Effects of Mindfulness-Oriented Recovery Enhancement Versus Social Support on Negative Affective Interference During Inhibitory Control Among Opioid-Treated Chronic Pain Patients: A Pilot Mechanistic Study

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Abstract

Background Among opioid-treated chronic pain patients, deficient response inhibition in the context of emotional distress may contribute to maladaptive pain coping and prescription opioid misuse. Interventions that aim to bolster cognitive control and reduce emotional reactivity (e.g., mindfulness) may remediate response inhibition deficits, with consequent clinical benefits.

Purpose To test the hypothesis that a mindfulness-based intervention, Mindfulness-Oriented Recovery Enhancement (MORE), can reduce the impact of clinically relevant, negative affective interference on response inhibition function in an opioid-treated chronic pain sample.

Methods We examined data from a controlled trial comparing adults with chronic pain and long-term prescription opioid use randomized to either MORE ($n = 27$) treatment or to an active support group comparison condition ($n = 30$). Participants completed an Emotional Go/NoGo Task at pre- and post-treatment, which measured response inhibition in neutral

and clinically relevant, negative affective contexts (i.e., exposure to pain-related visual stimuli).

Results Repeated-measures analysis of variance indicated that compared with the support group, participants in MORE evidenced significantly greater reductions from pre- to post-treatment in errors of commission on trials with pain-related distractors relative to trials with neutral distractors, group $\times$ time $\times$ condition $F(1,55) = 4.14$, $p = .047$, $\eta^2_{\text{partial}} = .07$. Mindfulness practice minutes and increased nonreactivity significantly predicted greater emotional response inhibition. A significant inverse association was observed between improvements in emotional response inhibition and treatment-related reductions in pain severity by 3-month follow-up.

Conclusions Study results provide preliminary evidence that MORE enhances inhibitory control function in the context of negative emotional interference.

Keywords Cognitive control • Go/NoGo • Inhibitory control • Mindfulness • Opioid • Pain

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Introduction

Response inhibition (alternately construed as inhibitory control) is crucial to executing adaptive behaviors, particularly under conditions of duress. Response inhibition is the ability to restrain inappropriate or nonadvantageous overt behaviors and is vital to suspending or editing actions in ways that facilitate goal attainment. Due to its clinical relevance, researchers have become increasingly interested in response inhibition and how it relates to various health conditions, including chronic pain [1], substance use disorders [2, 3], and

affective disorders [4]. Indeed, neurocognitive models propose that deficits in response inhibition propel the downward spiral linking chronic pain to opioid misuse [5]. Many chronic pain patients rely on prescription opioids to manage pain; yet, prolonged opioid use typically results in physical dependence and tolerance, requiring increasing opioid doses to treat pain [6]. Such opioid dose escalations may lead to opioid misuse, a problem evidenced by one fifth to one third of chronic pain patients [7]. In the absence of effective response inhibition capacity, chronic pain patients may lose control over opioid use.

In the laboratory, the Go/NoGo task is a well-validated protocol used to measure response inhibition [8], in which one responds to frequent “Go” stimuli while withholding responses to infrequent “NoGo” stimuli. The Go/NoGo task creates a prepotent (or automatic) response pattern to frequently presented stimuli and thereby presents an inhibitory control challenge during presentation of an infrequent NoGo stimulus to which responses should be withheld. Thus, inhibitory control failure on the task is reflected by errors of commission (i.e., making a response to a NoGo stimulus when a response should be withheld). This challenge is intensified in Emotional Go/NoGo tasks, which introduce emotional stimuli to serve as distractors, providing affective interference during cognitive control efforts that reduce task performance [9, 10]. Performing the task with this additional emotional context more accurately reflects the daily life challenges faced by many individuals with chronic pain, psychopathology, and substance use disorders, who may struggle to inhibit prepotent, maladaptive habitual coping responses (e.g., opioid misuse) triggered by stress and negative emotions.

Chronic Pain and Response Inhibition

Though acute pain delivered via electrical stimulation to healthy individuals increases commission errors on the Go/NoGo task [11], chronic pain patients are particularly vulnerable to response deficits in cognitive control functions [1]. For instance, individuals with chronic low back pain [12] and those with chronic pancreatitis pain have significantly delayed response times on the Go/NoGo task [13]. Such behavioral deficits may be linked with neural dysfunction in brain regions during response inhibition. Indeed, patients with fibromyalgia exhibit attenuated inhibitory control-related BOLD response in premotor and midcingulate cortices [14, 15]. Overall, the extant literature suggests that chronic pain is associated with response inhibition deficits subserved by deleterious changes in circuitry mediating inhibitory control.

Opioid Use and Response Inhibition

Moreover, chronic opioid use and opioid dependence are associated with diminished cognitive control functions, including deficits in response inhibition [16–19], which can persist beyond cessation of and withdrawal from opioid use [20, 21]. Opioid-dependent individuals exhibit attenuated inhibitory control-related fMRI BOLD signal in medial prefrontal circuitry, including the anterior cingulate cortex [22, 23] and medial prefrontal cortex [24], and have worse behavioral performance compared with nonopioid-dependent persons across a broad range of task probes of response inhibition including the arrow task [25], the standard Go/NoGo task [22], and the affective Go/NoGo task [26]. Taken together, these studies suggest that opioid use and dependence may be associated with impairments in response inhibition, especially among chronic pain patients who may already be subject to impaired response inhibition due to the effects of prolonged pain on inhibitory control brain circuitry.

Mindfulness as a Means of Augmenting Response Inhibition

Due to the adverse social, occupational, and clinical consequences of deficient response inhibition, therapies are needed to remediate this cognitive function among opioid-treated chronic pain patients. Mindfulness-based interventions (MBIs) represent one class of promising treatments for response inhibition deficits in this patient population due to their demonstrated ability to reduce chronic pain symptoms [27], attenuate risk of opioid misuse [28], and strengthen multiple domains of cognitive control [29]. Mindfulness can be defined as a metacognitive state characterized by nonjudgmental awareness of and attention to moment-by-moment cognition, emotion, and sensation without fixation on thoughts of past and future [30]. Recurrent activation of the mindful state through various mindfulness meditation practices has been shown to influence brain regions responsible for a range of cognitive control functions, including those implicated in the regulation of attention and emotion [31]. Such neural effects are paralleled by improvements in cognitive performance, even under emotional load; for instance, mindfulness training has been found to increase accuracy on tests of working memory, executive functioning, and visuospatial processing [32] and also to facilitate inhibition of negative emotional interference on cognitive tasks [33], with concomitant effects on enhancing inhibitory control-related prefrontal cortical activation [34].

With respect to response inhibition generally, Mrazek et al. [35] found that mindfulness training

led to improvement in response inhibition metrics on the Sustained Attention to Response Task. Such mindfulness-induced enhancements in response inhibition capacity are durable and correlate with improved clinical outcomes [36]. With respect to the effects of mindfulness training on the Go/NoGo Task specifically, few randomized controlled studies have been conducted. However, using electroencephalography during a Go/NoGo task, Schoenberg et al. [37], found that Mindfulness-Based Cognitive Therapy increased an event-related brain potential response linked with cognitive and motor control during response inhibition (i.e., P300) on NoGo trials for adults diagnosed with attention-deficit hyperactivity disorder.

Current research suggests that mindfulness may (a) enhance response inhibition and (b) reduce emotional interference. Whereas mindfulness training has been shown to decrease interference by negative emotional information on dot probe tasks requiring attentional orienting in chronic pain samples [38, 39], to our knowledge, no studies of chronic pain patients have examined effects of mindfulness on response inhibition in pain-related emotional contexts via an Emotional Go/NoGo task. The aim of the present study was to test the effects of an MBI, Mindfulness-Oriented Recovery Enhancement (MORE), on emotional response inhibition among a sample of chronic pain patients receiving long-term opioid therapy. In the parent randomized controlled trial (RCT) from which the present unpublished Go/NoGo task data are derived, relative to a support group (SG) active control, MORE significantly reduced pain severity and opioid misuse [28]. Subsequent analyses of other mechanistic data from this trial revealed that MORE led to significant effects on autonomic responses during a dot probe task measuring attentional bias to emotionally salient cues [40], and significant effects on neurophysiological and cardiac responses during an affective picture viewing task designed to measure emotional reactivity [41, 42]. The present manuscript presents findings pertaining to a heretofore unexamined potential mechanism of MORE—emotional response inhibition. In light of the potential effects of mindfulness on emotion regulation and cognitive control, we hypothesized that participation in MORE, compared to the SG, would be associated with significantly greater reductions in errors of commission on NoGo trials with clinically salient, negative emotional distractors (i.e., pain-related images) relative to trials with neutral distractors. Furthermore, given evidence of neural-functional convergence between negative affect, inhibitory control, and pain intensity in the cingulate cortex [43], we hypothesized that improvements in emotional response inhibition would predict the

significant reductions in pain severity from pretreatment to 3-month follow-up observed in the parent trial from which the present mechanistic data were derived.

Materials and Methods

Procedures

The current pilot study examined unpublished cognitive task data from a previously published RCT (ClinicalTrials.gov identifier NCT01505101; see Garland et al. for a CONSORT diagram) of MORE versus SG for chronic pain and prescription opioid misuse [28]. Individuals from this RCT with complete reaction time data (MORE $n = 27$; SG $n = 30$) on an Emotional Go/NoGo task conducted 1 week before, and 1 week after, the 8-week treatments were selected for the present study. Rather than impute missing cognitive task data, we only included the 57 participants with complete pre- and post-treatment reaction time data in this study. The Emotional Go/NoGo task was one of three experimental tasks completed by the sample in the parent trial during a single psychophysiological assessment session at both pre- and post-treatment to assess potential therapeutic mechanisms of the MORE intervention; emotional response inhibition was one of the secondary outcomes of the parent trial. Findings from the other experimental tasks have been published elsewhere [40–42] and will not be reported here.

Participants were recruited from primary care, pain, and neurology clinics and met study inclusion criteria if they reported recurrent pain on more days than not stemming from chronic noncancer-related pain conditions and had taken opioid analgesics daily or nearly every day for at least the past 90 days [44]. Actively suicidal participants were excluded. Following a preliminary phone screening for eligibility, potential participants were screened in an initial interview in the first author's lab, and individuals who met eligibility criteria and consented to take part in the study completed a preintervention assessment where they first reported demographic and clinical information on questionnaires and then participated in the three experimental tasks, including an Emotional Go/NoGo Task. Following completion of this assessment, participants were randomly allocated to MORE or an SG (which served as the active control condition). Study assessments were conducted by project staff blind to each respondent's group assignment, which remained concealed throughout the study. After participants had completed 8 weeks of MORE or the SG intervention, they returned to the lab to complete a postintervention assessment including the Emotional Go/NoGo Task. All procedures were approved by the Florida State

University IRB (where the first author was located during data collection), and informed consent was obtained from each participant. Participants were paid \$200 for completing the study.

There were no significant between-group differences in clinical characteristics (see Table 1). Participants were mostly female (68%), with a mean age of 46.8 ($SD = 12.9$) years and moderate levels of pain severity ($M = 5.5$ out of 10, $SD = 1.5$). The most common form of chronic pain reported was low back pain (58%) followed by fibromyalgia (19%), and hydrocodone (39%) and tramadol (40%) were the most frequently reported types of opioids used by participants.

Measures

Emotional Go/NoGo task

The Emotional Go/NoGo task (see Fig. 1) used in this study conformed to the task validated by Albert et al. [9]. Go and NoGo stimuli consisted of two capital letters (“M” and “W,” respectively, presented in “Arial” font) superimposed over six images used as background contexts (three neutral and three pain-related images). Letter font was yellow and outlined in black to distinguish letters from the background image (Fig. 2). Images used as background contexts were taken from

Table 1 Demographic and Clinical Characteristics of Prescription Opioid-Using Chronic Pain Patients, by Treatment Group ($N = 57$)

Measure	MORE ($n = 27$)	Support group ($n = 30$)	Test statistic
Female, N (%)	19 (70)	20 (67)	$\chi^2 = 0.09, p = .76$
Age (M, SD)	46.8 ± 13.5	46.7 ± 12.6	$t = 0.001, p = .99$
Primary type of pain, N (%)			$\chi^2 = 2.27, p = .52$
Low back pain	14 (52)	19 (60)	
Fibromyalgia	5 (15)	7 (23)	
Joint or extremity pain	2 (7)	1 (3)	
Other	6 (19)	3 (10)	
Pain severity (BPI) at pretreatment (M, SD)	5.3 ± 1.4	5.7 ± 1.6	$t = 1.05, p = .30$
Primary prescription opioid type, N (%)			$\chi^2 = 4.36, p = .36$
Hydrocodone	8 (30)	14 (47)	
Oxycodone	4 (15)	2 (7)	
Hydromorphone/morphine	2 (7)	3 (10)	
Tramadol	11 (41)	11 (37)	
Other	2 (15)	0 (0)	

BPI Brief Pain Inventory-Short Form; MORE Mindfulness-Oriented Recovery Enhancement.

Fig. 1. Examples of Go and NoGo trials in a pain-related context block. Three images from the International Affective Picture system served as the background context for Go (the letter “M”) and NoGo (the letter “W”) stimuli. A random series of 93 Go and 40 NoGo trials were presented.

Fig. 2. Effects of Mindfulness-Oriented Recovery Enhancement (MORE, $n = 27$) versus a social support group ($n = 30$) on improvements from pre- to post-treatment in errors of commission (i.e., NoGo accuracy) in the presence of pain-related distractors relative to neutral distractors.

the International Affective Picture System (IAPS) [45] and selected on the basis of (a) their valence scores from the IAPS Technical Manual and (b) a matching (i.e., no significant difference) of neutral and pain-related images in mean luminance and spatial frequency [46]. Moreover, after the experimental task, each participant rated image valence on a scale from 1 to 10 (1 = extremely negative, 10 = extremely positive). Neutral (e.g., furniture, IAPS 7038, 7041, 7179) and pain-related images (e.g., injured limbs, IAPS 3102, 9405, 9582) significantly differed with regard to their respective affective valence ratings (neutral valence = 5.2 ± 0.7 , pain valence = 2.7 ± 1.0 , $t = -14.33$, $p < .001$).

Participants were instructed to press a button as fast and accurately as possible whenever the letter “M” (Go) was presented and to withhold pressing the button when the letter “W” (NoGo) was presented. They were asked to look continuously at the center of the screen to control eye-movement interference. Participants performed the task during two different emotional contexts generated by pictorial backgrounds: negative and neutral. The order in which the two emotional conditions were presented was randomized and counterbalanced across participants. Each emotional context contained 133 letters (93 Go and 40 NoGo) presented in three blocks. Each block within each emotional context had a different picture as background. Go and NoGo trials were presented in semirandom order within each block, such that NoGo trials could be preceded by one-to-four Go trials and there was never a consecutive presentation of two NoGo trials. Trials began with the presentation of the letter M or W (200 ms), followed by a fixation cross

(800 ms); 500 ms later, the next letter appeared. Between each block, participants were allowed to rest for 60 s. Before beginning the experiment, subjects completed a practice block of 12 trials (8 Go and 4 NoGo) with a neutral picture as a background. The Go/NoGo task was programmed using Eprime 2.0 software and presented on a computer monitor. In the present study, behavioral performance on the task was used to indicate effects of emotional interference on response inhibition—with errors of commission selected as the primary metric. Although some studies use neural-functional and electrophysiological indices of emotional interference, a number of studies have obtained effects of emotional valence on behavioral data with similar versions of the Emotional Go/NoGo Task [9, 47–49].

Pain severity

Pain severity was measured with the four-item pain severity subscale from the Brief Pain Inventory ($\alpha = .87$), a well-validated measure widely used to assess acute and chronic pain [50]. Participants reported their worst pain during the past week, least severe pain during the past week, average pain, and current pain severity. Response options ranged from 0 (*no pain*) to 10 (*pain as bad as I can imagine*). An overall pain severity score was computed by taking the mean of the four items.

Nonreactivity

The mindfulness facet of nonreactivity to distressing thoughts and emotions was measured with the 7-item nonreactivity subscale ($\alpha = .76$) of the Five Facet Mindfulness Questionnaire (FFMQ) [51]). This subscale, comprised items such as “When I have distressing thoughts or images, I ‘step back’ and I am aware of the thought or image without getting taken over by it,” aims to assess metacognitive decentering from aversive experiences. This FFMQ subscale was selected specifically for this study because it was shown to mediate effects of mindfulness on abdominal pain in patients with irritable bowel syndrome [52] as well as mediate effects of MORE on chronic pain severity in the parent RCT from which these data were derived [28]. Given this link between mindfulness-induced increases in FFMQ nonreactivity and reduced pain severity in the parent trial, as well as evidence for a link between pain severity and inhibitory control [43], we expected emotional response inhibition to be associated with increased nonreactivity.

Study Interventions

MORE intervention

MORE is a manualized, eight-session group intervention that unites complementary aspects of mindfulness

training, cognitive reappraisal, and principles from positive psychology into an integrative intervention strategy designed to target comorbid chronic pain and opioid-related problems [30]. MORE sessions involve training in mindfulness to enhance cognitive control over automaticity and cultivate nonreactivity to distressing emotions, training in reappraisal to restructure negative interpretations of stressful life events and motivations for opioid use, and training in savoring pleasant daily events to ameliorate deficits in positive affectivity. Sessions were held in groups of 8–12 individuals, were 2 hr in length, and were administered by a masters-level clinical social worker who had practiced mindfulness for over a decade and had extensive clinical experience providing mindfulness training to persons with psychiatric disorders. This individual was supervised by the developer of MORE (also an experienced, licensed psychotherapist). The first author reviewed video/audio-recordings of the sessions to monitor therapist adherence to the MORE treatment manual. No major protocol deviations were noted, and minor deviations were corrected in subsequent sessions. MORE participants were asked to engage in daily 15-min mindfulness practice sessions at home guided by a CD. Participants were asked to record number of minutes of mindfulness meditation practice per day (e.g., mindful breathing, body scan) on a practice log.

Support group intervention

The active control condition in this study consisted of 8 weekly, 2-hr conventional SG sessions composed of 8–12 participants, in which a masters-level clinical social worker led discussions of topics pertinent to chronic pain and opioid misuse. This SG format was derived from the active, evidence-based treatment condition outlined in the Matrix Model intensive outpatient treatment manual [53]. SG participants disclosed feelings and thoughts about group topics and provided emotional support to their peers. This intervention, which typifies a commonly available form of conventional group therapy for chronic pain, was found in prior RCTs to have equivalent perceived credibility to MBIs and to significantly reduce psychological distress among persons suffering from chronic pain [54] and addiction [55]. The first author reviewed video/audio-recordings of the sessions to monitor therapist adherence to the SG treatment manual; no major protocol deviations were noted, and minor deviations were corrected in subsequent sessions. SG participants were asked to engage in 15 min of journaling a day on chronic pain-related themes at home.

Statistical Analysis

To test our primary hypothesis that MORE would significantly decrease negative emotional interference on

NoGo trials relative to the SG, we used a 2 (group: MORE vs. SG) $\times$ 2 (time: pre- vs. post-treatment) $\times$ 2 (condition: neutral cue vs. pain-related cue) repeated-measures analysis of variance (RM-ANOVA). Next, to determine whether observed effects were due to general improvements in inhibitory control and not specific to emotional response inhibition, we conducted an RM-ANOVA to test whether MORE led to greater improvements in Go/NoGo accuracy than the SG on trials with only neutral distractors. We then used RM-ANOVA to examine group $\times$ time $\times$ condition interactions on d-prime and reaction time variability (i.e., coefficient of variation); because we had no a priori hypotheses concerning these alternative Go/NoGo performance metrics, these analyses were exploratory. To determine whether the mindfulness components of MORE improved emotional response inhibition, we then examined increases in the mindfulness facet of nonreactivity and total number of mindfulness practice minutes as predictors of NoGo accuracy. Last, to understand the clinical implications of these findings, we computed regression models to examine the association between pre-post treatment improvements in emotional response inhibition and reductions in pain severity from pretreatment to 3-month follow-up. Given the pilot nature of this study, we did not control for multiple comparisons; an alpha level of .05 was used as the threshold for statistical significance.

Results

NoGo Trial Performance (Errors of Commission)

Go/NoGo task performance data are depicted in Table 2. For NoGo trial accuracy, the main effect of condition was significant, $F(1,55) = 5.57$, $p = .02$, $\eta^2_{\text{partial}} = .09$, indicating that, overall, participants made more errors of commission on trials when pain-related cues were present versus when neutral cues were present, suggesting the presence of emotional interference effects on response inhibition. The main effect of time was also significant, $F(1,55) = 9.15$, $p = .004$, $\eta^2_{\text{partial}} = .14$, indicating that across both groups, participants made fewer errors of commission at the post-treatment assessment compared with pretreatment. Germane to our primary hypothesis, there was a significant group $\times$ time $\times$ condition effect, $F(1,55) = 4.14$, $p = .047$, $\eta^2_{\text{partial}} = .07$, indicating that compared with the SG, the MORE group experienced significantly greater improvements in NoGo accuracy (i.e., fewer errors of commission) over the course of treatment on trials with pain-related distractors relative to trials with neutral distractors. There was no significant group $\times$ time effect on NoGo trials with neutral distractors, $F(1,55) = 1.44$, $p = .24$, $\eta^2_{\text{partial}} = .03$.

Table 2 Emotional Go/NoGo Task Performance of Patients Participating in Mindfulness-Oriented Recovery Enhancement (MORE, $n = 27$) or a Support Group (SG, $n = 30$) Treatment for Chronic Pain and opioid-Related Problems

	Pretreatment		Post-treatment	
	Neutral cue	Pain cue	Neutral cue	Pain cue
NoGo accuracy				
MORE	0.92 (0.08)	0.88 (0.08)	0.93 (0.05)	0.92 (0.06)
SG	0.88 (0.10)	0.87 (0.10)	0.91 (0.08)	0.89 (0.08)
Go accuracy				
MORE	0.88 (0.12)	0.91 (0.12)	0.88 (0.14)	0.88 (0.18)
SG	0.87 (0.12)	0.86 (0.17)	0.91 (0.08)	0.88 (0.15)
Go reaction times				
MORE	144.93 (65.45)	157.51 (73.11)	159.84 (73.29)	167.13 (77.07)
SG	134.60 (50.34)	143.90 (48.08)	156.51 (58.65)	158.27 (51.38)

NoGo and Go accuracy are expressed as the average proportion of correct trials out of the total number of trials for NoGo and Go trial types, respectively. Go reaction times are expressed in milliseconds.

Go Trial Performance (Errors of Omission)

For Go trial accuracy, the main effect of condition was non-significant, $F(1,55) < 0.01$, $p = .99$, $\eta^2_{\text{partial}} < .01$, as was the main effect of time, $F(1,55) = 0.21$, $p = .65$, $\eta^2_{\text{partial}} = .004$, indicating that, the presence of pain-related cues did not modulate errors of omission and that on average, no changes in such errors were observed from pre- to post-treatment. The group $\times$ time $\times$ condition effect was also non-significant, $F(1,55) = 0.08$, $p = .79$, $\eta^2_{\text{partial}} = .001$. For Go trial reaction times, the main effect of condition was significant, $F(1,55) = 8.77$, $p = .005$, $\eta^2_{\text{partial}} = .14$, indicating that, overall, participants were slower to respond on trials when pain-related cues were present versus when neutral cues were present, suggesting the presence of emotional interference effects. The main effect of time was also significant, $F(1,55) = 4.55$, $p = .04$, $\eta^2_{\text{partial}} = .08$, indicating that across both groups, participants reaction times slowed from pre- to post-treatment. The group $\times$ time $\times$ condition effect was non-significant, $F(1,55) = 0.05$, $p = .82$, $\eta^2_{\text{partial}} = .001$.

Other Go/NoGo Metrics

With regard to analysis of d-prime, neither the effect of condition ($F(1,55) < 0.01$, $p = .98$, $\eta^2_{\text{partial}} < .001$), time ($F(1,55) < 0.01$, $p = .96$, $\eta^2_{\text{partial}} < .01$), nor the group $\times$ time $\times$ condition interaction was significant ($F(1,55) = 2.16$, $p = .15$, $\eta^2_{\text{partial}} = .04$). With regard to analysis of reaction time variability (i.e., coefficient of variation), although the effect of time was significant indicating reduced variability from pre- to post-treatment ($F(1,55) = 4.93$, $p = .03$, $\eta^2_{\text{partial}} = .08$), the effect of condition ($F(1,55) = .62$, $p = .43$, $\eta^2_{\text{partial}} = .01$)

and the group $\times$ time $\times$ condition were not significant ($F(1,55) = 0.17$, $p = .68$, $\eta^2_{\text{partial}} \leq .01$).

Associations Between Improvements in Nonreactivity, Mindfulness Practice, and Changes in Emotional Interference on Response Inhibition

Relative to the SG, RM-ANOVA indicated that MORE significantly increased scores on the nonreactivity facet of the FFMQ ($F(1,52) = 5.79$, $p = .02$, $\eta^2_{\text{partial}} = .10$). Entering this FFMQ facet as an independent variable in a regression model predicting improvements in NoGo accuracy on trials with pain-related distractors (and adjusting for NoGo accuracy on trials with neutral distractors), increases in nonreactivity significantly predicted improvements in NoGo accuracy on trials with pain-related distractors, $\beta = 0.31$, $p = .02$. Similarly, after adjusting for NoGo accuracy on trials with neutral distractors, greater number of minutes of mindfulness meditation practice over the course of treatment predicted improvements in NoGo accuracy on trials with pain-related distractors, $\beta = 0.40$, $p = .03$.

Association Between Chronic Pain and Changes in Emotional Interference on Response Inhibition

As previously reported [28] in the parent RCT from which the present data were derived, participation in MORE was associated with significantly greater reductions in pain severity from pretreatment to 3-month follow-up than the SG ($p = .01$, $d = 0.63$). Consistent with our hypothesis, across both groups in the present study we observed an inverse association between pre- and post-improvements in adjusted NoGo accuracy on trials with

pain-related distractors and reductions in pain severity from pretreatment to 3-month follow-up, $\beta = -0.32$, $p = .04$, such that individuals who exhibited the greatest increases in NoGo accuracy reported the greatest reductions in pain severity by follow-up.

Discussion

Study results indicate that although participants in both treatment conditions demonstrated improvements in NoGo accuracy over the course of treatment, MORE, relative to an SG control condition, enhanced response inhibition in the context of negative emotional interference among a sample of chronic pain patients on long-term opioid therapy. Compared with SG participants, participants in the MORE intervention evidenced a modest yet statistically significant improvement in accuracy on NoGo trials with negative emotional visual distractors (i.e., pain-related images) relative to trials with neutral distractors from pre- to post-treatment. Moreover, regardless of treatment condition, increases in NoGo accuracy from pre- to post-treatment were associated with reductions in pain severity at 3-month follow-up. To our knowledge, this is the first study to demonstrate that a mindfulness-based intervention may improve performance on an Emotional Go/NoGo task, suggesting therapeutic effects on reducing negative emotional interference on ongoing and subsequent cognitive control relevant to the experience and management of chronic pain.

Chronic pain patients in the present sample evidenced significant emotional interference during response inhibition, indicated by greater errors of commission on trials with negative emotional visual distractors relative to trials with neutral distractors. Though participants in both study intervention groups became more accurate over time regardless of the distractor type, MORE significantly outperformed the social support control condition in ameliorating interference from negative affective distractors on response inhibition. This finding converges with two studies that used the Affective Stroop task to measure emotional response inhibition in healthy individuals: a cross-sectional investigation demonstrating an association between meditation practice and decreased neural indices of emotional interference [56], as well as a randomized longitudinal experiment demonstrating effects of mindfulness training on reaction time metrics of emotional interference and concomitant increases in prefrontal inhibitory control function [34].

Other studies have demonstrated protective effects of mindfulness practice on preventing declines in inhibitory control on the Sustained Attention to Response Task (SART) in high-stress contexts [57] and improved

inhibitory control on nonaffective versions of the Stroop task [58, 59]. Thus, MBIs might modulate “cold cognition” in addition to emotion–cognition interactions to improve response inhibition performance. Because the Emotional Go/NoGo task used in this study measures the capacity for response inhibition in negative emotional contexts, it is unclear whether the observed benefits derive from enhanced cognitive control, reduced negative emotional reactivity, or the interaction of these mechanisms. Pure cognitive control explanations of the present findings are unlikely, however, given that no significant between-group differences were observed for trials with only neutral distractors. Furthermore, MORE significantly improved the mindfulness facet of nonreactivity to distressing thoughts and emotions, and improvements in this facet of mindfulness, as well as total number of mindfulness practice minutes, were associated with greater capacity to inhibit responses when pain-related negative affective distractors were present, suggesting that the nonreactive mental stance engendered by the mindfulness meditation practices in MORE (e.g., mindful breathing, body scan) might reduce negative emotional interference during cognitive control. In support of this notion, in a laboratory experiment, focused attention meditation combined followed by mindful awareness of emotional responses to negative affective stimuli enhanced neural indices of performance monitoring during inhibitory control [60].

Prominent theories of mindfulness construe response inhibition as integral to the emotion regulatory effects of mindfulness; for instance, Vago and Silbersweig posit that both focused attention and open monitoring forms of mindfulness practice engage response inhibition mechanisms in facilitating decentering from distressing thoughts and emotions [61]. Similarly, the Mindfulness-to-Meaning Theory proposes that inhibitory control processes facilitate self-regulation of negative cognitive appraisals and maladaptive coping behaviors (like opioid use) stemming from affective perturbations [62, 63]. Thus, by enhancing response inhibition, mindfulness may facilitate downstream emotion regulatory processes. As such, although we observed associations between emotional response inhibition, mindfulness practice, and the mindfulness facet of nonreactivity, MORE includes training in mindfulness, reappraisal, and savoring skills, and therefore, it is plausible that emotion regulation via reappraisal (or savoring) practice could have contributed to the observed decreases in negative emotional interference. Indeed, emotion regulation strategies like reappraisal have been shown to modulate inhibitory control performance [64]. Future studies should employ dismantling designs to isolate effects of each of these therapeutic techniques on response inhibition. Regardless of their precise mechanism of action, the

observed effects on response inhibition specifically within the context of negative emotional distractors have potentially important clinical implications.

In that regard, treatment-related improvements in emotional response inhibition predicted decreases in pain severity by the 3-month follow-up. Speculatively, this association may be understood in light of neurocognitive models explicating the overlapping roles of the anterior midcingulate cortex (aMCC) in regulating cognitive control and processing pain and negative affect. Converging neuroscience findings suggest that the aMCC serves a role in regulating aversively-motivated behaviors that are elicited by stimuli with affective and nociceptive relevance [43]. Moreover, a body of data indicate that negative affect, inhibitory control, and pain compete for the limited functional resource executed by the aMCC [65, 66]. Integrating these neurobiological and behavioral findings, Shackman et al.'s adaptive control hypothesis [43] posits that the aMCC processes punishment-related information (e.g., cues representing the experience of pain) and implements the deployment of cognitive control resources to avoid future punishment (e.g., chronic pain symptoms). If mindfulness training through MORE enhances adaptive control via augmented aMCC function, enhanced response inhibition during affective interference may reflect overall improvements in self-regulatory capacity that can be directed in service of pain regulation. In support of this speculation, it should be noted that in the same sample of patients studied in the present manuscript, MORE was found to enhance autonomic regulation during attention to emotional information on dot probe and affective picture viewing tasks. Given imaging data that implicate the MCC in the regulation of autonomic activity during adaptation to emotional provocations [67], findings across these various tasks suggest that MORE may target this functional convergence zone crucial to adaptive control. Alternatively, if mindfulness facilitates inhibitory gating in the brain, as suggested by Schoenberg et al. in interpreting electrocortical effects of mindfulness training during a nonaffective Go/NoGo Task [37], it is plausible that the mindfulness practices in MORE could inhibit the gating of nociceptive information, leading to reductions in pain coupled with reduced corticothalamic brain activity, as observed in neuroimaging studies of mindfulness-based analgesia [68]. To test these alternative neurophysiological mechanistic hypotheses, neuroimaging approaches are now indicated.

Although MORE outperformed the SG with regard to augmenting emotional response inhibition, the main effect of time on NoGo performance was significant, indicating that errors of commission decreased on average for both groups following treatment. How might social support impact the executive function of response

inhibition? Multiple studies have demonstrated positive associations between social support and cognitive performance [69]. To explain this phenomenon, social support has been hypothesized to buffer the deleterious consequences of emotional distress (such as the distress induced by chronic pain) on cognitive function by reducing loneliness and its effects on neuroimmune function [70]. In addition, the observed association between increased emotional response inhibition and decreased pain severity was common to both MORE and the SG. Hence, it is plausible that increasing emotional response inhibition through a variety of therapeutic approaches (e.g., MORE, social support, cognitive training, pharmacotherapy) might be an efficacious means of alleviating pain.

The present study was limited in several respects. The primary limitation of this study was that we were unable to obtain a reliable, quantitative measure of opioid dosing. We could not obtain accurate opioid dosing data for the whole sample due to nonresponses and ambiguous responses (e.g., reporting the opioid dose without reporting number of pills taken per day) on our self-report measure of opioid dose. Consequently, we do not know whether enhancing cognitive control in the face of emotional interference may have reduced opioid use or whether reduced opioid use as a result of MORE may have led to the observed increases in cognitive control. This latter interpretation is plausible, though the data are decidedly mixed as to whether and to what extent opioids impair executive functions [71–73]. To that end, future studies should carefully track opioid dosing and other psychotropic medication usage via a multipronged approach including self-report, prescription history, pill count, and urine and serum toxicology screens. Furthermore, because the Go/NoGo task in the present study did not include a stimulus block that presented negative stimuli unrelated to pain, we cannot determine if the observed task effects were due to specific interference from pain-related imagery or general negative emotional interference. In addition, study findings may not be generalizable to opioid-naïve chronic pain patients. It should also be noted that we did not correct for multiple comparisons in the present study, given power limitations due to the pilot nature of this research. Confirmatory studies attempting to replicate this result should be fully powered to employ statistical corrections for analyses of mechanistic and clinical outcome data. Finally, this study lacked multiple fidelity assessors to provide independent ratings of therapist competence and adherence to the MORE treatment manual via a validated fidelity measure; future studies of MORE should involve multiple raters using fidelity measures with high inter-rater reliability.

These limitations notwithstanding, study results provide preliminary evidence that MORE enhances response inhibition in the context of negative emotional interference. These findings could be important not only for individuals experiencing chronic pain, but potentially for persons experiencing response inhibition deficits in other clinical contexts. Given the significance of inhibitory control as a transdiagnostic mechanism implicated across a wide range of disorders, interventions that boost this capacity may be especially useful in addressing the complex comorbidities associated with chronic pain.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Authors' Contributions All authors were involved in the preparation of this manuscript and read and approved the final version.

Ethical Approval This study was approved by the University of Utah IRB and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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