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Mindfulness Training and Stress Reactivity in Substance Abuse: A Randomized, Controlled Pilot Study

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in Partial Fulfillment of the Requirements for the
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by
Justin Albert Chen
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Abstract

MINDFULNESS TRAINING AND STRESS REACTIVITY IN SUBSTANCE ABUSE:
A RANDOMIZED, CONTROLLED PILOT STUDY.
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There is substantial evidence for the central role of stress in the inception and
maintenance of substance use disorders. The use of mindfulness training (MT) has
demonstrated promise in a number of stress-related conditions. However, no studies to
date have compared MT to empirically validated treatments such as cognitive behavioral
therapy (CBT) for substance use disorders or assessed its impact on response to stress
provocation. The specific aim of this investigation was to engage in the first randomized,
controlled trial of a manualized mindfulness based therapy for the treatment of substance
use disorders. The hypotheses to be tested were: (1) MT would be tolerated equally as
effectively as CBT in terms of retention rates and subjective measures of treatment
tolerability; (2) Participants undergoing MT would demonstrate reduced reactivity on
both subjective and objective measures during stress provocation as compared with CBT;
and (3) Participants undergoing MT would have reduced substance use as compared with
CBT following completion of the intervention. 36 individuals with alcohol and/or cocaine
use disorders were randomly assigned to receive group MT or CBT in an outpatient
community setting. After treatment completion, subjective and physiologic responses to
personalized stress provocation were measured by self report, skin conductance, heart
rate, and heart rate variability. Subjects exposed to MT demonstrated reduced
psychological and physiological indices of stress during provocation compared with
subjects exposed to CBT, as evidenced by the laboratory paradigm conducted post-

treatment among treatment completers. There were no significant differences in retention, treatment satisfaction, or abstinence rates between individuals assigned to MT versus CBT. This pilot study provides preliminary evidence for the use of MT in targeting stress for substance use disorders.

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I. Introduction

Over the past several decades, cognitive-behavioral approaches have become the most prevalent and widely researched of all evidence-based, non-pharmacologic interventions for substance use disorders (1). CBT's prominence as a therapeutic modality is attributable to repeated demonstrations of its efficacy for reducing substance use in randomized clinical trials (2) as well as robust theoretical explanations for its mechanism of action. Specifically, the theory underlying the use of CBT in addictive disorders posits that deficits in the ability to cope with life stress in general and drug cues in particular serve to maintain excessive drug use and lead to a resumption of use following cessation attempts. The various forms of CBT all share some form of skills training to address cognitive and behavioral coping deficits, including identification of specific situations where coping inadequacies occur, and the use of instruction, modeling, role-plays and behavioral rehearsal to address these inadequacies. In their review of cognitive-behavioral treatment for alcohol dependence, Morgenstern and Longabaugh summarize CBT's strengths as follows: "A strong theoretical base, impressive efficacy data and weak evidence for effective alternative treatments have led to the ascendancy of CBT as the dominant paradigm for treating alcohol dependence within the research community" (2).

More recently, however, preliminary evidence has also accumulated for the efficacy of mindfulness based therapies in the treatment of tobacco, alcohol, and drug use disorders (1, 3-8). For example, Zgierska and colleagues found significant reductions in anxiety, depression, and stress in individuals with alcohol dependence who were enrolled in an eight-week mindfulness meditation regimen after completing an intensive outpatient program (3). Bowen and colleagues reported significant reductions in alcohol and drug use after release from prison in individuals who had undergone a 10-day vipassana meditation course while incarcerated, compared to those

that had received treatment as usual (7). In seeking to understand the potential role for mindfulness based therapies in the treatment of substance use disorders, it is helpful to first establish a precise definition of mindfulness, and then discuss the theoretical links between mindfulness, stress reactivity, and addiction. This discussion will then be followed by a more general discussion of the theoretical basis for the use of mindfulness oriented therapies in the treatment of substance use disorders.

As taught as a component of Buddhist philosophy for over two millennia, the practice of mindfulness involves an attitude of openness, inquisitiveness, and acceptance of moment-to-moment experience (9-11). A recent consensus definition of mindfulness emphasizes two complementary elements: 1) the placement of attention on the immediate experience; and 2) adopting an open, curious, accepting attitude toward that experience (9). The premise behind cultivating mindfulness is that observing one's immediate circumstances with an open attitude of acceptance is helpful for identifying automatic, habitual patterns of reactivity to internal and external events as they arise. This perspective, in turn, allows one to learn to respond more intentionally to environmental stimuli rather than thoughtlessly reacting. While the terms meditation and mindfulness are occasionally used interchangeably, they do not refer to the same concept. Rather, meditation is a specific technique or practice that has been used to cultivate the quality of mindfulness over time (12).

According to Buddhist philosophy, one of the primary effects of continued mindfulness practice is the development of awareness regarding the ever-changing nature of reality, whether in terms of the physical body, internal states, or external circumstances. Through this awareness comes greater understanding of how one's views of reality may clash with actual events, resulting in discord and suffering. With these insights and gradual nonjudgmental acceptance of

experience comes greater skill at releasing habitual thought patterns or behaviors that may contribute to various psychological conditions, such as depression or substance addiction, thus providing a possible means by which to decrease one's suffering.

While meditation has been practiced for thousands of years in the East, it did not come to the attention of Western medical science until much more recently. Specifically, a seminal study published by Goleman and Schwartz in 1976 reported that meditation experience helped to reduce stress reactivity—i.e., cognitive and physiological reactions to stress (13). The investigators reported that when exposed to disturbing video images of death and dismemberment, experienced meditators demonstrated attenuated heart rate and phasic skin conductance responses as well as less subjective anxiety when compared with subjects who had no experience with meditation. These findings led them to conclude that "meditation can produce a psychophysiological configuration in stress situations opposite to that seen in stress-related syndromes" (13). Just three years later, one of the first meditation-based treatment modalities was developed through the outpatient Stress Reduction Clinic at the University of Massachusetts Medical Center. This modality, known as Mindfulness-Based Stress Reduction (MBSR), was developed as an adjunct to medical care and intended to optimize health outcomes for people with chronic medical problems (14). Mindfulness based therapies such as MBSR and Mindfulness-Based Cognitive Therapy (MBCT) are sometimes referred to generically as "Mindfulness Training" (MT).

It is believed that while the capacity for mindfulness is inherent, without MT or specific meditation practices the majority of individuals move through life on "auto-pilot" (10) and perform daily activities based on habitual behavioral patterns while their minds are elsewhere (e.g., thinking about the past or worrying about future experiences) rather than purposefully

focusing attention on the present moment. Mindfulness is developed through the continual practice of "awakening" to present-moment experiences. Traditionally, this skill is taught through meditation exercises that focus on developing concentration capacities by repeatedly bringing attention to a specific object (e.g., the touch sensation of one's breath as it flows in and out of the nostrils), then broadening it to include all physical and mental events that are consciously experienced (e.g., bodily sensations, emotions, and thoughts). Instruction for mindfulness practice can be as simple as: "When sitting, know you are sitting; when walking, know you are walking; when thinking, know you are thinking."

While the basic instructions for mindfulness practice appear quite straightforward, Jon Kabat-Zinn, the developer of MBSR and one of the central figures responsible for the elucidation of mindfulness' clinical applications in general, has described the challenges surrounding its actual employment: "Detached self-observation is not a trivial task. The mind has a strong tendency to wander and invariably becomes preoccupied with the content of thoughts and emotions, which often take form as memories, anticipations, ideas, opinions, and desires. The result is a reduction or complete loss of moment-to-moment attention and observation. When recognition of this drift from awareness occurs, the meditator simply brings attention to a detail of momentary reality, usually the breath or a sensation, to (re)anchor the attention in the present. When the faculty of detached observation becomes stable, the field of awareness is allowed to expand again. With practice, any event that arises in the field of one's awareness momentarily becomes the object of meditation until the next event (which may also be the experience of "absence of event") arises. In awareness meditation practice, no event is considered a distraction (not even the wandering of the mind); it is simply another object of observation." (15).

Mindfulness has been operationalized to include the two distinct components described in the consensus definition above: 1) attention that is maintained on the immediate experience, and 2) the maintenance of an attitude of acceptance/non-judgment towards the object of attention (9). Recent studies have suggested that as few as 8 weeks of MT can have direct and measurable effects on both attentional processes as well as neuronal activation (16, 17). The format of MT generally follows an 8 to 10-week schedule, with groups usually composed of 10–40 participants who meet for single 1.5- to 2.5-hour sessions each week occurring in a sequential order (18). During a standard course of MBSR, each session would include experiential meditation practice as well as an educational/discussion component. Meditation exercises that might be used during these sessions include mindful body scanning, sitting meditation, walking meditation, and basic yoga. Participants are encouraged by the facilitator to be increasingly mindful in their day-to-day activities, such as when eating a meal, and to practice meditation between sessions (18).

Since the early days of research into meditation's "psychophysiological" effects, the more standardized mindfulness oriented therapies such as MBSR (15) and MBCT (19) have demonstrated efficacy in the treatment of a wide variety of stress-related disorders, including anxiety (20), depression (19, 21), chronic pain (11), insomnia (22), eating disorders (23, 24), suicidality (25, 26), and even psoriasis (which can be exacerbated by psychological stress) (27). MBCT for prevention of relapse in depression has shown an absolute reduction of 44-50% in the relapse/recurrence rate for those with three or more episodes of depression in both initial and replication studies (19, 21).

Given the accumulating evidence of MT's efficacy in the treatment of stress-related conditions, as well as the established importance of stress reactivity in the inception and maintenance of addiction (28-32), researchers have more recently begun to investigate a

potential role for MT in the treatment of substance use disorders, with some preliminary evidence of promise as described above. There is substantial theoretical rationale for attempting to use MT to target stress reactivity in patients with substance use disorders. Considerable clinical evidence suggests that exposure to stress can produce an increased arousal state similar to that induced by drug cues (33). Furthermore, preclinical data suggest that acute stress may provoke an increase in self-administration of drugs such as amphetamines (34), cocaine (35, 36), and alcohol (37, 38). These findings are consistent with incentive conditioning models, which suggest that exposure to drug-related cues produce conditioned responses, which in turn serve as a cue for subsequent drug-seeking behavior and substance use (39).

Additionally, as drugs have been shown to activate stress circuitry, and hypothalamic-pituitary-adrenal (HPA) activation has been shown to reciprocally increase mesolimbic dopamine transmission, exposure to stress may provide a common neural substrate by which stress enhances drug-seeking behavior and relapse risk (29, 33). Not surprisingly, stressful events and psychological distress are frequently cited reasons for relapse to drug use among individuals with substance use disorders (30, 40-42). These data support the hypothesis that mechanisms related to stress are critical in the establishment of addictions and their continued propagation as chronic disorders (43, 44).

Beyond MT's obvious role in targeting stress reactivity, newer research suggests that mindfulness oriented therapies may act on other pathways and neuroanatomic regions that are important in the pathophysiology of addictions. The remainder of this introduction will review the recent research regarding these other pathways as well as theoretical justifications for the use of mindfulness oriented therapies in the treatment of substance use disorders.

Intentional, sustained attention on a chosen focus is a core practice in mindfulness meditation. As described in the quote by Kabat-Zinn above, whenever the mind strays from the object of attention or is distracted by other stimuli, the meditator is instructed to gently bring his or her attention back to the intended focus. This practice could be described as targeting stimulus-independent thought (SIT). SIT refers to automatically generated verbal or visual experience, "stream of consciousness" (10, 45, 46), or the default tendency to have "narrative process" when there is no demand to respond to external stimuli (47). The medial prefrontal cortex (mPFC) has been shown to play a role in linking subjective experiences through time (48, 49), holding memory of traits of the self (50, 51), reflected self-knowledge (52, 53), and aspirations for the future (54). These findings suggest that midline cortical structures are involved in producing a "narrative self reference," or a sense of identity through time (55, 56). Brain activation in midline cortical structures during narrative self-reference has shown similarities with the proposed "default mode" of resting attention (57, 58). Thus, it appears that a "wandering mind" prone to SIT may be the default mental state even in the absence of external stimuli.

The mechanisms by which mindfulness training influences narrative self-reference/default mode functioning are the subject of current investigation. In one recent study, participants were instructed to either elaborate on current cognitions (narrative focus, NF) or to attend to somatic sensations and merely note the presence of any cognitions without elaborating on them (experiential focus, EF). The investigators found increased midline cortical activation with the NF condition as compared to EF (17). Indeed, after eight weeks of mindfulness training, midline cortical structures showed decreased activity in EF vs. NF (17). One interpretation of these data is that momentary self-experience may provide a non-self-related cortical "task"

which may lead to suppression of midline cortical activity. These findings are corroborated by behavioral studies showing improved attentional regulation with meditation training (16, 59, 60). Another study demonstrated a correlation between trait mindfulness and reduced amygdalar activation during affect labeling (matching facial expressions with corresponding affect words) (61). Together, these data suggest that present-centered attentional focus not only moves the individual away from the habitual default-mode thought process, but also manifests itself in behavioral processes.

The link between attention training and treatment of depression and addiction may not be initially apparent. It has been hypothesized that focusing and sustaining attention on present experience increases the ability to notice overlearned behavioral patterns as they arise, allowing for individualized interventions (whether cognitive, emotional, or behavioral) that interrupt the cyclical nature of these patterns (1, 9, 62). For example, preliminary findings suggest efficacy of mindfulness-based treatment for obsessive compulsive disorder (OCD, a disorder characterized by overly active habit-related neural networks). Treatment response has been positively correlated with decreases in overactive brain regions such as the dorsal striatum, suggesting that mindfulness may modulate these pathways, leading to fewer compulsive behaviors (63).

Similar cognitive habit patterns are reflected in the rumination that often occurs in clinical depression. Early in the course of major depressive episodes, associations between depressed mood and depressive, negativistic thought patterns are established, and these can be reactivated during periods of dysphoria (64, 65). Ruminative patterns can then precipitate future depressive episodes (66, 67). With continued practice of mindfulness, individuals may be better able to notice these patterns, allowing for disengagement from the thoughts (i.e., not being caught up in the thoughts and thus believing them to be "true") and an increased sense of choice

as to how to relate to the experience, rather than automatically following the thoughts (typically into deepening dysphoria) (10, 68). Studies have shown that decreases in distress scores following mindfulness training are mediated by a decreased tendency to ruminate (69). It is posited that similar mechanisms may operate in the relationship between mindfulness practice and the prevention of relapse to depression, especially given repeated observation of its effectiveness in individuals with three or more depressive episodes, but not in those with fewer. These findings suggest mindfulness practices may be effective in targeting more habitual patterns or ruminative thinking, rather than situational depression (19, 21).

Efforts to avoid or suppress "unwanted" thoughts are commonly used in patients' attempts to manage cravings and relapse (70). However, these strategies may in fact be counterproductive. For example, thought suppression has been shown to lead to stronger expectancies after cue exposure (71). Interestingly, decreases in alcohol consumption following mindfulness-based treatment have been shown to be partially mediated by decreases in thought suppression indices such as avoidance (4). These findings suggest that bringing attentional focus to arising thoughts may be more effective than attempts to suppress them in decreasing their influence on behavior. This intentional focus correlates with changes in activation of midline cortical structures in healthy volunteers (17). A similar mechanism is hypothesized to exist in individuals with substance use disorders. Future neuroimaging studies of attentional tasks and craving paradigms in individuals with addictions who have received mindfulness training will help to test this and other hypotheses regarding the mechanism of mindfulness and its effects on brain activation.

The second major component of mindfulness, acceptance, involves a non-judging/non-attached, "objective" view of experiences. This perspective, referred to as "de-centering" or

"meta-cognition" (72), leads to an understanding of thoughts and sensations as "transient mental events" rather than as reality or a reflection of the self. As with attentional focus, de-centered observation has been hypothesized to reduce perpetuation of harmful thought patterns by shifting one's perspective away from automatically regarding uncomfortable or unpleasant thoughts as "real" or "true," and instead cultivating a more open attitude that recognizes such thoughts as merely passing mental events. Awareness of thoughts that might arise improves tolerance of negative affect, lessens reactivity, and decreases attempts to avoid or suppress experience, measures which have all been linked to worsened outcome (73, 74). It should be noted here that as the capacity for acceptance is emphasized and reported to be beneficial in mindfulness training as well as therapies that incorporate mindfulness such as Acceptance Based Therapy (ACT) and Dialectical Behavioral Therapy (DBT) (75, 76), it is yet unclear whether a de-centered viewpoint fosters acceptance, acceptance fosters a de-centered viewpoint, or whether the effects are bidirectional.

It has been posited that much emotional reactivity is rooted in self-referential thinking, and that by reducing this secondary emotional processing, meditators "experience less stress and react to problems with greater composure and equanimity" (74). Indeed, Farb and colleagues have provided some of the first evidence in favor of this perspective with their functional connectivity analysis, which revealed a decoupling of insular-ventromedial prefrontal cortical (vm-PFC) activity and an increased coupling of the insula with the dorsolateral prefrontal cortex (dl-PFC) with mindfulness training (17). In further support of these findings, meditation practice has been associated with a thickened right insular cortex, somatosensory cortex, inferior temporal gyrus, and inferior parietal lobule (77, 78). These data suggest a movement away from

self-referential experiences (associated with midline structural activation) toward those that are more objectively observed.

This non-attached vantage point may explain the effectiveness of mindfulness for prevention of depression relapse in MBCT, which posits that emotional challenges are often closely connected to thoughts, and which trains individuals to recognize thoughts as "mental events" rather than "reality" (10). As in the case of attentional tasks and craving paradigms for individuals with substance use disorders, future neuroimaging studies will help identify neural correlates of these processes, furthering progress toward a greater understanding of mindfulness' specific mechanisms of action.

The utility of a de-centered mode of processing experience in individuals with addictions is becoming increasingly clear. The majority of individuals with substance use disorders report experiencing "urges" to use substances and state that the experience of an urge is increasingly tolerated and managed when working with a mindfulness approach (6, 79-81). In addition, decreases in substance use following engagement in meditation training have been shown to be partially mediated by decreased avoidance, but not decreased frequency, of intrusive thoughts (4).

Meta-cognitive skills developed through practice of mindfulness can be delineated as follows: the ability to sustain attention, shift attention, inhibit secondary elaborative processing of objects of awareness, and process information related to current experience since attentional capacity is not being consumed by elaborative thinking (9, 16). Because mindfulness involves enhancement of attentional control and increased awareness of mental and behavioral process, it holds promise as a tool for interrupting patterns of self-destructive habitual thoughts and behaviors (6, 10, 19, 21, 82, 83). Development of a defined, prescribed attitude toward

experience is thought to decrease avoidance of negative aspects of experience, thereby increasing tolerance of negative affect and raising emotional awareness (9).

Another important aspect of mindfulness training is the concept of compassion. Compassion practice has shown effects on stress induction and immune function (84). Expert meditators have demonstrated increased activity in the insula when practicing compassion meditation, which is based on generating feelings of "loving kindness," and which has been hypothesized to affect emotional responses to stimuli (85). Additionally, these practices are increasingly being incorporated into mindfulness-based relapse prevention programs (79). Whether these practices foster meta-cognitive skills, increase acceptance, or have other mechanistic utility remains to be determined. Future work in defining and measuring compassion practices both in basic science and clinical realms will move us closer to understanding their neural mechanisms and therapeutic efficacy.

One potentially important aspect of mindfulness training, particularly interesting in the context of treatment of substance use disorders, is the practice of "abstinence" (86), i.e., response prevention by sitting motionless and abstaining from impulsive reaction to both pleasant and painful thoughts or feelings. The behavioral practice of non-reaction might "de-link" the thought/feeling from the response (86), moderating maladaptive habitual behaviors. Future studies might compare traditional mindfulness vs. more standard behavioral treatment in the dual diagnosis population.

Despite the efficacy of mindfulness based therapies in the treatment of a variety of stress-related disorders, as well as the extensive theoretical benefits of applying mindfulness training to the treatment of addictions as outlined above, to date no randomized controlled trials have been

run comparing MT to empirically validated treatments for substance use disorders, such as CBT (87).

II. Statement of Purpose

The purpose of this investigation was to engage in the first randomized, controlled trial of a manualized mindfulness based therapy for the treatment of substance use disorders. This report describes the clinical and laboratory outcomes from a Stage I pilot trial in which a manualized version of MT was modified for individuals with substance use disorders, and the following specific parameters were evaluated: (1) MT's feasibility compared with another empirically validated therapy (CBT); and (2) MT versus CBT's subjective and objective effects on stress, as evaluated by both self-report measures and reactivity during stress provocation using a stress paradigm established in previous studies on stress and addiction (88). The hypotheses to be tested in this investigation were: (1) MT would be tolerated equally as effectively as CBT in terms of retention rates and subjective measures of treatment tolerability; (2) Participants undergoing MT would demonstrate reduced reactivity on both subjective and objective measures during stress provocation as compared with CBT; and (3) Participants undergoing MT would have reduced substance use as compared with CBT following completion of the intervention.

III. Methods

<u>Participants</u>

Participants were recruited from media advertisements and clinician referrals for individuals seeking treatment at the Substance Abuse Treatment Unit (SATU), a community-based outpatient treatment facility in New Haven, CT. Participants were English-speaking adults who met DSM-IV criteria for alcohol and/or cocaine abuse or dependence in the past year. Exclusion criteria were minimal to facilitate recruitment of a clinically representative group of individuals seeing treatment in a community setting. Thus, individuals were excluded only if they were currently at clinically significant risk for suicide or homicide, had a current psychotic disorder, were cognitively impaired to the point where they were unable to complete clinic demographic or study-related questionnaires, were on beta-blocker treatment (which may influence heart rate measurements), or were intoxicated at the time of initial study interview.

As shown in the participant flow diagram (Figure 1), all of the 36individuals who were screened were determined to be eligible for the study, provided written informed consent, and were randomly assigned to a treatment condition (MT or CBT), following a complete description of the study and provision of written informed consent approved by the Yale University School of Medicine's Human Investigations Committee. Of the 36 subjects assigned to treatment, 25 were exposed to their protocol treatment and 14 completed treatment. Thus, full outcome data are available only for the 14 individuals who completed treatment. Laboratory data are available for the 13 participants who completed treatment and the lab session as described below.

Treatments

All participants received weekly group treatment that was matched for time (approximately one hour, once weekly). All treatments were manualized and delivered by PhD-level therapists experienced in CBT or MT respectively. CBT was used for the comparison condition because of its well-established role in the non-pharmacologic treatment of substance use disorders, as described above. Groups were structured in a psychoeducational format, allowing for both experiential discussion and didactic instruction. This investigator was involved in the testing and adaptation of the MT format for the purposes of this study.

CBT was delivered by one PhD-level therapist using the National Institute on Drug Abuse (NIDA) CBT manual over a 12-week period (89). Groups were delivered in a continuous fashion and individuals could enter based on a weekly rolling admission process. Groups were capped at eight to ensure optimal treatment.

Participants randomized to MT received a modified form of manualized group Mindfulness-Based Relapse Prevention (MBRP) over a nine-week period (3, 82). Briefly, the MBRP course is based on MBSR and traditionally delivered via eight, two-hour weekly group sessions. Participants are taught relapse prevention techniques through learning to attend mindfully to relapse triggers such as thoughts, emotions, and bodily sensations. Themes for the eight sessions of MBRP are as follows: "1. Automatic pilot and its relation to craving"; "2. Triggers, thoughts, emotions and cravings"; "3. Mindfulness in everyday life"; "4. Staying present and aware in high-risk situations"; "5. Balancing acceptance and change"; "6. Seeing thoughts as just thoughts"; "7. How can I best take care of myself? Build support networks and taking action"; and "8. Balanced

living and using what has been learned." During sessions, individuals learned various meditation techniques, including sitting and walking meditations as well as "urge surfing" techniques to help them tolerate urges as they arose.

Three major adaptations to MBRP were implemented. First, after the initial session (renamed Introduction), the seven sequential sessions were divided into two, four-week modules that could be completed in either order (i.e., Introduction, then Module 1, then Module 2; or Introduction, then Module 2, then Module 1). This was done to assess "real-world" delivery of the treatment by providing minimal waiting time for individuals to enter treatment. Another benefit was to facilitate equal pre-group clinic intake periods for individuals who were randomized to MT or CBT (roughly 3 weeks from initial clinic intake and individual clinician evaluation to the start of group treatment for both groups). Module 1 included sessions 2, 6 and 7. Two additional sessions were added: the first specifically targeted working with anger as a trigger for stress, drug use or relapse (90), and had originally been developed for MBSR, while the second involved instruction for using compassion-based loving-kindness/"*metta*" techniques to facilitate working with difficult emotions or thoughts as part of MT (91). Module 2 included sessions 3, 4, 5, and 8.

The second major adaptation was the elimination of yoga meditation from the training in order to minimize the possibility of confounding effects, especially given evidence for yoga's potential beneficial effects as a stand-alone treatment for stress reduction and drug use (92, 93).

The final major adaptation was to shorten the weekly sessions to approximately one hour each (mainly by shortening the guided meditation exercises). This was done for

two reasons: 1) as the "dose-response" curve for mindfulness acquisition and treatment

has not been determined, we wanted to determine whether shorter sessions would be

sufficient for individuals to attain adequate mindfulness skills for benefits to be seen; and

2) we wanted to mimic as closely as possible group community session length—which,

as with the CBT sessions, is typically approximately one hour in length.

Assessments

Participants were assessed before treatment initiation, weekly during treatment,

and at the time of treatment termination. Participants were administered the Structural

Clinical Interview for DSM-IV (SCID) alcohol and drug use sections before

randomization in order to establish substance use diagnoses (94). This investigator was

trained to administer the SCID alcohol and drug use sections. Diagnoses were confirmed

by an individual evaluation by a psychiatrist. The Substance Use Calendar was

administered weekly during treatment to collect detailed day-by-day self-reports of drug

and alcohol use throughout treatment (95). Participant self-reports of drug use were

verified by random breathalyzer and urine toxicology screens (approximately once every

two weeks). One hundred percent of the breathalyzer and 98.4% (62/63) of the urine

specimens were consistent with participant self-report.

A variety of psychometric and self-report measures were used to assess study

participants. This investigator was involved in the research, compiling, and adaptation of

these measures for the purposes of this investigation. The *Five Facet Mindfulness*

Questionnaire (FFMQ), a 39 item self-reported psychological measure of mindfulness

skills, was administered at baseline and treatment completion to assess mindfulness skills

acquisition (96, 97). The items are presented on a 5-point Likert scale ranging from 1 (almost always) to 5 (almost never). The *Treatment Credibility Score questionnaire (TCS)*, an eight item self-reported measure of treatment acceptability was administered at the end of treatment. The TCS consisted of questions related to how agreeable and practical each treatment was for drug use, depression and anxiety, and was also rated on a 5-point Likert scale ranging from 1 (not at all) to 5 (very much). Questions included: "How confident do you feel that your therapy can help with your drug/alcohol use?"; "How much does it make sense to you that your therapy would help with drug/alcohol use?"; and, "How confident do you feel recommending your therapy to a friend with similar problems?"

Laboratory Paradigm

At the conclusion of treatment, subjects participated in a single one-hour laboratory session that included two imagery conditions: one with neutral-relaxing imagery and the other with stressful imagery (29, 31, 33, 88, 98-100). In a separate session several weeks prior to the laboratory session, these imagery scripts had been developed for both the stress and neutral-relaxing situations as (29, 31, 33, 88, 98, 99). The stress imagery script was developed by having subjects identify a recent stressful experience they had personally experienced as "most stressful." The quality of "most stressful" was determined by asking the subjects to rate an experience perceived as stressful by them in the past year on a 10-point Likert scale, where 1 = "not at all stressful" and 10 = "the most stress they have felt in the past year." Only situations rated as 8 or above on this scale were accepted as appropriate for script development. Stressful

situations related to drug use were not allowed. Examples of acceptable stressful situations include unemployment-related stress, such as being fired from work, or a verbal argument or physical altercation with a significant other or family member. The neutral-relaxing script was developed from a commonly experienced relaxing scene that did not include drug or alcohol use (*e.g.*, reading a book in bed, listening to music, walking on the beach). Each script was edited by two individuals who were blinded to treatment group to ensure consistency between participants. Scripts were then digitally recorded by a female research associate who was blinded to treatment condition and unknown to participants.

Approximately 45-60 minutes before each laboratory session, participants were fitted with skin conductance electrodes on the non-dominant hand to measure galvanic skin responses (GSR), a respiratory rate monitor, and two electrocardiogram (ECG) leads to measure heart rate and heart rate variability (HRV). This allowed for acclimatization before the start of the laboratory sessions. At this time the participants were taught relaxation procedures to help them follow the guided relaxation before the start of each script, such that they were in a standardized, relaxed state at the onset of each script. Physiological measurements were recorded using a Biopac MP100 system running AcqKnowledge 3.9 software (Biopac Systems Inc., USA). The Biopac electrodermal activity amplifier module (GSR 100c) was set at a channel sampling rate of 31 Hz and a gain of 5 μSiemens (μS) per volt (resulting in a resolution of 0.0015 μS), the electrocardiogram amplifier (ECG 100c) was set at a channel sampling rate of 1000 Hz for the laboratory sessions, and the respiratory amplifier (RSP 100c) was set at a channel sampling rate of 62.5 Hz.

Participants were seated in a comfortable reclining chair for the duration of the laboratory session and were separated by a physical partition from the experimenter. Each imagery condition was presented in a 30-minute block, beginning with guided relaxation before presentation and an 8-minute recovery period between conditions. The order of the stress and neutral-relaxing imagery scripts was randomized for each subject. The subject was not informed of the order of imagery conditions. The recorded scripts were played via noise-reduction headphones (iTunes, Apple Inc., USA). Subjective responses after each script were recorded on a laptop computer positioned next to each participant using the ePrime software package v. 2.0 (Psychology software Tools Inc. USA).

After each imagery script was played, participants rated situational vividness on a 10-point visual analog scale (VAS, with 1 = not at all clear, and 10 = perfectly clear image) for how "clearly and vividly" they were able to imagine the scenario. Participants then rated their anxiety and drug/alcohol cravings on a 10-point visual analog scale (VAS) for each condition. Subjects also completed an abbreviated 30-item version of the Differential Emotion Scale after each condition, in which five adjectives are used to describe each of six emotional states and subjects are asked to rate on a 5-point Likert scale the extent to which each word describes the way they feel at the present time (DES; (101)). In the laboratory sessions, average vividness ratings for the stress imagery were 8.1 ± 1.1 and 8.6 ± 0.5 for MT and CBT, respectively, average vividness ratings for the neutral imagery were 8.0 ± 1.1 and 8.2 ± 0.4 for MT and CBT, respectively, with no significant differences between the groups or conditions.

Data Analysis

This investigator was responsible for extracting and compiling the subjective and objective data obtained during this study, which involved extensive communication and collaboration with the makers of the AcqKnowledge software in order to convert data for heart rate, heart rate variability, respiratory rate, and galvanic skin responses into an applicable format (as described below).

The principal data analytic strategy was analysis of variance (ANOVA) for between-group comparisons of drug use and scores on the FFMQ and TCS. Chi-square analysis was used to determine treatment retention differences. DES, anxiety and drug craving VAS scores were compared by 2-tailed t-tests. A within-subjects ANOVA was used to evaluate GSR differences by treatment condition (between subjects) and testing condition (within subjects). GSR "events" were thresholded at 0.05 µS with a 0.05 µS high pass filter applied and responses under 10% of maximum were excluded (of note, a *post-hoc* analysis with no thresholds yielded essentially unchanged numbers of events in all participants). Stress reactivity was calculated by subtracting the mean skin conductance from the maximum skin conductance within each testing condition (stressful and neutral) using a covariate of a five-minute period before each condition to control for baseline GSR measurements. These models were also run on the mean skin conductance, the maximum skin conductance, and the number of GSR events, or stress reactivity score. Within-subjects ANOVAs were run on the mean skin conductance, the maximum skin conductance, the number of GSR events, or stress reactivity score with treatment condition, testing condition, and the interaction of treatment and testing condition as the predictors.

Within-subjects ANOVAs evaluated influences of sympathetic and vagal tone, with treatment condition, testing condition, and the interaction of treatment and testing condition as the predictors using HRV power algorithms. Briefly, ECG heartbeat dropouts were manually filtered, then each PQRST complex was bandpass filtered at 17 and 5 hz to create discrete signal nodes. From these nodes, power spectral density analysis was performed using AcqKnowledge 3.9 software. The sympathetic ratio was defined as the percentage of the power spectral density (P) that occurs in the low frequency band (0.04 - .15 Hz): (P_Low) / (P_High + P_Low). The vagal ratio was defined as the percentage of the power that occurs in the high frequency band (.15 - .4 Hz): (P_High) / (P_High + P_Low) (102). The sympathetic/vagal ratio was calculated from dividing the sympathetic by the vagal ratio.

Data are reported as mean $\pm$ standard error of the mean unless otherwise noted.

IV. Results

Group Description

       Table 1 presents baseline demographic and substance use characteristics of the 36

individuals who were randomized for this study. Most of the participants (72%) were

male, 64% were White, 24% Black, and 12% Hispanic. Most were single or divorced

(76%), did not have a college degree (76%), and were not employed full-time (72%). The

majority met SCID criteria for alcohol dependence (68%) and/or cocaine dependence

(48%). Analysis of variance and chi-square analysis indicated no significant differences

by treatment condition except that more participants assigned to the CBT group were

married (57%) than in the MT group (6%) ($F/X^2 = 8.5$, p = .04). No differences in

baseline drug or alcohol use were found between individuals who completed treatment

and those who did not complete treatment.

Feasibility: Treatment retention, satisfaction, and substance use outcomes

       To evaluate the feasibility and acceptability of MT relative to a more established,

empirically validated therapy (CBT), we compared retention across the two treatment

conditions. Of the 36 individuals who entered the study, 9/21 (43%) completed MT,

while 5/15 (33%) completed CBT (p = .563, Figure 1). Of those who initiated treatment,

participants attended 65% of expected sessions in MT vs. 34% of sessions in CBT (F =

4.89, p = .04, Figure 2). Participants who completed treatment in both groups rated their

treatments as highly satisfactory as assessed by TCS (4.2 $\pm$ .18 for MT vs. 4.4 $\pm$ .21 for

CBT, p = .37).

Despite active cocaine or alcohol use in the month prior to treatment initiation in 8/9 (89%) of completers in the MT group and only 2/5 (40%) in the CBT group, we found that substance use did not differ by treatment groups. Of the completers, the percent of days of cocaine use during treatment was 5.4 ± 2.7 in MT vs. $0.0 \pm .00$ in CBT groups (F = 2.1, p = .17). The percent of days of alcohol use during treatment was 24.3 ± 9.4 vs. $0.0 \pm .00$ in MT vs. CBT groups (F = 3.6, p = .09).

Specificity of MT: Effects of Treatment on Mindfulness Skills Acquisition and Implementation

To determine whether the paradigm employed in this investigation adequately fostered mindfulness skills development, the FFMQ was measured before and after treatment. There were no observed differences in the FFMQ between groups at baseline (MT = 126.5 ± 5.6, CBT = 122.6 ± 6.0, p = .64). Additionally, no differences were noted between completers at baseline (MT = 122.1 ± 8.6, CBT = 118.8 ± 12.9, p = .82). Although participants in the MT group showed greater overall increases in FFMQ scores compared to CBT after treatment, these differences did not reach statistical significance (MT = 144.2 ± 6.1; CBT = 131.4 ± 12.2, p = .04 by time, p = .54 group by time). These gains were primarily seen in the observing (p = .01 by time, p = .44 group by time), non-judging of experience (p = .03 by time, p = .87 group by time), and the non-reactivity to inner experience facets (p = .07 by time, p = .59 group by time).

Specificity of MT: Subjective and Objective Responses to Stress Provocation

To determine whether MT differentially influences psychological responses to stress, responses to a personalized stress challenge were compared for individuals who completed MT vs. CBT. Participants who received MT showed significantly attenuated anxiety in both VAS and DES scores in stress vs. neutral conditions compared to those who received CBT (VAS: $1.5 \pm .68$ for MT vs. $4.6 \pm .73$ for CBT, p = .01, Figure 3a; DES: 1.50 ± 1.7 for MT vs. 7.0 ± 1.4 for CBT, p = .03, Figure 4). These attenuations were echoed in attenuated responses in several other negative emotions (Figure 4). Though not statistically significant, individuals receiving MT also reported roughly half the levels of stress-induced drug craving compared to those receiving CBT (1.1 ± 1.3 vs. 2.0 ± 1.4, p = .65, Figure 3b).

Another goal was to determine whether MT would exert any influence on physiological measures of stress. We found large differences in galvanic skin responses between stress and neutral stories that were not different between groups (MT: 10.0 ± 2.9 for stress vs. 4.5 ± 2.6 for neutral; CBT: 7.0 ± 2.9 for stress vs. $0.8 \pm .49$ for neutral, F = 12.36, p = .01 for condition). Additionally, no differences were noted in respiratory rate (data not shown). However, whereas the expected increases in maximum heart rate during stress were observed in the CBT group, no increases in were seen in the MT group (81.4 ± 2.5 vs. 98.7 ± 16.8, F = 1.97, Figure 5a). These findings were not significant (p = .19), but the η^2 showed this effect size to be large (0.15; scores >.14 are considered "large"). Corresponding differences were seen in heart rate variability measures: individuals in the MT group showed decreased sympathetic/vagal ratios, a measure of

autonomic activation, when compared to those in the CBT group (4.01 $\pm$ .18 vs. 4.20 $\pm$

.10, F = 7.97, p = 0.02, effect size = .42, Figure 5b).

V. Discussion

<u>Overall conclusions</u>

This Stage I pilot trial sought to evaluate both the feasibility and specificity in terms of stress reactivity of manual-guided MT versus CBT for individuals with substance use disorders. Although attrition in both groups was substantial, MT did not differ from CBT in participant retention, treatment satisfaction, or frequency of substance use. However, those who completed MT demonstrated attenuated psychological and physiological responses to stress provocation compared to those participants who completed CBT. While the sample size was small and the results preliminary, this investigation represents the first randomized clinical trial comparing MT to an empirically validated treatment for substance use disorders, and the first to assess responses to stress provocation in this population. It adds to the emerging positive literature on MT for addictions by extending it to randomized controlled trials, as well as evaluating MT's effects on indices of stress reactivity a major trigger for use/relapse (29, 99).

<u>Stress and Addiction</u>

As noted above, stress has been shown to activate neural circuitry important in addictions, induce cravings, and lead to relapse (29-32). The stress paradigm described in this study provided robust psychological and physiological responses as evidenced by increases in emotional and craving ratings, and increases in GSR and HR measures. Importantly, the number of GSR events increased in stress vs. neutral stories in both groups, which suggests that all individuals engaged in, and thus did not employ

avoidance or suppression strategies, while listening to stressful stories. Such strategies have been shown to lead to increased numbers of intrusive drug-related thoughts (70) and linked to worse outcomes (73, 74). Importantly, the results of this investigation showed that subjective measures of stress were reduced in MT compared to CBT during stress provocation. This is consistent with the idea that MT fosters an active but *non-attached* participation in events (including cravings and stressful situations) (22, 103). It has been proposed that emotional reactivity is rooted in self-referential thinking, and that by reducing this secondary emotional processing, people trained in mindfulness may respond to stressful events with greater composure and equanimity (74). Indeed, Farb and colleagues have shown a decoupling of brain regions involved in sensing bodily states (insula) from those that are thought to be involved in self-reference (medial prefrontal cortex) after MT (17).

In addition to differences in self-reported anxiety and emotion, we also found objective evidence of differences in stress reactivity after MT. Previously, we and others have found increases in HR indices in individuals with addictions undergoing stress (33, 104, 105). In this study, the data demonstrate an attenuation of increase in HR among the MT group but not the CBT group. This finding provides objective corroboration of individuals' report of attenuated anxiety and negative emotions.

Sympathetic and vagal tone, which reflect autonomic nervous system (ANS) activity, were calculated as additional measures of subject arousal. ANS activity is important for psychological and physiological allostasis (106-109). The two major branches are the sympathetic ANS, associated broadly with energy utilization (*i.e.*, "fight or flight" responses) and the parasympathetic ANS, associated with restorative functions

(110). The heart is dually innervated by both the sympathetic and parasympathetic (vagus nerve) branches of the ANS (102, 110). In healthy individuals, the heart is under tonic, parasympathetic inhibitory control. This allows for adaptive responses to environmental conditions given the short time course of parasympathic effects (milliseconds) compared to sympathetic effects (seconds) (110). ANS imbalance, often characterized by predominance of the sympathetic branch, has been linked to a range of pathological conditions (111). HRV represents a reliable index of ANS balance and has been associated with increased mortality (112).

In this study, the data demonstrate a decreased sympathetic/vagal ratio among participants in the MT compared to the CBT group. This finding is consistent with the idea that MT promotes a de-centered stance toward environmental stimuli: as individuals are able to engage but not be "caught up" in thoughts or emotions, they are more able to adapt to changing internal and external environmental cues and conditions. As vagal tone has been shown to be a peripheral indicator of prefrontal cortical control of downstream sympathetic responses (*e.g.*, anxiety and/or fear) (113), decreases in the sympathetic/vagal ratio also suggest the possibility of prefrontal cortical circuits playing a mechanistic role in MT's mediation of stress. This is an intriguing possibility as we have previously found that prefrontal cortical activation during a cognitive control task (Stroop) is associated with improved treatment outcomes (114). Future studies using functional magnetic resonance imaging will help to determine specific brain regions that may be altered by MT and how this affects individual responses to stress.

Treatment implications

In this preliminary evaluation of the feasibility of MT, manual-guided MT was not significantly different from group CBT in treatment retention, substance abuse outcomes, or participant satisfaction with treatment. There are several important implications from these findings, as 1) MT has not previously been compared head-to-head to CBT, 2) the length of sessions was significantly shortened compared to standard mindfulness-based paradigms and 3) MT was delivered in a modular rather than sequential format. First, although preliminary given our small sample sizes, these data suggest that MT may be a viable treatment strategy. Second, individuals who have undergone mindfulness training through programs that utilize sequential sessions of approximately two hours a week for eight weeks have shown self-reported mindfulness "acquisition" which has recently been shown to correlate with outcomes (115). However, the "dose-response" curve for mindfulness acquisition and treatment delivered in a block design has not been studied. These data suggest that shorter MT sessions may still provide enough training to establish efficacy. Third, these results suggest that a modular format is a viable delivery option.

The latter two points have important implications for community-based treatment programs. Developing treatments that are shorter than typical mindfulness-based approaches will be more viable financially for community clinics and are less of a time burden for patients, ultimately supporting their attendance and treatment completion. Additionally, providing modular formats may be hypothesized to reduce logistical administrative burdens and allow for fewer trained therapists to treat a great number of patients. Such an effect has been successfully demonstrated in programs such as

dialectical behavioral therapy (116). However, future studies directly comparing modular vs. sequential delivery will be important in order to test these hypotheses.

Strengths and Limitations

Strengths of this trial include random assignment of a diverse group of participants in and representative of a community clinic, a robust, validated laboratory stress paradigm that utilized discrete psychological and physiological measures, and the use of CBT as the comparison condition, which provides good controls over attention, activity level, and therapist involvement.

This study has several limitations as well. In particular, the sample size was small and outcome data were based on the minority of individuals in both conditions who completed treatment. Also, it included a heterogeneous population both in substance use disorders (alcohol and cocaine) and drug use status at study entry. Although this arguably provides greater ecological validity, enrolling only individuals who were actively using a single substance at study entry may have provided more homogenous data with regards to substance use outcomes. Additionally, this study was performed at a single site using single therapists for each condition and measures of treatment fidelity or discriminability were not included. The randomization of subjects resulted in uneven groups, with differences in one of the demographics (marital status) approaching statistical significance. While there are no known explanations for this discrepancy, it may have had some impact on the study. Finally, given the robustness of CBT as an evidence-based, non-pharmacological treatment for relapse prevention in addictive disorders, its

use in the control condition may have made it more difficult to detect subtle treatment benefits attributable to MT.

Despite these concerns, this randomized-controlled pilot study suggests that MT may have promise as a component of addiction treatment, and that further studies of its effects on stress reactivity may be warranted.

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VII. Figure references and legends


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┌─────────────────────────────────────────────────┐
│        Assessed for Eligibility (N=36)          │
└─────────────────────────────────────────────────┘
                        │
┌─────────────────────────────────────────────────┐
│      Included in Randomization (N=36)           │
└─────────────────────────────────────────────────┘
           │                           │
┌──────────────────────────┐  ┌──────────────────────────┐
│ Assigned to CBT (N=15)   │  │ Assigned to MT (N=21)    │
│ Assigned non-starters    │  │ Assigned non-starters    │
│ (N=8)                    │  │ (N=3)                    │
│ Exposed to treatment     │  │ Exposed to treatment     │
│ (N=7)                    │  │ (N=18)                   │
│ Completed treatment (N=5)│  │ Completed treatment (N=9)│
│ Did not complete         │  │ Did not complete         │
│ treatment (N=2)          │  │ treatment (N=9)          │
└──────────────────────────┘  └──────────────────────────┘
           │                           │
┌──────────────────────────┐  ┌──────────────────────────┐
│ Completed laboratory     │  │ Completed laboratory     │
│ session (N=5)            │  │ session (N=8)            │
└──────────────────────────┘  └──────────────────────────┘
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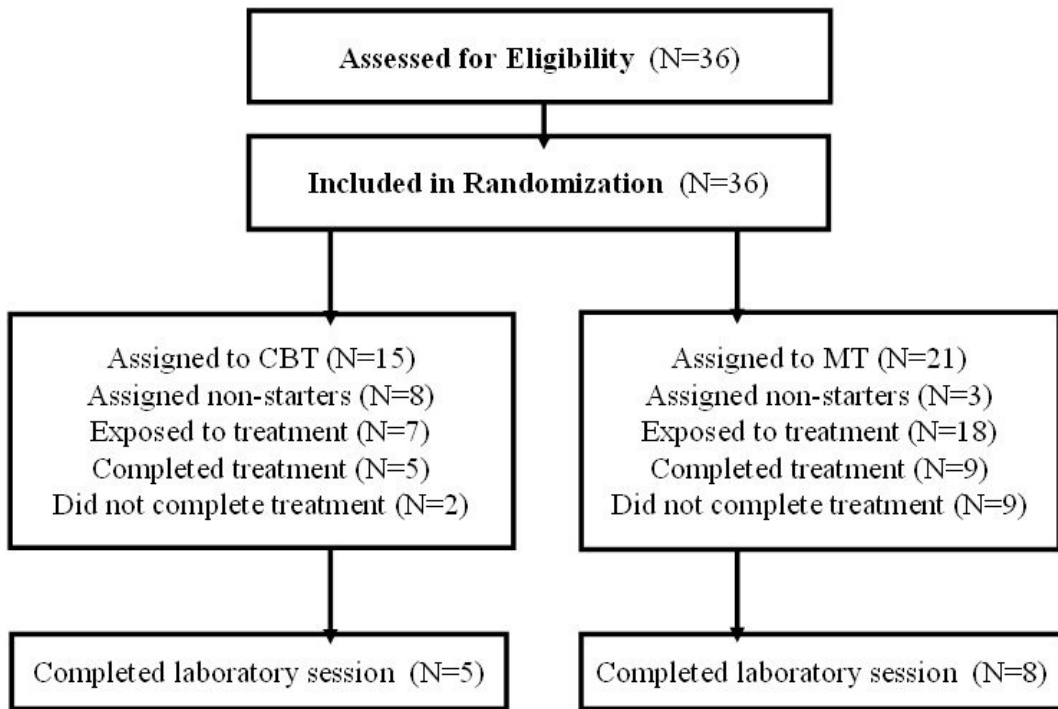
FIGURE 1. *CONSORT Diagram: Flow of Participants Through the Study Protocol.*
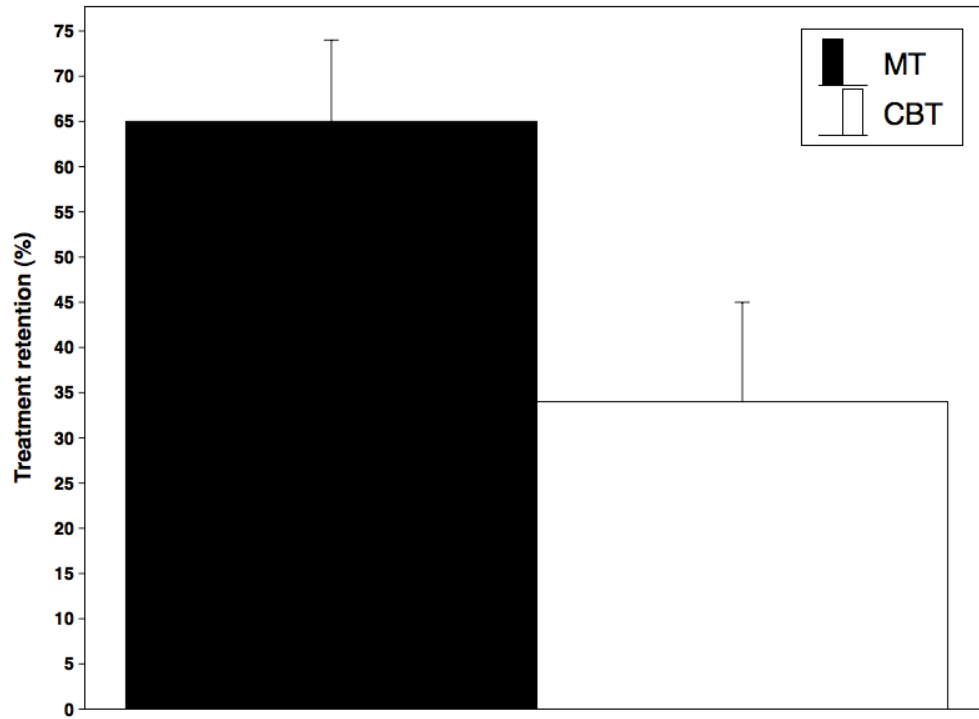CBT = Cognitive Behavioral Therapy, MT = Mindfulness Training

FIGURE 2. *Subjects Receiving MT Showed Increased Treatment Retention.*
Treatment retention was calculated from the number of sessions attended divided by the total number of sessions.
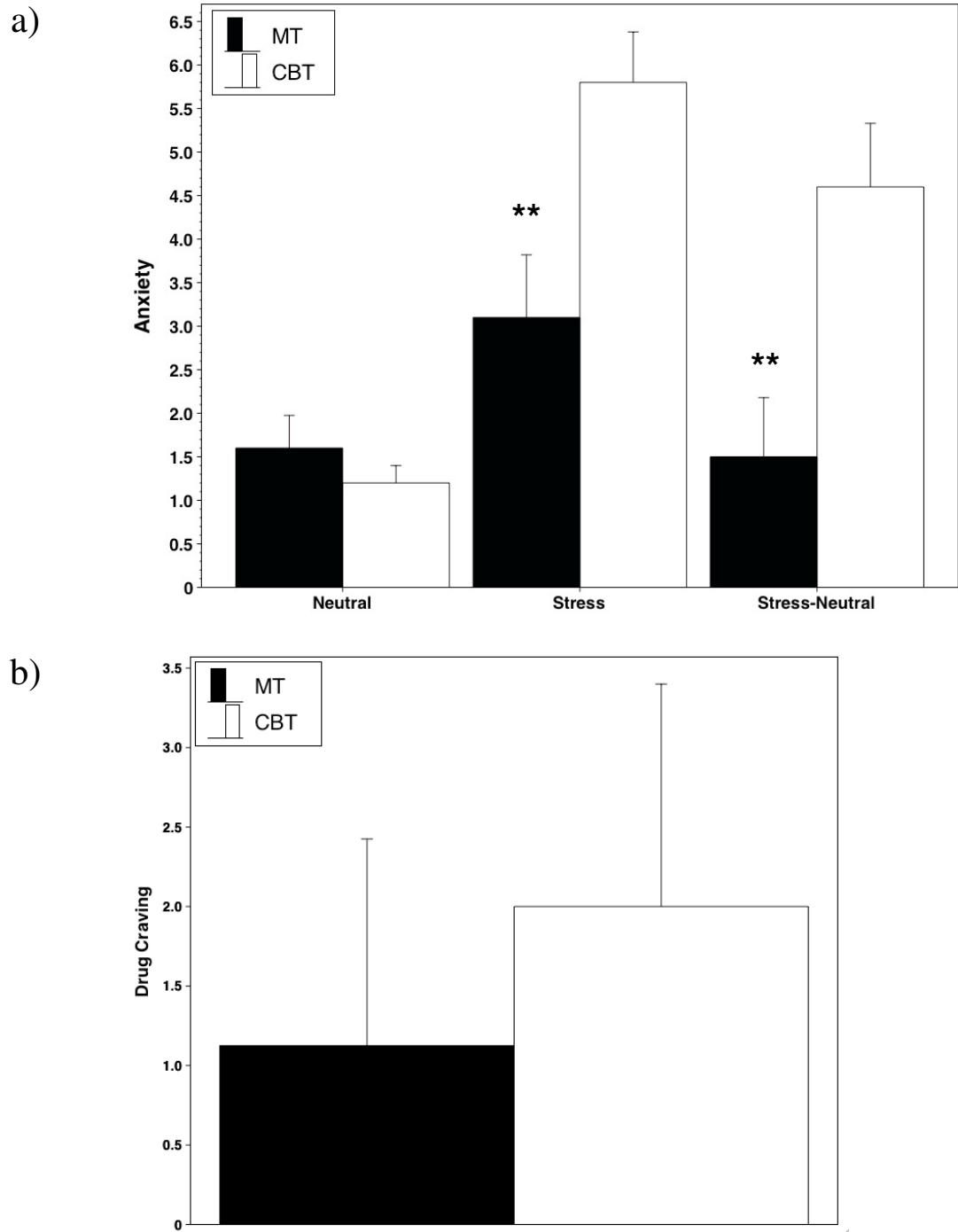
a)

b)

FIGURE 3. *Mindfulness Training is Associated with Attenuated Anxiety with Stress Provocation.* Y-axis denotes reported visual analog scale (VAS) scores after listening to personalized neutral or stressful stories. a) Anxiety scores; bars on far right indicate normalized scores (stress minus neutral). b) Normalized drug craving scores (stress minus neutral). ** indicates $p = 0.01$ between treatment groups.
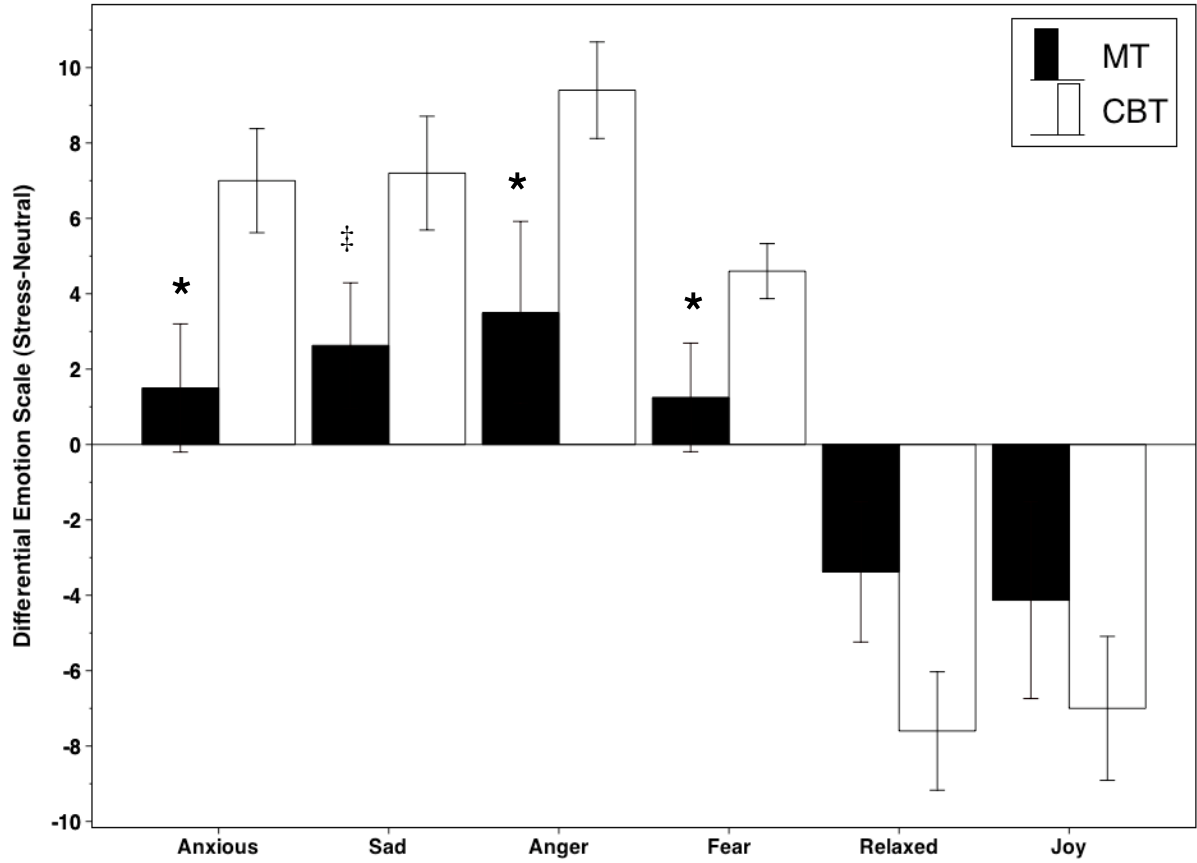
FIGURE 4. *Mindfulness Training is Associated with Attenuated Emotional Reactivity.* Y-axis denotes normalized Differential Emotion Scale scores after stress provocation (stress minus neutral). * indicates p < .04, ‡ indicates p = .07 between treatment groups.
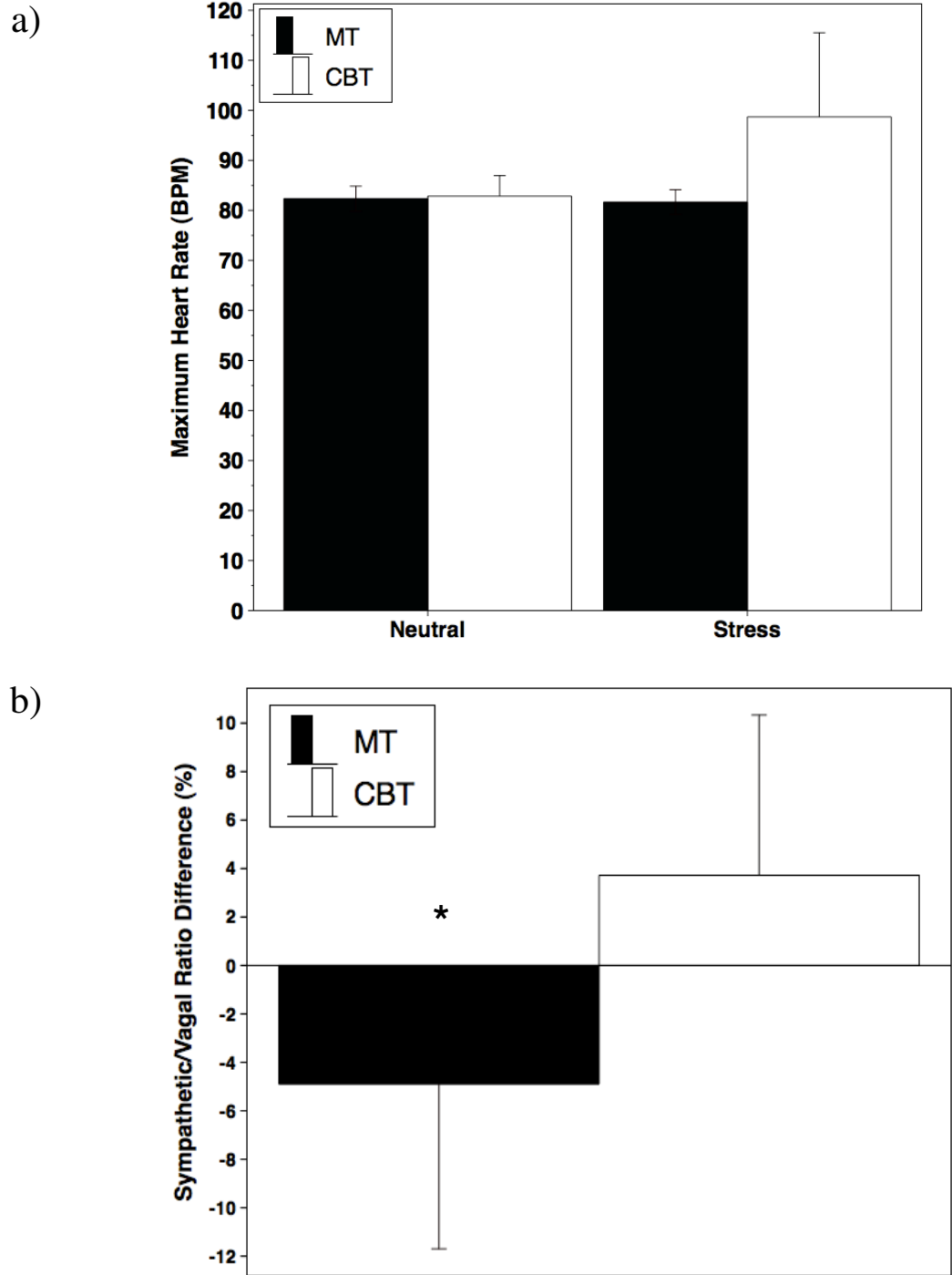
FIGURE 5. *Mindfulness Training is Associated with Lower Maximum Heart Rate and Sympathetic Tone During Stress Provocation.* a) Heart rate during neutral and stressful stories. b) Percent change in sympathetic/vagal ratio in stress versus neutral stories. * indicates F = 7.97 in treatment by condition (p = .02).

VIII. Tables

TABLE 1. Baseline Demographic Variables and Substance Use by Treatment Condition

	CBT (N=15)	MT (N=21)	Total (N=36)			
Sex	N (%)	N (%)	N (%)	F/X^2	df	p
Male	5(71.4)	13(72.2)	18(72)	0.002	1	.968
Female	2(28.6)	5(27.8)	7(28)			
Race						
White	6(85.7)	10(55.6)	16(64)	3.092	2	.213
Black	0	6(33.3)	6(24)			
Hispanic	1(14.3)	2(11.1)	3(12)			
Education level						
College or grad school	3(42.9)	2(13.3)	5(22.7)	3.216	2	.200
Partial college	1(14.3)	7(46.7)	8(36.4)			
High school/GED or part. HS	3(42.9)	6(40)	9(40.9)			
Marital status						
Never married	2(28.6)	11(61.1)	13(52)	8.504	3	.037
Married	4(57.1)	1(5.6)	5(20)			
Separated	0	1(5.6)	1(4)			
Divorced	1(14.3)	5(27.8)	6(24)			
Employment Status						
Full time	6(40)	4(19)	10(27.8)	2.843	3	.417
Part Time	3(20)	8(38.1)	11(30.6)			
Unemployed lt 1 month	1(6.7)	3(14.3)	4(11.1)			
Unemployed gt 1 month	5(33.3)	6(28.6)	11(30.6)			
Occupational level						
Higher executive	0	1(5.9)	1(4.2)	5.906	5	.315
Business manager RN	3(42.9)	4(23.5)	7(29.2)			
Administrative	2(28.6)	1(5.9)	3(12.5)			
Clerical or sales	1(14.3)	1(5.9)	2(8.3)			
Skilled manual	1(14.3)	6(35.3)	7(29.2)			
Machine operator	0	4(23.5)	4(16.7)			
Alcohol SCID Diagnosis						
Absent	2(28.6)	5(27.8)	7(28)	0.407	2	.816
Dependence	5(71.4)	12(66.7)	17(68)			
Abuse	0	1(5.6)	1(4)			
Cocaine SCID Diagnosis						
Absent	5(71.4)	8(44.4)	13(52)	1.47	1	.225
Dependence	2(28.6)	10(55.6)	12(48)			
Abuse	0	0	0			
MJ positive baseline	0	3(21.4)	3(15)	1.513	1	.219
Cocaine positive baseline	0	3(21.4)	3(15)	1.513	1	.219

TABLE 1 Continued

	CBT (N=15)		MT (N=21)		Total (N=36)				
	Mean+SD	N	Mean+SD	N	Mean+SD	N	F	df	p
Age	45+13.5	7	35.6+10.4	18	38.2+11.9	25	3.487	1	.075
Years of Education	13.7+2.2	7	13.1+2.4	18	13.2+2.3	25	.386	1	.541
Days of alcohol use in the past 28 days	0	5	.06+.24	17	.05+.21	22	.284	1	.600
Days of Marijuana use in the past 28 days	0	5	.19+.40	16	.14+.36	21	1.044	1	.320
Days of cocaine use in the past 28 days	0	5	.06+.24	17	.05+.21	22	.284	1	.600
Days of tobacco use in the past 28 days	.20+.44	5	.53+.52	15	.45+.51	20	1.654	1	.215
Number of inpatient psychiatric treatments	.57+1.5	7	.56+1.0	18	.56+1.1	25	.001	1	.975
Number of outpatient psychiatric treatments	1.3+2.0	7	.56+1.2	18	.76+1.5	25	1.291	1	.268
Number of inpatient drug treatments	.71+1.1	7	1.3+1.6	18	1.2+1.5	25	.899	1	.353
Number of outpatient drug treatments	.86+1.5	7	.89+.96	18	.88+1.1	25	.004	1	.950
Age of first alcohol use	13.8+2.0	5	12.5+2.6	8	13+2.34	13	.941	1	.353
Age of first cocaine use	13.5+17.2	4	17.6+3.7	7	16.1+10.1	11	.390	1	.548