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Autonomic and Affective Mediators of the Relationship Between Mindfulness and Opioid Craving Among Chronic Pain Patients

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Abstract

Prescription opioid misuse among chronic pain patients is associated with self-regulatory deficits, affective distress and opioid cue reactivity. Dispositional mindfulness has been associated with enhanced self-regulation, lower distress, and adaptive autonomic responses following drug cue exposure. We hypothesized that dispositional mindfulness might serve as a protective factor among opioid-treated chronic pain patients. We examined heart rate variability (HRV) during exposure to opioid cues and depressed mood as mediators of the association between dispositional mindfulness and opioid craving. Data were obtained from a sample of chronic pain patients (N=115) receiving long-term opioid pharmacotherapy. Participants self-reported opioid craving and depression, and HRV was measured during an opioid-cue dot probe task. Dispositional mindfulness was significantly positively correlated with HRV, and HRV was significantly inversely associated with opioid craving. Dispositional mindfulness was significantly negatively correlated with depression, and depression was significantly positively correlated with opioid craving. Path analysis revealed significant indirect effects of dispositional mindfulness on craving through both HRV and depression. Dispositional mindfulness may buffer against opioid craving among chronic pain patients prescribed opioids; this buffering effect may be a function of improved autonomic and affective responses.

Keywords

trait mindfulness; opioids; craving; phasic heart rate variability; self-regulation

Introduction

The ability to flexibly respond to a perpetually changing environment is crucial to survival. As affectively-valenced cues in the environment elicit appraisals of potential threat and

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Disclosures

All authors contributed to the final draft of the article. ELG conceived the study aims and hypotheses, and provided oversight in data collection, analysis, and manuscript preparation. AKB spearheaded analysis and manuscript preparation, and ELG contributed to data analysis and editing of this manuscript.

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reward, flexible responding is largely made possible through the capacity to self-regulate in order to approach appetitive stimuli or avoid aversive stimuli. Within a dynamical systems framework, self-regulation is enacted through two key regulatory mechanisms, attention and emotion, which are inextricably linked through an integrated neurovisceral network that subserves flexible adaptation of the organism to the environment (Thayer & Lane, 2000, 2009). Within this network, the central nervous system deploys attention to orient the individual to salient environmental stimuli and then generates emotions to provide feedback regarding the threat or reward value of those stimuli, coupled with autonomic activation to mobilize an appropriate behavioral response (Schwartz, 1986). Hence, self-regulation is thought to be facilitated by the interplay between attentional, emotional and autonomic processes (Heilman, 1997).

According to the allostatic model, addictive behaviors dysregulate processing of threat and reward stimuli in limbic and striatal brain regions (Koob & Volkow, 2010; Koob & LeMoal, 2001). In this theoretical model, as addiction develops, attention is shifted from environmental cues representing natural reinforcers and instead becomes focused on drug-related stimuli (Field & Cox, 2008), resulting in decreased sensitivity to natural rewards (Volkow, Wang, Fowler, Tomasi, & Telang, 2011; Alcaro & Panksepp, 2011; Lubman et al., 2009). At the same time, recurrent substance use increases sensitization to stress and threat, ostensibly resulting in emotion dysregulation and higher baseline depression (Garland, Bell, Atchley, & Froeliger, in press; Krupitsky et al., 2015). Opioid-treated chronic pain patients may be especially vulnerable to addiction (Volkow & McLellan, 2016) and subsequent reward dysregulation by way of two conditioned responses, wherein pain relief and opioid-induced euphoria become associated with opioid cues via negative and positive reinforcement, respectively (Shippenberg, Bals-Kubik, & Herz, 1993; Fields, 2004). This conditioning process may result in opioid cue reactivity manifested in cue-elicited attentional and autonomic responses (Garland & Howard, 2014; Garland, Froeliger, & Howard, 2015; Back, Gros, McCauley, Flanagan, Cox, ... Brady, 2014). It appears that when opioid cue reactivity is coupled with depressed mood—arguably stemming from the emotion dysregulatory effects of addiction (Shurman, Koob, & Gutstein, 2010)—patients may experience an upwelling of craving (Martel et al., 2014; Wasan et al., 2012) and consequently engage in opioid misusing behaviors like unauthorized dose escalation. Hence, craving may arise as a result of dysregulated attentional and emotional processes that, in turn, ultimately lead to behavioral disinhibition and loss of control over substance use (Volkow, Fowler, Wang, & Goldstein, 2002). Intact self-regulatory capacity therefore appears to be crucial in the successful management of opioid craving and prevention of opioid misuse.

Individuals who are predisposed to misuse prescription opioids may have low self-regulatory capacity and thereby suffer from dysregulated negative emotions (Garland, Bell, Atchley, & Froeliger, in press; Garland, Bryan, Nakamura, Howard, & Froeliger, 2017). Indeed, approximately 25% of opioid-treated chronic pain patients self-report aberrant drug-related behaviors like misuse of opioids to self-medicate depressed mood and other negative affective states (Vowles et al., 2015). Compounding this potential pre-existing vulnerability, recurrent opioid misuse may impair brain circuits involved in self-regulation and reward processing through an allostatic process (Koob & Le Moal, 2001), resulting in the downward

spiral of behavioral escalation linking chronic pain to opioid misuse (Garland et al., 2013). In light of these clinically relevant considerations, research is needed to examine protective factors that may buffer against dysregulation of the integrated network of autonomic, attentional and affective processes that appear to precipitate medication adherence and opioid misuse.

Dispositional mindfulness may be one such protective factor. Defined as the trait-like propensity to exhibit mindful qualities in everyday life, dispositional mindfulness encompasses various facets of self-regulation including acceptance, nonreactivity to distressing thoughts and emotions, and awareness of interoceptive and exteroceptive sensations and perceptions (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006; Brown, Ryan, & Creswell, 2007). Though it is a naturally occurring trait, dispositional mindfulness can be enhanced through mindfulness training, such as that provided by mindfulness-based interventions (Kiken, Garland, Bluth, Palsson, & Gaylord, 2015; Carmody & Baer, 2008). Mindfulness has been associated with improved ability to regulate attention (Holzel, Tang, & Posner, 2015) and emotions (Garland, Farb, Goldin, Fredrickson, 2015; Teper, Segal & Inzlicht, 2013; Keng, Smoski, & Robins, 2011), as well as with increased autonomic flexibility (Garland, Gaylord, Boettiger, & Howard, 2010; Garland, Froeliger, & Howard, 2014; Mankus, Aldao, Kerns, Mayville, & Mennin, 2013). Dispositional mindfulness has also been inversely correlated with depressed mood (Pearson, Brown, Bravo & Witkiewitz, 2015; Paul, Stanton, Greeson, Smoski, & Wang, 2013), and drug craving (Garland, Roberts-Lewis, Kelly, Tronnier, & Hanley, 2014). Specific to opioid misuse, low dispositional mindfulness is associated with greater use of opioids to self-medicate depressed mood and other negative emotions (Garland, Hanley, Thomas, Knoll, & Ferraro, 2015). Moreover, opioid-treated chronic pain patients who participated in a mindfulness-based intervention demonstrated significantly greater increases in autonomic control and decreases in opioid craving during attention to opioid cues, relative to support group controls (Garland, Froeliger, & Howard, 2014). Taken together, these findings suggest that dispositional mindfulness may reflect the capacity to self-regulate attentional and emotional responses elicited by opioid cues.

Self-regulation has thus emerged as an important variable in both addiction and mindfulness research. According to the neurovisceral integration theory (Thayer & Lane, 2000, 2009), self-regulation during attention to appetitive stimuli can be indexed by phasic heart rate variability (HRV)—the beat-to-beat, high-frequency variation in heart rate governed by the autonomic nervous system and controlled by the cortico-limbic-striatal network that modulates attention and emotion (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). Recent meta-analytic research demonstrates a statistically significant, albeit small, relation between HRV and various measures of self-regulation (Holzman & Bridgett, 2017). While higher resting HRV is generally understood as an indicator of adaptive function, interpretation of phasic HRV is more nuanced. As Laborde, Mosley, and Thayer (2017) recently observed, higher phasic HRV may be interpreted as maladaptive in the absence of executive functioning requirements, but adaptive during tasks that require executive functioning, such as attentional engagement and disengagement in response to emotionally-salient information. Consistent with these interpretive parameters, research examining phasic HRV as a marker of self-regulatory capacity among opioid-misusing chronic pain patients shows

that, relative to non-misusers, opioid misusers have significantly lower phasic HRV during attention to opioid-related cues (Garland, Froeliger, & Howard, 2015). On the other end of the spectrum, phasic HRV also appears as a marker of self-regulation in mindfulness research. Dispositional mindfulness has been linked with faster recovery from acute stress, inferred from higher phasic HRV (Corey, Moran, Koslov, Daubenmier, Mendes, et al., 2012). Moreover, dispositional mindfulness has been associated with higher phasic HRV during exposure to alcohol cues (Garland, 2011)—a finding that parallels results from a RCT demonstrating mindfulness training increases phasic HRV in response to alcohol cues (Garland, Gaylord, Boettiger, & Howard, 2010). Associations between dispositional mindfulness and phasic HRV during attention to opioid cues, however, have not yet been explored.

To test whether dispositional mindfulness might serve as a protective factor to buffer against autonomic opioid cue reactivity, craving, and attendant depressed mood symptoms, we conducted a secondary analysis of baseline data obtained from a clinical trial of opioid-treated chronic pain patients (Garland, Manusov, et al., 2014). We formed a two-pronged hypothesis. First, we predicted that dispositional mindfulness would be directly associated with lower opioid craving, lower levels of depressed mood, and higher phasic HRV during attention to opioid-related cues. Second, we posited that depression and phasic HRV would mediate the relationship between dispositional mindfulness and opioid craving.

Methods

Participants

Individuals diagnosed with chronic pain conditions were recruited from primary care, pain, and neurology clinics in the Southeastern United States between 2011 and 2012. Participants met inclusion criteria if they reported chronic, non-cancer-related pain and had taken opioid analgesics at least 5 days of each week for no less than the past 90 days (Chou et al., 2009). Exclusion criteria were active suicidality or psychosis, assessed with the MINI International Neuropsychiatric Interview 6.0 (MINI; Sheehan et al., 1998).

Procedure

Prior to participant recruitment, the study was reviewed and approved by the institutional review board at Florida State University (where the second author was located during data collection). Individuals who met study inclusion criteria and consented to participate completed a battery of self-report measures that captured demographic and clinical information, followed by a psychophysiological assessment conducted by trained research assistants. All participants were compensated \$25 for completing the study.

Measures

Dispositional Mindfulness—Dispositional mindfulness was measured with the Five Facet Mindfulness Questionnaire (FFMQ; Baer, Smith, Hopkins, Krietemeyer & Toney, 2006), a 39-item self-report questionnaire with good reliability and internal consistency ($\alpha = .78$ in this study). The FFMQ is comprised of five mindfulness facets, including non-reactivity to internal experiences (captured by items such as “I watch my feelings without

getting lost in them”), observing one’s experiences (“I pay attention to sensations, such as the wind in your hair or the sun on my face”), and acting with awareness (“I find myself doing things without paying attention”) (Baer et al., 2006). Items are scored on a 5-point Likert scale (1 = “Never or very rarely true”, 5 = “Very often or always true”), and total scores are calculated as summations of sub-scale items. The FFMQ total score was used in this study.

Opioid Craving—Opioid craving was measured with a 10-item prescription opioid adaptation of the Obsessive Compulsive Drug Use Scale-Revised (OCDUS-R; Franken, Hendriksa, & van den Brink, 2002; Morgan et al., 2004; $\alpha = .91$ in this study). This instrument is designed to capture frequency of opioid craving over the past week, assessed by scores on a 5-point Likert scale (0 = no craving, 4 = extreme craving). The authors slightly adjusted wording of items to identify prescription opioid use, changing language such as “How strong is the drive to take drugs?” to “How strong is the drive to take your opioid pain medicine?”

Depressed Mood—Depressed mood was measured with scores from the Symptoms of Stress Inventory (SOSI; Carlson & Thomas, 2007) depression sub-scale ($\alpha = .89$ in this study). The depression subscale is comprised of eight Likert-type items tapping depressive symptoms on a scale from 1 (never) to 5 (very frequently), including feelings of loneliness and sadness, crying spells, and fatigue. The SOSI has been used as a validated measure of affective symptoms in opioid-treated chronic pain patients (Garland, Manusov et al., 2014; Garland, Brown, & Howard, 2016).

Phasic HRV during attention to opioid-related cues—Disposable Ag-AgCl adhesive electrodes were attached to participants’ right and left pectoral muscles and electrocardiogram (ECG) data were continuously sampled at 1,000 Hz on a Biopac MP 150 (Biopac Systems, Goleta, CA). Baseline HRV was collected during a 5-min period in which participants were asked to remain silent and motionless, after which they completed the dot-probe task. R-R intervals in the ECG waveforms were initially detected automatically in Acqknowledge 4.1 (BIOPAC, Inc.), and then visually inspected to correct missed or incorrectly identified R-waves.

Phasic HRV during attention to opioid-related cues was assessed with a computerized dot probe task (E-Prime, PST Inc., Pittsburgh, PA). A fixation cross was presented for 500 ms at the beginning of each trial. Then, pairs of photos containing one opioid-related image (e.g., pills, pill bottles) and one neutral image—matched for visual complexity, composition, and figure-ground relationships—were presented side-by-side on the computer screen for either 200 or 2,000 ms across 64 trials. Opioid cues consisted of 12 images of pills and pill bottles selected from media libraries on the Internet, and neutral cues consisted of 12 neutral images selected from the International Affective Picture System (IAPS; Lang et al., 1997). Presentation duration and left-right position of the images were randomized and counterbalanced. Both images disappeared simultaneously, followed by a 50 ms inter-stimulus interval, after which a target probe replaced one of the images. Probes appeared for 100 ms, and probe location was counterbalanced. The total epoch of the dot probe opioid

cue-condition was 2 minutes in length. Participants designated left or right probe location with a left or right button press.

Analysis

Kubios 2.0 (Biosignal Analysis and Medical Imaging Group, University of Finland) was used for time domain analysis of R-waves. The root mean square of successive differences (RMSSD) in R-R intervals was used to compute HRV (Thayer & Lane, 2000; Kleiger, Stein, & Bigger, 2005). Although some researchers suggest that RMSSD and other time-domain measures of HRV are less optimal than frequency-domain measures such as high-frequency (HF) HRV (Berntson, Quigley, & Lozano, 2007), we selected RMSSD as our measure of phasic HRV in this study given that it is considered to be less affected by respiratory influences than spectral HRV measures (Hill & Siebenbrock, 2009). Indeed, it has been suggested that RMSSD is preferable to spectral HRV measures in experiments where respiratory confounds are likely to be present (Penttila et al., 2001). In light of well-documented effects of opioids on respiratory depression Activation of opioid receptors does not appear to have an effect on HRV (Ellidokuz et al., 2008), but respiratory depression is a known side-effect of opioids (Boom, Niesters, Sarton, Aarts, Smith & Dahan, 2012; Jarzyna et al., 2011); thus, we selected RMSSD in an effort to remove the potentially confounding influence of respiration inherent to frequency-domain measures of HRV. RMSSD values were averaged across the 5-min baseline and the dot probe opioid cue condition.

For hypothesis testing, we used the following multi-stage analytic approach. First, we computed Pearson's correlations to assess the unadjusted, zero-order relationships between dispositional mindfulness, resting HRV, phasic HRV during opioid cue exposure, depression, and opioid craving. We also tested a linear regression model in which dispositional mindfulness served as the independent variable, HRV during opioid cue exposure was the dependent variable, and baseline resting HRV was used as a covariate. Next, we created a residualized HRV score representing phasic HRV during attention to opioid cues (HRV cue responsivity) by saving the residuals after co-varying resting HRV from HRV during opioid cue exposure. Finally, we conducted a multivariate path analysis with full-information maximum likelihood estimation using SPSS AMOS 24 to examine this phasic HRV variable and SOSI depressed mood scores as mediators of the association between dispositional mindfulness and opioid craving. Unstandardized indirect effects were computed for each of 1,000 bootstrapped samples, and the 95% confidence interval was computed by determining the indirect effects at the 2.5th and 97.5th percentiles. Significance of each indirect effect was indicated by the upper and lower limits of the 95% confidence interval not spanning zero (Preacher & Hayes, 2008). This method has been recommended as superior to a normal theory approach to testing mediation (e.g., Sobel test) because it does not assume normality of the indirect effect sampling distribution. Model fit was determined using fit indices recommended by Kline (1998), including a χ^2/df ratio between 1 and 3 (Carmines & McIver, 1981), comparative fit index (CFI) > 0.90, and the root-mean square error of approximation (RMSEA) 0.08 (Browne & Cudeck, 1993).

Results

Sample Characteristics

Data were obtained from chronic pain patients ($N = 115$) prescribed long-term opioid therapy for analgesia. A majority of participants were female (68%, mean age = 48.3 ± 13.6), Caucasian (65%), had completed some college-level education (70%), and a large portion (46%) reported annual incomes less than \$40,000. Demographics are depicted in Table 1.

Bivariate Associations Between Phasic HRV and Clinical Variables

Bivariate correlations confirmed expected directionalities of variable relationships. FFMQ scores were significantly positively correlated with resting HRV and phasic HRV during opioid cue-exposure—both with moderate effect sizes, and significantly negatively correlated with both depression and opioid craving—also with moderate effect sizes. Depression and opioid craving were positively correlated with a moderate effect size. In contrast, the small effect size correlation between HRV and depression was non-significant. Pearson's correlations are depicted in Table 2, and effect size interpretations are consistent with those outlined by Cohen (1988).

Linear Regression Analysis

Linear regression indicated that dispositional mindfulness was significantly positively associated with phasic HRV during opioid cue-exposure ($B = .58$, $SE = .23$, $p = .01$, model $R^2 = .57$), after controlling for baseline resting HRV.

Multivariate Path Analysis

Our multivariate path model (Fig. 1) revealed that phasic HRV and depression were partial mediators of the relationship between dispositional mindfulness and opioid craving during attention to drug-related stimuli ($\chi^2/df = .53$; CFI=1; RMSEA=.00). The regression coefficient between dispositional mindfulness and phasic HRV was statistically significant ($B = .56$, $SE = 0.20$, $p = .005$) with a medium effect size ($r = .24$), as was the regression coefficient between phasic HRV and craving ($B = -.08$, $SE = 0.25$, $p = .006$). The regression coefficient between dispositional mindfulness and depression was also statistically significant ($B = -.17$, $SE = 0.05$, $p = .001$) with a medium effect size ($r = .35$), as was that between depression and craving ($B = .44$, $SE = 0.12$, $p = .002$). With these two mediational pathways entered into the model, the direct effect of dispositional mindfulness on craving become non-significant ($B = .02$, $SE = .06$, $p = .44$). The bootstrapped, unstandardized indirect effect of dispositional mindfulness on craving through phasic HRV was $-.03$ ($SE = .02$), 95% BCI $[-.09, -.001]$, and through depression was $-.08$ ($SE = .03$), 95% BCI $[-.15, -.02]$, indicating phasic HRV and depression were both statistically significant mediators in the relationship between dispositional mindfulness and opioid craving, together accounting for 21% of the variance in the model.

Discussion

Self-regulation is an essential feature of adaptive behavior and is central to the effective management of drug cravings. According to the neurovisceral integration model (Thayer & Lane, 2000, 2009), self-regulation is achieved through attentional and emotional processes, in conjunction with downstream effects on autonomic responses. In the present investigation of a community sample of opioid-treated chronic pain patients, we found that dispositional mindfulness, a construct closely linked with heightened self-regulatory capacity, was positively associated with phasic HRV during opioid cue exposure, and with lower depressed mood—two potential mechanisms of action that mediated the inverse association between mindfulness and opioid craving.

Mindfulness, Heart Rate Variability, and Craving

Findings revealed that dispositional mindfulness was positively correlated with phasic HRV and phasic HRV was inversely correlated with opioid craving, with phasic HRV mediating the association between dispositional mindfulness and craving. The indirect effect of dispositional mindfulness on craving through phasic HRV may suggest that greater autonomic flexibility (Friedman, 2007) could be a key mechanism by which higher dispositional mindfulness buffers against addictive behaviors. This mediational mechanism might be understood through the lens of the dynamical systems model proposed by Thayer and Lane (2000), who discuss goal-directed behavior (e.g., drug consumption perpetuated by craving) as a product of a central autonomic network (CAN), including brain regions implicated in self-regulation of appetitive responses – including the medial prefrontal cortex, anterior cingulate cortex, insula, amygdala, and striatum (Benarroch, 1993, 1997). CAN outputs modulate heart rate during regulation of attention and emotion (Thayer & Lane, 2000), making phasic HRV a possible marker of flexible self-regulation in the face of appetitive cues. Hence, it seems that as phasic HRV increases from baseline levels, so too might the ability to inhibit maladaptive responding. In the context of the present analysis, this translates as lower drug craving among individuals exhibiting the enhanced autonomic flexibility associated with higher levels of dispositional mindfulness.

In light of literature supporting phasic HRV as an index of self-regulation (Segerstrom & Nes, 2007; Holzman & Bridgett, 2017), it seems reasonable to presume that higher phasic HRV observed among opioid-treated patients with high dispositional mindfulness scores may indicate greater capacity to self-regulate in the face of opioid cues. This interpretation is consistent with prior research demonstrating associations between dispositional mindfulness, reduced alcohol attentional bias, and higher phasic HRV following alcohol cue-exposure among a sample of alcohol-dependent individuals (Garland, 2011). Plausibly, it may be that dispositional mindfulness enables parasympathetic control during attention to emotional information, and thereby facilitates successful down-regulation of sympathetically-driven cue reactivity with consequent effects on reducing subjective craving. However, in light of the fact that RMSSD may capture both sympathetic and parasympathetic activity (Berntson, Lozano, & Chen, 2005), this physiological inference can only be taken as logical conjecture. Future research should aim to unpack these nuances to promote deeper understanding of how vagal tone influences craving.

Mindfulness, Depression, and Craving

Findings revealed that dispositional mindfulness was inversely correlated with depression and depression was positively associated with opioid craving, with depression also mediating the association between dispositional mindfulness and craving. The direct effect of dispositional mindfulness on depression is consistent with behavioral research demonstrating associations between dispositional mindfulness, depression, and psychological well-being (Brown & Ryan, 2003; Jimenez, Niles, & Park, 2010; Hanley & Garland, 2016). This direct effect is also unsurprising in light of neurobiological evidence that dispositional mindfulness is associated with reduced amygdala reactivity to negative emotional stimuli (Baldwin, Creswell, Eisenberger, & Lieberman, 2010) and with smaller amygdala volumes (Taren, Creswell, & Gianaros, 2013).

The observed association between depression and opioid craving may be understood as a function of conditioned negative reinforcement. That is, opioid cues could be associated with reprieve from the emotional suffering that accompanies chronic pain, thereby eliciting a conditioned response (i.e., craving) to promote opioid consumption and the desired emotional relief (Martel et al., 2014; Childress, McLellan, Ehrman, & O'Brien, 1988). A recent neuroimaging study of self-control deficits in the face of negative affect provides an alternative lens through which to understand the direct effect of depression on craving. Researchers found that, contrary to the widely accepted notion that self-regulatory deficits occur as a simple failure to recruit resources from the prefrontal cortex, these deficits actually appear to be a function of excessive self-regulatory taxation when disinhibition occurs in conjunction with negative emotion (Chester, Lynam, Milich, Powell, Anderson, & DeWall, 2016). From this perspective, it is possible that over-regulation of negative emotion may exhaust self-regulatory resources, thereby limiting an individual's capacity to manage craving.

The source of the direct effect of depression on craving may hold considerable implications for how to interpret the indirect effect of dispositional mindfulness on craving through depression. Insofar as individuals high in dispositional mindfulness may be subject to less negative affectivity (Brown & Ryan, 2003; Paulus, Langdon, Wetter, Zvolensky, 2017), lower depressed mood among mindful individuals may explain their comparatively lower levels of craving driven by a desire to ameliorate negative emotions. Alternatively, it could be that the heightened executive control associated with mindfulness (Teper, Segal, & Inzlicht, 2013) is made possible in part by greater self-regulatory resource availability associated with lower negative emotion (Chester et al., 2016), or vice versa. In this case, the indirect effect might be understood not as a function of reduced depression, but rather of the attenuation of depression's impact on the capacity for self-regulation. Future research may benefit from inclusion of additional measures, such as emotion regulation and executive functioning, to more clearly partition the relationships elucidated by the present study.

Conclusion

Extensive research has focused on illuminating the functional links specified by the neurovisceral integration model between central and autonomic nervous system structures implicated in attentional control and emotional experience (Nyklicek, Thayer & van

Doormen, 1997; Thayer, Friedman, & Borkovec, 2000; Thayer & Lane, 2000, 2009), and together these biobehavioral processes appear to subserve self-regulation and adaptive responding. The results of the present study provide support for the neurovisceral model in the context of addiction, capturing two pathways by which dispositional mindfulness attenuates craving: one through autonomic regulation of drug cue reactivity, the other through lower levels of negative affect.

While these findings hold preliminary implications for the role of mindfulness in prevention of and recovery from opioid misuse, there are several limitations to this study. First, causal inferences regarding directionality in the proposed mediational pathways are precluded by the cross-sectional design of this study. As Baron & Kenny (1986) outlined, changes in the mediator must precede changes in the dependent variable in order to establish causality. Future studies employing longitudinal designs could yield causal inferences by providing more insight into the directionality of associations evinced in this study. Similarly, without a control group, we could not provide a comparator to contextualize the sample with regard to the broader literature. Although data from the present study were limited to individual difference analyses, this analytic approach has long been recognized as a valid means of assessing psychobiological mediators of the relation between dispositional factors and physiological responses to environmental challenges (Kosslyn, Cacioppo, Davidson, Hugdahl, Lovallo, Spiegel, & Rose, 2002). Nonetheless, future iterations of this research would benefit from inclusion of not only healthy controls, but also chronic pain patients not on prescription opioids, to provide further clarity. Self-report measures are also potentially problematic features of the study's design, as social desirability bias may have influenced the extent to which constructs of interest were accurately captured. Finally, the unique clinical features of the sample may limit the generalizability of study results to chronic pain patients treated with extended opioid pharmacotherapy and might not be applicable to other forms of substance use and misuse.

In conclusion, higher levels of dispositional mindfulness were associated with lower opioid craving among this sample of chronic pain patients taking prescription opioid analgesics, and phasic HRV during attention to opioid cues and depression significantly mediated this relationship. These preliminary findings suggest that dispositional mindfulness may be a valuable buffer against physiological and emotional risk factors implicated in drug craving. As such, psychological interventions designed to cultivate mindfulness (e.g., Garland, Manusov et al., 2014) may be an effective, non-pharmacological means of ameliorating opioid craving and cue reactivity (Garland, Froeliger, & Howard, 2014) and help to stem the rising public health crisis of opioid misuse.

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Significance Statement

This study provides evidence that mindfulness as a personality trait may be associated with lower rates of opioid craving by way of adaptive autonomic responses, and either lower levels of negative emotion or higher levels of emotion regulation. This research helps identify possible mechanisms of recovery from opioid misuse, allowing interventions to be more carefully tailored to combat this rising public health epidemic.

Figure 1.

Multivariate path model testing the mediating role of HRV and depressive symptoms between dispositional mindfulness and opioid craving. Unstandardized path coefficients are shown next to arrows indicating each link in the analysis, with SEs in parentheses. The indirect effect through HRV (represented by the arrow under that variable in the figure) was statistically significant. The indirect effect through depressive symptoms (represented by the arrow under that variable in the figure) was also statistically significant. FFMQ indicates Five Facet Mindfulness Questionnaire, SOSI-DEP indicates depressive symptomology on the Symptoms of Stress Inventory, and OCDUS-R indicates Obsessive-Compulsive Drug Use Scale-Revised.

Table 1

Demographic and Clinical Characteristics of the Chronic Pain Sample (N = 115)

<u>Measure</u>	<u>N (%)</u>
Female	78 (68)
Age	48.3 ± 13.6
Work status, full time	29 (26)
Race	
Not responded	11 (10)
Indian American	4 (3)
African American	21 (18)
White	75 (65)
Other	4 (3)
Income Level	
Not responded	34 (30)
Below \$20,000	27 (23)
\$20,000–\$39,999	27 (23)
\$40,000–\$59,999	10 (9)
\$60,000–\$79,999	9 (8)
Over \$80,000	8 (7)
Education, some college	81 (70)

Table 2

Zero-order Correlations Between Study Variables (N=115)

	FFMQ	Dispositional Mindfulness	Resting HRV	Dot Probe HRV	Phasic HRV	SOSI-DEP Depression	OCDUS Craving
Resting HRV		.30**					
Dot Probe HRV	.39**		.74**				
Phasic HRV	.24*		.00	.68**			
SOSI-DEP	-.30**		-.08	-.16	-.17		
OCDUS	.23*		-.07	-.28**	-.29*	.34*	

Note. FFMQ = Five Facet Mindfulness Questionnaire; HRV = Heart Rate Variability; SOSI-DEP = Symptoms of Stress Inventory Depression Subscale; OCDUS = Obsessive Compulsive Drug Use Scale.

* $p < .05$

** $p < .01$