Reduced Fear-Conditioned Pain Modulation in Experienced Meditators: A Preliminary Study

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ABSTRACT

Objective: Mindfulness-based practice is a form of cognitive/affective training that may help reduce suffering by attenuating maladaptive anticipatory processes. This study's objective was to examine the pain modulating impact of classical fear learning in meditation practitioners.

Methods: The hyperalgesic effects of pain expectation and uncertainty were assessed outside formal meditation in 11 experienced meditators (>1000 hours) compared with meditation-naive controls during a Pavlovian classical fear-conditioning paradigm involving two visual stimuli (CS+/CS−), one of which (CS+) co-terminated with a noxious electrical stimulus (unconditioned stimulus) on 50% of trials. A Rescorla-Wagner/Pearce-Hall hybrid model was fitted onto the conditioned skin conductance responses using computational modeling to estimate two learning parameters: expected shock probability and associability (i.e., uncertainty).

Results: Using a scale ranging between 0 (no pain) and 100 (extremely painful), meditators reported less pain (M = 19.9, SE = 5.1 for meditators, M = 32.4, SE = 2.4 for controls) but had comparable spinal motor responses (nociceptive flexion reflex) to the unconditioned stimulus. Multilevel mediation analyses revealed that meditators also exhibited reduced hyperalgesic effects of fear learning on higher-order pain responses but comparable effects on the nociceptive flexion reflex. These results suggest that mindfulness affects higher-order perceptual processes to a greater extent than from descending inhibitory controls. Furthermore, meditators showed reduced hyperalgesic effects of fear conditioning with no significant group difference in conditioned learning as evidenced by discriminative anticipatory skin conductance responses and learning parameters derived from computational modeling.

Conclusions: These results highlight potential mechanisms underlying mindfulness-related hypoalgesia, relevant to clinical conditions in which repeated pain exposure might reinforce hyperalgesic processes through fear conditioning.

Key words: computational modeling, fear conditioning, mindfulness meditation, nociceptive flexion reflex, pain.

INTRODUCTION

Cultivated through the practice of meditation, mindfulness has gained worldwide scientific interest for its accessibility and its potential for attenuating symptoms in pathologies related to chronic pain as well as affect, anxiety, and stress (1–5). This state of awareness involves intentionally paying attention to the present-moment and monitoring mental/physical events in a detached and accepting manner (6). Findings from neuroimaging studies suggest that the hypoalgesic influence of the cognitive/affective training of mindfulness meditation is particular because it selectively affects higher-order brain centers linked to cognitive/affective elaboration of pain and not primary sensory aspects of nociceptive pain (7,8). More specifically, one of the premises underlying mindfulness is that relief from suffering occurs by detaching oneself from past events and future scenarios (6), which may reduce pain anticipation.

Indeed, the mechanisms of action through which mindfulness may attenuate pain have been suggested to operate by reducing neural activity in pain-related regions during the anticipation of pain (9,10). Electrophysiological and functional magnetic resonance imaging studies have reported that changes in anticipatory brain activity may contribute to the reduced pain sensitivity of experienced meditators (9). The net hypoalgesic effects of meditation may therefore reflect a reduction in anticipatory processes, i.e., reduced anticipation leading to reduced pain facilitation. However, an alternative possibility would be that anticipatory processes are triggered normally but their impact on pain is reduced, i.e., normal anticipation with reduced facilitation of pain by anticipation. In addition, a lack of low-level (spinal) assessments of nociceptive transmission is present in previous studies examining pain modulation by meditation. It remains unclear whether the underlying pain-modulation mechanisms from meditation operate specifically

CS = conditioned stimulus, **US** = unconditioned stimulus, **NFR** = nociceptive flexion reflex, **PH** = Pearce-Hall, **SCR** = skin conductance response, **RW** = Rescorla-Wagner

SDC Supplemental Content

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at higher-order perceptual levels of processing, lower-level spinal levels, or a combination of both. Therefore, it is important to clarify the contribution of pain modulation by meditation on different levels of pain transmission/modulation, such as spinal measures of nociception (nociceptive flexion reflex [NFR]) elicited by noxious electrocutaneous stimualtions (11).

In a previous independent report, we showed that the anticipation of noxious stimuli facilitated pain during classical conditioning (12). We demonstrated that pain facilitation during fear conditioning can be explained by specific fear-learning parameters (expectations and uncertainty) estimated from computational modeling of anticipatory responses (skin conductance responses [SCRs]) to fear-conditioned cues (CS+). Computational models of reinforcement learning are thought to best depict trial-by-trial variations in anticipatory behavior as a function of predictions, or expected shock probabilities, formed about the occurrence of pain, as well as the associability of CSs (13). The latter factor, "associability," is highest when predictions are unreliable, i.e., when the absolute magnitude of prediction errors experienced in previous trials is elevated. There is more to learn when contingencies are uncertain; therefore, associability is thought to reflect enhanced attention allocation to cues most informative about uncertain environmental contingencies (13). We showed that both fear leaning parameters, i.e., expected shock probabilities and uncertainty (henceforth referred to as associability), positively predicted trial-by-trial fluctuations in pain, and spinal NFR responses to noxious electrical US (12). In addition, we showed that low pain catastrophizing and high dispositional mindfulness attenuated the hyperalgesic impact of aversive learning processes.

Here, we examined the impact of extensive meditation experience on the effects of fear learning on pain and spinal responses to the US during a classical fear-learning task. The main objective of the present study was to determine whether effects of mindfulness meditation practice on pain are due to an impact of classically learned anticipation on pain-evoked responses. The secondary aim of this study was to investigate whether general hypoalgesic effects of mindfulness meditation occur exclusively by targeting higher-order pain response level of processing (i.e., perceptual), by influencing spinal responses to noxious stimuli (i.e., reflexive), or both.

Although brain correlates of pain anticipation had shown a reduction with meditation experience in previous reports (9,10), evidence specific to autonomic system reactivity showed that mindfulness meditation training does not eliminate fear-conditioned anticipatory SCRs (14) or amygdala responses to negative affective pictures (15). These inconsistent findings may indicate that meditation would be related to reduced anticipation signals sent to higher-order cortical centers (e.g., prefrontal or cingulate regions) from lower-level fear encoding regions (e.g., amygdala), yet that lower-level fear processing (autonomic and amygdala reactivity) remain intact. In light of findings specific to autonomic conditioned responses and meditation training (14), we hypothesized that meditation experience would not affect anticipatory SCRs to CSs but would reduce the impact of fear-learning parameters on pain (i.e., of expected shock probabilities of receiving pain and associability). Finally, because meditation experience is associated with reduced brain responses in regions related to cognitive/affective elaboration of pain and enhanced activation of regions related to sensory aspects of pain (7,8), we hypothesized that meditation experience would be related to reduced impact of fear learning on pain only at a higher-order level of processing (perceptual) (16).

METHODS

Participants

Meditators were recruited using advertisement posted in Zen and Bodhicitta meditation centers in Montreal and through word of mouth. The group consisted of 11 experienced meditators with a minimum of 1000 hours of practice involving the cultivation of mindfulness (ranging between 1050 and 9500 hours; 7 males, 4 females, aged between 28 and 68 years). Eight meditators practiced traditional Zen meditation. Two other meditators were from the Bodhicitta tradition, and one meditator was from the "Kadampa" tradition. These practices share common ground in that they typically involve an anchor for the focus of attention (e.g., the breath, the posture, mantra), while acknowledging distractions/sensations/thoughts nonjudgmentally and returning to the anchor of attention each time the mind wanders. In doing so, the field of attention tends to gradually expand to encompass a broader experiential span (17). The control group (n = 51, 24 males, 27 females, aged between 19 and 61 years) had no previous meditation training/experience and was recruited from advertisements in local university settings (Université de Montréal, McGill, and Concordia Universities). Recruitment calls (advertisements and word of mouth) were homogeneous across groups. The control group consisted of 47 participant described in a previous report to which we added four participants matching the age of the older meditators. Because of the unequal number of participants between groups, all of the analyses described in the present report were also conducted by comparing the group of experienced meditators with a subsample of 11 participants taken from the large control group and selected to match the meditators for age, sex, and number of years of education. The control individuals from the control group matching meditators on demographic variables were randomly chosen (using computerized randomization algorithm) to be incorporated in the subsample control group. The timeframe for data collection was between September 2012 and September 2014 and was received ethical approval by the Comité d'Ethique de la Recherche of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montreal. The present study used the same methods and experimental protocol developed and in our recent study (12).

Exclusion criteria for participating in the study are described in the Supplemental Digital Content 1, http://links.lww.com/PSYMED/A513. Participants were invited to visit the Laboratory of the Neuropsychophysiology of Pain of the *Centre de recherche de l'Institut universitaire de gériatrie de Montréal* (Canada) for a screening and familiarization session to assess their pain thresholds and physiological responsivity (skin conductance and NFR) and for a second visit to complete the experimental paradigm. Twelve participants (9 meditation-naive controls and 3 experienced meditators) were not retained after the familiarization session for one of the following reasons: extremely low/high pain thresholds, excessive use of alcohol, drugs, or analgesic medication, discomfort with the nature of the noxious stimuli (electrical stimulations), or oversensitivity of skin at the site of electrical stimulation, or absent/unstable skin conductance or NFRs to the painful stimuli. Sixty-five participants participated in the experimental session, but three meditation-naive control participants were excluded from data analysis because of poor electrodermal signal or very inconsistent NFRs.

Measures and Materials

The conditioned stimuli (cue1 and cue2) consisted of visual stimuli, i.e., colored fractal images (see Supplemental Digital Content 1, http://links.lww.com/PSYMED/A513, for further details).

Unconditioned stimuli (US) were transcutaneous electrical stimulations (30 milliseconds), and each consisted of a train of ten 1-millisecond pulses (delivered at a frequency of 333 Hz), administered using two electrodes at

the level of right sural nerve (behind the ankle). NFR thresholding was conducted to determine stimulus intensity (135% of the intensity corresponding to NFR threshold) to be administered during the experimental paradigm for each participant. Further details on shock delivery, administration, and thresholding procedure (11,18–20) are presented in the Supplemental Digital Content 1, http://links.lww.com/PSYMED/A513, as well as acquisition and analysis of physiological recordings (electrodermal activity and electromyographic activity).

Pain Ratings

The pain level elicited by each US was evaluated using a visual analog scale. Anchors were set as 0 (no pain) to 100 (extremely painful). This scale consisted in a graduated horizontal bar with a cursor that participants moved using response keys on a computer keyboard. Pain ratings were normalized into z-scores across all trials of the fear-conditioning task for each participant before being included in data analyses, to account for differences in pain levels between individual participants and to parallel the processing of NFR responses.

Fear-Conditioning Paradigm

The fear-conditioning paradigm (Figure 1), adapted from previous work (21), included an acquisition phase (composed of 2 blocks, approximately 13 minutes each), a reversal phase (composed of 2 blocks), and an extinction phase. In the acquisition phase, one of the visual stimuli was paired with the US on 50% of trials (CS+), whereas the other was presented alone (CS−). The reversal phase was identical to the acquisition phase, but cue-shock pairings were reversed: the cue that had been paired with the shock during acquisition became the CS−, and the cue that had been presented alone during acquisition became paired with the shock on 50% of trials (CS+). The last phase was an extinction phase (1 block) in which CSs were presented alone. The fear leaning paradigm, as well as the experimental testing procedure, is described in more detail in Supplemental Digital Content 1, http://links.lww.com/PSYMED/A513.

Data Analyses

Data analyses performed with respect to sample characteristics, effects of meditation on pain and the NFR, and fear-conditioned SCRs are fully described in Supplemental Digital Content 1, http://links.lww.com/PSYMED/A513.

Computational Modeling of Fear Conditioning

Different computational learning models were fitted to individual trial-by-trial SCR data to the unreinforced cues (CS− and CS+ unpaired). This allowed estimating the fear-learning parameters to the CS+ paired trials and, in the second part of the analysis, to assess how these parameters predicted ongoing fluctuations in the shock-evoked pain responses. The following models were tested: Rescorla-Wagner (RW model, which depicts learning as a function of prediction errors), a RW/Pearce-Hall hybrid model (RW/PH hybrid, learning occurs as a function of prediction errors, and associability dynamically modulates the learning rate at each trial). Lastly, an inter-cue dependent RW/PH hybrid model (12) was tested. This model is a variant of the RW/PH hybrid model in which the expected shock probability (EShock) and associability are updated both for the cue, which was presented at trial *t*, as well as for the cue, which was not presented on this trial. The RW/PH hybrid inter-cue dependent model is fully described in Supplemental Digital Content 1, http://links.lww.com/PSYMED/A513, and, as in our previous report (12), was the best-fitted model to the data compared with the other models. A thorough description of model equations used for the RW and RW/PH models is provided in Supplemental Digital Content 1, http://links.lww.com/PSYMED/A513.

RESULTS

The group comparisons hereinafter are presented between experienced meditators and the large control cohort of participants. Because of size inequality of groups and a difference in age ($t_{(57)} = -4.53$, $p < .001$) between the large control cohort and experienced meditators, all of the analyses were conducted additionally in comparison with the matched control subsample. All results are reported for the large control group, and statistical conclusions were corroborated with the matched subsample. The only instance in which this was not the case is with respect to the effects of meditation experience on pain modulation by fear learning, as described and discussed hereinafter. Table S1 (Supplemental Digital Content 1, http://links.lww.com/PSYMED/A513) illustrates demographic and questionnaire variables for the experienced meditators and the control groups.

Effects of Meditation Experience on Learning and Pain During Fear Conditioning

Meditation Experience and Fear Conditioning of the SCR

First, we examined the impact of meditation experience on fear-conditioned SCR using multilevel regression analyses, revealing significant increases in SCRs to the CS+ (M = 0.296, SE = 0.096) compared with the CS− (M = 0.140, SE = 0.054) across both groups of participants, consistent with discriminative learning (β = 0.22, SE = 0.06, $p < .001$). There were no significant group differences in discriminant SCRs (β = −0.13, SE = 0.10, $p = .13$). These results indicate successful acquisition of fear-conditioned responses across both groups of participants. In addition, there were no significant group differences in the free individual parameters of the learning model reflecting basic associative learning mechanisms (all *p*'s < .05). Parameters averaged for each group of participants are listed in Supplemental Digital Content 1, http://links.lww.com/PSYMED/A513.

Meditation Experience and Impact of Fear Learning on Pain

To tackle our main objective as to the impact of fear-learned anticipatory responses on pain, the effects of both fear-learning parameters on pain and the NFR were examined at the trial level (first level) and then at the group level (second level) to assess the moderating effect of meditation on the modulation of pain/NFR by fear. The mediation models of Eshock and Associability are shown in Figures 2A and D, respectively. Table 1 reports second-level moderator effects of meditation group on each path of the mediation models. Figure 2 also illustrates the moderating effects of group on the direct effects (c′) of Eshock (2B-C) and associability (2E-F) on the NFR (2B and 3E) and on pain (2C and 3F).

At the first level, as reported in our recent study (12), expected shock probability significantly predicted pain ratings (*a*) directly, i.e., after taking into account the mediating effects of NFRs (path c′: β = .79, SE = .25, $t = 3.18$, $p = .002$) and (*b*) indirectly via mediation effects of the NFR (path a × b: β = .09, SE = .03, $t = 3.07$, $p = .003$). The same pattern of results was found in the model of associability (path c′: β = .93, SE = .35, $t = 2.63$, $p = .011$; path a × b: β = .19, SE = .06, $t = 3.02$, $p = .004$).

At the second level, in the model of expected shock probability, the significant group differences in the total effect of Eshock on pain ratings (path c) and in the effect on the NFRs (path a) were significant in the analysis performed with the large control group

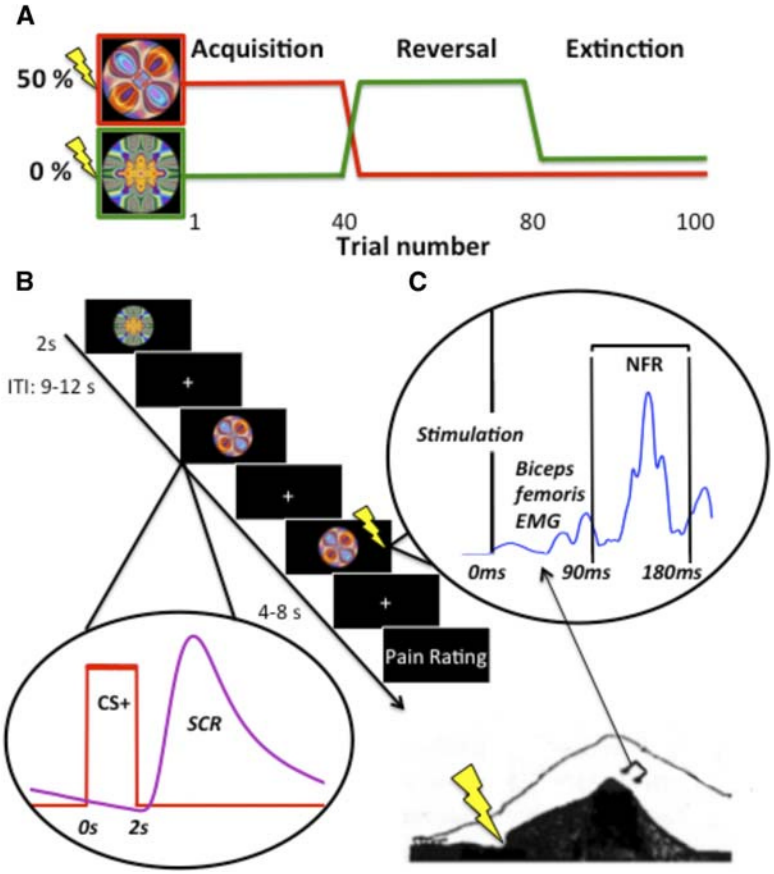

FIGURE 1. Experimental paradigm. A, In the acquisition phase (trials 1–40), one cue had a 50% chance of co-terminating with an electric shock (CS+), whereas the other cue was never presented (0% chance) with the shock (CS−). In the reversal phase, cue-shock contingencies between the two cues were reversed: the cue previously assigned as the CS+ became the CS−, whereas the cue previously assigned as the CS− became the CS+. In the extinction phase, both cues had a 0% chance of being presented with the shock. B, An example of each type of trial (CS−, CS+, and CS+ paired) is shown: each trial started with the presentation of one of the two cues for a 2-second duration. On trials involving shock administration ("CS + paired" trials), the cue co-terminated with an electric shock (30 milliseconds) to the right sural nerve and participants rated their pain after a time interval (randomized between 4 and 8 seconds). The next trial began after a random intertrial interval of 9 to 12 seconds. No pain ratings were assessed for unreinforced trials (CS + unpaired and CS−) and SCRs (with a typical latency between 0.5 and 2 seconds) to visual cues were obtained from electrodermal activity recordings. C, The electromyographic signal was recorded with electrodes at the level of the right biceps femoris (above the sural nerve stimulated) to assess the NFR, observable at a 90- to 180-millisecond latency after electrical stimulation onset. Color image is available only in online version (www.psychosomaticmedicine.org).

but did not reach significance using the matched control subsample (p = .071 for path c, p = .27 for path a). Hence, these differences are displayed and explained in Figure 2 (see blue dotted line in Figure 2A) but are not discussed further. However, meditators showed a significant reduction in the direct effect of Eshock on pain ratings after accounting for the mediating effect of the NFR (moderator effect on path c′: $\beta = -1.63$, SE = .65, $t = -2.51$, p = .015) (Figure 2C). This moderating effect of meditation on path c′ was confirmed with the smaller subsample (p = .050).

In the model of associability, meditators also showed significant reduction in the direct effect of associability on pain ratings (moderator effect on path c′: $\beta = -2.36$, SE = .93, $t = -2.54$, p = .014). This effect was replicated yet fell slightly short of statistical significance, in the age-matched control subsample (moderator effect on path c′: $\beta = -2.20$, SE = 1.09, $t = -2.02$, p = .062). Nonetheless, the Bayes Factor obtained for this group difference was 3.56:1 against the null hypothesis, representing substantial odds against the null hypothesis of no difference between groups (22). Follow-up simple multilevel regression analyses on the direct effect indicated that meditators showed a significant reduction in the direct effect of associability on pain ratings (second-level moderator effect: $\beta = -2.11$, SE = 1.02, $t = -2.01$, p = .047) (Figure 2D). Other moderation effects did not approach significance (path a, b and ab, p's > 0.50) or were not confirmed in the age-matched subsample (path c) (Table 1).

Figure 3 shows mean fear-learning parameters to CS+ paired trials averaged across both groups of participants (A). As can be seen in an exemplar participant from each group of participants, fear-learning parameters (weighted by regression coefficients) do not predict the pain rating trajectory during learning for the experienced meditator (B) but accurately depict the pain rating time course of the control participant (C). Individual participant data are displayed for experienced meditators in Supplemental Digital Content 1, http://links.lww.com/PSYMED/A513 (see Figure S1).

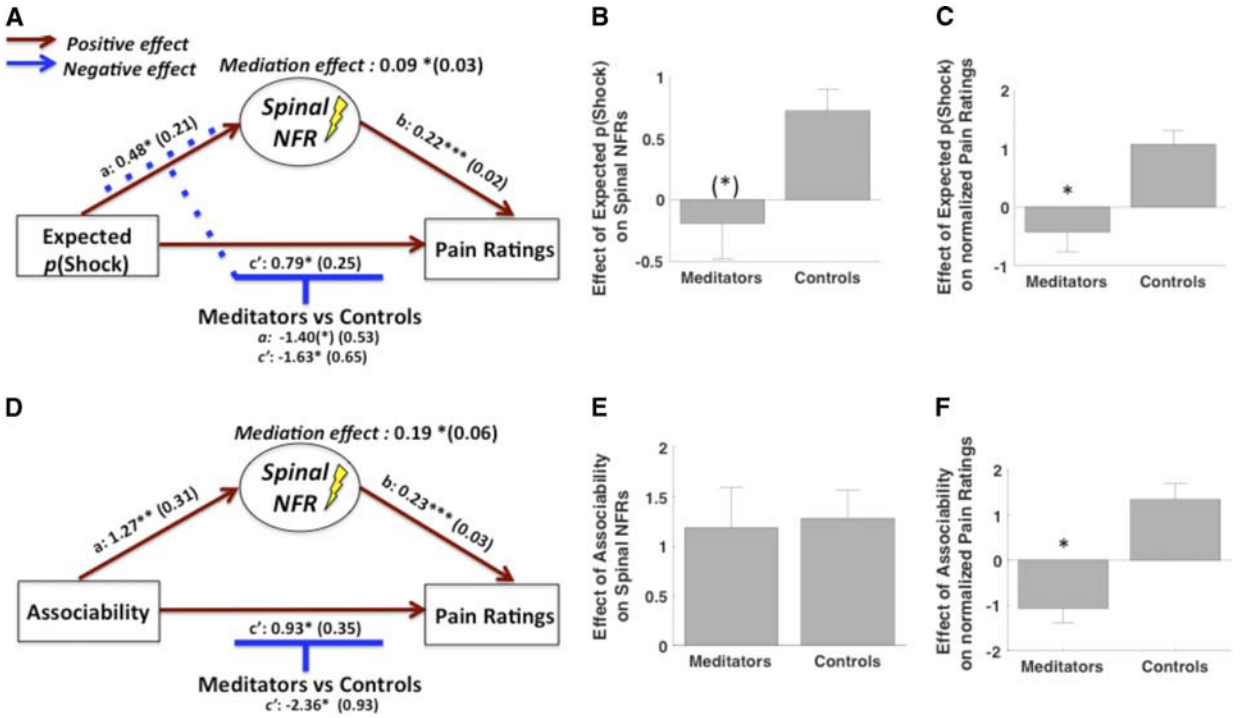

FIGURE 2. Multilevel mediation models of the effects of fear learning parameters (A) expected probability of shock (expected p(shock)) and (B) associability on pain ratings. Both models confirmed an overall direct effect on pain (path c′) and an indirect effect (mediation) through changes in spinal nociception (path ab). Coefficients are shown for each path and mediation effects with standard errors in parentheses. The negative moderating effects of meditation group are shown with grey lines. Bar graphs illustrate the moderating effect of the group on β values for the direct effects on the NFR and on pain. Meditators showed significant decreases in the direct effects of both fear learning parameters, i.e. (A) expected p(shock) and (B) associability on pain ratings. $^{**}p < .001$, $^{*}p < .05$, $(^{*})p < .05$ not confirmed with an age-matched control subsample. Color image is available only in online version (www.psychosomaticmedicine.org).

TABLE 1. Mediation Models of Fear Learning Parameters-Expected Shock Probabilities or Associability-as Predictors of Pain Ratings with spinal NFRs as a Mediator and Meditation Group as the 2nd level Moderator

Mediation Model of Expected Shock Probabilities				
	2nd Level Moderating Effects of Meditation Group on Each Path			
	β	SE	*t*	*p*
Path a: Effect of *Expected p(Shock)* on spinal NFRs	−1.40	.53	−2.63	(*).011
Path b: Effect of spinal NFRs on pain	−.01	.07	−.18	.86
Path c: Total effect of *Expected p(Shock)* on pain	−1.50	.64	−2.36	(*).022
Path c′: Direct effect of *Expected p(Shock)* on pain (after accounting for mediator)	−1.63		−2.51	*.015
Path ab: Indirect effect of *Expected p(Shock)* on pain via spinal NFRs	.08	.08	.99	.33
Mediation Model of Associability				
	2nd level Moderating Effects of Meditation Group on Each Path			
Path a: Effect of *Associability* on spinal NFRs	−.21	.81	−.26	.80
Path b: Effect of spinal NFRs on pain	−.04	.07	−.64	.53
Path c: Total effect of *Associability* on pain	−2.01	.89	−2.27	(*).027
Path c′: Direct effect of *Associability* on pain (after accounting for mediator)	−2.36	.93	−2.54	*.014
Path ab: Indirect effect of *Associability* on pain via spinal NFRs	.09	.16	.59	.56

NFR = nociceptive flexion reflex.

Results from moderated multilevel regression analyses.

$^{*}p < .05$, $n = 51$ for control group, $n = 11$ for group of meditators.

$(^{*})p < .05$ not confirmed with the smaller age-matched control subsample ($n = 11$).

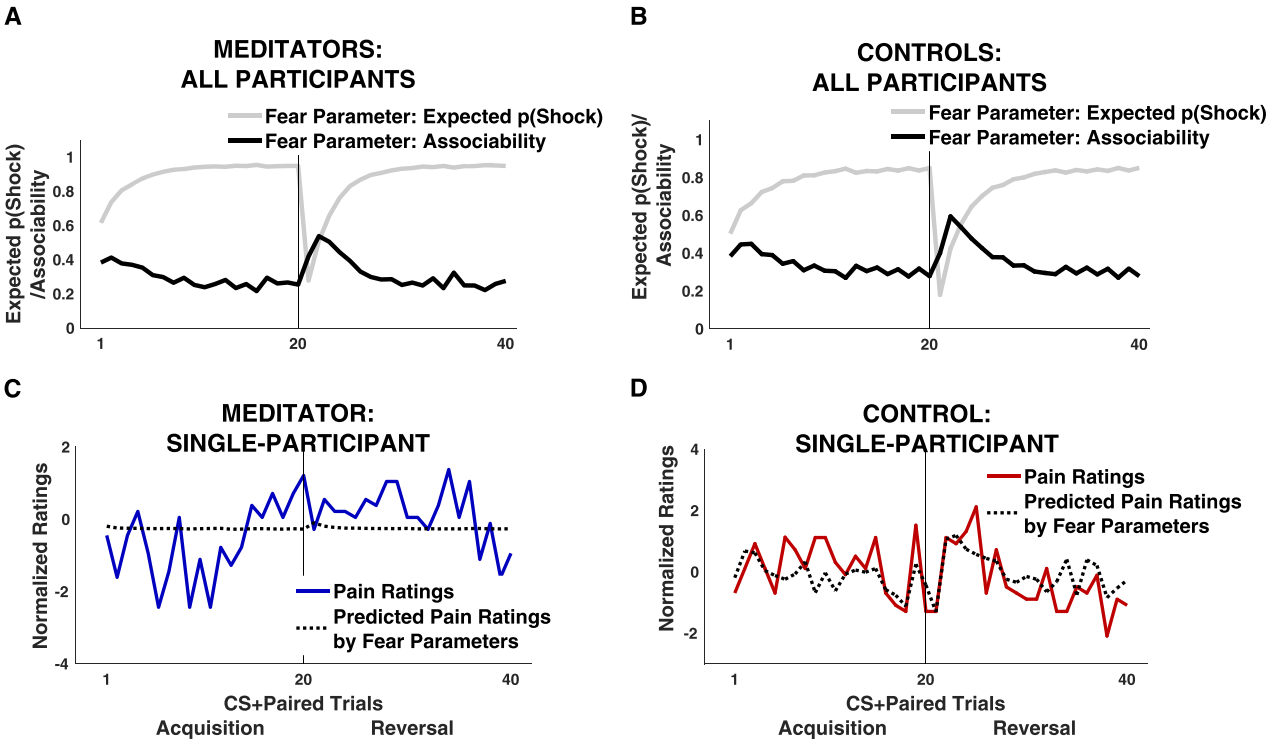

FIGURE 3. Relationship between expected shock probabilities (expected p(shock)), associability, and pain ratings for reinforced (CS + paired) trials in a meditator and a control participant. A and B, Average associability and expected p(shock) estimates in experienced meditators and controls respectively. C, Relationship between pain ratings and associability/expected p(shock) estimates for control participants (C), and a meditator participant (D). Trial-by-trial associability and expected p(shock) estimates were weighted by their regression coefficients to illustrate the multilevel regressions. CS = conditioned stimulus. Color image is available only in online version (www.psychosomaticmedicine.org).

Impact of Meditation Experience on Pain Outcomes and Descending Inhibitory Control

Effects of Meditation on Baseline Pain Assessments and NFR Threshold

Independent samples *t* tests indicated that meditators did not exhibit any difference compared with their control counterparts with respect to the electrical stimulation intensity corresponding to the NFR threshold ($t_{(60)} = -.98$, $p = .33$) or pain threshold ($t_{(60)} = -.20$, $p = .84$). Meditators and controls also received similar stimulus intensity levels, adjusted to 135% of the NFR threshold, during the fear-conditioning task ($t_{(60)} = -.43$, $p = .68$). One-way analyses of variance revealed that baseline NFR responses to the US assessed before fear-conditioning were similar between meditators and controls ($F_{(60)} = 0.90$, $p = .35$). However, meditators reported significantly lower levels of perceived pain at baseline ($F_{(60)} = 10.82$, $p = .002$; see means and standard deviations in Table S1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A513).

Effects of Meditation on Pain Outcomes and Descending Pain Controls During Fear Learning

Pain outcome measures (pain ratings, NFR, and SCRs) to US through the entire fear-learning paradigm were then compared between groups to determine the impact of meditation experience on pain sensitivity (Figure 4, A and B). A mixed-measures trial (40 US trials) by group (meditators, controls) analyses of variance, performed on each dependent variable, revealed a significant group effect on pain ratings ($F_{(1, 60)} = 6.31$, $p = .015$) with experienced meditators rating the US as less painful compared with controls (M = 19.9, SE = 5.1 for meditators, M = 32.4, SE = 2.4 for controls). In contrast, meditation experience had no significant effect on the NFRs ($F_{(1, 60)} = 0.79$, $p = .38$). This replicates effects reported previously in the baseline measures before fear conditioning.

In sum, our data indicate that experienced meditators displayed reduced perceived pain induced by the US before and during fear conditioning but had comparable NFR. In the following sections, we compare groups on fear-learning processes and on the trial-by-trial modulation of pain and the NFR by the learning parameters expected probabilities of receiving shock and associability.

DISCUSSION

The results of the present study can be summarized as follows. First, an overall hypoalgesia (decreased pain ratings) to the noxious US was observed both before and during fear conditioning in meditators. Second, meditation experience did not affect the discriminant anticipatory responses (SCRs) significantly, consistent with preserved fear-learning processes. Finally, results show that meditation experience reduced the effects of anticipatory processes on pain. These effects are further detailed in the following paragraphs.

First, as hypothesized, the overall hypoalgesia we observed during the fear-conditioning task are directly in line with previous reports that meditation experience reduces pain perception and sensitivity (8,16,23). The fact that we did not observe group differences

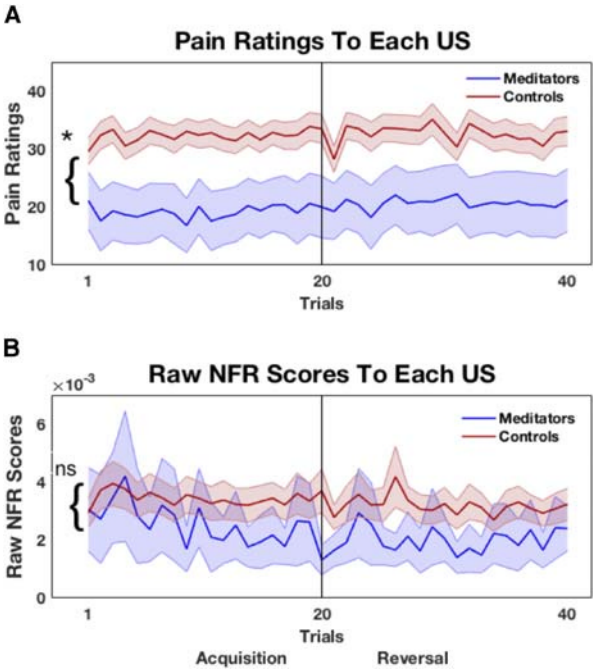

FIGURE 4. Mean (SEM) pain responses (A) and NFRs by group for each CS + paired trial during the fear-conditioning task. (*$p < .05$). Color image is available only in online version (www.psychosomaticmedicine.org).

in nocifensive spinal reflexes to nociceptive stimuli demonstrates that the general hypoalgesic effects of meditation do not operate by activating inhibitory descending control of pain. Rather, our results support the notion that the hypoalgesic effects of meditation selectively target cognitive/affective elaboration. This is consistent with neuroimaging studies on the pain-modulating effects of meditation showing reduced activity in brain regions associated with the mental elaboration/evaluation of pain but not in regions receiving nociceptive signals directly from the spino-thalamo-cortical pathways (7,8). These results are directly in line with premises taught in meditation: aversive experiences are welcomed and are not suppressed or changed, but they are not further elaborated upon (6).

Second, the fact that extensive mindfulness experience did not yield any detectable differences with respect to the production of anticipatory SCRs to the CSs is consistent with previous results (14). Specifically, Holzel et al. (2016) (14) showed that short-term meditation experience, i.e., an 8-week mindfulness-based stress-reduction program, did not affect fear-conditioned SCRs assessed pre- and posttraining. The hypoalgesic impact of meditation experience we observed on pain perception did not lead to reduced anticipatory responses. Thus, the meditation-related reduction in neural activity during the anticipation of pain observed by others (9,10) does not reflect an absence of anticipatory processes at a psychophysiological level. Rather, the present results show that previous findings of hypoalgesic effects of meditation via reduced neuronal anticipation (9,10) may reflect a reduced effect of anticipation on pain rather than a reduced ability to learn about pain and to predict its occurrence. Present findings further show that individuals with extensive meditation experience exhibit preserved basic associative learning mechanisms. Mindfulness training may attenuate the aversive quality of US but does not interfere with the "teaching function" provided by noxious events in terms of forming predictions about the occurrence of impending harm or allocating attention to critical moments informative of CS-US contingencies (13). These results show that mindfulness meditation does not achieve its attenuating effects on pain by abolishing fear-conditioned anticipatory behaviors altogether. This finding is also in line with the premise that mindfulness promotes the acceptance of all (aversive, neutral, or positive emotional) feelings/sensations as opposed to the *suppression* of low-level aversive emotional responses (15).

Finally, our results indicate that the reduced hyperalgesia influenced by anticipation in experienced meditators operates by disrupting the *influence* of associative learning on pain responses mainly at a higher-order perceptual level of processing. Meditation experience did not abolish the critical ability to learn from associative cues in the environment to predict impending harm or to allocate more attention to associative cues when uncertainty is high. Specifically, meditation experience reduced the hyperalgesic effects of expectations about the probability of occurrence of impending harm. This attenuation of pain facilitation at higher-order levels of processing possibly reflects a detached or nonreactive stance toward the probability of the upcoming aversive event.

Meditation experience also reduced the effects of associability on higher-order pain perception directly, independently from effects produced on the spinally mediated NFR. Associability is encoded in the amygdala (24) and is thought to reflect attention allocation, vigilance to cues informative of CS-US contingencies at moments critical to learning (i.e., after large prediction errors) (13). The hyperalgesic effects of associability on pain may provide an important "teaching function" in the sense that pain perception is enhanced in trials critical to the association between environmental predictive cues and sources of harm: the information may be better integrated if the US is more saliently/aversively experienced. Thus,

meditation experience may preserve from such pain enhancement, especially at the beginning of a learning phase when associability/uncertainty is highest, without weakening the learning processes.

Nonetheless, the present study is not without its limitations. Although the study of highly trained individuals provides unique insight onto mechanisms underlying a given expertise, such study is characteristically constrained by the limited sample size. The cross-sectional design inherent to such study also precludes drawing causal inferences on the effects of the practice of meditation per se because confounding individual variables cannot be extensively controlled. Thus, future longitudinal studies should be conducted to examine the effects of short-term, and ideally long-term meditation training on pain and pain modulation by classical conditioning. In addition, our sample of experienced meditators was mainly composed of Zen practitioners, as well as other types of Buddhist traditions. Therefore, the present results warrant further replication in experienced meditators homogeneous in their meditation tradition or comparing effects between types of traditions. In addition, although no significant between-group differences were observed in anticipatory conditioned responses, it is possible that the reduced pain/aversiveness from the US influenced the effect of fear learning on pain. Thus, the present results should be replicated by comparing groups in which US are calibrated using pain ratings, relative to participants whose US are calibrated based on objective spinal nociception responses. Finally, future studies should also replicate these methods to investigate effects of fear learning on pain in experienced meditators and novice meditators, to account for baseline differences characterizing individuals with an intrinsic interest for these practices.

With respect to clinically oriented work, previous reports in chronic pain patients (25) using event-related potentials during pain and pain anticipation showed that anticipatory brain responses had decreased after a mindfulness training intervention. In contrast, patients who had not undergone such training showed enhanced anticipatory activity, possibly reflecting a conditioning effect that had been suppressed in the mindfulness intervention group. In light of the findings of our study, the suppressed anticipatory activity in the meditation group may have reflected reduced higher-order anticipatory processes. Our observation that control participants with no previous mindfulness meditation experience displayed pain-modulating effects of learned expectations and uncertainty (associability) during fear conditioning may shed some light onto a potential mechanism explaining the central maintenance of pain and pathological manifestations of repeated exposure to noxious stimuli. This latter hypothesis is speculative in nature and would warrant investigation in studies using longitudinal designs and clinical populations and studies, which address the limitations of the present work (3,4).

In conclusion, our results show that meditation experience (1) achieves its hypoalgesic effects by selectively targeting higher-order perceptual mechanisms rather than by activating descending inhibitory controls, (2) does not alter the anticipatory learning process, but rather (3) reduces the interaction between anticipatory processes and pain perception at higher-order levels of processing. Importantly, this is achieved without compromising the adaptive value of pain signal in aversive leaning. The results of this study highlight potential mechanisms underlying mindfulness-related analgesia. This may be relevant to clinical conditions where anticipation may increase pain and in which repeated pain exposure might reinforce hyperalgesic processes through fear conditioning.

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