

HEART RATE VARIABILITY (HRV) BIOFEEDBACK TRAINING WITH
YOUNG ADULT MALE PATIENTS IN TREATMENT FOR ADDICTION

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ABSTRACT

Persons in treatment for substance use disorders often experience stress and craving which are major precipitants of relapse. The present study examined the psychophysiological function of heart rate variability (HRV), its relation to clinical symptoms of stress and craving, and the feasibility of a brief HRV biofeedback (BFB) intervention as an addendum to a substance use disorder (SUD) treatment as usual. The HRV BFB training was implemented in a traditional 28-day SUD inpatient treatment program. Forty-eight young adult male patients received either treatment as usual plus three sessions of HRV BFB training over three weeks, or treatment as usual only. Participants receiving HRV BFB training were instructed to practice daily using a hand-held HRV BFB device. HRV BFB training was well tolerated by participants and supported by treatment staff. Overall, lower values for various HRV indices that suggest diminished neurocardiac adaptability were associated with reasons for drinking, higher craving, and higher levels of stress. Patients who received HRV BFB training in addition to treatment as usual demonstrated a greater, medium effect size reduction in alcohol and drug craving compared to those receiving treatment as usual only, although group differences did not reach statistical significance. In addition, HRV indices at baseline were significantly correlated with change in craving scores. Specifically, lower basal HRV was associated with less reduction in craving scores across groups. Higher respiration frequency indices in the last session were positively correlated with increased craving scores after discharge. Results suggest that HRV indices may be potential psychophysiological markers of decreased autonomic cardiac control and need for more intensive treatment, although replication and extension with larger samples is needed prior to reaching firm conclusions. Given that alcohol and drug craving often precipitates relapse, HRV BFB intervention merits further study as an adjunct treatment to ameliorate craving experienced by persons with substance use disorders.

Key words: Heart rate variability biofeedback, substance use disorders, craving

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CHAPTER I

INTRODUCTION

Alcohol abuse and dependence are common psychiatric disorders, estimated in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) to affect 17.8 million Americans (Grant et al., 2004). A variety of adverse consequences are associated with alcohol use disorders, including medical, social, and legal problems (Caetano & Cunradi, 1997). The estimated annual cost of alcohol abuse in the US is nearly \$ 185 billion (Harwood, 2000). Epidemiologic data demonstrated that the prevalence of drug use increases with age during adolescence and peaks in young adulthood (Johnston, O'Malley, Bachman, Schulenberg, & Bethesda, 2008). This indicates the need for further research and development of treatment programs aimed specifically at the adolescent to young adult population. In addition, although gender differences in alcohol use in adolescence are typically modest (Hicks et al., 2007; Johnston et al., 2008), adult studies consistently show higher levels of alcohol consumption and a greater prevalence of alcohol use disorders among males (Prescott, 2001; Sher, Grekin, & Williams, 2005).

Current treatment model

Substance Use Disorder is the diagnostic term for substance abuse and dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders (Text Revision; DSM IV-TR) (APA, 2000). Substance dependence, which includes alcoholism, is a chronically relapsing disorder characterized by at least three of the following within the past twelve-month period: tolerance; withdrawal; substance of choice is often taken in larger amounts or over a longer period than was intended; a persistent desire or unsuccessful efforts to cut down or control substance use; a great deal of time is spent in activities necessary to obtain the substance, use substance or recover from its effects; important social, occupational, or

recreational activities are given up or reduced because of excessive substance use; or substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance. Successful treatment for substance dependence typically consists of detoxification from the target substance such as alcohol followed by rehabilitation and long-term follow-up (Kenna, McGeary, & Swift, 2004). Pharmacologic approaches can be integrated into therapy, but psychosocial treatments (e.g. residential programs, individual and group therapy, twelve-step programs) have historically been the mainstay (Kenna et al., 2004). Psychosocial therapy effectively decreases using and promotes short-term abstinence however, 40 to 70% of patients typically resume substance use within one year post-treatment (Finney, Hahn, & Moos, 1996). Moos and Moos (2006) found that 60.5% of individuals who did not participate in treatment relapsed, whereas 42.9% of individuals who received treatment eventually relapsed, in this 16-year follow-up study (Moos & Moos, 2006).

Cognitive-behavioral treatment (CBT) models are among the most extensively evaluated interventions for alcohol or drug use disorders. Based primarily on Marlatt and Gordon's (Marlatt, 2005; Marlatt & Gordon, 1985) model of relapse prevention, these treatments target cognitive, affective, and situational triggers for substance use and provide skills training specific to coping alternatives. Alongside brief motivational interventions, contingency management, family-based interventions, and self-help approaches, CBT approaches for SUDs were found to be efficacious across diverse samples and rigorous conditions (Magill & Ray, 2009). In existing SUD treatments such as behavioral therapy, medication, and case management, it is notable that the focus largely lies on individual and psychosocial aspects of the maintenance of addiction, and individuals with SUD are encouraged to form alliances with professionals and/or peers to reduce the risk of relapse. In

behavioral treatments, professionals provide incentives for patients to remain abstinent, modify their attitudes and behaviors related to substance abuse, and increase their life skills to handle stressful circumstances and environmental cues that may trigger intense craving for alcohol or drugs and prompt another cycle of compulsive abuse (Budney, Moore, Rocha, & Higgins, 2006; Carroll et al., 2006; Carroll et al., 2005).

Emotional regulation, stress, and craving in SUD

It is known that emotional regulation is an important motivation for alcohol and other drug use (Pandina, Johnson, & Labouvie, 1992) and individuals with depression and anxiety use alcohol to combat intrusive emotional states (Grant, Stewart, & Mohr, 2009). According to Baker et al. (2004), the inability to effectively adapt to negative emotional challenges is central to the development and persistence of alcohol and other drug use disorders (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004). In the context of substance use, good emotional regulation involves the ability to reduce excessive arousal and deal with negative emotions such as sadness and anger (Thayer & Siegle, 2002). In a study with younger adolescents, individuals with higher ability to regulate their emotions showed less exacerbation in their substance abuse despite negative life events (Wills, Ainette, Stoolmiller, Gibbons, & Shinar, 2008). Further, impulsivity and affect lability increased the relation between alcohol use level and problems in college population (Simons, Carey, & Wills, 2009). Bates and Buckman (2011) posit that individual differences in the efficiency of psychological and physiological systems that modulate emotional arousal may make some individuals more susceptible to the use of alcohol and other drugs to regulate emotions. In turn, alcohol use both immediately and chronically interferes with the individuals' ability to self-regulate emotions at multiple physiological and cognitive levels (Bates & Buckman, 2011). Thus, although efficacious behavioral and/or pharmacological therapies in the treatment of addiction exist, it is well

known that relapse rates in addiction remain high (O'Brien, 2005; Vocci, Acri, & Elkashef, 2005). Exposure to stress, substance-related stimuli, and substances themselves may each reinstate substance-craving behavior and increase relapse susceptibility in addicted individuals (Shaham & Hope, 2005; Weiss, 2005). It is known that craving is strongly manifested in the context of stress exposure and substance-related cues and is a risk factor for relapse (Childress et al., 1993; Foltin & Haney, 2000; Rohsenow, Childress, Monti, Niaura, & Abrams, 1991). In chronic substance use, stress and craving represent not only cognitive and behavioral states but also physiological processes, which may occur outside of conscious awareness (Diamond & Aspinwall, 2003; Forgas, 2008; O'Brien, Childress, Ehrman, & Robbins, 1998).

Emotional regulation depends on a person's ability to adjust physiological arousal on a momentary basis (Gross, 1998). A key system involved in the generation of this physiological arousal is the autonomic nervous system (ANS). A flexible autonomic nervous system allows for rapid modulation of physiological states according to the situational demands (Porges, 2009). In this context, heart rate variability (HRV) reflects the degree to which cardiac activity can be modulated to cope with these situational demands (Appelhans & Luecken, 2006), if measured in situations where physiological coping responses are needed.

Stress has long been known to increase vulnerability to addiction (Del Pozo, Gevirtz, Scher, & Guarneri, 2004). The term stress refers to processes involving perception, appraisal, and response to harmful, threatening, or challenging events or stimuli (Lazarus, 1993). Stress experiences can be emotionally or physiologically challenging and activate adaptive processes to regain homeostasis (Cohen, Kessler, & Gordon, 1995; McEwen, 2007).

Emotional and physical stressors activate the same neuroendocrine systems as well as lead to physiological changes including inflammation and haemostatic activation that challenge the

cardiovascular system (Brotman, Golden, & Wittstein, 2007). A hallmark of the stress response is the activation of the ANS, hypothalamic-pituitary-adrenal (HPA) axis, and the immune, metabolic, and the cardiovascular systems. A normal stress response is essential in surviving a potentially threatening situation, without activating inadequate or excessive adrenocortical or autonomic functions (Brotman et al., 2007; McEwen, 2007). The brain affects body organs in response to acute stress through the peripheral sympathetic system, especially the heart and vasculature (Tsigos & Chrousos, 2002). For example, the amygdala receives a range of neural inputs from cortical and subcortical structures including the hypothalamus and controls behavioral and physiological responses to stressful experiences (Iwata, Chida, & LeDoux, 1987). The stress reaction is bi-directional, in that the amygdala receives information from the hypothalamus and in turn, projects to the hypothalamus and brainstem that are involved in blood pressure control (De Olmos, Alheid, & Beltramino, 1985; Pitkänen, 2000). Physiological pathways exist through which chronic stress could potentiate cardiovascular disease including increased blood pressure or coronary atherosclerosis after adjusting confounding variables such as life style variables (e.g., smoking, medical noncompliance) (Bonnet et al., 2005; Brotman et al., 2007)

There is a substantial literature on the significant association between acute and chronic stress and the motivation to use addictive substances (Khantzian, 1985; Wills & Shiffman, 1985). Many theories of addiction identify an important role of stress in addiction processes. These range from psychological models of addiction that view drug use as a coping strategy to deal with stress, to self-medicate, and to decrease withdrawal related distress (Baker, Piper, et al., 2004; Marlatt & Gordon, 1985; Russell & Mehrabian, 1975). There is considerable evidence from clinical studies supporting a positive association between acute and chronic stress and addiction vulnerability (Barrett & Turner, 2006; Cooper,

Russell, & Frone, 1990; Newcomb & Harlow, 1986). This evidence can be categorized into three types including 1) negative life events (Wills, Vaccaro, & McNamara, 1994), 2) trauma, maltreatment, and chronic stress (Clark, Lesnick, & Hegedus, 1997), and 3) cumulative adversities including socioeconomic status, family history of substance use, and comorbid psychiatric disorders, all of which contribute to addiction vulnerability (Lloyd & Turner, 2008; Turner & Lloyd, 2003).

Craving has been defined as a self-reported characteristic of a state that may promote and maintain substance dependence and that often serves as a cue immediately before self-administration (Martin, Fillmore, Chung, Easdon, & Miczek, 2006). A recent brain imaging study identified a biological cue-induced craving response among alcohol dependent persons (Weiss, 2005) and craving has been used as an outcome measure alcohol treatment studies (O'Brien, 2005). It is known that symptoms of irritability, anxiety, sleep problems, dysphoria, aggressive behaviors, and drug craving are common during early abstinence from alcohol, cocaine, opiates, nicotine, and marijuana (Budney & Hughes, 2006; Mulvaney, Alterman, Boardman, & Kampman, 1999). The severity of these symptoms has been associated with treatment outcomes (Baker, Brandon, & Chassin, 2004; Paliwal, Hyman, & Sinha, 2008). Drug craving is conceptually different from other negative emotions as it comes from desire towards a hedonic stimulus. In chronic substance use, the term is often associated with a physiological need such as wanting to seek out the desired object, thereby representing the more compulsive aspects of craving and drug seeking identified by addicted patients (O'Brien et al., 1998; Sayette et al., 2000; Wikler, 1948). Thus, the addicted patient's wanting the desired substances continued despite diminished liking of them (Robinson & Berridge, 1993; Tindell, Smith, Berridge, & Aldridge, 2009). The craving experience includes both obsessive and compulsive features such that substantial effort is required to resist thoughts and the

impulse to use (Anton, 2000).

Emotional regulation and heart rate variability

Emotions represent a person's subjective experience while interacting with the environment and includes not only challenges and threats but also an individual's ability to respond or cope with them (Frijda, 1988). The emotions that human experience while interacting with their environment are associated with varying degrees of physiological arousal (Levenson, 2003). The neurovisceral integration model (Thayer & Lane, 2000) conceptualizes substance use disorder as disorder of cognitive, emotional, and behavioral dysregulation and highlights the role of autonomic nervous system (ANS).

Heart rate variability (HRV) reflects the degree to which cardiac activity can be modulated to cope with these situational demands (Appelhans & Luecken, 2006). The term HRV refers to the beat-to-beat changes in the duration of RR intervals (RRI) in the electrocardiogram (ECG). Stable and healthy systems are characterized by oscillations that reflect the operation of multiple homeostatic reflexes (Lehrer & Vaschillo, 2003). Both the amplitude of these oscillations and the complexity of these rhythms are related to adaptive capacity (Lombardi, 2000). These oscillations are seen as 1) a measure of autonomic activity (i.e., sympathetic and parasympathetic balance) or 2) a measure of adaptive capacity (Lehrer & Vaschillo, 2003). HRV is a dynamic process of bidirectional communication between the cardiovascular and central nervous systems (Benarroch, 1997; Thayer & Brosschot, 2005). Psychophysiological models consider various HRV indices as measures of the continuous interplay between sympathetic and parasympathetic influences on heart rate. This yields information about autonomic flexibility and represents the capacity for regulated emotional responding (Appelhans & Luecken, 2006). When measured in situations requiring physiological, emotional, and cognitive response, changes in heart rate can reflect an

individual's ability to respond. For example, patients with closed head injury showed smaller heart rate response to cognitive tests (Brouwer & Van Wolffelaar, 1985). In another study, non-assertive women showed smaller heart rate responses to challenge requiring assertion (Tomaka et al., 1999).

Various physiological and environmental factors influence HRV, but the influence of the ANS on cardiac activity and ANS regulation by the central autonomic network (CAN) are particularly prominent (Appelhans & Luecken, 2006; Quintana, Guastella, McGregor, Hickie, & Kemp, 2013). The autonomic influences on heart rate are regulated in large part by the distributed network of brain areas composing the CAN (Benarroch, 1993). The CAN is known to oversee bidirectional communication related to maintaining steady autonomic function as well as reflexive and adaptive autonomic reactions. The CAN includes the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), insular cortex (IC), extended amygdala (AMYb), hypothalamus (HYP), periaqueductal gray (PAG), parabrachial nucleus (PBN), nucleus tractus solitarius (NTS), nucleus ambiguus (NAmb), and the ventral lateral medulla (VLM). In nearly all cases, these structures are reciprocally interconnected (Bates & Buckman, 2013). Importantly, the brain and the body communicate bi-directionally, meaning the body signals stress to various brain regions and, conversely, the brain also conveys stress to the body. Difficulties in regulating emotional challenges when experiencing stress and craving may be related to impairment in this feedback loop, especially in the context of alcohol and drug addiction. As the CAN supports regulated emotional responding by flexibly adjusting physiological arousal in accordance with changing situational demands (Appelhans & Luecken, 2006), alcohol and drug impairments to brain areas may interfere with neural control of autonomic functions. This may contribute to mind-body states involved in addiction, including craving, inability to regulate emotions, and stress responses (Bates &

Buckman, 2013).

As a physiological marker of autonomic flexibility, HRV reflects the moment-to-moment output of the CAN and one's capacity to generate regulated physiological responses in the context of emotional expression (Thayer & Lane, 2000; Thayer & Siegle, 2002). Specifically, low basal HRV reflects withdrawal of modulatory reflex action that reflects the body's inability to respond adequately, and can be associated with excessive cardiac sympathetic modulation and inadequate parasympathetic modulation (Task-Force, 1996), sudden cardiac death in myocardial infarction patients (Bigger, Fleiss, Rolnitzky, & Steinman, 1993), hypertension (Schroeder et al., 2003), depressive symptomology (Glaser & Glaser, 2002; Grippo & Johnson, 2002), anxiety symptoms (Watkins, Grossman, Krishnan, & Sherwood, 1998), generalized anxiety disorder (Vaschillo, Vaschillo, & Lehrer, 2006), panic disorder (Cohen et al., 2000), and post-traumatic stress disorder (Cohen et al., 1997). According to previous findings, low basal HRV is consistently associated with undesirable physical and psychological health conditions, and can be conceptualized as a marker of decreased autonomic health. On the other hand, higher levels of basal HRV have been found after successful clinical treatments with anti-depressants, beta sympathetic blockers, or psychotherapy for depression (Balogh, Fitzpatrick, Hendricks, & Paige, 1993; Ross, Quitkin, & Klein, 2002; Stein et al., 2000).

Lower basal HRV was identified in individuals with alcohol use disorders (Bennett et al., 2001), drug use disorders (Brody, Krause, Veit, & Rau, 1998), and high-craving alcohol users in comparison to a control group (Ingjaldsson, Laberg, & Thayer, 2003). Lower basal HRV was significantly correlated with higher perceived emotional stress, regardless of confounding variables such as age, trait anxiety, and various physiological indices that could impact HRV (Dishman et al., 2000). In sum, HRV is a measure of adaptive

neurophysiological regulation (Porges, 2007). Lower levels of resting state HRV predict increased vulnerability to stress (Giardino, Lehrer, & Feldman, 2000) and less active coping skills (Fabes & Eisenberg, 1997), and resting state HRV is chronically depressed in alcohol use disordered persons (Ingjaldsson et al., 2003). Existing literature thus suggests that HRV is not only an indicator of the bidirectional communication between cardiovascular and central nervous system (Thayer & Brosschot, 2005), but is also related to emotional regulation, craving, and stress in the context of substance use disorder.

Mechanism of HRV biofeedback

HRV biofeedback targets the baroreflex system, homeostatic reflexes that modulate blood pressure (Eckberg & Sleight, 1992), and thereby strengthening one of the body's important self-regulatory reflexes. When individuals try to increase their HRV, they slow their breathing to about 0.1 Hz, the first resonant frequency of the cardiovascular system, and resonance at that frequency is caused by the baroreflex activity (Lehrer & Vaschillo, 2003). In previous clinical studies, maximal increases in the amplitude of heart rate oscillation were produced when the cardiovascular system was rhythmically stimulated by breathing paced at a frequency of about 0.1 Hz (6 breaths per minute) (DeBoer, Karemaker, & Strackee, 1987; Ursino & Magosso, 2003; Vaschillo, Lehrer, Rishe, & Konstantinov, 2002; Vaschillo, 1984). This effect is linked to resonance properties of the cardiovascular system resulting from activity of the heart rate baroreflex (Vaschillo et al., 2006). The baroreflex as any other autonomic reflex can be modeled as a "closed loop" control system with feedback (Hammer & Saul, 2005; Ringwood & Malpas, 2001). The baroreflex closed loop system includes the combined effects of mechanical feed-forward from heart rate to blood pressure through changes in cardiac output and feedback from blood pressure to heart rate via baroreceptors, stretch receptors in the aorta and carotid arteries (Saul et al., 1991). Due to the baroreflex,

increase in blood pressure trigger heart rate decreases, while decreases in blood pressure trigger heart rate increases (Eckberg & Sleight, 1992).

There is substantial evidence that the human cardiovascular system has resonant features (DeBoer et al., 1987) with resonance occurring at a specific resonance frequency in the low frequency range (Lehrer & Vaschillo, 2004). When people breathe at resonance frequency, it stimulates the baroreflex, and breathing occurs for the same period as the baroreflex takes to affect blood pressure. When heart rate rises, blood pressure rises after a 5 second delay and when heart rate falls, blood pressure falls for about 5 seconds. A phase shift of 180° was found at a frequency near 0.1 Hz, corresponding to a delay of 5 seconds between the oscillations in heart rate and blood pressure (Vaschillo et al., 2006). Thus, heart rate and blood pressure oscillate 180° out of phase, while heart rate and respiration oscillate in phase with each other (Vaschillo et al., 2002). The consequent resonance effects produce large increases in both HRV and baroreflex gain, and over time can produce increases in baroreflex gain and peak air flow during a forced expiratory maneuver (Lehrer et al., 2003). At resonance frequency, the highest amplitude of heart rate oscillation occurs, and respiration and heart rate occurs in phase only at this rate, usually between .075-.120 Hz averaging around .092 Hz. This procedure, known as HRV biofeedback, produces an interaction between baroreflex and respiratory effects on HRV, both primarily mediated by the parasympathetic system. Because participants are instructed to breathe at low frequency (LF) range (.05-.15Hz), vagally mediated respiratory effects are found in the LF range (Vaschillo et al., 2006). LF HRV is the sum effect of parasympathetically mediated baroreflex regulation of HRV and sympathetically mediated baroreflex regulation of vascular tone, depending on the circumstances of the assessment (Appelhans & Luecken, 2006; Cevese, Gulli, Polati, Gottin, & Grasso, 2001; Vaschillo, Vaschillo, Buckman, Pandina, & Bates, 2011). LF activity

when measured during slow, deep breathing, or in the supine position is believed to be vagally controlled (Grasso, Schena, Gulli, & Cevese, 1997; Pomeranz, Macaulay, & Caudill, 1985). The baroreflex is mediated by the Nucleus Tractus Solitarius (NTS), which communicates directly with the insula and amygdala, the emotion-regulating centers. The NTS is the primary site of termination of afferent fibers originating from various visceral organs, including the arterial baroreceptors located in the blood vessels (Loewy, 1990). In recent studies, results suggest that the central nucleus of the amygdala may influence directly the baroreceptor reflex control of blood pressure at the level of NTS (Saha, 2005; Saha, Drinkhill, Moore, & Batten, 2002).

HRV biofeedback produces large increases in heart rate variability, usually within a few minutes of the beginning of training (Vaschillo et al., 2006). During HRV biofeedback training, the following features in the cardiovascular system are used to determine an individual's resonance frequency (Vaschillo, Vaschillo, & Lehrer, 2004). First, paced breathing at the resonance frequency elicits the highest possible amplitude of heart rate oscillation. Secondly, respiration and heart rate oscillations occur in phase (i.e., heart rate rises simultaneously with inhalation and decrease simultaneously with exhalation) only when the participant breathes at the resonance frequency (Vaschillo et al., 2004).

Decreased baroreflex gain has been indicative of physiological impaired regulatory capacity associated with poor aerobic fitness, heart failure, hypertension, and anxiety (Wheat & Larkin, 2010). Similarly, lower resting state HRV has been related to an array of health indices that are similar to those reflected in baroreflex activity. In contrast, relatively higher resting state HRV has been linked to emotional resilience and stress vulnerability (Thayer, Hansen, & Johnsen, 2010), a person's overall physical health (Britton et al., 2007), and higher flexibility (Goldberger, Peng, & Lipsitz, 2002).

HRV biofeedback training leads to acute and chronic increases in baroreflex gain (Lehrer et al., 2003). It improved symptom severity in disorders related to ANS dysfunction including asthma (Lehrer et al., 2004), hypertension (McCraty, Atkinson, & Tomasino, 2003), as well as anxiety (Thurber, Bodenhamer-Davis, Johnson, Chesky, & Chandler, 2010; Wells, Outhred, Heathers, Quintana, & Kemp, 2012), depression (Karavidas et al., 2007), craving in patients with post-traumatic stress disorder (Zucker, Samuelson, Muench, Greenberg, & Gevirtz, 2009), and food craving in high food cravers (Meule, Freund, Skirde, Vögele, & Kübler, 2012). HRV biofeedback training effectuates acute improvements during biofeedback practice whereas the presence of short-term and long-term carry-over effects is less clear (Wheat & Larkin, 2010). The utilization of HRV biofeedback training to increase individuals' resting state HRV level and ability to regulate affect better could provide an additional treatment approach to existing substance use interventions.

Current study and predictions

The present study extends previous research on substance use treatment by examining whether an additional treatment component that addresses autonomic flexibility and capacity for regulated emotional responding provided additional treatment benefit compared to treatment as usual (TAU). HRV biofeedback training was evaluated as an additional component added to substance abuse treatment as usual that included psycho-educational lectures, process groups focused on addiction, community activities, 12-step meetings, and family treatment program during a one-month stay at the facility. Treatment benefit of adding HRV biofeedback training was examined based on differences between the TAU group and the TAU plus HRV BFB group in treatment outcome variables including changes in craving scores across sessions, and post-treatment HRV and abstinence.

The current study utilized a protocol for HRV biofeedback developed by Lehrer,

Vaschillo, and Vaschillo (Lehrer, Vaschillo, & Vaschillo, 2000). It explored the efficacy of HRV biofeedback training that included individual practice using portable biofeedback devices, with young adult males who were voluntarily admitted to a residential addiction treatment program for alcohol and/or other drug use treatment. A brief, modified version of the HRV biofeedback approach that had shown efficacy in other clinical groups was used to explore whether a feasible, add-on component to an established treatment would be efficacious. Following are specific aims, rationale, and hypothesis of the present study.

Specific Aim 1. To investigate the relationship between pre-treatment HRV and pre-treatment craving and stress scores among men in treatment for substance use disorder.

Rationale: Previous findings have suggested the association between lower HRV and heightened craving (Ingjaldsson et al., 2003) and stress symptoms (Dishman et al., 2000). These relations were examined in an SUD population at treatment entry.

Hypothesis: Pre-treatment HRV will be negatively correlated with pre-treatment craving scores and stress scores in men beginning treatment for substance use disorders.

Specific Aim 2. To examine if higher pre-treatment HRV predicts better treatment outcome represented by reduced craving, more days of post-treatment abstinence, and increased likelihood of attending aftercare treatment after discharge.

Rationale: Relatively higher levels of HRV have been linked consistently to better adaptability in terms of emotional regulation and regulating autonomic arousal (Appelhans & Luecken, 2006), which theoretically should lead to less drug craving and less use of drugs to regulate emotion.

Hypothesis: Higher pre-treatment HRV will predict improvement of symptoms indicated by pre-treatment to post-treatment decreases in craving, more days of post-treatment abstinence, and increased likelihood of attending aftercare treatment after discharge compared to lower

HRV levels.

Specific Aim 3. To determine whether participants who received HRV biofeedback training demonstrate better treatment outcomes reflected by physiological indices and psychological treatment outcome variables compared to patients who received treatment as usual.

Rationale: Previous research indicated that total HRV increased during HRV biofeedback practice (Karavidas et al., 2007; Lehrer et al., 2003), after treatment (Del Pozo et al., 2004; Swanson et al., 2009; Zucker et al., 2009), and that there were chronic improvements in anxiety (Paul, 2012; Thurber, 2010; Wells, 2012), depression (Karavidas, 2007), craving in patients with PTSD (Zucker, 2009), and food craving (Meule, 2012). This is the first study that will evaluate the treatment efficacy of HRV biofeedback training with patients in recovery from substance use disorder.

Hypothesis: The HRV BFB group will exhibit higher post-treatment HRV gain, pre-treatment to post-treatment change of craving score, more days of post-treatment abstinence, and increased likelihood of attending aftercare treatment after discharge, compared to the control group.

CHAPTER II

METHODS

Participants

Participants were 48 men recruited from a Residential Addiction Treatment Services Center and part of Caron Treatment Centers Network in Wernersville, PA. Caron Treatment Center offers primary, relapse, and long-term treatment in a gender separate campus for adolescents, young adults, and adults. After a 28-day intensive care treatment, residents are encouraged to continue their aftercare at longer-term rehabilitation centers including Caron Renaissance in Boca Raton, FL. Male patients at the Young Adult Male (YAM) units (age 20-25) who met the inclusion and exclusion criteria were eligible for participation. Inclusion criteria included fluency in the English language, at least seventy-two hours since last use of alcohol or other drugs to guard against acute withdrawal effects, and near 20/20 or corrected vision. Exclusion criteria included any serious medical condition (pacemaker, hypertension, diabetes), psychiatric condition (e.g., psychosis), neurological condition (e.g., Parkinson's Disease) that would complicate physiological assessment and interpretation. Participants with cardiac arrhythmia were excluded due to difficulties in performing the HRV Biofeedback training, where arrhythmic beats may interfere with following the cardiometer tracing. Patients currently taking medications such as MAOIs, alpha/beta blockers, anti-psychotics, or detoxification medications (e.g., chlordiazepoxide, methadone hydrochloride) were excluded due to these drugs' large effects on HRV. Patients who had previously participated in biofeedback training were planned to be excluded as this may interfere with interpretation of results, but no one had received previous biofeedback training.

In total, 42 participants completed all three sessions (22 experimental and 20 controls). Out of 26 recruited patients in the experimental condition, four participants

dropped out of the study due to attrition from the treatment facility (three completed two of three study sessions). Out of 22 participants in the control group, two dropped out of the study and treatment facility. One additional experimental participant was excluded from analysis due to an ECG recording error. The experimental and control groups were on average 21.7 (SD= 1.8) and 22.0 (SD= 1.9) years of age, respectively, and reported the same average level of education, with the majority of participants reporting some college or technical education. The majority of the participants were non-Hispanic/Caucasian in terms of their ethnicity, with the exception of two participants of Hispanic origin in each group. Of note, residents were of higher socioeconomic status (SES), able to afford the 28-day private-pay treatment facility.

All 48 initial participants had clinical diagnosis of substance use disorders for alcohol dependence, opiate dependence, cannabis dependence, or amphetamine dependence. All patients had more than two clinical diagnoses of substance use disorders and met criteria for dependence on at least one substance (13 with both alcohol and other drug use disorders). There were no significant differences between the experimental and control groups, or between completed and dropped-out participants in terms of mean age or clinical diagnosis as shown in Table 1 and Table 2.

Table 1. Participants' Substance Use Disorder Diagnoses by Group

	Alcohol	Opiate	Cannabis	Stimulant	Sedatives	Hallucinogen	Average # per Person	Comorbidity
HRV BFB	7	9	11	8	2	0	1.94	6
Control	3	12	13	3	0	1	1.78	5

Table 2. Participants' Psychopathology Diagnoses by Group

	Anxiety	Dep.	Bipolar	ADHD	Cluster A	Cluster B	Cluster C	Comorbidity (Axis I)	Comorbidity (Axis II)
HRV BFB	6	6	2	6	0	2	2	14	3
Control	7	5	2	6	0	2	0	13	2

Physiological Measures

Electrocardiogram (ECG). To record ECG output, positive, negative, and ground electrodes were attached to each participant's arms and ankle (ECG sensor; model SA9306M by Thought Technology Inc.). The sensors are pre-amplified electrocardiograph sensors, for directly measuring heart electrical activity with 1000/sec sampling rate. *Respiration.* To record respiration, a high durability strain gauge latex rubber band fixed with Velcro respiration belt (SA9311M) was placed around the navel section of the abdomen. The respiration sensor converts the expansion and contraction of the abdominal area to a rise and fall of signal on the screen. Respiration volume was calibrated via an 800cc plastic bag. Finger pulse, skin temperature, and skin conductance were assessed as part of another study.

Sequences of heart beat-to-beat intervals (RRI) were recorded via ECG and exported to WinCPRS software (Absolute Aliens Oy, Turku, Finland) for analysis and calculation of HRV indices and mean HR. The RRI sequence was measured with the length of the bins of approximately 8 ms (7.8125 ms=1/128 seconds) that corresponds to the precision of current equipment (Task-Force, 1996). The complete signal was carefully edited using visual checks and manual corrections of individual RRIs. After cubic interpolation of the non-equidistant waveform, the RRI sequence was checked for artifacts and irregular beats and edited manually where necessary, using interpolation. Cubic interpolation of the non-equidistant

waveform of the RRI sequence was completed to recover an evenly sampled signal from the irregularly sampled event series, and RRIs were resampled at 4 Hz (Tarvainen, Ranta-aho, & Karjalainen, 2002). Mean respiration frequency was calculated from the abdominal respiration record. All physiological measures were calculated for each task, and then analyzed using time and frequency domain methods. Frequency domain HRV indices were calculated using Fourier analysis (Cooke et al., 1999; Taylor, Carr, Myers, & Eckberg, 1998). HR, expressed as beats per minute, was derived by calculating the average number of R-spikes in the ECG signal occurring during the entire 5-minute recording period. HRV was calculated from edited sequential RR intervals derived from the ECG signal.

Time domain indices included the standard deviation of all normal-to-normal intervals (SDNN) and the root of the mean squared differences of successive normal-to-normal intervals (Rmssd). SDNN reflects all the cyclic components responsible for variability in the period of recording and therefore encompasses short-term high frequency variations as well as the lowest-frequency components during the duration of recording. Rmssd is one of the most commonly used measures derived from interval differences and is a measurement of short-term variation that estimates high-frequency variations in heart rate (Task-Force, 1996). SDNN is the estimate of overall HRV whereas Rmssd is an estimate of short-term components of HRV. Time domain HRV measures assessing overall HRV (SDNN) provide most reliable prognostic information (Task-Force, 1996). Both SDNN and Rmssd provide useful estimates for gauging autonomic activity. The number of pairs of adjacent normal-to-normal intervals differing by more than 50ms throughout each 5min recording (NN50) was used to derive the percentage of NN50 (pNN50), a sensitive measure of fine-grained changes in parasympathetic vagal activity. These measurements of short-term variation estimate high-frequency variations in heart rate and thus are highly correlated (Task-Force, 1996).

Frequency domain indices of HF HRV (0.15–0.4 Hz) and 0.1-Hz HRV index were calculated, measured as the maximum amplitude of the RRI spectral power at 0.1 Hz (0.075–0.108 Hz). The 0.1-Hz HRV was measured within this narrow range (0.075–0.108 Hz) to accommodate individual differences in the specific cardiovascular resonance frequency (Vaschillo et al., 2002, 2006). Frequency domain statistics provided information about how power distributed as a function of frequency (Task-Force, 1996). When individuals are breathing in the high frequency range, Hf HRV activity is primarily parasympathetically mediated by vagal activity (Berntson, et al., 1997; Task-Force, 1996). In those times, Hf HRV provides insight into respiratory sinus arrhythmia, that is, changes in heart rate driven by respiration, which conserves energy, minimizes cardiac workload, and is indicative of a well-functioning system. However, individuals breathe in the low frequency range during HRV biofeedback training, thus Hf HRV does not reflect respiratory sinus arrhythmia or vagal activity.

In addition to Hf HRV, low frequency variability (Lf: 0.04–0.15 Hz) and very low frequency variability (VLf: 0.005–0.04 Hz) were calculated. LF HRV is the sum effect of parasympathetically mediated baroreflex regulation of HRV and sympathetically mediated baroreflex regulation of vascular tone (Appelhans & Luecken, 2006; Cevese et al., 2001; Vaschillo et al., 2011). VLf HRV is thought to exclusively reflect fluctuations in the sympathetic nervous system (Berntson et al., 1997) that mediate baroreflex control of vascular tone (Vaschillo et al., 2011).

In general, high respiration rate associates with high sympathetic arousal and weak vagal activity whereas lower frequency range, especially resonance frequency, stimulates the baroreflex and leads to greater HRV amplitude and baroreflex gain (Vaschillo et al., 2002). To assess the effect of respiration rate in relation with HRV, two respiration indices were

included; mean respiration frequency (RVFMean) and standard deviation of respiration frequency (RVFDev). However, there is evidence that slower respiration can lead to higher respiratory sinus arrhythmia independently of vagus nerve traffic. Saul et al. (1989) proposed that R-R interval changes follow breathing, not pressure, with a nearly fixed time delay. During slow respiration, the acetylcholine released by the vagus during exhalation may have more time to effect slowing of the heart rather than the blood pressure and baroreflex system (Saul, Berger, Chen, & Cohen, 1989). Eckberg (2009) posited a non-baroreflex but respiratory causation of respiratory R-R interval changes (Eckberg, 2009).

Psychosocial Measures

Demographic Information Questionnaire. This demographic questionnaire included questions about participants' contact information, age, ethnicity, marital status, income, and highest level of education.

Perceived Stress Scale (PSS). This 10-item questionnaire assessed patients' stress at the first and last session (Cohen, Kamarck, & Mermelstein, 1983). Items ask about how frequently participants have felt that they were under stress in the past month (e.g., "In the last month, how often have you felt nervous and "stressed"?). These items are measured on a 5-point, Likert-type scale ("never" to "very often"). Per Cohen et al. (1983), this measure has been widely used for the perception of stress with robust reliability in various clinical samples ($\alpha=.86$) and substantial evidence for concurrent and predictive validity.

Reasons for Drinking Questionnaire. This 29-item questionnaire (Labouvie & Bates, 2002) assessed reasons that an individual engages in drinking or using drugs. The original scale only measured reasons for alcohol use and was adapted to assess drug use in the present study. It contains three subscales (social, disinhibition, and suppression), which are differentially correlated with risk for escalation of use and negative consequences from use.

Although moderately correlated with each other, they exhibited distinct relationships with other use variables including use intensity and use problems. All items were coded on a 3-point scale from “Not at all important” to “Very Important.” The questionnaire has demonstrated good internal consistency ($\alpha=.82$), sound factor structure, and validity (Labouvie & Bates, 2002; Mun, von Eye, Bates, & Vaschillo, 2008).

Penn Alcohol Craving Scale (PACS). The PACS is a five-item self-administered instrument for assessing craving (Flannery, Volpicelli, & Pettinati, 1999). Frequency, intensity, and duration of thoughts about drinking are assessed along with ability to resist drinking. The final item asked to provide an average rating of craving over the course of the past week. The questions used descriptors coupled with numerical ratings ranging from 0 to 6. Garland and Lewis (2013) modified the PACS to measure drug craving by changing key words in the questionnaire. This adapted version of the PACS was found to have similar internal consistency to the original form ($\alpha=.90$). In the current study, the instruction was revised to include craving for either alcohol or drug depending on the individual’s specific craving area. Cronbach’s alphas for this modified PACS were .90, .93, and .94 respectively for the first, second, and third administrations of the questionnaire in the present study. The scale has demonstrated sound reliability ($\alpha=.85$), (Flannery, Poole, Gallop, & Volpicelli, 2003) and construct/predictive validity in clinical samples. As shown in Table

A 23-item follow-up questionnaire, based on the follow-up questionnaire utilized by the Caron Foundation, was used to measure craving, depression, anxiety, somnolence, and confidence of maintaining sobriety in the coming month. It was telephone administered at one, two, and three months after treatment.

Procedures

Rutgers research staff members consisted of two doctoral students of the Cardiac

Neuroscience Laboratory at the Rutgers Center of Alcohol Studies (CAS). Rutgers research staff provided Caron research staff with a standard recruitment script to assist in gauging the interest of potential participants. Participation in this study was strictly voluntary and did not in any way affect their access to other care or services offered by Caron. Written informed consent, approved by the Rutgers Institutional Review Board (IRB), was obtained from each patient prior to participating in the study. Participants were not charged to participate in the study, nor were they paid to do so. Rolling admissions entering the treatment facility were offered the opportunity to participate in the study. Taking part in the study occurred simultaneously with the patients' entering the treatment facility during their first week at the Caron institute. The HRV BFB condition was conducted at a separate time from the control condition to prevent contamination on the unit. The experimental group was run from March 2011 to December 2011, followed by the control group from December 2011 to February 2012. All participants in the experimental group were discharged from the unit before the control group started. After discharge, an attempt was made to administer the follow-up questionnaire once per month for three months to assess whether participants had used alcohol and/or other drugs, their level of craving, worry about staying sober after discharge from treatment, sleeping issues, depressive symptoms, medications, other treatments, smoking, and whether they continued to use the breathing techniques.

HRV Biofeedback Group

HRV BFB group participants completed three 60-75 minute sessions (one per week) of physiological monitoring and breathing training during a three-week period. Three psychosocial questionnaires (demographic information, reasons for drinking, and PSS) were completed in session 1 only, while the adjusted PACS craving measure was administered at the start of each session.

In session 1, after calibrating their respiration volumes by breathing into a standardized breathing bag, participants performed a standardized low-cognitive-demand baseline task, the *plain vanilla* task (Jennings, Kamarek, Stewart, Eddy, & Johnson, 1992) in which they viewed rectangles of various colors appearing one at a time on a computer screen and were asked to silently count the number of rectangles of an assigned color. This pre-test baseline task was designed to elicit minimal cognitive burden to compare with the physiological reactivity during the breathing training which also involves minimal cognitive functioning on the part of participants while they breathed following a visual pacer.

After the plain vanilla task, participants were introduced to the EZ-Air Plus visual breathing pacer (Biofeedback Foundation of Europe, Montreal, PQ, Canada), a pacer designed to guide inhalation and exhalation according to a visual stimuli, and were asked to breathe along with the pacer set at six-breaths per minute (BPM).

After breathing at 6 BPM, participants were asked to breathe at five different breathing frequencies (4.5, 5, 5.5, 6, & 6.5 BPM) to identify their resonance frequency (RF). The optimal RF was determined based on 1) HRV amplitude, the HRV spectral peak at respiratory frequency, 2) average LF activity, and 3) respiration oscillation occurring in phase with heart rate. Paced breathing at the RF elicits the highest possible amplitude of heart rate oscillation. At this rate, heart rate rises simultaneously with inhalation and decreases simultaneously with exhalation. Next, participants were asked to breathe with the breathing pacer set at their RF for 5 minutes. The first session ended with a repeat of the baseline task.

As homework, participants were asked to practice breathing at their RF for two 20 minute sessions each day on their own, using HeartMath EmWave portable biofeedback devices (Quantum Intech, Inc.; Boulder Creek, CA). They were instructed to breathe along the pacer as they have practiced during sessions. Of note, HRV BFB group participants

reported practicing outside of sessions with the EmWave biofeedback device for an average of 21.02 minutes per day ($SD = 12.01$).

In session 2, participants were asked to breathe along with the EZ-Air Plus pacer set at their identified RF. Physiological data were monitored to determine if participants were accurately breathing at their RF. If not, they were coached in how to do so, or asked to breathe at a rate 0.5 BPM faster or slower until a more accurate RF was identified. Specifically, the biofeedback trainer closely monitored whether participants' heart rate rose simultaneously with inhalation and decreased simultaneously with exhalation. Next, for the biofeedback component of the training, the participant's instantaneous heart rate and respiration rate data were shown on the screen (shown as cardiometer and respiratory tracings). They were asked to breathe at a rate that maximized HRV as well as synchronized heart rate and respiration rate as closely as possible.

In session 3, experimental group members completed respiration calibration, the plain vanilla baseline task, breathing with the visual pacer set at their RF, breathing with the cardiometer tracing lines, and the post-test plain vanilla task.

Control Group

In session 1, control group participants were administered the plain vanilla baseline task after respiration calibration. To provide additional physiological data, they performed 5 minutes of paced breathing at 6 BPM. However, no theoretical education, instruction or biofeedback was provided, and participants were not instructed to practice any kind of paced breathing. The session ended with a repeat of the plain vanilla task.

Control participants completed the adjusted PACS at session 2 but no physiological recording took place. In session 3, participants completed respiration calibration, the baseline plain vanilla task, 5 minutes of paced breathing at 6 BPM, and post-test plain vanilla task.

In an attempt to encourage continuous participation and reduce attrition, control group participants were offered instruction in HRV BFB after the final follow-up.

An overview of both experimental and control group sessions are presented in the following Table 3.

Table 3. Overview of experimental and control group sessions

Experimental Group

Task	Session 1 (Week 1)	Session 2 (Week 2)	Session 3 (Week 3)
1	Plain Vanilla* (Baseline) (5min)	Resonance frequency breathing (5min)	Plain Vanilla (5min)
2	6 breaths per minute (5min)	Res. freq. breathing with instruction (5min)	Resonance frequency breathing (5min)
3	Resonance frequency assessment (10min)	HRV BFB instruction (5min)	HRV BFB (5min)
4	Resonance frequency breathing (5min)	HRV BFB (5min)	Plain Vanilla (5min)
5	Plain Vanilla (5min)		

Control Group

Task	Session 1 (Week 1)	Session 2 (Week 2)	Session 3 (Week 3)
1	Plain Vanilla (Baseline) (5min)	X	Plain Vanilla (5min)
2	6 breaths per minute (5min)	X	6 breaths per minute (5min)

Risks, benefits, and confidentiality

Participants in the HRV BFB group were informed that they may receive direct benefits from participating in this training, including decreased stress levels; however, they were informed that these methods have not been used in patients in addiction rehabilitation, and that they may receive no direct benefit. The risk that participants may feel symptoms of hyperventilation, such as lightheadedness or dizziness, due to regulation of the depth of breathing was disclosed. Participants were advised against "trying too hard" which could potentially lead to hyperventilation. The biofeedback trainers reiterated the purpose of the training, which is to help participants to relax, not to push themselves over the limit. The potential risks to participants were minimal and reasonable in relation to the potential personal benefit of participation and the importance of knowledge that may result from the present study. Individual results from the physiological measures were not provided to participants or to Caron staff. One exception was that if a cardiac abnormality was detected during our assessment, participants were informed that there may be an indication of abnormality, and they should follow up with their physician.

Analysis

All psychological measures were coded by two undergraduate research assistants and were matched and cleaned by doctoral-level researchers using the SAS software (SAS[®] 9.3., 2013). Preliminary analyses consisted of examining means, standard deviations, and distributional properties of all measures. Analysis of variance was used to investigate within group and between group differences in physiological and psychological measures. Linear regression was used to investigate associations between basal HRV levels (HR, pNN50, SDNN, Rmssd, Hf/Lf/Vlf HRV, and respiration frequency), baseline stress scores, baseline craving scores, and outcome measures (change in craving scores and post-treatment outcome variables).

CHAPTER III

RESULTS

Preliminary Analysis

All questionnaire (Reasons for Drinking, Perceived Stress Scale and Penn Alcohol Craving Scale) and physiological indices (HR Mean, SDNN, pNN50, Rmssd, Hf, Lf, Vlf HRV, RVFMean, RVFDev) were checked for skewness and kurtosis and normalized using logarithmic transformation. Testing for multivariate outliers was conducted using Mahalanobis distance (D2) with a criterion set at $p < .001$ (de Maesschalck, Jouan-Rimbaud, & Massart, 2000). No outliers were detected. Baseline craving data for one participant was lost. The experimental group and control group were not significantly different on baseline measures of craving, stress, or HRV (all $p > .05$; Table 4).

Pearson product correlations were used to examine associations between all physiological indices and psychological questionnaires administered in baseline, Session 1, across all participants. In baseline session 1, before any of the training components were implemented, most psychological variables (Reasons for Drinking, Perceived Stress Scale, and Penn Alcohol Craving Scale) were highly correlated (Table 5), although social reasons for substance use were not significantly correlated with disinhibition and suppression reasons for use. As shown in Table 5, social, disinhibition, and suppression reasons for substance use were positively correlated with craving and stress scores in both groups. Table 5 shows the results of correlational analysis between all psychological measures in the study, including baseline reasons for drinking, craving, and stress, subsequent craving scores in later time points, change of craving scores¹, and how much participants were worried about staying sober².

¹ Session 3 PACS scores were subtracted from session 1 PACS scores

² The more worried, the higher the score in a 1 (Not worried) to 10 (Extremely worried) scale

Table 4. Between group differences in heart rate variability, perceived stress, and craving at baseline session 1

Variable	Experimental Group	Control Group	<i>t</i>	<i>df</i>	<i>p</i>
	<i>n</i> = 21	<i>n</i> = 20			
HR (log)	4.32 (0.15)	4.31 (0.14)	−0.25	39	.81
pNN50 (log)	2.31 (1.42)	2.57 (1.22)	0.63	39	.53
SDNN (log)	3.84 (0.45)	3.93 (0.45)	0.62	39	.54
Rmssd (log)	3.44 (0.71)	3.62 (0.56)	0.87	39	.39
Hf HRV (log)	5.67 (1.50)	6.08 (1.20)	0.96	39	.35
Lf HRV (log)	6.39 (1.09)	6.56 (1.18)	0.47	39	.64
Vlf HRV (log)	6.11 (0.80)	6.15 (1.01)	0.16	39	.88
Respiration freq. (log)	−1.38 (0.31)	−1.34 (0.18)	0.48	39	.63
Perceived Stress (log)	3.31 (0.24)	3.21 (0.26)	−1.27	39	.21
Craving (log)	2.58 (0.76)	2.50 (0.77)	−0.34	38	.73

Notes. Standard deviations in parentheses; HR= heart rate, pNN50= percent of normal-to-normal intervals greater than 50ms, SDNN= standard deviation of normal-to-normal intervals, Rmssd= square root of the mean squared difference of successive normal-to-normal intervals, Hf HRV= high frequency range of the power spectral analysis, Lf HRV= low frequency range of the power spectral analysis, Vlf HRV= very low frequency range of the power spectral analysis, Perceived Stress= total Perceived Stress Scale score, Craving= Total PENN alcohol and drug craving score.

Table 5. Correlations between all psychological measures

	1	2	3	4	5	6	7	8	9	10
1. Social Reasons (log)	-									
2. Disinhibition (log)	.08	-								
3. Suppression (log)	-.02	.72***	-							
4. Craving Session 1 (log)	.13*	.50***	.57***	-						
5. Craving Session 2 (log)	-.13*	.60***	.58***	.77***	-					
6. Craving Session 3 (log)	-.07	.39***	.54***	.62***	.78***	-				
7. Craving Follow-up (log)	.20**	-.14	.02	.49***	.42***	.65***	-			
8. Craving Change (S1-S3)	-.19**	-.09	-.14**	-.46***	-.05	.23***	-.10	-		
9. Stress (log)	.52***	.31***	.24***	.48***	.39***	.22***	.30***	-.31***	-	
10. Sober Follow-up (log)	-.07	.28***	.36***	.46***	.38***	.41***	.52***	-.08	.02	-

Note. * = $p \leq .05$, ** = $p \leq .01$, *** $p \leq .001$.

As shown in Table 5, disinhibition and suppression reasons for drinking were positively correlated with craving scores ($r = .39 - .60, p < .001$). Both reasons were also positively correlated with how much participants were worried about staying sober after discharge from treatment by the first follow-up interview ($r = .28, .36, p < .001$), whereas social reasons were not. Feeling worried about staying sober was also positively correlated with craving indices ($r = .38 - .52, p < .001$). It is notable that the baseline stress score was strongly positively correlated with all craving indices ($r = .22 - .48, p < .001$) and all three reasons for drinking subscales ($r = .24 - .52, p < .001$).

HRV indices were all highly correlated ($r = .54 - .96$; all $p < .001$), therefore, only frequently used and widely validated time-series measures (SDNN, Rmssd & pNN50), and spectral indices (Hf HRV, Lf HRV & Vlf HRV) were used in the following analyses. In relation to physiological indices, suppression reasons for drinking were negatively correlated with Lf HRV ($r = -.36, p < .05$), whereas social reasons for drinking approached significance with Vlf HRV ($r = -.27, p = .08$) and SDNN ($r = -.27, p = .08$) at baseline, Session 1.

Relationship between Pre-treatment Craving, Stress, and HRV

The first hypothesis, that pre-treatment HRV will be inversely correlated with pre-treatment levels of craving and stress, was tested using Pearson's r coefficients. As predicted, HRV indices measured during the baseline task of Session 1 were inversely correlated with baseline stress score: SDNN ($r = -.44, p < .01$), Rmssd ($r = -.34, p < .05$), Hf HRV ($r = -.30, p = .05$), Lf HRV ($r = -.36, p < .05$), and Vlf HRV ($r = -.32, p < .05$). However, significant correlations were not found between baseline HRV indices and craving scores.

The anticipated association between baseline HRV indices and stress and craving scores was observed in Session 3. HRV indices measured during the baseline task were inversely correlated with craving and stress scores across groups. Craving scores were

inversely correlated with SDNN ($r = -.35, p < .05$), Rmssd ($r = -.32, p < .05$), pNN50 ($r = -.31, p < .05$), Lf HRV ($r = -.40, p < .05$), and Hf HRV ($r = -.29, p = .06$) approached significance. In terms of stress scores, a regression analysis confirmed that stress score (session 1) predicted SDNN ($\beta = -.16, t(39) = -2.02, p = .05$) and Lf HRV ($\beta = -.08, t(38) = -2.43, p < .05$) in Session 3, and explained significant proportions of variance in them (SDNN: $R^2 = .09, F(1, 39) = 4.08, p = .05$, Lf HRV: $R^2 = .16, F(1, 39) = 7.68, p < .01$).

Relationship between Pre-treatment HRV and Post-treatment factors

To investigate the second hypothesis that pre-treatment HRV will be correlated with improvement of symptoms indicated by lower post-treatment craving score, post-treatment abstinence, and continuous treatment participation, Pearson correlation coefficients (2-tailed) were computed. There was no significant association between pre-treatment HRV and post-treatment craving or sober² scores from the first follow-up interview. However, three HRV indices measured during the HRV breathing task (6 BPM, Session 1) significantly predicted change in craving scores from session 1 to session 3, measured in the beginning of each session. Specifically, lower levels of the three HRV indices measured during the breathing task were significantly associated with less change in craving scores across groups.

Lower levels of SDNN indices measured in session 1 significantly predicted less change in craving scores, $\beta = -.03, t(38) = -2.11, p < .05$. SDNN explained a significant proportion of variance in craving change scores, $R^2 = .10, F(1, 38) = 4.45, p < .05$. Similarly, lower levels of Rmssd ($\beta = -.04, t(38) = -2.33, p < .05$) and Hf HRV ($\beta = -.08, t(38) = -2.43, p < .05$) indices also significantly predicted less change of craving scores and explained significant proportions of variance in them (Rmssd; $R^2 = .13, F(1, 38) = 5.45, p < .05$, Hf HRV; $R^2 = .13, F(1, 38) = 5.90, p < .05$). In addition, pNN50 ($\beta = -.05, t(38) = -1.91, p = .06$)

² How worried participants were about staying sober after discharge from treatment

and Lf HRV ($\beta = -.05$, $t(38) = -1.76$, $p = .08$) approached significance towards the anticipated direction, yielding small effect sizes³ of .09 (pNN50) and .08 (Lf HRV) in explaining the variance of change of craving scores.

As an additional finding, respiration frequency indices measured during the last session were positively correlated with post-treatment craving score in the first follow-up interview (RVFDev; $r = .59$, $p = .001$), or approached significance (RVFMean; $r = -.36$, $p = .06$).

Physiological changes during HRV breathing training

As a manipulation check of the HRV breathing training in the experimental group, we compared HRV measures during the baseline and RF breathing tasks of session 1. The manipulation check was performed on session 1 to ensure that participants in the experimental group were breathing as instructed without difficulty in the beginning of the training period. Statistically significant physiological and respiratory changes in the expected direction were observed (Table 6), indicating that participants were able to perform the breathing training.

³ f^2 A effect sizes of 0.02, 0.15, and 0.35 are termed small, medium, and large, respectively, at Jacob Cohen (1988). Statistical Power Analysis for the Behavioral Sciences (second ed.). Lawrence Erlbaum Associates.

Table 6. Physiological changes in experimental group from baseline to resonance frequency breathing task during session 1

Variable	Baseline Assessment (SD)	Resonance Frequency Breathing (SD)	<i>t</i>	<i>p</i>
HR (log)	4.31 (0.15)	4.32 (0.13)	0.18	.86
pNN50 (log)	2.43 (1.31)	2.87 (0.96)	1.35	.18
SDNN (log)	3.84 (0.45)	4.42 (0.43)	9.88*	<.01
Rmssd (log)	3.44 (0.71)	3.87 (0.59)	5.26*	<.01
Hf HRV (log)	5.67 (1.50)	6.09 (1.24)	1.98	.06
Lf HRV (log)	6.39 (1.09)	8.45 (0.93)	9.27*	<.01
Vlf HRV (log)	6.11 (0.80)	5.95 (0.92)	-0.66	.52
Respiration freq. (log)	-1.36 (0.25)	-2.32 (0.15)	-16.73*	<.01

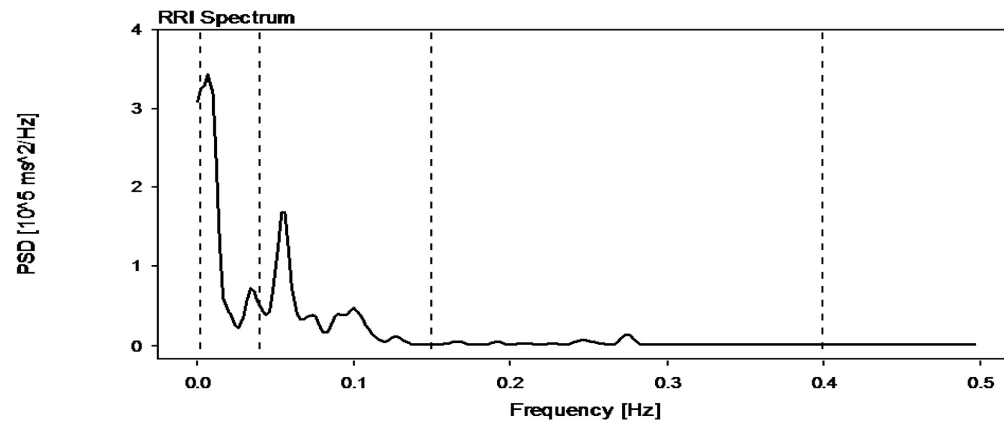
As further evidence that the twenty cumulative minutes of HRV biofeedback training resulted in significant increases in HRV levels from baseline, statistically significant physiological and respiratory changes in the expected direction were found (Table 7). Specifically, low frequency variability (Lf: 0.04-0.15 Hz) exhibited significant change both from baseline to resonance frequency breathing task and from pre-session to end of session baseline tasks. A graphic example of a participant's physiological change from baseline task, breathing at 6-breaths-per-minute, and breathing at a resonance frequency of 4.5-per-minute is shown in Figure 1.

Table 7. Physiological changes in experimental group from pre-session to end of session in session 1

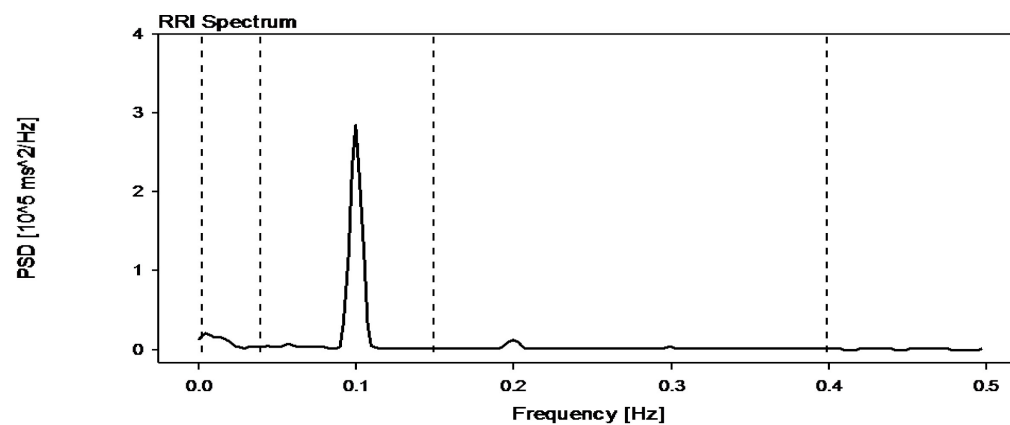
Variable	Pre-session (SD)	Post-session (SD)	<i>t</i>	<i>p</i>
HR (log)	4.31 (0.14)	4.29 (0.13)	−0.49	.62
pNN50 (log)	2.43 (1.31)	2.39 (1.32)	−0.14	.88
SDNN (log)	3.84 (0.45)	4.06 (0.41)	3.33 [*]	<.01
Rmssd (log)	3.44 (0.71)	3.60 (0.66)	1.67	.11
Hf HRV (log)	5.67 (1.50)	5.91 (1.45)	1.42	.17
Lf HRV (log)	6.39 (1.09)	7.13 (1.04)	3.48 [*]	<.01
Vlf HRV (log)	6.11 (0.80)	6.37 (0.73)	1.36	.19
Respiration freq. (log)	−1.36 (0.24)	−1.67 (0.39)	−3.27 [*]	<.01

Figure 1. Spectral analysis of various physiological changes at baseline (experimental group participant #44)

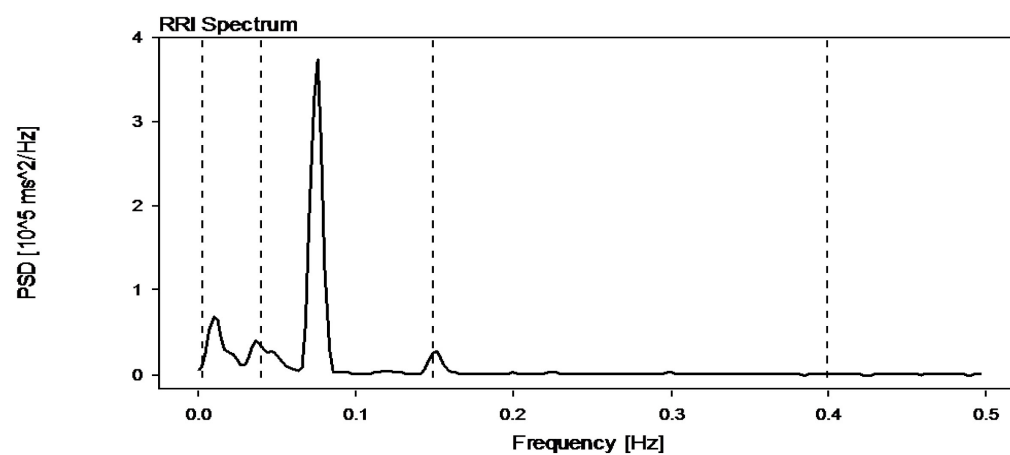
Session1, Task 1 (Baseline / Plain Vanilla)



Session1, Task 2 (breathing at 6 breaths per minute)



Session1, Task 3 (breathing at resonance frequency - 4.5 breaths per minute)



Group differences in post-treatment HRV, craving, and other factors

It was predicted in the third hypothesis that the HRV biofeedback training group would exhibit higher post-treatment HRV, lower post-treatment craving score, higher post-treatment abstinence, and continuous treatment participation compared to the control group.

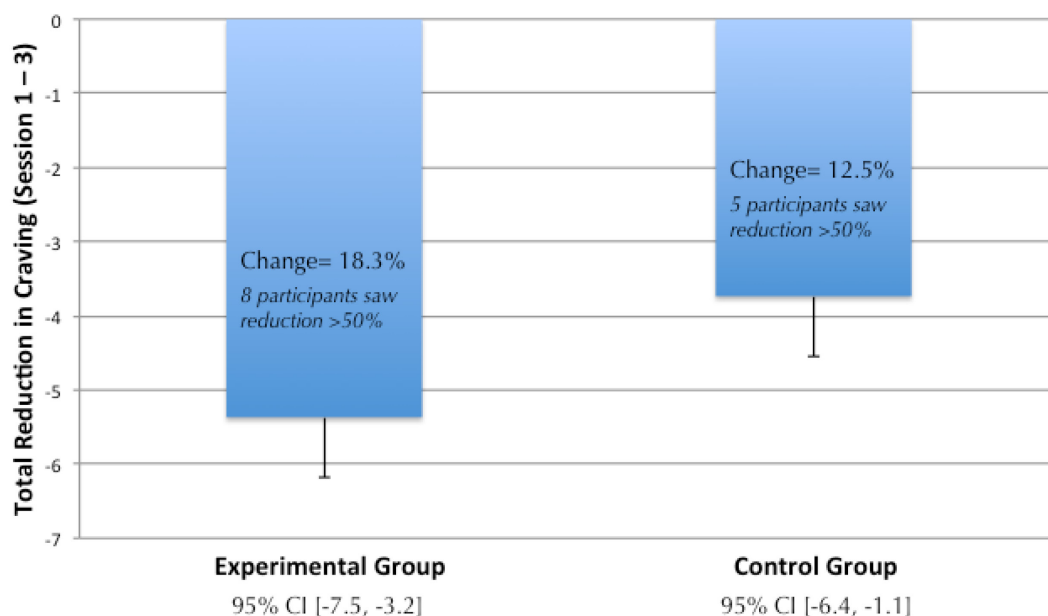
There were no significant physiological differences between the HRV biofeedback and control groups at baseline in session 3, indicating that two weeks of HRV biofeedback training and additional individual practice were not sufficient to effect chronic changes in HRV in this sample (Table 8). None of the anticipated group differences in HR, time series HRV, spectral HRV, or respiration frequency indices approached significance.

Table 8. Physiological differences between experimental and control groups at baseline, session 3

Variable	Experimental Group <i>n</i> = 21	Control Group <i>n</i> = 20	<i>t</i>	<i>df</i>	<i>P</i>
HR	82.10 (17.01)	77.20 (12.35)	−1.05	39	.30
pNN50	14.39 (16.61)	16.19 (13.80)	−0.25	39	.80
SDNN (log)	3.90 (0.61)	3.86 (0.33)	0.29	31	.80
Rmssd (log)	3.40 (0.83)	3.47 (0.52)	0.29	34	.78
Hf HRV (log)	5.60 (1.64)	5.87 (1.06)	0.61	39	.54
Lf HRV (log)	6.77 (1.44)	6.61 (0.80)	−0.04	32	.66
Vlf HRV (log)	6.00 (1.10)	6.17 (0.91)	0.53	39	.60
Respiration freq.	0.24 (0.09)	0.26 (0.06)	1.14	33	.26

The HRV BFB group showed a larger mean reduction in alcohol and drug craving over the course of treatment than controls (mean reduction= 5.5 points versus 3.7); the effect size was medium (Cohen's $d=.35$), however, the difference was not statistically significant, $t(39)= .99, p= .33$, (figure 1). In terms of percentage, the average percent change in craving score in the experimental group was 18.3 %, whereas the average percent change in craving score in control group was 12.5 %. Participants who showed greater than fifty percent reduction in craving, a typical clinical cutoff rate, were eight in the experimental group (38%) and five in the control group (25%).

Figure 2. Total reduction in alcohol and drug craving from session 1 to session 3, by group



There was a significant group difference in telephone follow-up interview completion rate at one month, $\chi^2 (1, N= 41)= 5.85, p < .05$, two months, $\chi^2 (1, N= 41)= 15.93, p < .0001$, and three months, $\chi^2 (1, N= 41)= 11.11, p < .001$. The first, second and third follow-ups were completed by 18, 15, and 11 participants in the HRV BFB group, respectively. In the control group, nine, two, and one participants completed the three respective follow-ups. Thus, planned group comparisons at follow-up could not be completed.

CHAPTER IV

DISCUSSION

This present study investigated the relationship between various HRV indices and psychological variables including craving and stress, and the efficacy of a brief heart rate variability biofeedback intervention offered in the context of inpatient substance use disorder treatment program. Lower levels of HRV at baseline were associated with increased vulnerability to stress as well as less decrease in craving scores in the overall sample. Also, higher respiration frequency indices by the end of treatment were indicative of increased craving after discharge. Persistent changes in HRV were not found, but the HRV BFB group demonstrated a medium effect size trend of greater overall reduction in craving from session 1 to session 3, supporting potential clinical benefit of adding HRV BFB to TAU.

According to Labouvie and Bates (2002), increases in suppression and disinhibition reasons lead to increases in use problems and maintenance of high levels of both reasons during treatment should predict poorer treatment outcomes. In the present study, actual alcohol or drug use intensity was not measured, but stress, craving, and worrying about staying sober were all highly correlated with disinhibition and suppression reasons, indicative of participants' difficulties related to craving and stress that could potentially increase the risk of problematic usage after treatment.

In this context, Lazarus' (1993) cognitive meditational approach offers a conceptual link between the cognitive aspect of drinking (reasons for drinking) and the affective component (craving, stress, and worrying). As shown in results, craving and feeling worried about staying sober were highly correlated throughout sessions, as was stress and craving scores. According to Lazarus (1991), the most important cognitive content in the emotion process consists of beliefs and appraisals of person-environment encounters as harms, threats,

or challenges. In this context, alcohol and drug consumption produces reliable impairments in cognitive functioning and information processing (Hull & Bond, 1986; Paterniti, Bisserbe, & Alperovitch, 1999), thereby diminishing the ability to regulate affect through regulation of cognitive activity and cognitive content (Lazarus, 1991; Wenzlaff & Wegner, 2000).

In line with this theory, Carpenter and Hasin (1998) suggest that, “experiences of alcohol as disrupting one’s appraisal of incoming negative information and/or as facilitating distraction from such information and, thereby, as facilitating the avoidance or suppression of unwanted thoughts result in the development of suppression reasons for drinking”. Thus, suppression of negative thoughts is likely to reduce negative affect and stress, at least temporarily. Consequently, suppression reasons are strongly related to use problems (Labouvie & Bates, 2002). In line with these previous findings, suppressive reasons were associated with HRV indices representative of diminished autonomic function and the baroreflex system in the current study. Specifically, the Lf HRV index during the HRV BFB procedure of breathing 6 BPM was inversely correlated with suppression reasons for substance use. Typically, low HRV is associated with decreased autonomic health and capacity to modulate cardiac activity to meet changing situational demands (Appelhans & Luecken, 2006). In the present study, suppression reasons exhibited a relationship with physiological indices indicative of decreased autonomic health.

Relationship between Pre-treatment Craving, Stress, and HRV

As predicted in the first hypothesis, various HRV indices (SDNN, Rmssd, Hf HRV, Lf HRV, and Vlf HRV) measured during the baseline task of the first session were inversely correlated with baseline stress scores. This supports the hypothesized association between lower levels of resting state HRV and increased vulnerability to stress, suggested in previous studies (Giardino et al., 2000). This association was not found for baseline craving scores in

Session 1. However, HRV indices measured during the baseline task were negatively correlated with craving and stress scores in Session 3 across groups. These findings are in accordance with a recent study that observed that resting state autonomic cardiac control predicted levels of overall craving related to alcohol in a population of alcohol dependent outpatients (Quintana et al., 2013). This study indicates that alcohol craving may help to characterize those less likely to respond to treatment. This emphasizes the potentially important role of autonomic cardiac control in alcohol use disorders (Quintana et al., 2013). Similarly, results from the present study indicated that patients with lower basal HRV may require more intensive treatment, as they exhibited reduced capacity for self-regulation and ability to inhibit craving as reflected in their resting state physiology.

Relationship between Pre-treatment HRV and Post-treatment factors

HRV indices measured during the baseline HRV breathing task (6-breath-per-minute) were associated with change of craving scores from session 1 to session 3, in the full sample. Three HRV indices (SDNN, Rmssd, Hf HRV) were significantly negatively correlated with change in craving scores. Thus, lower basal HRV was associated with less decrease in craving scores across groups. A follow-up regression test was conducted to examine the effect size of various HRV indices predicting change of craving scores and results indicate that basal SDNN, Rmssd, and Hf HRV significantly predicted change of craving scores. In addition, the relationship of change in craving to pNN50 and Lf HRV approached significance, although the effect size was small. This indicates that HRV may reflect self-regulatory effort required to cope with cravings, and that autonomic cardiac control plays an important role in self-regulation (Thayer, Hansen, Saus-Rose, & Johnsen, 2009). According to Garland et al. (2011), alcohol dependent patients who were less likely to relapse had increased HF HRV, indicative of greater self-regulatory effort required to tolerate alcohol-related cues. Combined with

Quintana et al. (2013) and findings from the present study, this suggests that basal HRV could function as a biological marker that could inform treatment in relation to self-regulation, craving, and post-treatment abstinence. The relatively stronger prediction of craving scores by HRV indices during 6-breath-per-minute breathing periods suggests that differences in baroreflex activity might be involved in this prediction.

Additionally, respiration frequency indices measured in the last session were significantly positively correlated with post-treatment craving score in the first follow-up interview (RVFDev), and approached significance (RVFMean). These observations are consistent with previous findings about high respiration rate being associated with high sympathetic arousal and weak vagal activity, whereas the lower frequency range, and especially the resonance frequency, stimulates the baroreflex and leads to greater HRV amplitude and baroreflex gain (Vaschillo et al., 2002). Thus, higher RVFMean associates with lower HRV, and respiration frequency in the current study exhibited a tendency of positive correlation with post-treatment craving score. Namely, higher respiration frequency indices observed by the end of the treatment were indicative of increased craving after discharge.

Group differences in post-treatment HRV, craving, and other factors

The primary within treatment outcome measure used in the present study was alcohol and drug craving. Craving decreased in both groups as would be expected given that all received 28 days of inpatient SUD treatment. Although there were no significant differences between the HRV BFB group and control group in craving at the final session, participants receiving HRV biofeedback did demonstrate a small to medium effect size trend of greater overall reduction in craving from session 1 to session 3, supporting an interpretation of potential added clinical benefit from HRV biofeedback, even within the context of intensive inpatient treatment as usual. Future research is needed to replicate this finding in a sample

with more power to empirically support the hypothesis of enhanced efficacy.

There were no significant differences in HRV between the experimental and control groups at pre-session baseline in session 3, indicating that two weeks of HRV biofeedback training and practice did not affect chronic changes in HRV. One limitation of the present study was that participant report of daily practice was not verified. Thus, it is not certain that the average reported 20 plus minutes of daily practice accurately reflected their actual time spent practicing. Nonetheless, the absence of a chronic increase in HRV is consistent with the findings of some other studies that HRV biofeedback did not induce persistent changes in HRV, even though it affected improvements in clinical symptoms such as craving and depression (Hassett et al., 2007; Zucker et al., 2009). According to a post-hoc power analysis, 102 or more participants are need per group to have 80% power of detecting a medium effect size ($\alpha = 0.5$). Longer period of training (4-12 weeks) has led to increased effect size in other clinical studies (Hassett et al., 2007; Karavidas et al., 2007; Zucker et al., 2009). In addition, the current results are also limited to young adult males and may not generalize to women or older age groups.

Although we anticipated HRV biofeedback would ameliorate craving through chronic improvements in autonomic flexibility, it is possible that participants trained in HRV biofeedback used the resonance frequency breathing technique to help regulate acute states of alcohol and drug craving in the moment when they occurred. Interestingly, some participants in the experimental group anecdotally reported that they used HRV biofeedback to successfully subdue acute anxiety and panic symptoms. At follow-up, three participants with panic disorder noted that the technique effectively offset full-blown panic attacks when practiced at the first sign of panic symptoms. It may be that after HRV biofeedback training, individuals use resonance frequency breathing in the moment when the experience or

anticipate affective challenges in order to regulate autonomic arousal or state. Conceivably, such strategic use of this breathing technique could initiate automatically after extended practice in a full HRV biofeedback protocol, or could be implemented consciously and effortfully. Further research is needed to determine whether such strategic use could at least partially underlie the salutary clinical effects of HRV biofeedback found in previous studies.

With respect to feasibility of implementation, it is noteworthy that HRV biofeedback participants were generally enthusiastic about the intervention and counselors on the unit were supportive of the intervention. Anecdotal reports from patients to counselors about the benefits of HRV biofeedback led the Young Adult Male Unit at the treatment facility to incorporate HRV biofeedback training into their standard inpatient treatment protocol.

With respect to post-treatment outcomes, attrition, especially in the control group, precluded between-group analyses. One challenge in this substance use disordered population was that upon leaving inpatient treatment, patients are routinely advised to change their phone number to make it difficult for persons in their previous substance use network to contact them. Further, in keeping with the treatment site's best care policies, almost all participants were referred to extended care after inpatient treatment. Patient privacy laws made contacting individuals at these facilities difficult. Although participants were asked at their final session to add the experimenters to their 'safe contact list' once they arrived at their extended care treatment facility, few did. Follow-ups with the experimental group were more successful, than with the control group. The experimental group had substantially more contact with the researchers compared to the control group: two 20-minute sessions for controls compared to three 60-75 minute sessions for the experimental group. Thus, extent of contact was conflated with group assignment in this preliminary study. This may have contributed to heightened rapport between researchers and the experimental group that

enhanced follow-up. Further, involvement in HRV biofeedback training appeared to increase adherence to the research protocol. It is possible this effect may generalize to affect an increase in treatment motivation.

The present study, though unable to discern statistically significant effects of brief HRV biofeedback, did provide potentially promising results. Effect size estimates suggest that participants receiving HRV biofeedback exhibited additional reductions in craving through the course of intensive inpatient treatment, compared to the treatment as usual controls. In addition, participant feedback was extremely positive and the intervention was well received by clinical staff at the Caron Foundation. The results support the potential utility of further examination of HRV biofeedback as an addendum to SUD treatment as usual.

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APPENDICES

Appendix 1. Brief description of each session in experimental and control group

Experimental group (HRV biofeedback group)

Session 1 (Recording session): Orientation/Administer all questionnaires - Hook up physiological instruments (respiration belt, ECG, BVP, skin temperature, skin conductance) - Respiration calibration - Collect baseline physiology data - Breathe with pacer at 6 BPM - Determine resonance frequency (RF) - Breathe with pacer at RF - Recollect baseline physiology data - Assign homework practice

Session 2 (Training session): Discuss homework/craving questionnaire - Hook up physiological instruments (respiration belt, ECG) - Breathe with pacer at RF - Provide instruction and practice for pursed-lips & abdominal breathing - Breathe with pacer at RF using pursed-lips & abdominal breathing - Introduce cardiometer tracing line - Breathe with pacer at RF with tracing line - Breathe with tracing line again - Assign homework

Session 3 (Recording session): Discuss homework/craving questionnaire - Hook up physiological instruments (respiration belt, ECG, BVP, skin temperature, skin conductance) - Respiration calibration - Collect baseline physiology data - Breathe with pacer at RF - Breathe with cardiometer tracing line - Recollect baseline physiology data - Final discussion

Control group

Session 1 (Recording session): Orientation/Administer all questionnaires - Hook up physiological instruments (respiration belt, ECG, BVP, skin temperature, skin conductance) - Respiration calibration - Collect baseline physiology data - Breathe with pacer at 6 BPM - Recollect baseline physiology data

No Session 2: Filled out craving questionnaire

Session 3 (Recording session): Craving questionnaire – Physiological instruments (respiration belt, ECG, BVP, skin temperature, skin conductance) - Respiration calibration – Collect baseline physiology data - Breathe with pacer at 6 BPM - Recollect baseline physiology data – Final discussion
