each experience as it arose”). All items are rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). A mean state mindfulness score (Cronbach’s α = 0.80) was computed, as well as the decentering (Cronbach’s α = 0.67) and curiosity (Cronbach’s α = 0.85) subscale scores. Higher scores were indicative of higher state mindfulness levels. German and French adaptations of the questionnaire (translated and back-translated in line with recommended guidelines from the International Test Commission (2017)) were also devised specifically for the purpose of this study (see Appendix S2).

2.6.4 | Situational pain catastrophizing scale

The Situational Pain Catastrophizing Scale (SCS; Campbell et al., 2010) is a 6-item adaptation of the PCS, which aims to capture catastrophizing cognitions during a specific experimental pain procedure on a 5-point Likert scale, with higher scores indicative of higher catastrophizing levels. Items scores (e.g. “I thought that the pain might overwhelm me”) were averaged to obtain a mean situational pain catastrophizing score (Cronbach’s α = 0.82). Similar to the TMS,

German and French adaptations were again devised for this study (using the trait French and German (trait) PCS as basis) (see Appendix S3).

2.6.5 | Anticipatory anxiety and pain (VAS) ratings

Anticipatory anxiety (i.e. anxiety level of the participant before each pain stimulus), pain intensity (i.e. intensity of the pain stimulus) and pain unpleasantness (i.e. aversiveness of the pain stimulus) were assessed via visual analogue scales (VAS), ranging from 0 (not anxious/intense/unpleasant at all) to 100 (extremely anxious/intense/unpleasant). Furthermore, original instructions from Price et al., (1983) were used to clarify the distinction between pain intensity and pain unpleasantness to participants.

2.6.6 | Manipulation checks

A post-experiment multiple-choice manipulation check item was administered to assess whether participants successfully noticed the cue-stimulus contingency during the acquisition phase (see Appendix S4). Participants also reported their level of confidence in their response on a Likert scale of 1 (not confident at all) to 5 (fully confident). In addition, participants were asked to rate (i) the clarity of the audio instructions, (ii) the extent to which they followed the instructions, (iii) how easy it was for them to follow the instructions and (iv) how successful they thought they were in applying the instructions, on a scale of 1 (not at all) to 7 (very much so).

2.7 | Procedure

Upon arrival, participants provided written informed consent and completed the FFMQ and the PCS. Next, participants were tested in a laboratory room dedicated to experimentally induced pain research. Participants were seated in a reclining chair approximately 110 cm away from a 24-inch screen monitor and used a lap desk fitted with a mouse and keyboard to respond to the VAS scales and manipulation check items. Participants first carried out the pain calibration procedure to derive individual temperatures for the low, medium and high pain stimuli. This was followed by the acquisition phase of the pain-cueing task. Once the acquisition procedure was completed, participants were randomly assigned (using an AB-BA block randomization procedure) to listen to either the mindfulness or the suppression audio recording and then underwent the testing phase of the pain-cueing paradigm. Participants filled in the TMS,

the SCS and the manipulation checks questionnaire upon completion of the testing phase. Finally, they were fully debriefed as to the purpose of the study.

2.8 | Data analysis

Inspection of the manipulation check items revealed that six participants failed to correctly report the cue-stimulus contingency. As previous studies have reported evidence of conditioned hypoalgesia and hyperalgesia even in the absence of explicit awareness of the conditioning stimuli (Jensen et al., 2015), we conducted separate one-way repeated measures ANOVAs to determine whether Cue Type (low vs. novel vs. high) elicited different anticipatory anxiety, pain intensity and pain unpleasantness ratings, respectively. The analyses revealed no significant effect of Cue Type (i.e. conditioning effects) within this sub-sample of six participants (all p 's > 0.10). As we were specifically interested in how the mindfulness and suppression conditions modulate the magnitudes of conditioned hypoalgesia and hyperalgesia, we excluded these six participants from the final analyses. Nevertheless, we would like to point out that supplementary analyses, including data from these six participants, showed a similar pattern of results to that reported in this manuscript. As a preliminary check, we also conducted independent t tests to determine whether the language in which the study was conducted influenced the scores on the study items. The between-group comparisons showed no significant effect of language (all p 's > 0.10).

Next, we ran between-group multivariate GLM comparisons on the pre-experimental measures (FFMQ, PCS, temperature thresholds derived from the calibration procedure and pain ratings during the acquisition phase) to test whether our randomized participant allocation procedure was successful. We then ran similar analyses on the post-experimental measures (TMS, SCS and manipulation check items) to assess the effectiveness of our experimental manipulation.

To test our main hypotheses, we conducted separate two-way mixed ANOVAs, with Cue Type (low vs. novel vs. high) as the within-subjects factor and Group (mindfulness vs. suppression) as the between-subjects factor, for anticipatory anxiety, pain intensity and pain unpleasantness ratings, respectively. Greenhouse-Geisser corrections were applied wherever assumptions of sphericity were violated. Planned Bonferroni-adjusted ($p = 0.05/4$) follow-up pairwise comparisons were conducted to test whether ratings on novel-cued trials differed from low and high pain-cued trials respectively, across each group. Furthermore, we used a difference score approach to test whether the magnitudes of conditioned hypoalgesia and conditioned hyperalgesia differed between the mindfulness and suppression groups. Conditioned hypoalgesia (i.e. difference between novel-cued trials and

low-cued trials) and conditioned hyperalgesia (i.e. difference between high-cued trials and novel-cued trials) magnitudes were computed for anticipatory anxiety, pain intensity and pain unpleasantness ratings separately. Individual two-way mixed ANOVAs, with Group (mindfulness vs. suppression) as the between-subjects factor and Direction of modulation (conditioned hypoalgesia vs. conditioned hyperalgesia) as the within-subjects factor, were conducted for the anticipatory anxiety, pain intensity and pain unpleasantness ratings, respectively. We were specifically interested in any potential interaction effects, i.e. whether the two groups differed in terms of conditioned hypoalgesia and conditioned hyperalgesia magnitudes, respectively. Bonferroni-adjusted follow-up pairwise comparisons ($p = 0.05/2$) were again used to probe any significant interaction effects. Finally, we conducted exploratory (two-tailed Pearson) correlational analyses to test for potential associations between the self-report mindfulness and pain catastrophizing questionnaires (i.e. FFMQ, TMS, PCS and SCS) and cue-induced hypoalgesia and hyperalgesia.

3 | RESULTS

3.1 | Baseline measures

The mindfulness ($N = 31$) and suppression ($N = 31$) groups did not differ in terms of gender distribution ($\chi^2(1, N = 62) = 0.07, p > 0.10$) or age ($t(60) = 0.33, p > 0.10$). Furthermore, no group differences in trait questionnaires scores or in temperature thresholds required to elicit low, medium and high pain during the calibration procedure were found. Finally, there were no group differences in anticipatory anxiety, pain intensity and pain unpleasantness ratings on low and high pain-cued trials during the acquisition phase, confirming that our randomization procedure was successful. Table 1 summarizes the group means, SDs and statistics for the baseline measures.

3.2 | State and manipulation check measures

Between-group multivariate GLM comparisons revealed that the two groups did not significantly differ in overall state mindfulness (TMS) scores, $F(1,60) = 2.43, p = 0.12, \eta_p^2 = 0.04$. However, when analysing the subscales, results indicated that the mindfulness group scored significantly higher than the suppression group on the decentering subscale, $F(1,60) = 7.88, p < 0.01, \eta_p^2 = 0.12$. No group differences were found for the curiosity subscale, $F(1,60) = 0.10, p = 0.92, \eta_p^2 = 0.00$. In addition, the mindfulness group reported marginally lower SCS scores than the suppression group, $F(1,60) = 2.89, p = 0.095, \eta_p^2 = 0.046$. Analyses of

TABLE 1 Mean (SD) and F values for baseline measures

	Mindfulness ($N = 31$)	Suppression ($N = 31$)	$F(1, 60)$
FFMQ (1–5)	3.27 (0.27)	3.23 (0.40)	0.19
PCS (0–52)	20.55 (9.26)	19.26 (9.55)	0.29
Pain thresholds (°C)			
Low	45.63 (0.85)	45.24 (0.81)	3.33
Medium	46.63 (0.80)	46.29 (0.77)	2.77
High	47.65 (0.78)	47.32 (0.76)	2.84
Acquisition Phase			
Low-cued ratings (0–100)			
Anticipatory Anxiety	23.27 (11.60)	26.25 (15.52)	0.78
Pain Intensity	33.19 (10.54)	37.53 (11.36)	2.43
Pain Unpleasantness	30.55 (11.17)	32.46 (10.49)	0.48
High-cued ratings (0–100)			
Anticipatory Anxiety	40.56 (16.27)	48.40 (22.98)	2.41
Pain Intensity	80.33 (7.83)	81.20 (6.89)	0.21
Pain Unpleasantness	79.96 (7.82)	82.33 (7.55)	1.48
Pain Unpleasantness	79.96 (7.82)	82.33 (7.55)	1.48

Abbreviations: FFMQ, Five Facet Mindfulness Questionnaire; PCS, Pain Catastrophizing Scale.

Scale ranges are provided alongside each measure Note: *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$

the manipulation check items indicated that the mindfulness group reported significantly greater confidence in their cue-stimulus contingency awareness response, $F(1,60) = 5.04, p = 0.03, \eta_p^2 = 0.08$. No group differences were observed for the other manipulation check items (p 's all > 0.10). Table 2 summarizes the group means, SDs and statistics for the state and manipulation check measures.

3.3 | Cue-induced anxiety and pain modulation: Mindfulness versus Suppression

3.3.1 | Anticipatory anxiety

The two-factor ANOVA conducted on the anticipatory anxiety ratings showed a significant main effect for Cue Type ($F(2,120) = 26.16, p < 0.001, \eta_p^2 = 0.30$) but not for Group ($F(1,60) = 2.74, p > 0.10, \eta_p^2 = 0.04$). Bonferroni-adjusted follow-up pairwise comparisons revealed lower anticipatory anxiety levels on the low-cued trials ($t(61) = -5.36, p < 0.001$) relative to the novel-cued trials, but no differences between high-cued and novel-cued trials ($t(61) = 0.83, p > 0.10$). There was also a marginal, but non-significant, Cue*Group interaction, $F(2,120) = 2.60, p = 0.08, \eta_p^2 = 0.04$. This marginal interaction was driven by marginally higher

TABLE 2 Mean (SD) and F values for state measures and post-experimental manipulation checks

	Mindfulness ($N = 31$)	Suppression ($N = 31$)	$F(1,$ $60)$
SCS (0 – 4)	0.73 (0.57)	1.02 (0.74)	2.89
TMS (0 – 4)	2.55 (0.67)	2.30 (0.60)	2.43
Curiosity	2.49 (0.87)	2.47 (0.78)	0.10
Decentering	2.60 (0.70)	2.15 (0.56)	7.88**
Testing Phase			
Low-cued ratings (0 – 100)			
Anticipatory Anxiety	15.47 (16.16)	20.11 (18.82)	1.09
Pain Intensity	32.97 (20.70)	28.97 (21.36)	0.56
Pain Unpleasantness	25.96 (19.66)	25.59 (20.97)	0.01
Novel-cued ratings (0 – 100)			
Anticipatory Anxiety	20.75 (18.15)	29.11 (20.52)	2.89
Pain Intensity	36.74 (21.18)	39.78 (19.61)	0.34
Pain Unpleasantness	29.80 (20.35)	36.92 (21.14)	1.83
High-cued ratings (0 – 100)			
Anticipatory Anxiety	20.87 (18.92)	30.99 (21.89)	3.79
Pain Intensity	44.23 (20.58)	44.65 (20.62)	0.01
Pain Unpleasantness	36.37 (22.10)	41.76 (21.82)	0.93
Manipulation Checks			
Confidence (1 – 5)	4.39 (1.02)	3.81 (1.01)	5.04*
Clarity (1 – 7)	5.77 (1.09)	6.23 (0.99)	2.93
Followed (1 – 7)	5.55 (0.99)	5.71 (1.07)	0.38
Ease (1 – 7)	5.16 (1.34)	5.00 (1.48)	0.20
Success (1 – 7)	5.10 (1.01)	5.39 (0.99)	1.31

Abbreviations: SCS, Situational Catastrophizing Scale; TMS, Toronto Mindfulness Scale.

Confidence (confidence in cue-stimulus contingency report), Clarity (clarity of instructions), Followed (extent to which instructions were followed), Ease (perceived ease in following instructions), Success (perceived successiveness in applying instructions); scale ranges are provided alongside each measure Note:

*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$

anticipatory anxiety ratings in the suppression group for novel-cued ($t(60) = 1.70, p = 0.09$) and high-cued trials ($t(60) = 1.95, p = 0.06$) relative to the mindfulness group, with no group differences observed for low-cued trials ($t(60) = 1.04, p = 0.30$).

Analyses of the computed difference scores for the anticipatory anxiety ratings revealed that the suppression group reported larger overall cued changes in anticipatory anxiety ratings than the mindfulness group, $F(1,60) = 5.84, p = 0.02, \eta_p^2 = 0.09$. We observed no significant Direction of modulation*Group interaction, $F(1,60) = 0.19, p > .10, \eta_p^2 = 0.003$.

3.3.2 | Pain intensity

Analyses of the pain intensity ratings again revealed a significant effect for Cue Type ($F(1.57,94.18) = 67.74, p < 0.001, \eta_p^2 = 0.53$) but no effect for Group ($F(1,60) = 0.001, p > 0.10, \eta_p^2 = 0.00$). The Bonferroni-corrected follow-up

comparisons ($p = 0.05/2$) suggested that the paradigm was successful in inducing conditioned hypoalgesia and hyperalgesia, with low-cued trials resulting in lower pain intensity ratings ($t(61) = -6.30, p < 0.001$) and high-cued trials resulting in higher pain intensity ratings ($t(61) = 7.19, p < 0.001$), compared to novel-cued trials.

In addition, we also observed a significant Cue*Group interaction effect, $F(1.57,94.18) = 4.71, p = .02, \eta_p^2 = 0.07$. Bonferroni-corrected follow-up pairwise comparisons ($p = 0.05/4$) showed that low-cued trials resulted in significantly lower pain intensity ratings compared to novel-cued trials in the suppression group ($t(30) = -6.61, p < 0.001$), but failed to do so in the mindfulness group ($t(30) = -2.31, p = 0.07$). High-cued trials resulted in higher pain intensity ratings than the novel-cued trials in both the mindfulness ($t(30) = 6.17, p < 0.001$) and suppression group ($t(30) = 4.01, p < 0.001$).

Analyses of the computed difference scores for the pain intensity ratings revealed a significant Direction

of modulation*Group interaction ($F(1,60) = 10.62, p < 0.01, \eta_p^2 = 0.15$), but no main effect for Direction of Modulation ($F(1,60) = 0.57, p > 0.10, \eta_p^2 = 0.009$) or Group ($F(1,60) = 2.49, p > 0.10, \eta_p^2 = 0.04$). Bonferroni-corrected follow-up pairwise comparisons ($p = 0.05/2$) showed reduced conditioned hypoalgesia magnitudes in the mindfulness compared to the suppression group, $t(43.65) = -3.04, p < 0.01$. There were no group differences in conditioned hyperalgesia magnitudes, $t(60) = 1.53, p > 0.10$.

3.3.3 | Pain unpleasantness

Analyses of the pain unpleasantness ratings revealed a significant effect for Cue Type ($F(1.64, 98.53) = 61.32, p < 0.001, \eta_p^2 = 0.51$) but not for Group ($F(1,60) = 0.62, p > 0.10, \eta_p^2 = 0.01$). The main effect for Cue Type was again driven by lower pain unpleasantness ratings for low-cued trials ($t(61) = -6.41, p < 0.001$) and higher pain unpleasantness ratings for high-cued trials ($t(61) = 6.05, p < 0.001$), relative to novel-cued trials.

There was a significant Cue*Group interaction, $F(1.64, 98.53) = 5.31, p = 0.01, \eta_p^2 = 0.08$. Bonferroni-corrected ($p = 0.05/4$) follow-up comparisons revealed that the low-cued trials resulted in significantly lower pain unpleasantness ratings compared to novel-cued trials in the suppression group ($t(30) = -6.77, p < 0.001$), but not in the mindfulness group ($t(30) = -2.29, p = 0.08$). Both

the mindfulness ($t(30) = 4.93, p < 0.001$) and suppression ($t(30) = 3.62, p < 0.01$) groups reported higher pain unpleasantness for high-cued trials, relative to the novel-cued trials.

Analyses of the computed difference scores for the pain unpleasantness ratings revealed a main effect for Group, with the suppression group reporting larger overall cue-induced changes in pain modulation than the mindfulness group ($F(1,60) = 4.03, p = 0.049, \eta_p^2 = 0.06$), but no main effect for Direction of Modulation ($F(1,60) = 1.41, p > 0.10, \eta_p^2 = 0.02$). More importantly, we observed a significant Direction of modulation*Group interaction effect, $F(1,60) = 8.45, p < 0.01, \eta_p^2 = 0.12$. Bonferroni-corrected follow-up pairwise comparisons ($0.05/2$) showed smaller conditioned hypoalgesia magnitudes in the mindfulness compared to the suppression group, $t(41.71) = -3.17, p < 0.01$. There were no group differences in conditioned hyperalgesia magnitudes, $t(60) = 0.92, p > 0.10$.

Overall, while we observed cue-induced hyperalgesia in both groups, we found evidence for cue-induced hypoalgesia only in the suppression group. Importantly, there were no group differences on novel-cued trials, suggesting that the different patterns of results observed across the two groups were unlikely to be driven by differences in unconditioned pain ratings. Cue-induced anxiety, intensity and unpleasantness modulation across both groups are illustrated in Figure 2. Computed hypoalgesia and hyperalgesia difference scores across both groups are illustrated in Figure 3.

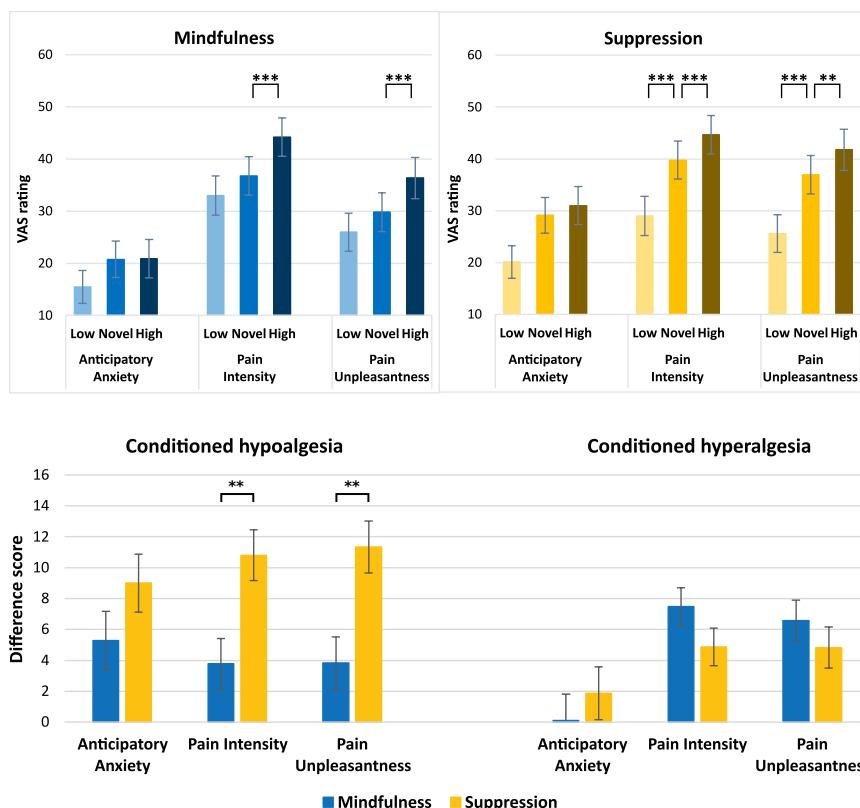


FIGURE 2 Mean anticipatory anxiety, pain intensity and pain unpleasantness ratings on low, novel and high-cued trials across both groups. Error bars indicate standard errors. Note: *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$

FIGURE 3 Computed conditioned hypoalgesia and hyperalgesia magnitudes (using a difference score approach) across both groups. Error bars indicate standard errors. Note: *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$

3.4 | Cue-induced anxiety and pain modulation: Associations with trait and state mindfulness and pain catastrophizing measures

We first ran preliminary two-tailed Pearson correlations to test for any significant association between the self-report mindfulness and pain catastrophizing questionnaires and the VAS ratings on the (unconditioned) novel-cued trials. The analyses revealed a significant negative correlation between state mindfulness scores and state pain catastrophizing scores ($r = -0.41, p = 0.001$). Importantly, higher levels of state mindfulness were associated with lower anticipatory anxiety ($r = -0.44, p < 0.001$), pain intensity ($r = -0.29, p = 0.02$) and pain unpleasantness ($r = -0.31, p = 0.01$) ratings. In contrast, higher state pain catastrophizing levels were associated with increased anticipatory anxiety ($r = 0.37, p < 0.01$), pain intensity ($r = 0.35, p < 0.01$) and pain unpleasantness ($r = 0.43, p < 0.001$) ratings. We also observed a significant negative correlation between trait mindfulness and trait pain catastrophizing ($r = -0.26, p = 0.04$). However, neither measure correlated significantly with the outcome or state self-report measures (p 's all > 0.10). Subsequent partial correlational analyses (controlling respectively for anxiety, intensity and unpleasantness ratings on novel-cued trials) revealed that higher state mindfulness scores were linked to

higher pain intensity ratings on the low-cued trials (i.e. reduced cue-induced hypoalgesia) but lower anticipatory anxiety levels on the high-cued trials (see Table 3). Conversely, state catastrophizing was associated with increased anticipatory anxiety and pain intensity ratings for the high-cued trials (i.e. increased cue-induced hyperalgesia).

Finally, correlational analyses conducted on the computed difference scores revealed a similar pattern of results (see Table 4). Higher state mindfulness scores were associated with smaller conditioned hypoalgesia magnitudes for pain intensity ratings and marginally smaller hypoalgesia magnitudes for the pain unpleasantness ratings ($p = 0.08$). Higher levels of state pain catastrophizing were associated with larger conditioned hyperalgesia magnitudes for the anticipatory anxiety ratings.

4 | DISCUSSION

The current study aimed to investigate how instructed use of a mindfulness or a suppression strategy modulates pain perception during a classical pain conditioning task. The findings partially support the hypothesis that a brief mindfulness induction reduces sensitivity to pain-cueing procedures. While we found evidence for conditioned hyperalgesia in

TABLE 3 Partial correlations (controlling for novel-cued trials) between the self-report questionnaires and VAS ratings on low and high-cued trials

	Low pain cue			High pain cue		
	Anxiety	Intensity	Unpleasantness	Anxiety	Intensity	Unpleasantness
State mindfulness (TMS)	-0.12	0.28*	0.14	-0.29*	-0.06	-0.13
Curiosity	-0.11	0.17	0.05	-0.24	-0.09	-0.17
Decentering	-0.10	0.32*	0.19	-0.25	-0.01	-0.06
State Pain Catastrophizing	0.26*	-0.10	-0.11	0.33**	0.27*	0.22
FFMQ	-0.07	-0.04	-0.12	0.02	0.12	0.03
PCS	0.03	-0.10	-0.11	-0.08	0.13	0.07

Note: *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$.

TABLE 4 Correlations between the self-report questionnaires and the computed difference scores

	Conditioned hypoalgesia			Conditioned hyperalgesia		
	Anxiety	Intensity	Unpleasantness	Anxiety	Intensity	Unpleasantness
State mindfulness (TMS)	-0.10	-0.31*	-0.22	-0.21	-0.01	-0.12
Curiosity	-0.06	-0.20	-0.13	-0.19	-0.05	-0.15
Decentering	-0.13	-0.35**	-0.26*	-0.17	0.04	-0.05
State Pain Catastrophizing	-0.05	0.15	0.23	0.27*	0.20	0.19
FFMQ	0.00	0.06	0.14	0.03	0.09	0.02
PCS	0.05	0.08	0.09	-0.10	0.15	0.07

Note: *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$.

both the mindfulness and suppression groups, only the latter reported lower pain intensity and pain unpleasantness ratings on the low-cued trials (i.e. conditioned hypoalgesia).

The absence of conditioned hypoalgesia in the mindfulness condition could be construed as indicative of reduced effectiveness in pain attenuation, relative to the suppression condition. This interpretation, however, is inconsistent with the lower, albeit non-significant, pain ratings reported by the mindfulness group on the unconditioned (novel-cued) trials. Previous studies comparing mindfulness and suppression strategies have likewise either reported no group differences in unconditioned pain ratings or reduced pain ratings in their mindfulness condition (Kohl et al., 2012). We would argue, therefore, that the lack of conditioned hypoalgesia in the mindfulness condition is instead a by-product of contrasting mechanisms underlying mindfulness-driven versus conditioning/expectancy-driven pain modulation. This argument is supported by neuroimaging evidence showing that pain alleviation during mindfulness is associated with a pattern of neural activity opposite to that observed in placebo hypoalgesia (Zeidan et al., 2015). Furthermore, recent studies have shown that while administration of an opioid antagonist (naloxone) was successful in nullifying hypoalgesic effects induced by a placebo saline infusion, the antagonist failed to reverse mindfulness-induced hypoalgesia (Wells et al., 2020; Zeidan et al., 2016). These findings suggest that mindfulness may alleviate pain via unique neuropsychological mechanisms which bypass opioidergically mediated descending pathways typically involved in the cognitive modulation of pain (King et al., 2013; Sprenger et al., 2012).

Nevertheless, while the results supported our prediction of reduced conditioned hypoalgesic effects following mindfulness training, we failed to observe the hypothesized mindfulness-induced reductions in conditioned hyperalgesia. These asymmetrical findings may have resulted from the disparate neuropsychological mechanisms underlying conditioned hypoalgesia versus conditioned hyperalgesia. Freeman et al., (2015) previously demonstrated that, while behavioural responses evoked by placebo and nocebo procedures are significantly correlated, placebo conditioning elicited changes in the insula, orbitofrontal cortex, and periaqueductal grey while nocebo conditioning was linked to altered striatal activity, with no overlapping activation across the two conditions. Alternatively, the preserved conditioned hyperalgesia may also be explained by an increased difficulty in modulating nocebo-like effects. Previous studies have shown conditioned nocebo effects to be significantly more resistant to extinction than conditioned placebo effects (Colagiuri et al., 2015; Colloca et al., 2008), presumably due to the higher adaptive cost associated with information about impending threat (i.e. high pain cue). It is, however, important to highlight the limited generalizability of the current mindfulness manipulation to the practice and construct of mindfulness as a whole. Our

brief mindfulness induction is unlikely to capture the full phenomenological complexity of mindfulness as experienced by expert practitioners or even novice practitioners who have completed introductory mindfulness-based courses. Accordingly, it must be noted that the mindfulness group scored higher than the suppression group on the decentering subscale, but not on the overall state mindfulness measure. This may potentially be explained by the fact that the TMS was administered as a retrospective measure after the testing phase of the study, rather than immediately after the mindfulness induction, as is common practice. Furthermore, Ireland et al., (2019) recently raised some doubts as to the sensitivity of the curiosity subscale of the TMS in assessing potential group differences, which may explain why we only observed group differences on the decentering subscale. Nevertheless, concerns may be raised as to the extent to which mindfulness was successfully induced, and if so, whether the observed results may have been driven by some extraneous variables. However, we think this is unlikely given that the correlational analyses conducted between the state mindfulness scores and conditioned hypoalgesia and hyperalgesia revealed a similar pattern of results, irrespective of group membership. Higher state mindfulness levels were associated with reduced conditioned hypoalgesia for pain intensity ratings (and marginally reduced conditioned hypoalgesia for unpleasantness ratings), but not with conditioned hyperalgesia. Nevertheless, we cannot rule out the possibility that a sample of experienced mindfulness practitioners may show improved resistance to conditioned hyperalgesia. Recent evidence from Taylor et al., (2018) showing that experienced meditators (>1,000 hr of practice) exhibit reduced conditioned hyperalgesic effects compared to meditation-naïve controls during a classical fear-conditioning paradigm suggests that this may indeed be the case. Importantly, meditators did not differ from controls in nocifensive reflexes elicited by the conditioned cues, suggesting that meditation experience does not weaken the critical ability to learn from associative cues. The authors argued that meditation may instead reduce cue-induced pain modulation by limiting the influence of such associative learning and anticipation on pain perception.

Some further limitations of the current study also need to be acknowledged. Firstly, we did not include a (no-instructions) control group. We opted to use a suppression condition as our comparison group to minimize the potential heterogeneity in coping strategies that is likely to arise from a no-instructions group condition (Van Ryckeghem et al., 2018). The downside to this approach, however, is that it does not allow for any definitive conclusions to be drawn regarding the directional influence of the two conditions. In other words, inclusion of a no-instructions group would be necessary to determine whether the group differences in conditioned hypoalgesia were driven by reduced sensitivity to conditioning procedures during mindfulness, increased sensitivity during suppression

or a combination of both. Likewise, it would be important to extend the paradigm to other forms of cognitive strategies (e.g. reappraisal, distraction, hypnosis) to determine whether the observed modulatory effects are unique to mindfulness. Secondly, unconditioned pain ratings were assessed on the premise that responses on novel-cued trials should be free from any influence of the conditioning procedure. Although the introduction of novel cues is common practice in classical conditioning paradigms, it cannot be fully ruled out that participants may have assumed the novel cue to be predictive of an intermediate temperature level.

Notwithstanding the aforementioned caveats, our findings, together with those of Taylor et al., (2018), provide initial support for the notion that mindfulness may minimize the biasing influence of expectations on pain perception. Recently formulated predictive coding models provide a promising unifying framework within which to explore the interplay between prior expectations (i.e. predictive value of the conditioned cues), sensory information (i.e. heat stimulation) and (mindful) attention modulation (Farb et al., 2015; Lutz et al., 2019; Pagnoni, 2019). According to these models, the key prescriptions of heightened sustained attention towards current sensory experience during mindfulness practice, coupled with increased stability in interoceptive and proprioceptive anchoring (via immobility of posture and gaze), may result in an increase in the precision of ascending sensory information. Conversely, the reallocation of attention from habitually activated mental content (e.g. during mind-wandering) to the non-elaborative monitoring of arising sensations and thoughts should lead to a curtailing of top-down mental processes fuelled by expectations, desires and schemas. Together, these effects may combine so that perceptual experience in mindfulness is less likely to be shaped by prior expectations and beliefs (i.e. descending predictions from higher cortical areas (Atlas & Wager, 2012)). This interpretation is also consistent with the unique neural pattern of reduced prefrontal activity and increased sensory processing-related activity observed in neuroimaging studies of mindfulness-induced hypoalgesia (Gard et al., 2011). Nevertheless, further research is required to substantiate this purported link between these neural mechanisms to the pain conditioning effects observed here. In line with previous reports that reduced functional connectivity between executive and sensory-related brain areas are associated with increased pain tolerance in mindfulness practitioners (Grant et al., 2011), we would expect similar functional decoupling to also predict the reduced cue-induced pain modulation observed here. Nonetheless, it is important to note that while the current evidence is consistent with the predictive processing view of mindfulness, the study did not aim to provide a direct test of the mechanistic postulates derived from these models. For instance, reduced cue-induced hypoalgesia, as per this framework, could be explained by either higher

weighting of afferent sensory information, lower weighting of prior information or an integration of both mechanisms. Our paradigm, however, does not allow us to tease apart the relative contributing influence of these different processes. Computational modelling of trial-by-trial changes in conditioned pain ratings based on the tenets of predictive coding (e.g. Hoskin et al., 2019) and effective connectivity studies of related neural activity (e.g. Sevel et al., 2015) provide promising pathways towards addressing these research questions.

While the hypoalgesic effects of mindfulness practice have been the subject of increasing empirical interest, the current study offers a first glimpse into how pain modulation may in itself deepen our understanding of the underlying mechanisms of mindfulness. Importantly, our findings provide novel evidence suggesting that mindfulness and expectancy-driven hypoalgesia may not only involve contrasting, but also counteracting, mechanisms. Nevertheless, the merging of pain cueing paradigms with neuroimaging and computational modelling techniques in samples of experienced practitioners represent important steps in advancing this line of investigation.

ACKNOWLEDGEMENT

The authors would like to thank Sam Bernard for his assistance in data collection and in the translation of testing instructions and questionnaires. We are also grateful to all participants for their time and interest in the study.

CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception of the study design. Data collection was carried out by SV. SV ran the analyses and drafted the manuscript, with critical discussion and revisions from all authors. All authors have read and approved the final version of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Vencatachellum, S., van der Meulen, M., Van Ryckeghem, D. M. L., Van Damme, S., & Vögele, C. (2021). Brief mindfulness training can mitigate the influence of prior expectations on pain perception. *European Journal of Pain*, 25, 2007–2019. <https://doi.org/10.1002/ejp.1817>