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Re-Training the Addicted Brain: A Review of Hypothesized Neurobiological Mechanisms of Mindfulness-Based Relapse Prevention

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Abstract

Addiction has generally been characterized as a chronic relapsing condition. Several laboratory, preclinical, and clinical studies have provided evidence that craving and negative affect are strong predictors of the relapse process. These states, as well as the desire to avoid them, have been described as primary motives for substance use. A recently developed behavioral treatment, Mindfulness-Based Relapse Prevention (MBRP), was designed to target experiences of craving and negative affect and their roles in the relapse process. MBRP offers skills in cognitive behavioral relapse prevention integrated with mindfulness meditation. The mindfulness practices in MBRP are intended to increase discriminative awareness, with a specific focus on acceptance of uncomfortable states or challenging situations without reacting "automatically." A recent efficacy trial found that those randomized to MBRP, as compared to those in a control group, demonstrated significantly lower rates of substance use and greater decreases in craving following treatment. Furthermore, individuals in MBRP did not report increased craving or substance use in response to negative affect. Importantly, areas of the brain that have been associated with craving, negative affect, and relapse have also been shown to be affected by mindfulness training. Drawing from the neuroimaging literature, we review several plausible mechanisms by which MBRP might be changing neural responses to the experiences of craving and negative affect, which subsequently may reduce risk for relapse. We hypothesize that MBRP may affect numerous brain systems and may reverse, repair, or compensate for the neuroadaptive changes associated with addiction and addictive behavior relapse.

Keywords

neurobiology; mindfulness; substance use disorders; craving; relapse; mindfulness-based relapse prevention

Addiction has generally been characterized as a chronic relapsing condition (Leshner, 1999), with relapse defined as the process of returning to a problematic addictive behavior following a period of abstinence or moderation. Understanding and predicting the relapse process has been a primary research goal and treatment target for the past 30 years, with

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several candidate intrapersonal and interpersonal predictors being hypothesized and studied. Across numerous investigations of relapse precipitants in both animal and human models, two factors have emerged as the most commonly endorsed relapse risk factors: craving and negative affect.

Craving, the subjective experience of an urge or desire to use substances (Kozlowski & Wilkinson, 1987), has been shown to strongly predict relapse for all major drugs of abuse (e.g., Hartz, Frederick-Osborne, & Galloway, 2001; Hopper et al. 2006; Shiffman et al., 2002), as well as gambling behavior (Young & Wohl, 2009). Craving is a complex construct, and operational and conceptual definitions vary widely, yet clinicians, researchers, and clients agree that the subjective experience of craving is an essential facet of substance use disorders (Skinner & Aubin, 2010). Negative affect, which has been defined as a negative subjective, evaluative feeling state in response to an internal or external stimulus (Kassel, 2006), has also been shown to be a prominent predictor of relapse in both laboratory and clinical studies (e.g., Sinha & O'Malley, 1999; Wheeler et al., 2008). The roles of craving and negative affect in predicting addiction treatment outcomes have more recently been investigated within the context of neurobiological studies, with numerous studies identifying differences in brain structure and functioning that predict relapse, craving, and negative affective states among individuals with addictive disorders (e.g., Breese, Sinha, & Heilig, 2011; Goodman, 2008; Heinz, Beck, Grusser, Grace, & Wrase, 2008; Myrick et al., 2004; Sinha & Li, 2007; Weiss, 2005; Wexler et al., 2001).

A recently developed cognitive behavioral treatment for addiction, Mindfulness-Based Relapse Prevention (MBRP; Bowen, Chawla, & Marlatt, 2010; Witkiewitz, Marlatt, & Walker, 2005), was designed to target experiences of craving and negative affect and their role in the relapse process. In the tradition of Mindfulness-Based Stress Reduction for chronic pain (MBSR; Kabat-Zinn, 1990) and Mindfulness-Based Cognitive Therapy for relapse to depression (MBCT; Segal, et al., 2002), MBRP integrates mindfulness meditation practices with cognitive behavioral relapse prevention skills (e.g., identifying high-risk situations; coping skills training; Marlatt & Gordon, 1985), retaining mindfulness practice as its primary focus (Bowen et al., 2010). Other behavioral treatments that incorporate mindfulness practice, such as Acceptance and Commitment Therapy (ACT; Hayes, Strohsal, & Wilson, 1999) and Dialectical Behavior Therapy (DBT; Linehan, 1993), are similar to MBRP in that they involve practices emphasizing awareness and acceptance (Hayes, Follette, & Linehan, 2004). However ACT and DBT are dissimilar from MBRP and other mindfulness-based treatments in that they are multi-component therapies that include mindfulness as one element, rather than as the primary foundation.

The mindfulness practices in MBRP are intended to increase awareness of external triggers and internal cognitive and affective processes, increase the clients' ability to tolerate challenging cognitive, affective, and physical experiences (Bowen et al., 2009), as well as enhance the clients' metacognitive abilities (Teasdale et al., 2002). Indeed, studies have shown that mindfulness practices taught in MBRP may lead to greater attentional (Chambers, Lo, & Allen, 2008) and inhibitory control (Hoppes, 2006) by teaching clients to observe challenging or uncomfortable emotional or craving states without habitually reacting. In contrast to the various strategies commonly employed in substance abuse interventions (e.g., cognitive-behavioral interventions and twelve-step groups) such as thought-stopping, avoidance of negative or challenging experience and emotions, or reliance on will power, MBRP practices emphasize intentional awareness and acceptance of all experiences, including those that are uncomfortable or unwanted, and teach skills to better relate to these experiences. MBRP clients are taught to practice a curious and nonjudgmental approach to discomfort, learning to investigate emotional, physical and cognitive components of experience as they occur in the present moment rather than attempting to

suppress or ameliorate the discomfort, fostering approach- vs. avoidance-based coping. Importantly, these skills can be practiced regardless of the underlying cause of negative affect (e.g., acute withdrawal, drug-induced mood disorder, or depressive disorders).

More generally, as summarized in Table 1, the mindfulness meditation exercises used in MBRP were incorporated to help clients increase present-moment awareness and attentional control, improve their ability to observe and regulate their behavior (i.e., self-regulation) by not engaging in a prepotent response (e.g., using substances to alleviate craving), and approach discomfort from a nonjudgmental and nonreactive stance. Clients come into contact with stimuli, such as negative affective states or self-critical cognitions, which in the past have been triggers for substance use. Through targeted mindfulness practices, clients maintain contact with these states, engaging in a nonjudgmental examination of their physical, affective and cognitive aspects, rather than reactively attempting to avoid or ameliorate the experiences. Through repeated exposure and non-reaction, clients are able to build a repertoire of alternative responses to the cues. For example, in the SOBER space exercise (see Bowen et al., 2009; Bowen et al., 2010), the clients are taught to "Stop," "Observe," "Breathe", "Expand awareness," and "Respond mindfully." The intention of the *SOBER* breathing space is to help clients break habitual stimulus-response patterns, such as seeking an immediate "fix" to alleviate a craving experience, by teaching clients to pause and make conscious, mindful choices.

In recent studies, MBRP has shown potential as an effective aftercare treatment for substance use disorders (Bowen et al., 2009), and empirical evidence suggests that one mechanism of action is a reduction in self-reported craving (Bowen et al., 2009; Witkiewitz & Bowen, 2010). Given the association between executive cognitive control and craving (Blume & Marlatt, 2009), it may be that MBRP improves higher-order executive control of typically "automatic" reactions to discomfort (e.g., craving). These types of cognitive modulatory processes may be referred to as "top-down" processes. As such, hypothesized improvements in top-down modulation may ultimately allow for exposure to previously avoided experiences that cause discomfort (e.g. negative mood or drug cues) without habitual substance use responses.

Two candidate neural pathways have been proposed that may help explain the association between mindful attention and substance craving (Westbrook et al., in press), with the top-down pathway reflecting executive control over craving and the bottom-up pathway involving changes in the subjective experience of craving. Westbrook and colleagues adopt the term "regulation" to describe top-down modulation (i.e., executive control over craving), suggesting that higher cortical regions may operate in an inhibitory fashion over lower, subcortical processing. Alternatively, "bottom-up" pathways are proposed to serve in a "reactive" fashion by activating craving-related brain regions involved in brainstem-sub-cortical-limbic processing (i.e., subjective experience of craving; Brewer et al., 2009). For example, a bottom-up process would be operating if mindfulness was associated with decreased reactivity to craving-related stimuli or decreased reactivity to a stressor. Ultimately, perceiving and attending to bottom-up stimulus events will involve cortical processes, but the extent of that involvement may vary according to the saliency of the incoming (or afferent) information rather than being modulated in a top-down fashion via the prefrontal cortex. As such, it is especially notable that mindfulness has been associated with reduced activation of craving-related regions without the recruitment of the prefrontal regulatory regions that are involved in top-down processes (e.g., Way, Creswell, Eisenberger, & Lieberman, 2010; Westbrook et al., in press) suggesting that mindfulness may be operating on bottom-up or afferent processes when it comes to craving.

Seeking to understand the role of top-down executive cognitive control and other bottom-up brain functions in response to meditation has led to an increase in neurobiological investigations of mindfulness meditation and other forms of meditation in recent years (see Chiesa & Serretti, 2010; Hölzel et al., 2011a; Lutz, Slagter, Dunne, & Davidson, 2008; Rubia, 2009). As reviewed in more detail below, there is increasing evidence that both novice mindfulness practitioners (e.g., Farb et al., 2010; Kilpatrick et al., 2011; Tang et al., 2010) and experienced mindfulness practitioners (e.g., Luders, Toga, Lepore, & Gaser, 2009; Lutz et al., 2004) show structural and functional neurobiological differences, in comparison to non-meditators. Furthermore, longitudinal investigations conducted from pre- to post-meditation training have found that mindfulness meditation, and mental training more generally (e.g., Hölzel et al., 2011b; Lutz, Slagter, Rawling, Francis, Greischar, & Davidson, 2009; Slagter, Davidson, & Lutz, 2011), is associated with significant changes in brain structure and functioning.

The goal of the current review is to propose hypothesized brain mechanisms that may underlie the effectiveness of MBRP. Our review builds on two recent reviews: one on the neural mechanisms of mindfulness meditation (Hölzel et al., 2011a) and the other on the neuroscience of treatments for addiction (Potenza et al., 2011). Our review is unique from these prior reviews in that we propose neurobiological mechanisms of a specific manualized and empirically-supported mindfulness-based treatment for substance use disorders. First, we present an overview of recent data supporting the efficacy of MBRP, and of behavioral data from studies of MBRP that provide evidence in support of the hypothesized bottom-up and top-down brain mechanisms that may underlie the effectiveness of MBRP in the treatment of addictive behaviors. Second, we focus on the neurobiological correlates of addiction, addictive behavior relapse, craving, negative affect, and mindfulness meditation, with a specific focus on neuroimaging studies that have examined brain structure and function before and/or after mindfulness meditation. Our review concludes with suggestions for future research.

Mindfulness-Based Relapse Prevention: Efficacy and Mechanisms of Change

As reviewed by Zgierska and colleagues (2009), four independent studies have evaluated the effectiveness of MBRP, or a modified MBRP protocol, in the treatment of substance use disorders. Individuals who received these treatments reported reduced substance use or related improvements, such as reductions in craving and reduced reactivity to substance use cues (Bowen et al., 2009; Brewer et al., 2009; Vieten, Astin, Buscemi, & Galloway, 2010; Zgierska et al., 2008; see Bowen, Witkiewitz, Chawla, & Grow, 2011 for a review).

In the largest controlled trial of mindfulness-based treatment for substance abuse disorders conducted to date, Bowen and colleagues (2009) present pilot efficacy data on MBRP delivered as an aftercare program following inpatient and intensive outpatient treatment. Substance use outcomes were assessed up to four months following aftercare treatment among participants randomly assigned to either eight weeks of MBRP ($n = 93$) or treatment-as-usual (TAU; $n = 75$). The TAU condition was the standard aftercare treatment provided by the community treatment program, which included psychoeducation, 12-step, and relapse prevention groups. Of the 168 participants randomized to treatment, 133 (79%) completed a postintervention survey and the treatment retention rates did not significantly differ by treatment condition (MBRP: 82.7%; TAU: 74.7%). Repeated measures analyses revealed significant treatment effects on alcohol and other drug use two months following treatment, with participants in the MBRP group using alcohol and other drugs at rates averaging five times lower than participants in the TAU group. Compared to TAU, MBRP participants also reported significant increases in mindful awareness, acceptance, and decreases in

experiential avoidance. Finally, the MBRP group displayed significant decreases in self-reported craving over the 4-month follow-up period, whereas the TAU group did not evince a significant decrease in craving.

Witkiewitz and Bowen (2010) conducted secondary analyses of these data to assess the influence of group membership (MBRP vs. TAU) on the strength of the association between negative affect and craving in the prediction of posttreatment substance use. Results indicated that participation in the MBRP group attenuated the association between self-reported depression scores and self-reported craving, and craving significantly mediated the relation between treatment assignment and days of alcohol or drug use following treatment. In addition, the relation between depression scores and posttreatment alcohol and other drug use days was mediated by craving among TAU participants, but not among the MBRP group. This moderation effect was consistent with the purpose and hypothesized mechanisms of MBRP. Specifically, the mindfulness practices in MBRP were designed to help clients experience challenging situations, including negative emotional states, without automatically reacting, thereby effectively altering the conditioned response of craving in the presence of negative affect. Given that craving did not mediate the effect of negative affect on use in the MBRP group, it is reasonable to hypothesize differences in bottom-up and top-down neurobiological functioning in the craving circuits between treatment groups, which we discuss in more detail below. Additional analyses of the same data revealed that differences in craving between the MBRP and TAU groups at the end of treatment were significantly mediated by self-reported mindful acceptance, awareness, and nonjudgment (Witkiewitz, Bowen, Douglas, & Hsu, in press). In other words, the reductions in craving among individuals who received MBRP could be partially explained by greater mindful acceptance, awareness, and nonjudgment among those who received MBRP, in comparison to TAU. Together, these analyses (Witkiewitz & Bowen, 2010; Witkiewitz et al., in press) suggest that MBRP might be effective in part by reducing the subjective experience of craving potentially via changes in present moment awareness, increased non-reactivity to salient craving cues by practicing acceptance (accepting the craving state) and nonjudgment (being non-critical of craving; Witkiewitz et al., in press), and by changing the way individuals respond to negative affect (Witkiewitz & Bowen, 2010). Although these changes have been observed at the level of self-reported behavior, it is hypothesized that the effects of MBRP may be observable at a neurobiological level (as outlined in Table 1), via both top-down and bottom-up processes.

Neurobiology of Addiction

Numerous studies have identified key bottom-up and top-down processes involved in the development and maintenance of addictive behaviors (see Koob & Le Moal, 2005; Kuhn & Koob, 2010; Redish, Jensen, & Johnson, 2008). Neuroimaging studies have largely focused on two interconnected systems: the mesolimbic and the mesocortical systems, which together comprise the mesocorticolimbic system known as the brain reward system (also known as the pleasure circuit). Regions within this system include the ventral tegmental area (VTA), the ventral striatum (including the nucleus accumbens), amygdala, and the medial prefrontal cortex (Feltenstein & See, 2008). While the neuropharmacological profiles of drugs of abuse are varied, they all share in common their ability to affect the nucleus accumbens, which is associated with reward-related processing (Di Chiara et al., 2004). Subsequent neuroadaptations underlie compulsive drug seeking behaviors associated with abuse. For example, with repeated substance use, VTA input to the dorsal striatum is activated (Kauer & Malenka, 2007). Of particular interest within the dorsal striatum are the caudate nucleus and the putamen known for their roles in reward-based learning. This pathway from VTA to the dorsal striatum is often referred to as the habit circuit because of its vital role in conditioned learning.

It is generally acknowledged that alterations within both the pleasure and habit circuits are needed to explain addictive behavior (Koob, 2008; Volkow, Fowler, & Wang, 2003; Volkow, Wang, Fowler, Tomasi, & Telang, 2011). Volkow and colleagues (2011) offer that compulsive drug seeking and addiction is likely the result of bottom-up and top-down disruptions in the reward system as a whole, interacting with deficits in motivation, drive, conditioning, and inhibitory control aspects of executive functioning as coordinated by the prefrontal cortex (PFC; for overview of executive functions more generally see Cohen (2001) and Suchy (2009), and for an overview of these executive functions relevant to addiction see Feltenstein & See, 2008).

There is consistent evidence across multiple drugs of abuse that PFC dysfunction is associated with abuse, and severity of drug use is correlated with top-down PFC dysfunction, including lack of inhibitory control and poor decision-making (for a review see Feil et al., 2010). It has been noted that mindfulness meditation may be one method for targeting the disruptions in neural systems affected by addiction in order to prevent substance use relapse and support positive behavior change (Brewer, Bowen, Smith, Marlatt, & Potenza, 2010; Potenza et al., 2011). In Table 2, we list numerous aspects of addiction (e.g., reward, conditioned learning/memory, motivation, stress responses, interoception, and executive control), which have been associated with activity in specific neural circuits or brain areas, along with hypothesized targets in mindfulness-based treatments for addiction. The question of interest is whether MBRP impacts these hypothesized targets in such a way as to prevent addictive behavior relapse.

Neurobiology of Relapse

Numerous reviews on the neurobiology of relapse exist in both animal and human models (e.g., Brown & Lawrence, 2009; Heinz et al., 2008; Sinha & Li, 2007; Steketee & Kalivas, 2011; Stewart, 2008; Weiss, 2005). Our review will focus on recent research investigating the structural and functional neurobiological changes associated with relapse and craving.

Brain structure

Durazzo and colleagues have conducted numerous studies examining brain morphology and cortical perfusion among individuals who relapsed to alcohol use following treatment for alcohol dependence (e.g., Cardenas et al., 2011; Durazzo et al., 2011). In these studies, brain structure during treatment was used to prospectively predict relapse following treatment, thus longitudinal structural changes before and after treatment were not assessed. Most recently, a study by Cardenas and colleagues (2011) compared individuals who “relapsed” (defined as any alcohol use), in comparison to those who “abstained” (defined as no alcohol consumption) for approximately 8 months following entry to alcohol treatment using deformation-based morphometry. Individuals who relapsed had significantly smaller white matter volumes in the bilateral orbitofrontal cortex and smaller white matter and gray matter volumes extending into the posterior temporal-parietal region. A prior study by Durazzo and colleagues (2011), found that relapsers had significantly lower total volume in the brain reward system than abstainers, although it is still unclear whether brain volume serves as a neurobiological marker or trait for identifying individuals most at risk for relapse.

Rando and colleagues (2011) also identified morphological differences associated with relapse among alcohol dependent patients. Using voxel-based morphometry (VBM), the authors identified two regional clusters, medial frontal and parietal-occipital, in which small gray matter volumes were significantly associated with a shorter amount of time to any drinking, and with a shorter amount of time to heavy drinking. The authors concluded that volume deficits in these regions could potentially explain deficits in cognitive and impulse control, as well as difficulty in inhibiting prepotent responses to environmental alcohol cues.

It is important to note that studies of brain structure are correlational and the findings can only be evaluated within the specific context examined in the particular study. That is to say, the findings from these studies (Cardenas et al., 2011; Durazzo et al., 2011; Rando et al., 2011) are strictly relative to the samples obtained, and it is not always the case that volumetric decreases can be directly linked to behavioral deficits or that volumetric increases indicate better functioning (see Nuñez, Rousotte, & Sowell, 2011 for a discussion of this issue).

Brain function

As craving and negative affect are key predictors of relapse, the brain activity patterns associated with relapse have been probed using paradigms that expose participants to cues that induce either craving or stress (i.e., negative affect). Considerable research has identified both cortical and subcortical areas of neural activation during craving (both drug cue-induced and stress-induced). The cortical areas include: the dorsolateral PFC (dlPFC) known for its role in working memory, top-down cognitive control over behavior, and executive cognitive functioning; the ventral PFC including both the ventromedial area and the orbitofrontal cortex (OFC) which are involved in evaluation and inhibition of behavior; and the cingulate cortex including the anterior portion (part of the superomedial PFC), responsible for sustained attention, motivation, and conflict monitoring (i.e., processing of distracting events). Subcortical structures implicated in craving include the ventral striatum (nucleus accumbens) which is a primary target of the VTA as part of the pleasure circuit and the amygdala known for its role in stress and emotion processing (Heinz et al., 2008; Naqvi& Bechara, 2010; Sinha & Li, 2007; Wilson, Sayette, & Fiez, 2004). Two recent meta-analyses of drug-cue activation and craving assessed using functional magnetic resonance imaging (fMRI) found that cue-related Blood Oxygen Level Dependent (BOLD) signal activation was consistently identified in the OFC, ventral striatum, and the amygdala (Chase, Eickhoff, Laird, & Hogarth, 2011). Moreover, the ventral striatum and anterior cingulate cortex (ACC) signals were associated with drug-cue reactivity and self-reported craving for nicotine, alcohol, and cocaine (Kühn & Gallinat, 2011).

Two recent fMRI studies of cue reactivity and craving are particularly relevant to the hypothesized mechanisms of MBRP (Kober et al., 2010; Westbrook et al., in press). Kober and colleagues (2010) used a cognitive regulation of craving task that consisted of exposure to smoking and food cue images and (1) bringing one's attention to the "immediate feelings associated with smoking or overeating" (p. 14812); or (2) directing one's attention toward the long-term consequences of smoking or overeating. All participants were trained in both attention tasks and instructed to practice each attention task while being exposed to the smoking and food cues during functional imaging. The authors found that individuals who were told to attend to the long-term consequences of smoking and overeating self-reported significantly less craving. Imaging results indicated significant dlPFC activity (as measured by BOLD) and regulation-related decreases in craving was mediated by ventral striatum activity. These results suggest that during craving, recruitment of dorsolateral PFC regions may temper craving in a top-down fashion by acting on craving-related brain regions contributing to the pleasure circuit.

Kober and colleagues (2010) explicitly instructed clients to bring attention to the feelings associated with craving, but did not provide instruction on how to cope with those feelings. This is an important point; in MBRP, clients are specifically instructed to observe experiences of discomfort (including craving) and to approach them with a curious, accepting, and nonjudgmental stance. A recent study by Westbrook and colleagues (in press) provided instructions similar to those in MBRP within an fMRI cue reactivity experiment. Participants were instructed to attend to smoking picture cues in two separate conditions: (1) relax and look at the pictures; or (2) "mindfully attend" to the pictures by actively and

nonjudgmentally focusing on the thoughts, feelings, memories, and bodily sensations associated with the pictures. Participants self-reported significantly less craving and distress when they were instructed to attend mindfully to smoking images, compared to when they were instructed to relax and look at the pictures. Imaging results indicated that subgenual ACC, a region typically activated during craving, showed reduced activity during mindful attention of smoking images compared to looking at the images. Importantly the reduced activity of the subgenual ACC during mindful attention was not explained by increased activity of the PFC. Thus, neural reductions in reactivity to craving cues were observed without prefrontal top-down modulation of responses, supporting bottom-up changes. Furthermore, during mindful attention, there was significantly reduced functional connectivity between the subgenual ACC and other regions associated with craving, including the ventral striatum. These results suggest that nonjudgmental mindful attention to smoking cues may temper craving in a bottom-up fashion resulting in decreased activity in the subgenual ACC and by reducing functional coupling with other craving-related regions.

Westbrook and colleagues (in press) also found reduced functional connectivity between craving related regions (subgenual ACC and the bilateral insula) during mindful attention. The insula is associated with drug cue-induced activation in studies of cigarette, cocaine, alcohol, heroin, and marijuana craving (Filbey et al., 2009; see review by Naqvi & Bechara, 2010), which is particularly noteworthy given the well-known roles for the insula in viscersomatics including bottom-up processing of salient stimuli. As such, it has been proposed that the insula may contribute to the somatic, interoceptive processes that result in the subjective experience of drug craving (Craig, 2009; Garavan, 2010). Recently, Naqvi and Bechara (2010) proposed that the insula influences pleasurable bottom-up interoceptive effects of drug-taking, the representation of drug-taking as pleasurable in conscious memory, and top-down decision-making when confronted with the decision to use (invoking pleasurable memories) against the decision to not use (invoking negative interoceptive consequences of drug use). Thus, the pleasurable memories of drug use (which include the immediacy of the reward) outweigh the negative consequences of drug use (which tend to be delayed), ultimately tipping the impulsivity scale towards use.

More generally, research suggests that the insula plays a role in self-awareness and experiences that occur within the body in response to various stimuli, including emotional stimuli (Craig, 2009; Critchley et al., 2004; Damasio, 2000). The posterior insula provides the interoceptive representation of physiological sensations and the anterior insula is activated during subjective experiences of bodily sensations (e.g., craving) and emotions (e.g., negative affect; Craig, 2009; Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). Results from resting state connectivity analyses indicated that the anterior insula is functionally connected to the ACC and mid-cingulate cortex, which together may form an emotional salience monitoring system (Taylor, Seminowicz, & Davis, 2009). As such, Naqvi and Bechara (2010) theorize that the insula may modulate the associations between brain regions activated during craving such as the ACC, amygdala, and the dorsomedial and ventromedial PFC. Naqvi and Bechara further theorize that this modulation may ultimately affect the activation of the striatum and thus the motivation for drug-seeking behavior, which may lead to a habitual stimulus-response cycle. Similarly, Goldstein and colleagues (2009) suggest that interoceptive awareness of the subjective experiences of drug craving (involving the insula), disadvantageous choice selection (involving the ACC), and the automaticity of drug seeking behavior in the presence of drug-cues or stimuli (involving the dorsal striatum) may explain lack of insight among individuals who relapse to substance use. One of the primary goals of a mindfulness approach is to disrupt this type of habitual stimulus-response cycle by increasing self-awareness and engaging approach versus avoidance systems in relation to triggering experiences. Rather than a habitual avoidance-based behavior (e.g., substance use) following exposure to an aversive stimuli (e.g., negative affect), by which substance use

is reinforced, clients are repeatedly exposed to challenging external and internal stimuli (e.g., substance cues) while remaining engaged with their experience. Over time, it is hypothesized that this repeated exposure without responding may reduce cue reactivity (Drummond, 1995). Based on the studies described above, we hypothesize that MBRP may be impacting the neurobiology of the habitual stimulus-response cycle from the top-down (as shown by Kober et al., 2010) and the bottom-up (as shown by Westbrook et al., in press).

Cognitive-Behavioral Interventions Targeting the Neurobiology of Addiction

Although many studies to date have focused on pharmacological intervention (e.g., Koob, 2000), recent research has found that targeting specific neurobiological dysfunction using cognitive and behavioral treatment techniques may also prove valuable in the prevention of relapse (Devito et al., 2012; Feldstein Ewing, Filbey, Sabbineni, Chandler, & Hutchison, 2011; Goldstein et al., 2009; Naqvi & Bechara, 2010; Potenza, Sofuoglu, Carroll, & Rounsaville, 2011; Volkow et al., 2010). Potenza and colleagues (2011) provided a review of neural mechanisms that might underlie pharmacological and behavioral treatments for addiction. The authors suggest that behavioral treatments may be most effective at changing prefrontal cortical and executive functioning (e.g., top-down processes), while pharmacological interventions appear to be most effective in changing striatal reward pathways (e.g., bottom-up processes).

Consistent with these hypotheses, Volkow and colleagues (2010) trained individuals with cocaine use disorders to purposively inhibit cocaine craving responses, and found (using positron emission tomography) that the active cognitive inhibition of cocaine craving was associated with decreased metabolic activity in the nucleus accumbens and the right medial orbitofrontal cortex, in comparison to a group that did not attempt to inhibit cocaine craving. The authors concluded that cognitive interventions designed to strengthen inhibitory control and decrease impulsive drug seeking in response to drug-related stimuli may be beneficial in the treatment of addiction.

In another study, Janes and colleagues (2010) used fMRI to examine responses to smoking-related versus neutral images among 21 female current smokers, and then conducted follow-up surveys of their quit status during 8 weeks of a behavioral and pharmacological smoking cessation intervention. Those who smoked any cigarettes during the 8 weeks of treatment (n=9) showed increased BOLD response to smoking cues when assessed prior to quitting in the insula, amygdala, ACC, prefrontal cortex and numerous other areas. Functional connectivity analyses revealed decreased functional connectivity between prefrontal cortical regions and both the ACC and the insula, suggesting that those who smoked a cigarette might have had decreased top-down control with greater bottom-up interoceptive awareness of smoking-related cues. This thinking aligns with that of Goldstein and colleagues (2009; also see Naqvi & Bechara, 2010) who proposed that cognitive training to improve self-awareness and reduce attentional bias to drug cues (as mediated by the insula) may help prevent relapse. We hypothesize that a mindfulness-based treatment may be ideal for targeting each of these areas.

Neurobiology of Mindfulness Meditation

Contemplative neuroscience is an emerging field encompassing research on the neurobiology of mindfulness meditation and other contemplative practices (Lutz, Dunne, & Davidson, 2007; Wallace, 2007). Our review focuses specifically on mindfulness meditation as it is incorporated into MBRP, based on practices from the Vipassana tradition, and largely based on the related treatments of MBSR (Kabat-Zinn, 1990) and MBCT (Segal, et al.,

2002). We focus our review on studies that have focused on either brain structure or functional changes in response to mindfulness practice. For a general discussion on the mechanisms of mindfulness meditation, we direct the reader to a recent review by Hölzel and colleagues (2011a).

Brain structure

Ott, Hölzel, and Vaitl (2011) provided a narrative review of five recent morphometric studies that compared experienced meditators with control groups of non-meditators, with three of the studies examining the brain structure of experienced practitioners of Vipassana (Hölzel et al., 2008; Luders et al., 2009) and insight meditation (Lazar et al., 2005). Lazar and colleagues (2005) found greater cortical thickness in the right anterior insula and the PFC of highly experienced insight meditation practitioners (average 9 years of practice) in comparison to control participants without meditation or yoga experience who were matched for sex, age, race, and years of education. Importantly, the study did not find significant differences in mean thickness across the entire cortex, suggesting that meditators had greater cortical thickness in specific regions (e.g., insula, PFC). While the methods employed in this study are anatomical in nature, Lazar and colleagues (2005) suggest that greater cortical thickness in the insula may be relevant to bottom-up interoception including awareness of bodily sensations and emotions (and as part of the putative emotional salience network with the ACC), while increased cortical thickness in the prefrontal cortex is likely related to top-down executive control.

Extending the work of Lazar and colleagues (2005), Hölzel and colleagues (2008) used VBM to study anatomical differences between 20 non-meditators, who were matched for sex, age, education and handedness with 20 experienced meditators with an average of 8.6 years of meditation practice. Similar to Lazar and colleagues, Hölzel and colleagues (2008) identified greater gray matter concentration in the right anterior insula among experienced meditators in comparison to non-meditators. Additionally, VBM identified greater gray matter concentration in the left inferior temporal gyrus, and the right hippocampus among experienced meditators in comparison to non-meditators. Similarly, Luders and colleagues (2009) found greater gray matter volume in the left inferior temporal gyrus and in the right hippocampus among 22 experienced meditators with an average of 24.18 years of meditation (range = 5 to 46 years) in comparison to 22 non-meditators, who were matched for age and gender. The right orbitofrontal cortex (OFC) also revealed greater volume in meditators compared to non-meditators, which is noteworthy given the top-down roles of the OFC in appraisal of emotional stimuli and behavioral inhibition. The authors concluded that greater volume in the right OFC might “allow disengagement from automatic thoughts and habits, and therefore permit consideration of options that would be more congruent with needs and values” (p. 676; Luders et al., 2009).

More recently, Hölzel and colleagues (2011b) conducted a longitudinal VBM study to examine changes in gray matter concentration following participation in an 8-week MBSR course. In this study, Hölzel and colleagues recruited 16 psychologically and physically healthy participants upon entry into an 8-week MBSR course who were compared to a waitlist control group. Region of interest analyses identified pre- to post-MBSR increases in gray matter concentration in the left hippocampus in the MBSR group that were not observed in the control group. Whole-brain analyses identified significantly increased gray matter concentration in the hippocampus, posterior cingulate, left temporoparietal junction, and cerebellum among MBSR participants, which may be related to learning and memory, as well as emotion regulation, and perspective taking (Hölzel et al., 2011b). These findings are particularly interesting given the short duration of meditation training in the MBSR course, which suggests that the brain may be highly plastic even in the context of minimal exposure to mindfulness meditation.

A comparison across these three studies indicated that the pattern of effect sizes for gray matter volume differences between meditators and non-meditators maps on to the average amount of meditation practice among participants in each of the studies (Luders et al. (2009) 24.18 years; Hölzel et al. (2008) 8.6 years; Hölzel et al. (2011b) 8 weeks) and would suggest that more years of practice are associated with greater volume differences. Consistent with this idea, Hölzel et al. (2008) found that gray matter concentration in the left inferior temporal gyrus, the right insula, and the medial OFC was correlated with hours of meditation practice. Yet, Luders et al. (2009) did not find a significant correlation between gray matter volume and meditation years, and Hölzel et al. (2011b) did not find significant associations between changes in the identified gray matter concentrations and homework practice or change in mindfulness scores. These disparities suggest that multiple factors associated with practice may affect plasticity; however, none of the studies examined the associations among regional gray matter concentration, mindfulness practice, and other indices of top-down or bottom-up cognitive functioning. Also, as noted above, volumetric studies are limited in that changes in function cannot be directly ascertained from volumetric assessment; in other words greater gray matter concentration does not necessarily imply improved functioning.

Brain function

Over the past 10 years, there has been a steady increase in functional brain imaging research on experienced meditation practitioners, meditative states, and the effects of meditation training on brain functioning in novice meditators. Results from the majority of studies suggest that meditation experience and meditation practice are associated with different functional responses to environmental stimuli, pain, emotional responding, and present-moment versus self-focused attention (e.g., Farb et al., 2010; Orme-Johnson, Schneider, Son, Nidich, & Cho, 2006; Taylor et al., 2011). (For a more extensive review see Cahn & Polich, 2006; Chiesa & Malinowski, 2011; Hölzel et al., 2011a; Rubia, 2009; Slagter, Davidson, & Lutz, 2011).

One of the earliest functional imaging studies compared self-selected Vipassana meditators (average 8 years of practice) with non-meditators matched for sex, age, education, and handedness (Hölzel et al., 2007). The effect of a one-minute breath awareness exercise on the BOLD signal was assessed with fMRI. Results revealed stronger activity in the medial PFC (mPFC) and the most rostral aspect of the anterior cingulate cortex (rACC) during meditation in meditators compared to non-meditators. Given the roles of the mPFC and the rACC in emotional processing and regulation, the observed pattern of activation suggests that meditation may contribute to more cortical processing of emotion and potential top-down emotion regulation. However, the cross-sectional nature of the research limits the ability to determine whether meditators had greater cortical processing of emotion prior to engaging in meditation practice.

More recent research suggests that mindfulness meditation contributes to subcortical processing of emotion as well. For example, Taylor and colleagues (2011) found that mindfulness practice was associated with deactivation of the left amygdala while viewing either positive or negative emotional stimuli among a group of individuals who practiced meditation for a week prior to the study, whereas experienced meditators did not show such deactivation. Both the inexperienced and experienced meditators rated the emotional stimuli as less intense during mindfulness practice, suggesting that mindfulness may be associated with improved bottom-up emotion regulation, however the neural mechanisms involved in regulation varied according to level of experience. These results, combined with the finding that effect sizes for gray matter volume differences between meditators and non-meditators increased with amount of practice (on average; see comment above regarding the findings from Hölzel et al., 2008, 2011b; Luders et al., 2009), suggest it may be important for future

longitudinal studies to track the changes in brain structure as an individual gains more meditation experience. Given that none of the aforementioned studies had long term follow-ups and only one found an association between practice hours and gray matter volume difference between meditators and non-meditators (Hölzel et al., 2008), it is important to discern whether meditation practice explains the observed differences across these studies, or whether these differences existed prior to the individuals' initiation of practice, and may have led to their increased practice.

Functional connectivity studies have also identified numerous differences among experienced meditators in comparison to non-meditators or individuals who recently began training in meditation. Not surprisingly, given the intention in meditation to maintain awareness and attention, meditation has been associated with enhanced attentional focus and stability (Kilpatrick et al., 2011; Lutz et al., 2009), greater attention regulation (Brefczynski-Lewis, Lutz, Schaefer, Levinson, & Davidson, 2007; Jha, Krompinger, & Baime, 2007), and enhanced sensory processing and perceptual discrimination (Cahn, Delorme, & Polich, 2010; Kilpatrick et al., 2011; MacLean et al., 2010). Imaging research has also begun to illuminate differences in circuit activation by demonstrating either coupling (i.e., simultaneous activation) or decoupling (i.e., disconnected activation) of associated brain regions (e.g., attentional networks, the emotional salience monitoring network, anterior cingulate and medial frontal cortices) after one month of meditation training (Xue, Tang, & Posner, 2011) and among experienced meditators (Brewer, Worhunsky, Gray, Tang, Weber, & Kober, 2011; Hasenkamp & Barsalou, 2012; Hölzel et al., 2007). Farb and colleagues (2007) found that experiential focused meditation (i.e., focus on current experience without attaching meaning), in comparison to a narrative focus (i.e., cognitive elaboration of thoughts), was associated with a decoupling of the right insula and mPFC with a shift toward greater activity in the dlPFC among individuals who attended an 8-week course in meditation. In contrast, non-meditators evinced a strong coupling of the insula with the mPFC (Farb et al., 2007). The authors concluded that the uncoupling of the mPFC among meditators reflects a tendency toward self-detachment from interoceptive cues, while the increased BOLD signal in the dlPFC may represent enhanced present moment awareness. The greater recruitment of dlPFC in meditators is noteworthy given the roles of this region in top-down emotion regulation processes (Lieberman et al., 2007). Studies on functional connectivity have found altered connectivity between meditators and non-meditators during a "resting state," suggesting that connectivity changes are maintained outside of meditative states (Brewer et al., 2011; Hasenkamp & Barsalou, 2012; Xue et al., 2011). As such, MBRP may help individuals detach from craving and, at the same time, experience greater dlPFC functioning with concomitant enhanced present moment awareness and improved top-down emotion regulation.

At the center of the practices from numerous meditation traditions, and at the heart of MBRP, is a focus on present moment awareness. This often involves shifting one's attention away from internal dialogue and rumination to sensory experiences in the present moment. A recent study by Hasenkamp and colleagues (2012) examined neural activity using fMRI during fluctuating cognitive states of a proposed cognitive cycle that was defined by mind wandering, awareness of the mind wandering, shifting attention, and sustained attention. In this paradigm meditation on the breath was the intended task and the target of sustained attention. Experienced meditators were instructed to pay attention to their breath while in the scanner, and to press a button when they became aware of their mind wandering. When participants indicated awareness of mind wandering, there were robust activations in the anterior insula and dorsal ACC. The anterior insula and dorsal ACC were highly correlated, suggesting neural integration. This integration has been associated with various top-down and bottom-up processes including emotional awareness, goal directed behavior, cognitive-control (including conflict monitoring and error detection), self-regulation, and the detection

of salient external and internal events (Craig, 2009; Seeley et al., 2007). These findings, in conjunction with those of Farb and colleagues (2007), who found a decoupling of the insula with the mPFC and heightened BOLD signal in the dlPFC during meditation, provide evidence of specific activation patterns within the prefrontal and insula/ACC circuitry that may reflect present moment awareness. Given that a primary focus of MBRP is increasing present moment awareness, it follows that those who practice MBRP might evince changes in the PFC and insula/ACC circuitry that corresponds with their level of present moment awareness.

Hypothesized Mechanisms of Neurobiological Change During and Following MBRP

Drawing from the literature reviewed here, there are several plausible neurobiological mechanisms by which MBRP may be effective at reducing craving, negative affect, and relapse. The primary hypothesis guiding this review and integration of the literature is that mindfulness training in combination with cognitive behavioral skills training, as part of the MBRP curriculum, predicts changes in numerous brain systems and pathways that may reverse, repair, or compensate for the neuroadaptive changes associated with the development of addiction.

Hypothesized structural changes

Two brain regions have emerged across studies that demonstrate structural changes in response to mindfulness meditation: the hippocampus and the insula. Identifying these as regions of interest, Hölzel and colleagues (2010) demonstrated that an 8-week MBSR course resulted in increased gray matter concentration in the hippocampus, the cerebellum, and cortical regions implicated in emotion regulation and higher cognitive processes involved in body awareness and processing of one's sense of self. We hypothesize that an 8-week MBRP course would result in similar pre-post changes, although structural deficiencies among individuals with addictive disorders may affect the magnitude of such changes.

It is noteworthy that none of the prefrontal regions implicated in mindfulness effects via functional imaging as reviewed here demonstrated structural changes in response to the 8-week MBSR course in the study by Hölzel and colleagues (2010). Yet, studies investigating long-term practitioners did evince prefrontal differences (Lazar et al., 2005, Hölzel et al., 2008, Luders et al., 2009) as well as insular differences (Lazar et al., 2005, Hölzel et al., 2008). This disparity seems to suggest a temporal interplay such that more practice over time may be needed to significantly increase gray matter. Increased gray matter in brain regions implicated in top-down executive functions (PFC) as well as emotional saliency (insula) has the potential to repair or compensate for addiction induced gray matter loss. To test this hypothesis, the effects of longer treatment courses on regional brain matter change, as well as functional change, are needed.

Hypothesized functional changes

Changes in the insula and hippocampus as observed in the studies cited here suggested that such activation due to mindfulness meditation may cause a shift from recall processing of past associations that may be "viscerally embedded" within insular circuitry to present moment awareness and experiential processing. Concomitant activity in the ACC and PFC could allow one to filter incoming information and inhibit inappropriate emotional or behavioral responses. To the extent that mindfulness training may improve functional connectivity of the ACC with the PFC (Xue et al., 2011), as well as improve top-down cognitive control of emotions and greater coupling of the insula with the dlPFC (Farb et al., 2007), it follows that individuals who receive MBRP may be more likely to exhibit greater

top-down cognitive and inhibitory control. As noted by Goldstein and colleagues (2009), "interventions to strengthen ACC activity or interconnectivity may be beneficial to enhancing top-down monitoring and emotion regulation as a strategy to reduce impulsive and compulsive behavior in addiction" (p. 9453). Targeting the dlPFC, ACC and related circuits as regions of interest, along with functional connectivity analyses in fMRI, investigations of emotion regulation among those treated with MBRP would be one way to test the hypothesized effects of MBRP on top-down cognitive control and bottom-up reactivity to emotionally laden stimuli.

Two prior imaging studies have found that cognitive regulation of craving was associated with greater top-down monitoring (Kober et al., 2010; Volkow et al., 2010) as indicated by increased activity in frontal regions (dlPFC, Kober et al., 2010; right inferior frontal cortex) and decreased activity in striatal regions. Still, neither Kober and colleagues or Volkow and colleagues studied participants treated with MBRP and the cognitive strategies used in the fMRI paradigms of each study differ somewhat from MBRP strategies for focusing attention and regulating craving. The task used by Volkow and colleagues (2010) included relaxation, ignoring thoughts of craving, or focused distraction from craving. Interestingly, one of the first skills practiced in MBRP is focused attention on the breath, which often helps people feel more relaxed and focused on present experience (Brown, Davis, LaRocco, & Strasburger, 2010). However, the skills taught in MBRP stand in stark contrast to avoidance, thought suppression, and distraction. Given recent evidence that mindfulness may be more effective than thought suppression or distraction in reducing negative affect (Huffziger & Kuehner, 2009; Rogojanski, Vettese, & Antony, 2011) and substance use (Bowen & Marlatt, 2009), we expect MBRP would exert stronger top-down neural regulation over the craving circuit with more varied neural responses possibly in the ACC/insular emotional saliency circuitry in response to a craving regulation task during imaging than those exhibited by participants in the Volkow and colleagues (2010) study.

The cognitive strategies implemented in the regulation of craving task used by Kober and colleagues (2010) was somewhat akin to the teachings of MBRP (e.g., attending to experience of craving) thus we would expect our findings to align with Kober et al. in terms of top-down inhibition over craving circuits. We may find stronger effects given the 8-week nature or our MBRP course. Hölzel and colleagues (2011b) suggest that it may be the case that novice meditators require more cognitive control to actively change their emotional responses (i.e., re-appraisal), whereas more advanced meditators might be more skilled in bottom-up regulation of emotions without requiring top-down executive control of their response. If this were the case, we would expect individuals practicing mindfulness for a longer amount of time would regulate craving with more bottom-up than top-down activation. However, recent findings of Westbrook and colleagues (in press) show that non-meditators instructed to mindfully attend to craving had decreased craving reactivity from the bottom-up, suggesting that even those individuals with minimal experience with MBRP may benefit from the training.

It has been hypothesized that lack of self-awareness during experiences of negative affect and craving may increase vulnerability to relapse (Goldstein et al., 2010). Further, it is proposed that mindfulness practices might help prevent relapse by increasing self-awareness (e.g., Jang et al., 2010) and acting with awareness (Bowen et al., 2009), and by reducing reactivity to drug cues (e.g., Garland, Gaylor, Boettiger, & Howard, 2010) and negative affective states (e.g., Witkiewitz & Bowen, 2010). Changes to the insula and the connectivity between the insula and frontal cortical networks (including the ACC) during meditation training could contribute to both the increases in awareness and the reductions in the subjective experiences of craving reported by individuals following MBRP. Further, if participation in MBRP increases gray matter volume in the PFC (e.g, Lazar et al., 2005),

then the ability to disengage from the experience of craving as an automatic response to drug cues and related stimuli (e.g., negative moods) might allow individuals to make choices that are more congruent with maintaining treatment gains.

The extent to which mindfulness practice in MBRP decreases automatic responses to craving cues and negative affect may be reflected in part in hemodynamic responses to stress. In preliminary analyses of an ongoing MBRP study, we found significantly less heart rate reactivity and increased high-frequency heart rate variability (HF-HRV), a measure of cardiac vagal control and an indicator of self-regulation (Thayer & Lane, 2009), in response to a laboratory stressor among those treated with MBRP compared to those in treatment as usual (unpublished data). Increases in phasic HF-HRV during stress has been observed with mindfulness and is interpreted as a more adaptive, self-regulatory response to stress (e.g., Ditto, Eclache, & Goldman, 2006;Tang, et al., 2007). Thus, while the HRV data reveal that from the bottom-up there is a shift to a more favorable (less reactive) stress response in the MBRP group, the concomitant increase in HF-HRV suggests top-down processes are also being recruited to manage the stress response post-MBRP (see Thayer & Lane, 2000). This top-down management may further be reflected in the meta-cognitive coping strategies taught in MBRP aimed at taming automatic processes that promote relapse (Bowen et al., 2010). Specifically, MBRP practices that teach present moment awareness seek to reduce “automatic pilot” and subsequent behaviors that go unchecked by prefrontal top-down control mechanisms.

To summarize, in this paper we have called specific attention to interactions between prefrontal executive control systems and the ventral striatal pleasure circuitry as well as the dorsal striatal habit circuitry suggesting that relapse may be related to a functional deficiency in these systems, and that craving cues and negative affect generated by stress or other factors may exert more deleterious effects given this deficiency. Brain plasticity in response to mindfulness practices may positively affect brain recovery with functional benefits that may reverse, repair, or compensate for detrimental neuroadaptive changes brought on by addiction. Based on our review of relevant studies, as well as our own clinical research, we hypothesize that MBRP is affecting both bottom-up and top-down process changes among individuals with substance use disorders. Preliminary evidence from studies examining mindfulness training for substance use disorders, alongside our own preliminary data from MBRP participants, suggests that mindfulness practice influences bottom-up responding, particularly by reducing responsivity to stressors (unpublished data; Brewer et al., 2009) and by decreasing bottom-up reactivity to craving cues (Westbrook et al., in press). Changes in the stress response system, the emotional salience monitoring system (including insula/ACC circuitry and the amygdala), and automaticity of drug-seeking behavior (involving the striatum) may all contribute to changes in bottom-up responding following MBRP. Behavioral interventions for substance use disorders and mindfulness practices are associated with top-down changes in executive functioning, cognitive control, attention regulation, and emotion regulation (see reviews by Hölzel et al., 2011a; Potenza et al., 2011). Changes in inhibitory control, conflict monitoring, motivation, and decision making via the dlPFC, ventromedial PFC, OFC, hippocampus, ACC, and insula may all contribute to the changes in top-down monitoring following MBRP.

Limitations and Future Directions

Numerous limitations of the current review deserve mentioning. First, most trials of mindfulness meditation as a treatment for substance use disorders have been methodologically limited (Zgierska et al., 2009). Second, the published MBRP findings have been limited to the self-reported experiences of study participants and it is unclear to what

extent the self-reported changes in craving, negative affect, and relapse will be observed at the neurobiological level.

The neurobiological data reviewed herein was mostly from neuroimaging and psychophysiological studies, which introduce numerous scientific and methodological limitations. Nearly all of the studies presented in the current review relied on correlational data, which precludes any causal inferences. While numerous experimental procedures were employed in the reviewed studies it is still unclear to what extent mindfulness may *directly* influence the function or structure of relevant brain areas. For example, numerous studies assume that BOLD fMRI signal represents increased neuronal activation in a particular brain region, yet the properties of BOLD are not fully understood. Moreover, the fMRI signal observed by the research could be reflective of either excitation, inhibition, or some other neuronal process (Logothetis, 2008). It is important to consider that apparent differences in fMRI signal may be strongly related to drug-induced or meditation practice-induced changes that are downstream from the neural activity, such as vascular reactivity or cerebral blood volume (see Ianetti & Wise, 2007). Similarly, we have reviewed literature showing differences in brain volumes in meditators and non-meditators, as well as in individuals more or less susceptible to substance use relapse, and it has been shown that brain volume is associated with fMRI signal (Di, Kannurpatti, Rypma, & Biswal, in press). Thus, cue-induced or mindfulness-induced activations/deactivations could be partially explained by differences in brain volume. Likewise, as noted above, an increase in brain volumes observed across populations or over time does not necessarily reflect improvements in functioning. Multimodal studies that incorporate numerous methodologies could help ameliorate some of these problems, although these would still be associational studies. The development of human laboratory studies (Sinha, in press), animal models of mindfulness (see Matzel et al., 2011 for a description of an animal model of “attentional engagement”), and longitudinal randomized clinical trials that include pre- and post- multimodal imaging and psychophysiological assessments are all needed to test the hypothesized neurobiological mechanisms proposed in the current review.

Unpacking the brain-behavior mechanisms of change following mindfulness training will require research that addresses the ongoing debate on how to operationalize mindfulness, particularly as it relates to the treatment of addiction (see DiClemente, 2010). To advance our understanding of the neurobiology of mindfulness treatments, future research needs to focus on the development of objective or behavioral measures of mindfulness that could be incorporated into neurobiological research. While numerous self-report measures of mindfulness have been developed (see Baer, Smith, Hopkins, Krietemeyer & Toney, 2006), they tend to capture trait, rather than state, mindfulness. Also, as individuals develop mindfulness skills, they develop greater awareness of their wandering mind and may report lower levels of mindfulness than an individual who has lower meta-cognitive awareness. Behavioral measures of mind wandering (Davidson, 2010) or attentional control may be particularly useful (see review by Schooler et al., 2011). We hypothesize that behavioral measures may be more robustly associated with the underlying neurobiological mechanisms of MBRP than self-report measures.

It will also be important to examine whether neurobiological changes observed following MBRP are due to the formal meditation practice or whether other treatments that incorporate mindfulness (e.g., DBT) or other effective treatments for addiction (e.g., cognitive behavioral treatment) result in similar effects on brain structure and functioning. Given that mindfulness training appears to target both bottom-up and top-down processing, it would be interesting to study whether mindfulness training alone (without the cognitive behavioral components of MBRP) is associated with the same neurobiological changes as MBRP. It may also be useful to examine effects of MBRP on different types of negative affect (e.g.,

substance- vs. context-induced) and craving (e.g., aversion vs. reward driven; Gardner, 2011).

Similarly, it is unclear to whether there could be a temporal ordering of top-down and bottom-up changes following mindfulness training. Some data suggest that more meditation practice may be associated with greater bottom-up processing and less top-down regulation (Hölzel et al., 2011b), whereas other studies found that even novice meditators experienced reduced bottom-up reactivity without recruiting prefrontal regulatory regions (Westbrook et al., in press). Future research should examine whether mindfulness-induced changes in cognitive control (top-down) and craving-related (bottom-up) regions occur simultaneously or in a sequence (e.g., top-down changes precede bottom-up changes or vice versa).

Research that cuts across disciplines and integrates information across multiple levels of analysis (from brain to behavior) will be necessary to further elucidate mechanisms of behavior change following mindfulness-based treatments. The study of mechanisms of change and the application of neurobiological approaches to understanding mindfulness-based treatments is a promising new area of research, but there are also limitations. In addition to logistical barriers (e.g., scanning time, costs), researchers may have to contend with numerous potential limitations of neuroimaging for examining mechanisms of change, such as participant retention, potential intoxication, scanning contraindications, and the generalizability of responses in the scanner environment to real-world responses. Despite these challenges, an investigation of neurobiological changes associated with mindfulness-based treatment for relapse prevention among individuals with substance use disorders has potential to shed light on mechanisms by which the treatment is affecting behavioral outcomes in this population.

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Table 1

Hypothesized Mechanisms of Action in MBRP and Relevant Brain-Behavior Associations

Mechanism of Action	Proposed Process	Hypothesized Brain Areas Involved
Increased present moment awareness	Bottom-up processing of salient stimuli with or without top-down modulation of reactivity	Dorsolateral PFC, anterior cingulate cortex, ventral striatum, insula, amygdala
Improved attentional control	Top-down modulation of attention	PFC, anterior cingulate cortex
Greater self-regulation	Top-down improved inhibitory control	Medial PFC, orbitofrontal cortex, anterior cingulate cortex
Increased self-awareness	Bottom-up processing of salient stimuli	Anterior cingulate cortex, insula
Develop and implement new ways to approach discomfort	Top-down modulation of responses to discomfort and decision making	Ventromedial PFC, dorsal striatum, amygdala
Reduced reactivity to substance cues	Bottom-up reactivity	Anterior cingulate cortex, ventral striatum

Note. PFC = prefrontal cortex.

Table 2

Neurobiology of Addiction and Addictive Behavior Relapse as Potential Targets for Mindfulness Interventions

Neural Circuitry of Addiction	Associated Brain Areas	Target in Mindfulness Intervention
Reward (craving and pleasure circuitry)	Medial PFC, anterior cingulate cortex, nucleus accumbens, amygdala, ventral tegmental area	Increasing present moment awareness, sitting with discomfort
Conditioned learning and memory (habit circuitry)	Dorsolateral PFC, orbitofrontal cortex, dorsal striatum, amygdala, hippocampus, ventral tegmental area	Reduced reactivity to drug cues, sitting with discomfort without going on autopilot
Motivation and drive	Orbitofrontal cortex, anterior cingulate cortex, dorsal striatum, ventral tegmental area	Greater self-regulation, cultivating non-reactivity including reduced reactivity to drug cues, choice selection
Stress responses	HPA axis, amygdala and extra-hypothalmic CRF system	Increasing present moment awareness, sitting with discomfort, greater self-regulation, reduced reactivity to drug cues
Interoception	Anterior cingulate cortex, insula, temporo-parietal region	Increased self-awareness, reduced responses to drug cues.
Executive control	Ventromedial PFC, orbitofrontal cortex, dorsolateral PFC, anterior cingulate cortex	Greater self-regulation, enhanced attentional control, actively allowing discomfort via choice selection

Note. PFC = prefrontal cortex; HPA = hypothalamic pituitary adrenal; CRF = corticotrophin releasing factor.