HEART RATE VARIABILITY BIOFEEDBACK FOR COLLEGE STUDENTS
RECOVERING FROM SUBSTANCE USE DISORDER: A LONGITUDINAL
ANALYSIS OF CRAVING CHANGES

by

NOUR ALAYAN

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Lucille Eller, PhD, RN
and approved by

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ABSTRACT OF THE DISSERTATION

Heart Rate Variability Biofeedback for College Students Recovering from Substance Use Disorder: A Longitudinal Analysis of Craving Changes

By Nour Alayan

Dissertation Director:
Lucille Eller, PhD, RN

**Purpose:** The purpose of this dissertation was to provide longitudinal evidence on heart rate variability biofeedback (HRVB) as an anti-craving intervention for college students recovering from substance use disorder (SUD).

**Methods:** Previous studies showed promise of the therapeutic potential of HRVB to reduce substance craving. Gaps in the literature indicated the need for a longitudinal examination of craving changes that takes individual differences into consideration. Data from 46 college students recovering from SUD were used to examine craving changes before and during an eight-session HRVB intervention. Participants were assessed at four occasions in the control condition over the first 12 weeks followed by 8 occasions in the experimental condition, separated by an 11-week rest period. A longitudinal multilevel modeling approach was used with time at level-1 nested within persons at level-2. Unconditional and conditional multilevel models of change were estimated to model craving trajectories and predictor relationships over time.

**Results:** Significant reductions in substance craving were observed during HRVB compared to waitlist. HRVB seemed to enhance the efficacy of conventional therapies by
producing craving reductions that were not evident prior to the HRVB intervention despite usual treatment. A continued daily HRVB practice of more than 12 minutes was found to enhance treatment as usual outcomes and contribute to greater craving reductions over time. In our sample, younger participants seemed to be more committed to daily HRVB practice, although many did not achieve the recommended daily practice of 15 minutes twice daily. Increases in depressive symptoms were found to attenuate the effects of HRVB on craving. Anxiety and perceived stress were not significantly associated with craving in this study. The true $R^2$ for the final model indicated that 20.5% of the variance in craving was explained by age, daily HRVB $>12$ minutes, and the within-person aspect of depression.

**Conclusions:** HRVB is an easily accessible and affordable intervention that shows promise as a complementary anti-craving intervention. The outcomes of this study have implications for hypothesized HRVB practice-dose relationships. Nurses may help persons recovering from SUD to better manage the symptom of craving by the routine and strategic use of personal HRVB practice.
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DEDICATION

To my loving parents, Yumna and Ali. I am who I am because of your example of perseverance, sacrifice, and love. Mom, thank you for teaching me that nothing is impossible. I could have never done this without your example of determination.

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# TABLE OF CONTENTS

ABSTRACT OF THE DISSERTATION ......................................................... ii
ACKNOWLEDGMENTS ............................................................................ iv
DEDICATION ................................................................................................ v
LIST OF TABLES ...................................................................................... viii
LIST OF FIGURES ................................................................................... ix
LIST OF APPENDICES ........................................................................... x

CHAPTER ONE: OVERVIEW OF THE DISSERTATION ......................... 1

Introduction ............................................................................................ 1
Organization of the Dissertation .............................................................. 3

CHAPTER TWO: THE PROBLEM .......................................................... 5

Substance Use Disorders in College Students ......................................... 5
Substance Craving ................................................................................... 5
Heart Rate Variability Biofeedback and Craving ....................................... 6
Purpose and Specific Aims ....................................................................... 10
Research Questions ................................................................................ 11
Definition of Terms ................................................................................ 11
Significance of the Study ........................................................................ 13

CHAPTER THREE. Manuscript 1: Current Evidence On Heart Rate Variability Biofeedback As A Complementary Anti-Craving Intervention ................. 16

The Concept of Craving .......................................................................... 16
Substance Craving Treatments ................................................................. 18
The Heart Rate Variability Biofeedback Perspective ............................... 22
Significance of the review ........................................................................ 24
Methods .................................................................................................. 25
Results ..................................................................................................... 26
Strengths and Limitations ....................................................................... 43
Future Directions ................................................................................... 43
Conclusion ............................................................................................... 44

CHAPTER FOUR: METHODS .................................................................. 46

The Research Setting ............................................................................... 46
LIST OF TABLES

Table 1 - Features of Studies Investigating HRVB and Substance Craving ................. 29
Table 2 - Features of Studies Investigating CB Interventions and Substance Craving .... 33
Table 3 - Effect Size and Quality Ratings using SASQI ........................................... 39
Table 4 - Data Collection Protocol ........................................................................... 51
Table 5 - Sample Characteristics of Studies Testing PACS ......................................... 67
Table 6 - Sample Characteristics .............................................................................. 86
Table 7 - Mean PACS, PSS, BAI, and BDI Scores over Time ..................................... 87
Table 8 - Empty random Intercept and Quadratic Time Models (N=44) ..................... 90
Table 9 - Baseline and Final Model Parameters (N=44) ........................................... 93
Table 10 - Piecewise Model Parameters (N=44) ....................................................... 96
LIST OF FIGURES

Figure 1 - Graphic Illustrations of Fixed and Random Effects of Time ....................... 56
Figure 2 - Mean Daily HRVB Practice by Age Group .................................................. 88
Figure 3 - Mean and Individual Craving Trajectories .................................................. 92
LIST OF APPENDICES

Appendix A .................................................................................................................. 137
CHAPTER ONE: OVERVIEW OF THE DISSERTATION

Introduction

Substance craving is a key feature of addiction and recovery that was added to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders as a criterion for substance use disorder (SUD) (American Psychology Association [APA], 2013). Simply stated, craving is an overwhelming involuntary desire to use a drug that “if unfulfilled produces a powerful physical and mental suffering” (Manejwala, 2013, p. 2). From a psychological standpoint, craving is thought to be an automatic drive resulting from dysfunctional reward-related processes (Drummond, 2001) or higher order cognitive functions (Skinner & Aubin, 2010). On the other hand, psychobiological models attribute craving to neurobiological adaptations of various brain circuits resulting in pathological motivation towards the drug and alterations in behavioral control (Robinson & Berridge, 2008). Autonomic imbalances in sympathetic and parasympathetic systems have been reported with increased craving (Sinha, 2013). Experiences of craving are often associated with physiological responses such as increased salivation, heart rate, and blood pressure, as well as psychological responses such as depression and anxiety (Eddie, Vaschillo, Vaschillo, & Lehrer, 2015; Haass-Koffler, Leggio, & Kenna, 2014). The experience of craving is therefore associated with moment-to-moment changes in physiological states which contribute to the person’s behavior (Eddie et al., 2015; Kemp & Quintana, 2013; Quintana, Kemp, Guastella, Hickie, & McGregor, 2013). A flexible autonomic system provides the ability for rapid modulation of physiological states in accordance with situational demands resulting in improved behavioral flexibility (Lehrer & Eddie, 2013; Porges, 2007). Neurocardiac
dynamics, such as heart rate variability (HRV), underlie the heart-brain feedback loop that contributes to behavioral flexibility (Bates & Buckman, 2013). The integrated psychophysiological processes of craving underpin this study’s conceptualization of craving as a biobehavioral phenomenon. Biobehavioral interventions, such as HRV biofeedback (HRVB), may offer the advantage of addressing psychophysiological processes of craving to increase the efficacy of conventional anti-craving treatments.

Whether in inpatient or outpatient settings, nurses represent the largest number of mental health providers (Edward & Munro, 2009) and are key stakeholders in the treatment of patients with SUDs. While current empirically supported SUD treatments are primarily focused on pharmacological and psychosocial interventions, nurses provide a unique holistic perspective of symptom management which can integrate psychophysiological processes. Slow abdominal breathing as a therapeutic intervention has been widely used in nursing to facilitate post-operative recovery (Cassidy, Rosenkranz, McCabe, Rosen, & McAneny, 2013; Cronin et al., 2015), pain management (Friesner, Curry, & Moddeman, 2006; Kwekkeboom & Gretarsdottir, 2006), and stress and anxiety reduction (Hayama & Inoue, 2012; Kim et al., 2013). Furthermore, breathing techniques that improve HRV and autonomic balance have been used by nurses to improve quality of life in hemodialysis patients (Stanley, Leither, & Sindelir, 2011), enhance sleep quality in patients with depression (Chien, Chung, Yeh, & Lee, 2015), decrease depressive symptoms in patients with coronary heart disease (Chung et al., 2010), and reduce pre-procedural distress in pediatric cancer patients (Shockey et al., 2013). Therefore, HRVB training that is based on a paced breathing technique could be easily integrated within non-pharmacological mental health nursing interventions.
Organization of the Dissertation

This dissertation consists of six chapters that include three inter-related manuscripts. This chapter (Chapter one) introduces the problem, a brief background of the studied HRVB intervention, and their relation to nursing. Chapters two through six will include the following:

- Chapter two discusses the problem of substance craving and denotes the specific aims, research questions, definition of terms, and study delimitations.
- Chapter three (Manuscript 1) presents a detailed literature review of the problem.
- Chapter four describes the research design and methods, including a detailed explanation of longitudinal multilevel modeling. Manuscript 2 is included in this chapter.
- Chapter five (Manuscript 3) reports the dissertation results.
- Chapter six presents a summary of the dissertation, conclusions, and recommendations for future research.

Below, the specific aims of each manuscript are presented.

Manuscript 1 of this dissertation discussed the craving concept, conventional and complementary anti-craving treatments, and current evidence on the effectiveness of HRVB in reducing craving and the challenges of research in this area. The review was expanded to include additional evidence from controlled breathing studies due to the limited amount of HRVB studies investigating its effects on craving. Specific aims of this manuscript were to: (1) assess current evidence on the effectiveness of HRVB and other controlled breathing strategies in reducing craving; (2) identify relevant predictors of craving which may contribute to the relationship between HRVB and craving; and (3)
outline current methodological challenges and future directions for research examining HRVB as an anti-craving intervention.

Manuscript 2 reviewed the psychometric properties of the Penn Alcohol Craving Scale (PACS). Due to the subjective and temporal nature of substance craving, a careful examination of the instrument measuring this study’s outcome was conducted to facilitate interpretation of results and identify any measurement-related limitations. The specific aims of this manuscript were to: (1) evaluate the psychometric properties of PACS discussing its development, measurement validity, and reliability and (2) propose recommendations for future research.

Manuscript 3 builds on all previous chapters and reports this dissertation’s results. The specific hypotheses of this manuscript were: (1) Craving levels decline over time; (2) Craving reductions occur at different rates over time; (3) Length of abstinence is related to craving reductions over time; (4) The dose of daily HRVB practice predicts craving reductions over time; (5) Craving reductions in the experimental condition would be greater than reductions in the control condition, if any; and (6) Variations in depression, anxiety, and perceived stress are associated with craving changes over time.

This dissertation presents longitudinal evidence on the usefulness of HRVB as a complementary anti-craving intervention for college students recovering from SUD. A reproducible HRVB protocol was tested, a specific daily HRVB practice dose was determined, and potential relationships with other predictors of craving were explored. In addition, this dissertation suggests the potential integration of HRVB in nursing.
CHAPTER TWO: THE PROBLEM

Substance Use Disorders in College Students

In the United States, 41% of college students reported the use of any illicit drug in the past year (Johnston, O’Malley, Bachman, Schulenberg, & Miech, 2016), corresponding to more than four times the prevalence (9.4%) of drug use in Americans aged 12 years and older (NIDA, 2015). In 2007, a Columbia University report of a 1993-2005 national study alarmed the public about an alcohol and drug-related crisis among college students. Almost one in four college students were found to meet the criteria for SUD, corresponding to 2.5 times the prevalence of SUD in the overall population (Califano, 2007). Although more recent studies of college-specific SUD prevalence are not available, current statistics of alcohol and drug use trends among college students point to a significant SUD prevalence in this population (Johnston et al., 2016). The consequences range from unintentional injury to assault, sexual abuse, disability and death as a result of intoxication (National Institute on Alcohol Abuse [NIAAA], 2015; Palmer, McMahon, Moreggi, Rounsaville, & Ball, 2012). College students with SUDs also suffer from academic decline, increased risk taking behavior, loss of productivity, depression, suicidality, and other psychiatric comorbidities (Substance Abuse and Mental Health Services Administration [SAMHSA], 2014).

Substance Craving

Although SUD treatment can be successful across ages (SAMHSA, 2014; National Institute on Drug Abuse [NIDA], 2012), recovery is difficult to maintain and on average 67% relapse within the first year after treatment (SAMHSA, 2009). While many factors may be associated with relapse, craving is one of its strongest predictors and is

According to the incentive-sensitization theory of addiction, craving is the intense ‘wanting’ of a substance which leads to drug seeking, even when the individual becomes consciously aware that the drug’s hedonic effect is decreasing and negative consequences of use are increasing (Robinson & Berridge, 1993, 2008). The mechanism of craving is explained by neurobiological adaptations of various brain circuits regulating motivated behavior and cognitive decision-making. Repeated drug exposure sensitizes the brain to the drug and drug-associated stimuli resulting in pathological incentive salience, a motivational ‘wanting’ attribute given by the brain to reward-predicting stimuli ascribed to the drug. Sensitized incentive salience can be experienced either unconsciously through ‘unconscious wanting’ or consciously through ‘conscious craving’ and is accompanied by implicit and/or explicit affective and cognitive changes, which may affect the person’s ability to flexibly regulate behavior resulting in drug seeking. All these psychophysiological mechanisms intensify the persistent nature of craving and place the individual in the cycle of drug dependence and addiction (Robinson & Berridge, 1993, 2008).

**Heart Rate Variability Biofeedback and Craving**

**Heart Rate Variability**

HRV is the variability in R- to R-spike intervals of the electrocardiogram, representing the moment-to-moment flexibility of the heart in response to interoceptive and exteroceptive demands (Bates & Buckman, 2013; Berntson et al., 1997). HRV is regulated by neural mechanisms of the autonomic nervous system, namely preganglionic sympathetic and parasympathetic neurons innervating the heart. These mechanisms
express the interaction between the brain and the heart via baroreflexes and control the flexible regulation of affective states and cognition that support behavioral flexibility (Bates & Buckman, 2013; Kemp & Quintana, 2013). According to polyvagal theory, primary emotions are related to the vagal regulation of the heart and different types of vagal activity (e.g., withdrawal or activation) support different behaviors (Porges, 2007). HRV has been used as a noninvasive measure of parasympathetic function (Berntson et al., 1997) and provides insight into the neural mechanisms governing behavioral flexibility (Bates & Buckman, 2013; Kemp & Quintana, 2013). It is believed that higher amplitude HRV improves autonomic homeostasis and behavioral self-regulation (Porges, 2007). Thus, the low HRV often observed in persons with SUDs (Brody, Krause, Veit, & Rau, 1998; Malpas, Whiteside, & Maling, 1991) may be associated with increased craving levels (Thayer & Friedman, 2002; Thayer & Lane, 2009). This hypothesis was supported by the results of a recent pilot study that investigated a brief three-session HRVB intervention with inpatient young men with SUD. Results showed that low pretreatment HRV were associated with greater craving in the control group (Eddie, Kim, Bates, Lehrer, & Deneke, 2014). HRV was also related to alcohol craving in a cross-sectional study of outpatients with alcohol use disorder and explained 12.1% of the variance in craving after controlling for age, trait anxiety, and alcohol consumption levels (Quintana et al., 2013). Based on such evidence, it may be hypothesized that increasing HRV may produce craving reductions in persons with SUD.

**Heart Rate Variability Biofeedback Training**

Heart rate variability biofeedback (HRVB) is a form of cardiorespiratory feedback training that aims to increase HRV and enhance vagal heart rate control (Lehrer & Gevirtz, 2014; Lehrer, Vaschillo, & Vaschillo, 2000; Nolan et al., 2005). In HRVB, users
are trained to breathe at their own resonance frequency, which maximizes HRV by eliciting high-amplitude heart rate oscillations. HRVB training has shown efficacy in a non-clinical sample for increasing baroreflex gain, a reflex that is produced by the stimulation of baroreceptors (Lehrer et al., 2003). HRVB was also shown to improve symptom severity of various disorders such as asthma, depression and anxiety, fibromyalgia, and hypertension (Hassett et al., 2007; Karavidas et al., 2007; Lehrer & Vaschillo, 2004; McCraty et al., 2003). To date, four controlled studies investigated the relationship between HRVB and craving in different populations. A controlled pilot study of 38 patients in a SUD residential program showed no substance craving differences between the biofeedback group and the control group (Zucker, Samuelson, Muench, Greenberg, & Gevirtz, 2009). However, the biofeedback group showed a trend of craving reductions following a four-week daily practice of slowed breathing. In this study, craving was only measured twice (before and after the intervention) using a single questionnaire item. The measurement validity of craving may therefore be questionable and may have contributed to the lack of statistical significance in the results (Zucker et al., 2009). In a study of young men (N=41) receiving inpatient SUD treatment, a larger craving reduction trend was found in the HRVB group compared to the control group. This finding was not statistically significant despite a medium effect size (Cohen’s d = .35). This study used a three-session HRVB training program, with no validation of daily practice, which may have been an insufficient dose to produce clinically significant craving reductions (Eddie et al., 2014). On the other hand, in a study of high food cravers, assignment to a 12-session HRVB intervention was associated with decreased food cravings suggesting that more intensive training may be necessary (Meule, Freund,
Skirde, Kübler, & Vögele, 2012). Taken together, these results suggest that more evidence is needed to determine the efficacy of HRVB to reduce craving in persons with SUD and the dose of HRVB practice that is necessary to produce craving reductions. The present study addresses the need for a longitudinal analysis of craving changes in persons with SUD receiving intensive HRVB training over a prolonged duration.

**HRVB, Psychosocial Factors, and Craving**

Stress, anxiety and depression predict relapse (Sinha, 2011) and are associated with craving (Porges, 2007; Thayer & Lane, 2000). Stress and anxiety are positively correlated with craving across different substances (Eddie et al., 2014; Fox, Tuit, & Sinha, 2013). Converseley, HF-HRV is negatively associated with stress, anxiety, and depression (Dishman et al., 2000; Eddie et al., 2014). Also, controlled studies suggest that HRVB was a useful intervention for stress and anxiety in non-clinical samples (Thurber, Bodenhamer-Davis, Johnson, Chesky, & Chandler, 2010; Wells, Outhred, Heathers, Kemp, & Fontenelle, 2012), and a clinical sample of persons with major depression (Karavidas et al., 2007). Despite some evidence for the usefulness of HRVB in decreasing anxiety, depression, perceived stress, and craving, the relationships among these factors have not been previously evaluated. Investigating the associations among trajectories of perceived stress, anxiety, depression, and substance craving changes may provide more insight into the mechanisms underlying the relationship between HRVB and craving. It is especially important to evaluate these relationships in the SUD population in which anxiety, depression, and stress disorders are commonly co-occurring (Garland, Roberts-Lewis, Tronnier, Graves, & Kelley, 2016); roughly 45% of persons with SUD have at least one serious mental illness (SAMHSA, 2012).

**HRVB, Length of Abstinence, and Craving**
The length of abstinence from alcohol and drug use appears to be an important factor of craving. While baseline substance craving decreases with abstinence time, cue-induced craving shows time-dependent increases in both animal and laboratory studies (Li, Caprioli, & Marchant, 2015b). For example, methamphetamine users showed increases in cue-induced craving for up to three months of abstinence followed by reductions in cue-induced craving at 6 and 12 months of abstinence (Wang et al., 2013). Similarly, increases in cue-induced craving were shown in alcohol dependents until two months of abstinence (Li et al., 2015a) and heroin dependents during the first month of abstinence (Shi et al., 2009). The existing literature lacks evidence on whether length of abstinence is related to HRVB craving outcomes. Exploring this relationship may show differences in HRVB dose requirements that are dependent on length of abstinence.

**Purpose and Specific Aims**

The purpose of this study was to examine substance craving changes in college students recovering from SUD, during and before an eight-session HRVB intervention compared to a waitlist control condition over the course of 35 weeks. Participants were assessed at four occasions in the control condition over the first 12 weeks followed by an 11-week rest period (semester break) and 12 weeks in the experimental condition (8 occasions). The specific aims of the study included:

- **Aim 1:** To determine a trajectory of substance craving changes before and during the HRVB protocol.
- **Aim 2:** To determine the relationship between daily HRVB practice and substance craving reductions.
• **Aim 3**: To determine the effects of variations in depression, anxiety, and perceived stress on substance craving changes.

**Research Questions**

The following research questions were proposed:

1. What are the substance craving trajectories over 12 weeks in the control condition compared to 12 weeks in the experimental condition?
   a. What are the between-person versus within-person variation patterns across time?
   b. Does the rate of craving changes vary between conditions?

2. Do craving changes over time differ by intra-individual predictors including age, sex, length of abstinence, and dose of daily HRVB practice?

3. Do craving changes over time differ by inter-individual predictors including depression, anxiety, and perceived stress?

4. Are craving reductions during the HRVB intervention greater than craving reductions in the control condition?

**Definition of Terms**

**Substance Craving**

Craving is conceptually defined as a single-factor phenomenon of the subjective experience of thinking about using a substance or thinking about how this substance would make one feel and resisting such thoughts (Flannery, Volpicelli, & Pettinati, 1999). The characteristics of craving include the frequency, intensity, and duration of thoughts about craving, the ability to resist using the substance, and an average retrospective craving rating of the past week. Each of these characteristics is
operationally defined as an item score on the Pennsylvania Alcohol Craving Scale (Flannery et al., 1999). The wording of this scale was modified to measure drug craving (Garland & Roberts-Lewis, 2013) and alcohol and drug craving (Eddie et al., 2014) and showed similar internal consistencies to the original scale.

**Heart Rate Variability Biofeedback**

This study uses an eight-session HRVB protocol that is offered to participants in the experimental condition over a period of 14 weeks. The intervention is based on a protocol by Lehrer et al. (2000). In HRVB, users are trained to breathe at their own resonance frequency, which maximizes HRV by eliciting high-amplitude heart rate oscillations. Users are asked to breathe at five specific frequencies ranging from 4.5 to 6.5 breaths per minute (i.e., 0.075 to 0.108 Hz). Resonance frequency is identified when respirations and heart rate oscillations occur in phase (i.e. heart rate rises simultaneously with inhalation and decreases simultaneously with exhalation) (Eddie et al., 2015; Vaschillo, Vaschillo, & Lehrer, 2006). Users are then trained to practice breathing at their own resonance frequency with the help of visual pacers and electronic monitoring of the heart rate. The operational definition of HRVB is further detailed in Chapter 3 of this proposal.

**Depression**

Depression is conceptually defined as a mental state characterized by symptoms of depressed mood and/or loss of interest or pleasure accompanied by a variety of physical symptoms and negative feelings as stipulated in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (APA, 2000). The Beck Depression Inventory II (BDI-II) assesses the severity of depression symptoms
based on criteria from the DSM-IV. Depression is operationally defined as a total score on the BDI-II (Beck, Steer, & Brown, 1996).

**Anxiety**

Anxiety is conceptually defined as a mental state characterized by symptoms of restlessness or feeling on edge, irritability, and difficulty concentrating which may be accompanied with physical symptoms of muscle tension, fatigue, and difficulty sleeping (APA, 2000). The severity of anxiety is measured by the Beck Anxiety Inventory (BAI). Anxiety is operationally defined as a total score on the BAI (Beck & Steer, 1993).

**Perceived Stress**

Perceived stress is conceptually defined as the appraisal of stress in current life situations and the extent to which persons find their lives unpredictable, uncontrollable, and overloaded. Perceived stress is operationally defined as a total score on the Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983b).

**Delimitations**

This study consisted of an analysis of extant data collected from 46 college students who resided in Rutgers Recovery House, a 12-month on-campus housing option offered by the Alcohol and Other Drug Assistance Program for students recovering from SUD. Students with SUD are voluntarily enrolled in this housing option which facilitates access to recovery counseling, on campus 12-step meetings, and related medical services. Residents support each other’s sobriety while forming healthy relationships and college experiences.

**Significance of the Study**

The high prevalence of SUDs among college students (Califano, 2007) is a significant healthcare and public concern. Despite conventional treatments, high relapse
rates are evident in the general population of individuals with SUD (SAMHSA, 2014). Relapse after treatment in this population requires special consideration given the impact of situational stressors college students may be facing (Lee & Jang, 2015; Woolman, 2015). Since substance craving is known to be highly predictive of relapse (Paliwal, Hyman, & Sinha, 2008; Sinha, 2011), designing and testing interventions that target substance craving in this population is warranted. HRVB training aims to increase HRV and exercise the baroreflex, which are thought to subsequently increase behavioral control of symptoms, such as substance craving (Lehrer et al., 2000). Increases in HRV may help individuals manage substance craving at the psychophysiological level. A flexible autonomic nervous system allows for momentary adjustments of physiological states in response to situational demands (Bates & Buckman, 2013; Porges, 2007), which in turn may increase the person’s ability to control craving. This study provided longitudinal evidence that HRVB can help college students better manage substance craving and maintain recovery by improving their ability to control physiological arousal. In addition, this study explored the associations among inter- and intra-individuals predictors (including age, sex, length of abstinence, daily HRVB practice, depression, anxiety, and perceived stress) and substance craving changes over time.

HRVB methods may be effectively integrated in SUD treatments and continued care in order to manage the symptom of craving, prevent relapse, and provide a more solid physiological ground for prolonged recovery. HRVB training is consistent with nursing’s holistic approach to patient care and may be effectively integrated within non-pharmacological interventions nurses may provide to help patients with SUDs control the symptom of craving. The integration of HRVB may enhance nursing care of this
vulnerable patient population which may in turn promote better clinical outcomes and have broader implications for the development of contemporary mental health nursing practices.
CHAPTER THREE. Manuscript 1: Current Evidence On Heart Rate Variability

Biofeedback As A Complementary Anti-Craving Intervention

The Concept of Craving

Recovery from substance use disorder (SUD) is difficult to maintain. On average, 50 to 70% of persons recovering from SUD relapse within the first year of treatment (NIDA, 2012; SAMHSA, 2009). While many factors may be associated with relapse, craving is one of its strongest and most distressing predictors (Fatseas et al., 2015; Paliwal et al., 2008; Sinha, 2011). For years, craving was described as a symptom of alcohol or drug withdrawal. Research advancements in the last decade showed that persons recovering from SUD can still experience cravings years after abstinence, long after their withdrawal symptoms disappear (Addolorato, Leggio, Abenavoli, & Gasbarrini, 2005). Currently, craving is a criterion for SUD diagnoses as per the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (APA, 2013).

Treatment of substance craving is now considered an essential component of recovery maintenance and relapse prevention (NIDA, 2016; Tiffany & Wray, 2012).

Craving is a highly subjective experience with virtually no universal definition. Simply stated, craving is an overwhelming involuntary desire to use a drug that “if unfulfilled produces a powerful physical and mental suffering” (Manejwala, 2013, p. 2). Although craving has inspired thousands of articles in the literature, components of the craving construct remain controversial (Kavanagh et al., 2013; Tiffany & Wray, 2012). A review of 18 psychological and biological models of craving concluded that no single model addresses all aspects of craving, suggesting that this phenomenon needs to be considered from multiple angles (Skinner & Aubin, 2010). Psychological theories
present craving in the context of classical conditioning and cognitive frameworks. Conditioning-based models assume that cravings result from withdrawal- or reward-related processes (Drummond, 2001). On the other hand, cognitive models relate craving to higher order cognitive functions as opposed to an automatic or primal drive (Skinner & Aubin, 2010). Advances in neuroimaging research resulted in novel views of craving as a phenomenon of psychobiological origins (Drummond, 2001; Kavanagh et al., 2013).

Psychobiological models of craving highlight biological factors of craving with an emphasis on motivational components. Specifically, changes in the mesolimbic dopamine pathways, originating in the ventral tegmental area and extending to the nucleus accumbens have been recognized as sites for the reinforcing properties of addictive drugs (Haass-Koffler et al., 2014; Westbrook et al., 2013). Substance craving as a result of increased drug use is associated with increased activity in limbic, striatal, and cortical brain systems (Sinha, 2013; Westbrook et al., 2013). The most prominent theory from this view is the incentive-sensitization (IS) theory, which explains the mechanism of craving by neurobiological adaptations of different brain circuits regulating motivated behavior and cognitive decision-making. Repeated drug exposure sensitizes the brain to the drug and drug-associated stimuli resulting in pathological incentive salience, a motivational ‘wanting’ attribute given by the brain to reward-predicting stimuli ascribed to the drug (Robinson & Berridge, 1993, 2008). Dysregulation in dopamine, serotonin, gamma-aminobutyric acid (GABA), endogenous opioid peptides, and noradrenalin functions have been associated with activation of the brain’s reward center resulting in incentive salience (Addolorato et al., 2005; Robinson & Berridge, 2008; Sinha, 2013; Skinner & Aubin, 2010). From a neurobiological standpoint, craving is defined as an
“intense, urgent abnormal desire characterized by longing, yearning and physiological need for the drug” (Sinha, 2013, p. 649). Current pharmacological, behavioral, and combination treatments for substance craving are based on these premises (Konova, Moeller, & Goldstein, 2013).

**Substance Craving Treatments**

**Conventional treatments**

Treatment for substance craving is generally integrated within every stage of recovery from SUD starting with detoxification and onto maintenance and relapse prevention. Available treatment approaches include pharmacological interventions, behavioral counseling (such as cognitive behavioral therapy, contingency management, and motivational interviewing), support groups, and evaluation and treatment for co-occurring mental health issues (NIDA, 2016). A vast literature is available on pharmacological treatments for substance-specific craving (mainly nicotine, alcohol, and opioids), as opposed to substance craving in general. Bupropion and varenicline have been used to reduce nicotine cravings and prevent relapse showing moderate long-term efficacy (Carim-Todd, Mitchell, & Oken, 2013). Pharmacological treatments for alcohol cravings target three psychobiological pathways (Skinner & Aubin, 2010; Verheul, Van den Brink, & Geerlings, 1999). Opioid antagonists (such as naltrexone) and dopamine receptor antagonists (such as atypical antipsychotics) target the reward pathways involving the stimulating effects of alcohol. Selective serotonin reuptake inhibitors and 5-HT3 antagonists (such as ondansetron) target obsessive mechanisms resulting in intrusive thoughts about drinking (Haass-Koffler et al., 2014; Skinner & Aubin, 2010). Glutamatergic and GABAergic agents, such as baclofen and gabapentin, address the
dysregulation of relief circuitry (Addolorato, Leggio, Hopf, Diana, & Bonci, 2012; Skinner & Aubin, 2010). Craving for opioids is mainly treated by agonist and antagonist mu-opioid medications such as buprenorphine (NIDA, 2012). Trials of alpha-2 adrenoceptor agonists and NK1 receptor antagonists show future potential in reducing opioid and other drug craving by modulating stress (Sinha, Shaham, & Heilig, 2011). For example, clonidine showed a therapeutic anti-craving effect by dampening stress (Kowalczyk et al., 2015). Although no particular pharmacotherapies are approved for cocaine cravings, agents that affect dopaminergic, GABAergic, serotonergic, and glutamatergic systems have been utilized (Addolorato et al., 2012; Dackis, 2005). Future anti-craving options might exist with endocannabinoid antagonists, and more advanced serotonergic, and GABAergic agents (Addolorato et al., 2012). Notably, repeated studies show that no single approach to recovery maintenance is effective alone. Combinations of pharmacological and behavioral interventions are always more effective than a single approach in terms of long-term recovery outcomes (NIDA, 2016). Despite treatment advancements, patient outcomes have not changed significantly and maintaining recovery is still a major challenge (Behere, Muralidharan, & Benegal, 2009; Miller, Walters, & Bennett, 2001; NIDA, 2012; O'Brien, 2005). Since craving is one of the strongest predictors of relapse (Drummond, 2001; Witkiewitz, Bowen, Douglas, & Hsu, 2013), the need for identifying additional effective anti-craving interventions is evident.

**Complementary and alternative medicine in craving control**

The limitations of conventional therapies in maintaining abstinence and preventing relapse resulted in attempts at using complementary and alternative medicine (CAM) practices, which have their roots outside of conventional medicine (Baird, 2014).
CAM therapies such as mind-body practices, biofeedback and neurofeedback, auricular acupuncture, homeopathic and naturopathic medicine, ayurvedic preparations, and bioelectromagnetic therapies have been used in the treatment of SUD (Behere et al., 2009). Anecdotal evidence of the effectiveness of CAM therapies in SUD treatment existed for more than 25 years although research evidence has been limited (Baird, 2014). However, available evidence supports the use of some dietary supplements, mind-body practices, biofeedback, neurofeedback, and acupuncture as adjuvant therapies in the treatment of SUD. Supplementation with ibogaine (derived from the roots of tabernanthe iboga), L-tryptophan, and magnesium reduced substance cravings significantly. Animal studies showed that tabernanthe iboga reduced dopamine levels in the nucleus accumbens, showed mu- and kappa-opioid, NMDA, and nicotinic receptor antagonist properties, and also blocked serotonin uptake (Behere et al., 2009). Ibogaine, an indole alkaloid, is thought to be effective in the treatment of opioid addiction because it reduced craving and improved self-control (Richer, 2009). L-tryptophan is a dietary supplement that is essential in the synthesis of brain monoamines and endorphins. L-tryptophan reduced craving for alcohol, cannabis and nicotine (Behere et al., 2009) and showed less stress-induced craving when given to binge-drinkers (Nesic & Duka, 2014). Magnesium is an endogenous NMDA blocker which showed reductions in opioid cravings, although this finding needs to be confirmed in larger studies (Behere et al., 2009). Acupuncture is widely used as a CAM treatment for opioid addiction in both Western and Asian countries (Baird, 2014). However, a meta-analysis of 14 published acupuncture trials showed that treatment and control groups did not differ on opioid craving although symptoms of anxiety and depression were improved in treatment groups (Boyuan, Yang,
Positive results of greater craving reduction have been reported when acupuncture was used as an adjuvant treatment to methadone maintenance (Chan et al., 2014). Furthermore, mind-body therapies are widely used to reduce stress effects and have been used to reduce cravings. Such therapies focus on the interactions among brain, mind, body, and behavior. A review of 14 smoking cessation trials showed that yoga and meditation-based interventions were effective in reducing nicotine craving intensity (Carim-Todd et al., 2013). Qigong meditation also showed significantly greater substance craving reduction than stress management and relaxation training, when used as an adjuvant to residential treatment for SUD (Chen, Comerford, Shinnick, & Ziedonis, 2010; Smelson et al., 2013). Additionally, there is growing evidence on the efficacy of mindfulness meditation (Black, 2014), which was shown to reduce brain activity in regions related to craving (Witkiewitz et al., 2013). Mindfulness-based interventions showed reductions in craving for smoking (Ruscio, Muench, Brede, & Waters, 2016), alcohol (Murphy & MacKillop, 2014), and binge drinking in college students (Mermelstein & Garske, 2015; Vinci et al., 2014). Although mindfulness shows very positive post-intervention craving outcomes more evidence is needed on its long-term effectiveness (Penberth et al., 2015). Along with mind-body practices, biofeedback is a therapeutic procedure that facilitates mind-body interaction (Calderon & Thompson, 2004). Different biofeedback techniques, including neurofeedback training (Dehghani-Arani, Rostami, & Nadali, 2013; Hartwell et al., 2016) and heart rate variability biofeedback (Eddie et al., 2014; Penzlin, Siepmann, Illigens, Weidner, & Siepmann, 2015), showed promise in reducing substance craving. In this review we focus on heart
rate variability biofeedback that is based on slowed breathing, which has shown evidence for therapeutic potential.

**The Heart Rate Variability Biofeedback Perspective**

Biofeedback research has shown that humans can be trained, through operant conditioning, to control certain autonomic nervous system functions, such as cardiac responses, gastrointestinal contractions, and vasomotor activity (Calderon & Thompson, 2004; Glick & Greco, 2010). The objectives of biofeedback are to (1) help persons acquire awareness of the mind-body interaction, highlighting the interaction between thoughts and automatic physiological responses; (2) acquire methods to control maladaptive physiological responses with the help of physiologic monitoring; and (3) learn to regulate their thoughts and physiology in everyday life without the use of instrumentation (Calderon & Thompson, 2004; Lehrer & Eddie, 2013). The goal is to improve autonomic regulation by engaging the parasympathetic nervous system and recovering from stress-induced sympathetic responses (Gevirtz, 2013). Autonomic imbalances in sympathetic and parasympathetic systems have been reported with increased craving (Sinha, 2013). Experiences of craving are often associated with physiological responses such as increased salivation, heart rate, and blood pressure, as well as psychological responses such as depression and anxiety (Eddie et al., 2015; Haass-Koffler et al., 2014). The experience of craving is therefore associated with moment-to-moment changes in physiological states which contribute to the person’s behavior (Eddie et al., 2015; Kemp & Quintana, 2013; Quintana et al., 2013). These findings are in line with the IS theory which stipulates that sensitized incentive salience is accompanied by implicit and/or explicit affective and cognitive changes, which affect the
person’s ability to flexibly regulate behavior. A flexible autonomic system provides the ability for rapid modulation of physiological states in accordance with situational demands (Lehrer & Eddie, 2013; Porges, 2007). Neurocardiac dynamics, such as heart rate variability (HRV), underlie the heart-brain feedback loop that contributes to behavioral flexibility (Bates & Buckman, 2013; Lehrer & Gevirtz, 2014). HRV is the variability in R- to R-spike intervals of the electrocardiogram that is regulated by neural mechanisms of the autonomic nervous system. HRV represents the moment-to-moment flexibility of the heart in response to interoceptive and exteroceptive demands, reflecting efferent vagus and sympathetic nerve activity and afferent nerve activity mediated by the baroreceptors. High frequency (HF) HRV (i.e., Respiratory Sinus Arrhythmia) reflects high-frequency HR oscillations (0.15–0.4 Hz) mediated by vagal activity reflecting both baroreflex control and modulation of respiratory function. HF-HRV is also a noninvasive measure of parasympathetic function (Berntson et al., 1997). According to polyvagal theory, primary emotions are related to the vagal regulation of the heart, and different types of vagal activity (e.g., withdrawal or activation) support different behaviors. In line with this theory, evidence shows that HRV provides insight into the neural mechanisms of the flexible regulation of affective states and cognition (Bates & Buckman, 2013; Porges, 2007; Thayer & Lane, 2009). Research suggests that low levels of HF-HRV predict craving in individuals with SUD (Eddie et al., 2014; Quintana et al., 2013). Increasing HRV may therefore improve autonomic homeostasis and behavioral flexibility (Bates & Buckman, 2013; Lehrer et al., 2004; Porges, 2007) and thus enhance craving control. Heart rate variability biofeedback (HRVB) is a form of cardiorespiratory feedback training that aims to increase HRV and enhance vagal heart rate control (Lehrer
In HRVB, users are trained to breathe at their own resonance frequency, which maximizes HRV by eliciting high-amplitude heart rate oscillations. Users are asked to breathe at five specific frequencies ranging from 4.5 to 6.5 breaths per minute (i.e., 0.075 to 0.108 Hz). Resonance frequency is identified when respirations and heart rate oscillations occur in phase (i.e. heart rate rises simultaneously with inhalation and decreases simultaneously with exhalation) (Eddie et al., 2015; Vaschillo et al., 2006). Users are then trained to practice breathing at their own resonance frequency with the help of visual pacers and electronic monitoring of the heart rate. HRVB was shown to improve symptom severity of various disorders such as asthma attacks, depression, anxiety, fibromyalgia, and hypertension (Gevirtz, 2013; Karavidas et al., 2007; Lehrer et al., 2004; Lin et al., 2012). The effectiveness of HRVB in reducing substance craving will be discussed in this review.

**Significance of the review**

The limited success of current anti-craving interventions encourages research into new treatment strategies. Since craving is a biobehavioral phenomenon that is modulated by physiological as well as cognitive processes, biobehavioral interventions, such as HRVB, offer therapeutic potential to aid substance craving control as a complementary or alternative drug-free treatment option. This review discusses current evidence on the effectiveness of HRVB in reducing craving and the challenges of research in this area. Due to the limited number of studies investigating HRVB and craving, we expanded our review to include research studying controlled breathing as an intervention to control craving. Although HRVB and controlled breathing use different training methodologies, both approaches are based on slowed rhythmic breathing. Therefore, evidence from
controlled breathing studies may help support the relationship between HRVB and craving. The purpose of this review is to: (1) assess current evidence on the effectiveness of HRVB and other controlled breathing strategies in reducing craving; (2) identify relevant predictors of craving which may contribute to the relationship between HRVB and craving; and (3) outline current methodological challenges and future directions for research examining HRVB as an anti-craving intervention.

Methods

Literature search

A review of the existing literature was performed using various combinations of the search terms: craving, urge, desire, heart rate variability biofeedback, respiratory sinus arrhythmia biofeedback, cardiorespiratory feedback, and breathing. Databases searched included Social Sciences Citation Index, MEDLINE, PsycINFO, PubMed, Scopus, and Google Scholar. Only peer-reviewed articles were considered and abstracts were used to determine article relevance. No publication time limits were used. A separate literature search was conducted to identify additional predictors of substance craving that may be of relevance to the HRVB-craving relationship. Literature searches ended in August 2016.

Article selection

To be selected, studies had to assess a cardiorespiratory feedback or controlled breathing intervention using a study population of persons with SUD with substance craving as a primary or secondary outcome. The initial search yielded 103 articles. After abstract evaluation, 95 articles were excluded due to duplication, observational and/or cross-sectional data, or lack of intervention, yielding a total of 8 articles for final review.
Studies included controlled studies with or without randomization as well as non-controlled trials. The main features of the studies included in this review are shown in Table 1 and Table 2.

Quality assessment

Due to the limited number of published studies addressing our research question, a formal meta-analysis of the literature was not possible. However, effect sizes were calculated to provide a quantitative measure of the magnitude of observed effect for each study (Field & Gillet, 2010). Since most of the reviewed studies used pre-post-control designs, effect sizes were calculated using the pooled pretest standard deviation (abbreviated as \( d_{ppc2} \)) to estimate the differences of the pre-post-means (Lenhard & Lenhard, 2016). This method provides an unbiased estimate of the population effect size and handles violations of assumptions of independence and homogeneity of variance (Morris, 2008). In addition, a qualitative systematic approach was used to further explore challenges and future directions of research studying HRVB as an anti-craving intervention. The Scale for Assessing Scientific Quality of Investigations in CAM (SASQI-CAM) was used to evaluate the quality of each article, resulting in a numerical score between zero and 21. Satisfactory scientific quality has been attributed to studies with SASQI scores greater than 9. The SASQI approach takes into consideration challenges in CAM research such as establishing control conditions and blinding group assignment (Carim-Todd et al., 2013; Meeks, Wetherell, Irwin, Redwine, & Jeste, 2007).

Results

HRV Biofeedback studies
To date, four studies investigated the relationship between HRVB and craving using different populations, settings and training methods, without yielding a definite conclusion on the effectiveness of HRVB in reducing substance craving. Two of those studies showed a trend in craving reductions with no statistical significance (Eddie et al., 2014; Zucker et al., 2009). Both studies were conducted in a residential SUD treatment setting and used relatively brief HRVB interventions (3 to 4 weeks). Zucker et al. (2009) investigated substance craving changes in a controlled pilot study of 38 patients with elevated post-traumatic stress disorder (PTSD) symptoms, following a home-based HRVB intervention. Participants were trained for 30 minutes on the use of a portable biofeedback (BFB) device and were asked to practice slowed breathing for 20 minutes daily over the course of four weeks. Participants in the control group were asked to listen to a 20-minute progressive muscle relaxation (PMR) recording on a daily basis. No substance craving differences were found between the BFB group and the PMR group. However, the BFB group showed a trend of craving reduction following the intervention compared to no craving changes in the PMR group (Zucker et al., 2009). In this study, craving was only measured twice (before and after the intervention) using a single item. Poor measurement validity of craving may have therefore contributed to the lack of statistical significance in the results. In addition, the home-based nature of the intervention does not allow an assessment of adherence to the intervention. On the other hand, the study by Eddie et al. (2014) administered formal three-session HRVB training over three weeks to young men (N=41) receiving inpatient SUD treatment. A larger craving reduction trend was found in the HRVB group compared to the control group receiving treatment as usual. This finding was not statistically significant despite a
medium effect size (Cohen’s d = .35). The three-session HRVB training may have been insufficient to produce clinically significant craving reductions (Eddie et al., 2014). Studies using longer interventions showed more promising results although more evidence is needed on the dose necessary to produce craving changes. In a non-clinical (N=56) sample of high food cravers from a German university, participants showed statistically significant reduced food cravings following a 12-session HRVB intervention over four weeks (Meule et al., 2012). This study used an experimental group of high food cravers (craving-BFB group) and two control groups, a craving-control group of high food cravers and a low-craving control group of participants who reported low food cravings. Craving reductions were noted in the low-craving controls while no changes occurred in the craving-control group. Notably, standardized effect sizes were consistently higher in the craving-biofeedback group than in both control groups. BFB practice was limited to laboratory sessions, excluding home practice (Meule et al., 2012). Despite the promising evidence from this study, results may not be generalizable to clinical populations of substance users. A recent randomized controlled trial showed similar results in a sample of alcohol dependents from an inpatient rehabilitation center in Germany (Penzlin et al., 2015). Craving reductions occurred immediately following six 20-minute HRVB training sessions given over two weeks in addition to standard rehabilitation treatment, compared to no craving changes in the control group. However, participants in the control group showed larger craving reductions, than the experimental group, at three and six weeks after the intervention. These findings suggest that HRVB contributed to earlier craving reduction than standard treatment alone but the lack of HRVB effect and superiority of standard treatment at follow-up could not be explained.
(Penzlin et al., 2015). In conclusion, overall evidence suggests that HRVB can be an effective adjunct to conventional craving treatment. Larger trials are needed to confirm these results and provide more evidence on treatment duration and the daily BFB practice that are necessary to produce immediate and long-term craving reductions in persons with SUD.

Table 1 - Features of Studies Investigating HRVB and Substance Craving

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample</th>
<th>HRVB Training</th>
<th>Control</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eddie et al. (2014)</td>
<td>20-25 years 100% male</td>
<td>n=20; one 60-75 min session / week over 3 weeks (Total: 180 - 225 min)</td>
<td>n=21</td>
<td>HRVB intervention vs. control comparison</td>
</tr>
<tr>
<td></td>
<td>28-day intensive inpatient USA</td>
<td>Handheld EmWave device (20 min twice daily practice)</td>
<td>Rehabilitative treatment as usual (TAU)</td>
<td>Larger mean craving reduction (35.8% vs. 27.3%; t(39) = .99, p&gt;.05)</td>
</tr>
<tr>
<td></td>
<td>Craving Measure: PACS</td>
<td></td>
<td></td>
<td>No chronic HRV changes at post-treatment baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HRVB dose-response effect was not reported</td>
</tr>
<tr>
<td>Meule et al. (2012)</td>
<td>18-40 years 11% male</td>
<td>n=14; Twelve 20-min sessions over 4 weeks (Total: 240 min)</td>
<td>Non-craving-control (NCC; n=28)</td>
<td>HRVB intervention vs. control comparison</td>
</tr>
<tr>
<td></td>
<td>Non-clinical University setting Germany</td>
<td>No home practice</td>
<td>Craving-control (CC; n=14)</td>
<td>Larger mean craving reduction in the HRVB group (13%; t(13) = 2.81,p&lt;.05) vs. the NCC (7%; t(27) = 2.90, p&lt;.01). No changes in CC. Stronger standard effect sizes in HRVB group (.95) than in CC (.01) and NCC (.32)</td>
</tr>
<tr>
<td>Study</td>
<td>Age Range</td>
<td>Gender Distribution</td>
<td>Study Setting</td>
<td>Craving Measure</td>
</tr>
<tr>
<td>---------------------</td>
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<td>----------------</td>
</tr>
<tr>
<td>Penzlin et al. (2015)</td>
<td>25-59 years</td>
<td>71% male</td>
<td>Inpatient rehabilitation, Germany</td>
<td>No home practice</td>
</tr>
<tr>
<td>Zucker et al. (2009)</td>
<td>18-60 years</td>
<td>55% male</td>
<td>Urban residential program (6 months to 1 year), USA</td>
<td></td>
</tr>
</tbody>
</table>

*SDNN* refers to the standard deviation of normal-to-normal (NN) intervals.
Biofeedback training methods and practice time. The aforementioned studies used different BFB training methods ranging from a 30-minute handheld device training to a total of 240 minutes of laboratory-based HRVB training either with or without home breathing practice. An average 20-minute daily breathing practice did not seem to produce statistically significant craving reductions in two of the studies although both found craving reduction trends (Eddie et al., 2014; Zucker et al., 2009). Also, in one study no differences were found between high and low users of daily breathing practice in terms of craving changes (Zucker et al., 2009). It is difficult to assess whether these results were due to incorrect breathing practice or unreliable reports of daily practice time. On the other hand, the use of a total 120 minutes HRVB formal training over 2 weeks (Penzlin et al., 2015) and 240 minutes over 4 weeks (Meule et al., 2012) with no daily breathing practice showed statistically significant craving reductions post-intervention. Training session duration did not seem to affect craving reductions as much as the total amount of training in minutes regardless of the number of weeks. The exact amount and duration of HRVB training needed to produce craving reductions are still unclear. Future studies are needed to provide more evidence on the efficacy of daily breathing practice versus formal laboratory-based training. Identifying a specific training amount is essential to ensure a cost-effective intervention.

Controlled breathing studies

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**Biofeedback training methods and practice time.** The aforementioned studies used different BFB training methods ranging from a 30-minute handheld device training to a total of 240 minutes of laboratory-based HRVB training either with or without home breathing practice. An average 20-minute daily breathing practice did not seem to produce statistically significant craving reductions in two of the studies although both found craving reduction trends (Eddie et al., 2014; Zucker et al., 2009). Also, in one study no differences were found between high and low users of daily breathing practice in terms of craving changes (Zucker et al., 2009). It is difficult to assess whether these results were due to incorrect breathing practice or unreliable reports of daily practice time. On the other hand, the use of a total 120 minutes HRVB formal training over 2 weeks (Penzlin et al., 2015) and 240 minutes over 4 weeks (Meule et al., 2012) with no daily breathing practice showed statistically significant craving reductions post-intervention. Training session duration did not seem to affect craving reductions as much as the total amount of training in minutes regardless of the number of weeks. The exact amount and duration of HRVB training needed to produce craving reductions are still unclear. Future studies are needed to provide more evidence on the efficacy of daily breathing practice versus formal laboratory-based training. Identifying a specific training amount is essential to ensure a cost-effective intervention.

**Controlled breathing studies**
Our search yielded a total of four studies investigating controlled breathing (CB) interventions in the treatment of substance craving (Table 2). None of these studies reported the rate at which controlled breathing was conducted except for McClernon et al. (2004) that used a breathing rate of 5 breaths per minute (i.e., comparable to HRVB). Two of the CB studies used community samples of cigarette smokers who were asked to abstain from smoking for 12 to 24 hours before the intervention. Controlled breathing interventions were mostly based on relatively brief CB training and results were limited to acute craving changes immediately post-intervention. Sarkar et al. (2014) proposed a large (N=992) multi-cluster randomized controlled trial of a brief yogic breathing intervention targeting low-income areas in India. However, the research article was limited to the study’s protocol and no results were reported. It is not clear whether this study was conducted or not since no subsequent publications were found in the literature. Two studies of different CB techniques showed significantly larger craving reductions in cigarette smokers immediately after the intervention compared to control groups not receiving CB training (McClernon, Westman, & Rose, 2004; Shahab, Sarkar, & West, 2013). Both studies used the craving subscale from the Shiffman and Jarvik Smoking Withdrawal Questionnaire (SJWQ) to measure craving pre- and post-breathing training. Craving reductions were evident with both short (15 minutes) (Shahab et al., 2013) and long (240 minutes) (McClernon et al., 2004) CB breathing training although different breathing techniques were used. Shahab et al. (2013) reported a significant amount (average of 7.7 times) of CB practice outside lab hours over a period of 24 hours after training. At 24 hour follow up, no craving reductions were found except for participants who reported practicing yogic breathing 'often' or 'very often'. Similarly, McClernon et al.
(2004) concluded that craving reductions were related to continued use of deep breathing at a rate of 5 breaths per minute. Craving levels fluctuated, over the course of four hours, before and after each breathing exercise showing that craving reductions after the first breathing exercise were only maintained with continued use of deep breathing (McClernon et al., 2004). Based on these results, a dose-effect relationship between CB and craving reduction is therefore evident in cigarette smokers abstaining from smoking for a short period of time. Similar post-intervention craving reductions were reported in a sample of crack cocaine dependents (N=32) who were offered 10 minutes of deep breathing training (De Zeni & Araujo, 2009). However, the deep breathing intervention was accompanied with soft music and no control group was used for comparison. It is therefore difficult to discern whether the craving reductions resulted from the breathing intervention or the calming effect of soft music or both. In conclusion, brief controlled breathing exercises showed effectiveness in acutely reducing craving immediately after the breathing exercise. More evidence is needed on the long-term effectiveness of controlled breathing in terms of craving reduction and the amount of practice needed for this relationship to hold. Although the mechanism of CB was not assessed in the reviewed studies, CB may share the same HRVB mechanism in terms of parasympathetic activation and restoration of autonomic balance.

Table 2 - Features of Studies Investigating CB Interventions and Substance Craving

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample</th>
<th>CB intervention</th>
<th>Control</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Zeni et al. (2009)</td>
<td>18–40 years</td>
<td>n=32; Deep breathing</td>
<td>None</td>
<td>Mean craving reduction of 32.1% in CCQB scores ($t(32) = 4.55, p&lt;.001$) and</td>
</tr>
<tr>
<td></td>
<td>100% male</td>
<td>Total time: 10 min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CCQB: Craving, Craving, Craving, and Baseline*
<table>
<thead>
<tr>
<th>Study</th>
<th>Age/Gender</th>
<th>Setting</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>McClernon et al. (2004)</td>
<td>18-60 years, 33% male</td>
<td>Community sample, USA</td>
<td>Controlled breathing over 12 sec every 30 min over 4 hours (Total time: 240 min)</td>
<td>Stayed in quiet room (light reading)</td>
<td>Larger mean craving reduction ($F(1, 7) = 22.44, p=.002$). Means and SDs were not reported.</td>
</tr>
<tr>
<td>Sarkar et al. (2014)</td>
<td>&gt;23 years, Low-income community sample, India</td>
<td>Low-income community sample, India</td>
<td>Yogic breathing (YB), Single training session. Time not specified.</td>
<td>Very brief advice</td>
<td>Only protocol was reported. Results not published.</td>
</tr>
<tr>
<td>Shahab et al. (2013)</td>
<td>18-55 years, 54% male</td>
<td>Community sample, USA</td>
<td>Yogic breathing (Total time: 15 min), Over 24 hours</td>
<td>10 min video about YB</td>
<td>Immediately post-intervention, larger reduction in ‘strength of urges to smoke’ ($F(1, 96) = 16.1, p&lt;0.001$), ‘craving a cigarette now’ ($F(1, 96) = 16.1, p&lt;0.001$), and ‘desire to smoke now’ ($F(1, 96) = 6.6, p=0.012$).</td>
</tr>
</tbody>
</table>
Means and SDs were not reported.

At 24 hour follow up, no craving reductions found except for participants who reported practicing YB ‘often’ or ‘very often’ ($F(1, 46) = 4.0$, $p=0.048$)

$d=$Cohen’s d; $d_{ppc2}=$ effect size; CCQB=$Cocaine Craving Questionnaire-Brief$; SJWQ=$Shiffman and Jarvik smoking withdrawal symptom questionnaires$; VAS=$Visual Analogue Scale$; *same participants were randomized to control and treatment conditions

**Predictors of craving in relation to HRVB**

Taking into consideration the subjective and temporal nature of craving, predictors of craving were grouped into inter- and intra-individual variables. Inter-individual variables are considered constant (or time-invariant) and assess differences between people (i.e., between-person variation). Intra-individual variables are time-variant variables that may change with time and assess how a person differs from his or her own baseline over time (i.e., within-person variation) (Hoffman, 2015).

**Inter-individual variables (Sex, length of abstinence, and addiction severity).**

Various human laboratory studies indicated sex differences in cue-induced craving intensity. While women reported greater cue-induced craving for cocaine and heroin, male sex was associated with greater alcohol craving (Serre, Fatseas, Swendsen, & Auriacombe, 2015). Similarly, in a study employing ecological momentary assessment women reported greater past-hour craving for cocaine and heroin in response to all trigger types (Kennedy, Epstein, Phillips, & Preston, 2013). Also, women smokers showed greater nicotine craving, negative emotion, and stress ratings in response to negative affect/stress cues (Saladin et al., 2012). Sex differences appear to be prominent
in stress responses of substance dependent persons. Specifically, male sex is associated with a general dampened autonomic response while female sex is associated with a non-specific enhanced autonomic function in response to stress (Fox et al., 2009). Since stress and craving are correlated, sex differences in stress-induced craving may have implications for sex-specific anti-craving interventions. On the other hand, individuals’ length of abstinence appears to be an important factor of craving. While baseline substance craving decreased with abstinence time, cue-induced craving showed time-dependent increases in both animal and laboratory studies (Li et al., 2015b). For example, methamphetamine users showed increases in cue-induced craving for up to three months of abstinence followed by reductions in cue-induced craving at 6 and 12 months of abstinence (Wang et al., 2013). Similarly, increases in cue-induced craving were shown in alcohol dependents until two months of abstinence (Li et al., 2015a) and heroin dependents during the first month of abstinence (Shi et al., 2009). Furthermore, addiction severity was positively correlated with alcohol craving (Murphy, Stojek, Few, Rothbaum, & MacKillop, 2014) and predicted craving response to smoking cessation treatment in nicotine dependents (Canterberry et al., 2013; Thompson-Lake et al., 2015; Vollstadt-Klein et al., 2011). The existing literature lacks evidence on whether addiction severity predicts craving in persons addicted to substances other than nicotine. However, addiction severity and other intra-individual factors, including substance type, cigarette smoking during recovery, and age, are worth exploration. None of the reviewed HRVB studies examined such intra-individual variables in relationship to HRVB craving outcomes, which may be due to reduced statistical power in most reviewed studies (Mean=45.75, SD=8.01).
Intra-individual variables (stress, anxiety, and depression). Prior research showed that stress, anxiety and depression are associated with craving (Porges, 2007; Thayer & Lane, 2000) and predict relapse (Sinha, 2011). Stress and anxiety are positively correlated with craving across different substances (Eddie et al., 2014; Fox et al., 2013). The presence of stress when a substance-related stimulus is encountered may influence the rewarding value of that stimulus and induce a heightened craving intensity (Back et al., 2015; Sinha, 2001) and produce stronger and more frequent cravings (Law et al., 2016). Acute stress increased craving in cocaine-dependent individuals and sensitivity to stress-induced craving in alcohol dependents. Stress exposure increased subjective anxiety accompanied with increases in drug and alcohol craving and the susceptibility to abusing alcohol after treatment completion (Breese et al., 2005; Sinha et al., 2009). Furthermore, HF-HRV is negatively associated with stress, anxiety, and depression (Dishman et al., 2000; Eddie et al., 2014; Lin et al., 2016). Controlled studies suggest that HRVB may be a useful intervention for stress and anxiety in non-clinical samples (Thurber et al., 2010; Wells et al., 2012), and clinical samples of persons with major depression (Karavidas et al., 2007; Siepmann, Aykac, Unterdorfer, Petrowski, & Mueck-Weymann, 2008). Among the reviewed studies, Penzlin et al. (2015) reported simultaneous craving and anxiety reductions without changes in depression symptoms following a two-week HRVB intervention, while Zucker et al. (2009) found significant depression reductions without significant craving changes following a four-week portable HRVB intervention. Taken together, the literature provides some evidence on the usefulness of HRVB in decreasing anxiety, depression, perceived stress, and craving. However, the relationships among these factors have not been systematically evaluated in
a clinical sample of persons with SUD. Exploring the associations among perceived stress, anxiety, and depression in relation to HRV and substance craving changes may provide more insight into the mechanisms underlying the HRVB-craving relationship and potential treatment implications.

**Discussion**

**Effectiveness of HRVB and CB in reducing cravings**

The literature supports HRVB training and controlled breathing as candidates to assist craving reduction and relapse prevention in persons recovering from SUD although a definitive conclusion was not possible. Our review yielded a varied range of methodological quality levels and effect size (Table 3). The reviewed HRVB articles rated moderately on methodological rigor (SASQI = 14-15) but showed inconsistent magnitudes of calculated effect size (.074 to .727) across populations. The largest effect size was found in a non-clinical college population of high food cravers utilizing the longest HRVB training time of 240 minutes. A small to moderate effect size was found in SUD populations from inpatient/residential settings except for the Penzlin et al. (2015) study which showed nearly zero effect of the two-week HRVB on craving. On the other hand, two of the three CB studies indicated modest methodological quality due to the lack of control and randomization, while one CB study rated highly. Notwithstanding quality, all CB studies showed moderate to large effect size ranging from .413 to 1.498. The largest effect size was found in smoking cessation studies testing the same persons repeatedly (McClernon et al., 2004) and without control (De Zeni & Araujo, 2009). Effect size may have been inflated due to dependency which usually yields a higher
power (Lenhard & Lenhard, 2016) or to differences in substance type (cigarettes vs. alcohol vs. other drugs).

Table 3 - Effect Size and Quality Ratings using SASQI

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Intervention / duration</th>
<th>Effect size</th>
<th>SASQI score</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeZeni et al. (2009)</td>
<td>Pre-post</td>
<td>Deep breathing (10min)</td>
<td>$d_{CCQB}=1.026$</td>
<td>8/21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$d_{VAS}=.968$</td>
<td></td>
</tr>
<tr>
<td>Eddie et al. (2014)</td>
<td>Controlled trial</td>
<td>HRVB (3 weeks)</td>
<td>$d_{ppc2}=.232$</td>
<td>14/21</td>
</tr>
<tr>
<td>McClernon et al. (2004)</td>
<td>Crossover trial</td>
<td>Controlled breathing (4 hours)</td>
<td>$d=1.498$</td>
<td>7/21</td>
</tr>
<tr>
<td>Meule et al. (2012)</td>
<td>RCT</td>
<td>HRVB (4 weeks)</td>
<td>$d_{ppc2}=.727$</td>
<td>15/21</td>
</tr>
<tr>
<td>Penzlin et al. (2015)</td>
<td>RCT</td>
<td>HRVB (2 weeks)</td>
<td>$d_{ppc2}=.074$</td>
<td>14/21</td>
</tr>
<tr>
<td>Shahab et al. (2013)</td>
<td>RCT</td>
<td>Yogic breathing (24 hours)</td>
<td>$d_{post}=.728$</td>
<td>15/21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$d_{24hr}=.413$</td>
<td></td>
</tr>
<tr>
<td>Zucker et al. (2009)</td>
<td>RCT</td>
<td>Portable HRVB (4 weeks)</td>
<td>$d_{ppc2}=.329$</td>
<td>11/21</td>
</tr>
</tbody>
</table>

$SASQI=$ Scale for Assessing Scientific Quality of Investigations; $d=$ Cohen’s $d$; $d_{ppc2}=$ effect size based on pooled pretest standard deviation; $CCQB=$ Cocaine Craving Questionnaire-Brief; $RCT=$ Randomized Controlled Trial; VAS=Visual Analogue Scale

In general, CB studies were limited to brief pre-post assessment of craving which did not provide evidence on the long-term effectiveness of CB treatment. Taken together, of the seven studies reviewed, three HRVB and all three CB studies showed positive results with inconsistent effect size. The reasons behind this wide range of effect size may include cultural differences with 50% non-USA studies, treatment setting variations (which may impose various lengths of abstinence and treatment options), substance type,
individual variations and co-morbidities, treatment protocol and duration, and other methodological and validity related discrepancies. Although CB studies provided additional supportive evidence to the effectiveness of cardiorespiratory training in acutely reducing craving, more clinical trials with carefully monitored interventions are required to rigorously determine the long-term effects of HRVB as an anti-craving treatment.

**Challenges of HRVB studies**

**Craving measurement.** In the reviewed HRVB articles, craving was examined with different types of assessments (Table 1) that are based on dissimilar conceptualizations of the craving construct, ranging from single item to multi-dimensional assessments. The adjusted Pennsylvania Alcohol Craving Scale (PACS) is a five-item single-factor scale that measures characteristics of craving without asking about factors associated with craving, such as emotional states or incentives (Flannery et al., 1999). On the other hand, the Obsessive-Compulsive Drinking Scale (OCDS) is a multi-dimensional instrument that assesses the cognitive aspects of craving including thoughts and compulsions as well as addiction severity (Anton, Moak, & Latham, 1996). Similarly, the Food Craving Questionnaire – Trait (FCQ-T) is a multi-dimensional instrument that measures various aspects of food cravings such as food triggers, relief anticipation, and preoccupation/control over eating. From a validity perspective, the variety of theoretical assumptions underlying each of these instruments may have resulted in the measurement of different aspects of craving creating inconsistencies in trial outcomes such as those revealed in this review. Given the relatively rudimentary understanding of the phenomenon of craving, it is not yet possible to accurately assess what experiencing craving means to the patient, clinician, and researcher. Despite the
advantages of single-item ratings of drug craving and how highly they correlate with many multi-item questionnaires, this type of craving assessment may fail to assess urges and cravings if drug takers attribute such feelings to another psychological or physiological state, such as anxiety, excitement, or drug withdrawal (Rosenberg, 2009). Components of the construct of craving, including emotional, cognitive, physiological and behavioral responses, remain the subject of considerable debate, suggesting the need for using multiple types of craving measurement and perhaps for more grounded theory or phenomenological studies in this area.

**Training protocols and personal practice.** Despite the limited number of HRVB studies, various training protocols were used employing different session allocations and treatment durations. The study with the longest standardized training time (240 minutes) and treatment duration (4 weeks) (Meule et al., 2012) among the three other studies had the strongest effect in terms of craving reduction, although home practice was not employed. This observation is supported by previous clinical trials of HRVB that have produced clinically significant changes in fibromyalgia, depression, and PTSD symptoms with longer interventions of 8 to 10 weeks, although these studies included home practice of up to 20 minutes twice daily (Hassett et al., 2007; Karavidas et al., 2007; Tan, Dao, Farmer, Sutherland, & Gevirtz, 2011). Yet, it is unknown whether this dose-effect relationship holds in clinical SUD populations. In addition, the usefulness of personal HRVB practice outside training hours remains unknown. Although positive anecdotal reports have been conveyed (Eddie et al., 2014), a relationship between personal practice and craving has not been found. Participant reports of daily practice have not been
independently verified. The use of electronic monitoring to accurately assess actual time spent practicing could provide more useful information.

**Methods and statistical analysis.** Since craving is a highly subjective and temporal phenomenon, observed changes in craving may be either undirected fluctuations or systematic changes. Erroneous conclusions of craving changes are therefore likely when only pre-post measurements are used. A minimum of three observations is usually required to differentiate error from real change, thus the need for longitudinal data. The primary advantage of a longitudinal study lies in its capacity to inform about within-person, in addition to between-person, relationships (Hoffman, 2015). The discrepancies found in the literature highlight the predominance of individual differences in craving assessments and the necessity of interpreting craving changes as a function of intra- and inter-individual sources of variance. General linear models, such as the analyses of variance and regression analyses employed by all reviewed studies, fail to distinguish intra- and inter-individual differences because they do not examine sources of dependency (or strong correlations between residuals) (Hoffman, 2015; Holden, Kelley, & Agarwal, 2008). The use of multilevel modeling (MLM) (also known as general linear mixed models) and potentially structural equation modeling (SEM) in analyzing longitudinal data allows the simultaneous examination of between- and within-person relationships (Hoffman & Stawski, 2009; Hox, 2010). Many benefits have been reported of the use of MLM over traditional general linear models in analyzing longitudinal data. With repeated measures, dependency is expected between the individual’s responses over time, which violates the assumption of independence of data that is required for repeated measures analyses of variance and regression analyses. MLM overcomes this
shortcoming by partitioning the outcome’s residual variance into within- and between-person components. The covariance between residual components is therefore explored to identify sources of dependency and accurately distinguish individual and time-specific differences. Furthermore, MLM handles missing and unbalanced data while preserving statistical power and the generalizability of results, which overcomes the problem of listwise deletion with general linear models (Hoffman, 2015; Hox, 2010; Kwok et al., 2008).

**Strengths and Limitations**

Strengths of this review include the use of a quantitative assessment of effect size across studies, a qualitative systematic review approach, and an exploration of study attributes that were associated with craving reductions. Nonetheless, this review has several limitations. Although an exhaustive literature search was conducted, the limited volume of HRVB and CB studies investigating craving does not provide material for a systematic review. CB interventions may not share the same mechanisms as HRVB and have different training methods, which makes comparison difficult across studies. However, CB studies were informative and worthy of examination and provided additional support to the evidence from HRVB studies. The reliability and validity of the SASQI has not been empirically evaluated, and SASQI ratings for this review cannot be considered completely unbiased.

**Future Directions**

Further study of HRVB as an anti-craving intervention for persons recovering from SUD is required but would benefit from improved methodology as well as addressing the aforementioned challenges. Based on this review, the following
considerations are recommended: (1) use of reproducible HRVB training protocols and treatment duration of 8 to 10 weeks at a minimum, (2) longitudinal examination of craving changes over time to differentiate fluctuation from real change, (3) examination of the effects of personal practice outside HRVB training using accurate measurements of practice time and treatment fidelity, (4) further examination of confounding variables (such as substance type, co-morbidity, length of abstinence, treatment setting) and other predictors of craving in relationship to HRVB, (5) use of multiple craving instruments to ensure measurement validity of the currently debatable craving phenomenon, and (6) use of advanced statistical analyses that differentiate between- and within-person variations, such as multilevel modeling and structural equation modeling.

Conclusion

This review evaluated current evidence on the effectiveness of HRVB training as an adjuvant anti-craving treatment. Additional evidence from controlled breathing studies was reviewed due to the limited amount of HRVB studies investigating craving changes. Challenges of HRVB studies and future directions were explored. The impact of craving as a frequently experienced and strong predictor of relapse underscores the need for investigating innovative anti-craving interventions. HRVB training was shown to be of significant therapeutic potential. Most reviewed studies showed positive results and a relatively moderate effect size across SUD populations. However, due to the scarcity and limitations of the studies available, larger clinical trials are required with methodological improvements such as longer treatment duration, adequate control conditions, measures of adherence, longitudinal examination of craving changes differentiating undirected
fluctuation from systematic change, and more comprehensive methods to measure and assess the craving phenomenon.
CHAPTER FOUR: METHODS

This chapter explains the study’s research design and methods. The research setting, sample, instruments, data collection procedures, and plan for data analysis are described in detail. An overview of multilevel modeling is also provided to support the rationale for the analysis plan. This study proposed a longitudinal analysis of extant data from an original experiment that was based on a protocol developed by Lehrer et al. (2000). A waitlist control condition was contrasted with the experimental condition. Participants were assessed at four occasions in the control condition over the first 12 weeks followed by an 11-week rest period (semester break) and 12 weeks in the experimental condition (8 occasions).

The Research Setting

Participants were recruited between the spring semesters of 2011 and 2015 through Recovery Housing available for students who are in voluntary recovery from SUD and managed by the university’s drug assistance program. Information flyers were made available to the students affiliated with the recovery house. Interested students were directed to contact the research staff at the Center of Alcohol Studies. Participation in this study was strictly voluntary and participants were neither charged nor paid to participate in the study.

The Sample

Inclusion and Exclusion Criteria

A total of 46 college students were enrolled in the study. Inclusion criteria were as follows: (1) current student in voluntary recovery from a SUD who resided in Recovery Housing, (2) fluency in the English language, and (3) 20/20 or corrected vision.
Exclusion criteria included conditions that may contraindicate physiological assessment or confound interpretation of HRV including: (1) cardiovascular disease (CVD) (e.g. pacemaker, cardiac arrhythmia, and hypertension) or other medical condition which increases CVD risk (e.g. diabetes) or pregnancy, (2) psychiatric condition (e.g., psychosis), or neurological condition (e.g., Parkinson’s disease), (3) medications such as MAOIs, Alpha or Beta Blockers, anti-psychotics, or benzodiazepines, and (4) previous experience with HRVB.

**Power Analysis**

The Repeated Measures and Sample Size (RMASS) (Roy, Bhaumik, Aryal, & Gibbons, 2015) web application computes sample size for multilevel mixed-effects linear regression models for the analysis of clustered longitudinal data. The sample size determinations in this program are based on the requirements for a test of treatment by time interactions. The two-level model allows for random-effects of the time trends at subject-level. This approach allows for differential attrition rates over time (Roy, Bhaumik, Subhash, & Gibbons, 2007). In our calculation, we accounted for four time points and the actual attrition rate of 13%. Using a two-tailed significance level of 0.05 and a power of 0.8, RMASS calculated a sample size of 35 participants. Therefore, the sample size (N=46) meets the criteria.

**Instruments**

**Demographic Information Questionnaire**

A questionnaire was used to collect contact and demographic information including age, sex, employment, university status, and length of abstinence.

**Penn Alcohol Craving Questionnaire (PACS)**
The PACS is a unidimensional 5-item questionnaire that assesses the severity of an individual’s alcohol or drug craving. Items are coded on a 7-point scale from “0”, (Not present) to “6” (Severe). A total PACS score range of 0 to 30 is possible with higher scores indicating greater substance craving (Flannery et al., 1999). The PACS has been used extensively in the literature with evidence of established validity and reliability. Convergent validity of the PACS was initially evidenced by the significant moderate correlation of PACS with the Obsessive Compulsive Drinking Scale (OCDS) scores \((r = 0.55)\) and the Alcohol Urge Questionnaire (AUQ) scores \((r = 0.39)\), both of which are instruments used to assess craving (Flannery et al., 1999). In subsequent studies, higher correlations were reported between PACS and OCDS and PACS and the craving Visual Analogue Scale in a study of college binge drinkers (Rosenberg & Mazzola, 2007) and a study using the Korean version of PACS (Kim et al., 2008). In addition, discriminant validity of PACS was supported by the lack of significant relationships between PACS and various scales of dissimilar constructs such as the Addiction Severity Index (ASI) psychiatric severity scores \((r = 0.11)\) and interpersonal relationships scores \((r = -0.04)\) (Flannery et al., 1999). Adequate test-retest reliability has been reported at 1-day intervals \((r=0.769, p<0.01)\) (Kim et al., 2008). Adequate internal consistency has been widely reported with Cronbach’s alpha ranging from 0.87 to 0.92 (Nunnally & Bernstein, 1994). The original study on PACS reported a Cronbach’s alpha of 0.92 with high item-total correlations, ranging from 0.8 to 0.92 (Flannery et al., 1999). Cronbach’s alphas in subsequent studies ranged from 0.87 to 0.96 showing consistently appropriate reliability across substance-dependent populations, such as 0.87 in a general sample of inpatients with substance use disorders (Witkiewitz & Bowen, 2010), 0.88 in a sample of adult
opioid-dependents (Tsui, Anderson, Strong, & Stein, 2014), and 0.96 in a population of Turkish alcohol-dependent inpatients (Evren, Durkaya, Dalbudak, Cetin, & Evren, 2012). See Manuscript 2 for an in-depth review of PACS.

**Beck Anxiety Inventory (BAI)**

The BAI is a 21-item questionnaire that assesses the severity of an individual’s anxiety in the past week. Items are coded on a 4-point scale ranging from “0=Not at all” to “3=Severely”. A total BAI score range of 0 to 63 is possible with higher scores indicating greater anxiety symptoms (Beck, 1993). The BAI has been validated in studies involving populations with SUD showing adequate validity and reliability (Ali, Seitz-Brown, & Daughters, 2015; Thekiso et al., 2015).

**Beck Depression Inventory – II (BDI-II)**

The BDI is a 21-item questionnaire that assesses the severity of an individual’s depression in the past week. Items are coded on a 4-point scale from “0” to “3”. A total BAI score range of 0 to 63 is possible with higher scores indicating greater depression symptoms (Beck, 1996). The BDI has been validated in various studies involving populations with SUD showing adequate validity, good internal consistency, and test-retest reliability (Ali et al., 2015; Buckley, Parker, & Heggie, 2001; McPherson & Martin, 2010). The BDI-II was also found to discriminate between depression and other psychiatric disorders in substance-dependent patients with dual diagnosis (Lykke, Hesse, Austin, & Oestrich, 2008).

**Perceived Stress Scale (PSS)**

The PSS is a 10-item questionnaire that assesses stress frequency in the past month. An example item is “In the last month, how often have you felt nervous and
stressed?”. Items are measured on a 5-point, Likert-type scale (“0=Never” to “4=Very often”). A total PSS score range of 0 to 40 is possible with higher scores indicating greater perceived stress (Cohen, Kamarck, & Mermelstein, 1983). The PSS has well-established validity and reliability in various populations such as persons with chronic diseases (Lee, Chung, Suh, & Jung, 2015) and college students (Smith, Rosenberg, & Timothy Haight, 2014). It has been used in two studies involving persons with SUD and showed adequate hypothesis testing validity. Instrument reliability was not reported in these studies (Pedrero-Perez et al., 2015; Tavolacci et al., 2013).

**Procedure for Data Collection**

The study spanned over a period of 35 weeks. There were four occasions of measurement for the control condition and eight occasions of measurement for the experimental condition, each over the course of one semester (12 weeks), separated by a semester break (11 weeks). In the first semester of data collection (Spring 2012), participants were randomly assigned to either the HRVB condition (8 participants) or the waitlisted control condition with treatment as usual (TAU) (4 participants). From the second semester and on, participants were enrolled in a control condition of TAU followed by an experimental condition of HRVB. Appointments were made with each participant to conduct research measurements in a private area at the recovery house, accommodating the participants’ schedules to promote participant retention. The data collection protocol is presented in Table 4 with the number of weeks in the study representing the average week number across participants per occasion. The first 4 occasions of measurement constituted the control condition whereby participants responded to the PACS, BAI, BDI, and PSS. HRVB training started at occasion 5.
Participants in the HRVB condition responded to the PACS and PSS at each occasion and to the BDI and BAI on occasions 5, 8, 11, and 12 only. Participants in the HRVB condition engaged in a total of 7-8 hours of physiological monitoring and breathing training. Measures of ECG and respirations were obtained on occasions 5, 8, 11, and 12 to ensure appropriateness of the HRVB intervention. Occasions 6, 7, 9, and 10 included HRVB training with no physiological recording. In addition, participants were asked to practice resonance frequency breathing for 15-minute periods twice daily on their own, using portable biofeedback devices that were provided to them while in the study. Daily HRVB practice was logged on weekly basis based on participant self-report.

Table 4 - Data Collection Protocol

<table>
<thead>
<tr>
<th>Time/Week</th>
<th>PACS</th>
<th>PSS</th>
<th>BDI</th>
<th>BAI</th>
<th>ECG Recording</th>
<th>HRVB Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (week 1)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2 (week 3)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3 (week 6)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4 (week 12)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5 (week 23)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>6 (week 24)</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>7 (week 25)</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>8 (week 26)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>9 (week 27)</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>10 (week 28)</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>11 (week 30)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>12 (week 35)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Experimental Operational Definition

The HRV BFB intervention was based on a protocol developed by Lehrer et al. (2000). The protocol included the following sessions:
- Session 1 (Time 5): Obtaining initial estimates of resonance frequency.
- Session 2 (Time 6): Learning abdominal and pursed lips breathing techniques.
- Session 3 (Time 7): Review of pursed-lips, abdominal breathing, HRV BFB training, and learning how to breathe with cardiotachometer feedback.
- Sessions 4, 7 & 8 (Times 8, 11, & 12): Continued BFB practice and assessment.
- Sessions 5 & 6 (Times 9 & 10): Maximizing heart rate variability.

A descriptive summary of each session is provided in Appendix (A).

**Physiological Recording Instrumentation**

Physiological data were recorded using BioGraph Infiniti software (Thought Technology Ltd.; Montreal, Canada) and saved on a desktop PC. Electrocardiograms were recorded via a FlexComp Infiniti Encoder and Amplifier (Thought Technology Ltd.; Montreal, Canada). Beat-to-beat RR intervals (RRI) of the ECG signal were measured from three electrodes attached to the arms and ankle, digitalized at a rate of 2,048 samples per second. A respiration strain gauge belt was positioned around the abdomen (navel area), and participants' respiration volume was calibrated using an 800cc plastic bag into which participants briefly breathe through a disposable cardboard tube.

**Data Analysis**

**Preliminary Analyses**

All data analyses were conducted with the Statistical Package for the Social Sciences (SPSS) version 23.0. Measures of central tendency were computed to describe sample characteristics including demographics and symptom severity scores. The data were examined for distribution, skewness, outliers, and linearity using histograms, scatterplots, and skewness and kurtosis statistics. All variables met assumptions of
normal data distribution. In addition, the variables were carefully examined for missing data points. A minimum of three observations was required to differentiate fluctuation from real change. Two participants had less than three time points on the outcome variable and were thus excluded from the sample (Hoffman, 2015). Of the 44 remaining participants, four dropped out from the experimental condition because they felt too busy with school work. Furthermore, instrument reliability was determined using measures of internal consistency for each of the instruments measuring continuous variables. A Cronbach’s coefficient alpha of 0.7 or more was considered acceptable (Nunnally & Bernstein, 1994).

**Multilevel Modeling for Longitudinal Analysis**

A multilevel modeling (MLM) approach was used to perform a longitudinal analysis of substance craving changes over time and across conditions. The purpose of these analyses was to (1) describe the average pattern of craving changes over time, (2) describe the individual differences within these changes, and (3) predict between-person differences and the remaining within-person variation over time. A series of mixed effects random coefficient models were analyzed with observations at level-1 nested within persons at level-2. These analyses modeled within-person and between-person craving variations simultaneously. The effects of craving predictors including perceived stress, depression, anxiety, length of abstinence, and daily breathing practice time were also modeled at both levels.

**Levels of Analysis.** Longitudinal variables comprise two dimensions of sampling which results in two sources of variation in the data, namely between-person variation and within-person variation over time. Between-person variation refers to differences
between people or inter-individual variation, the type of variation that is considered constant (or time-invariant) and could be determined from cross-sectional data. The between-person level of analysis is the macro level of analysis, labeled as level 2. On the other hand, the micro level of analysis (level 1) refers to within-person (or intra-individual) variation reflecting how a person differs from his or her own baseline over time (Hoffman, 2015). In this study, observations of substance craving over time are nested within persons.

**Fixed and Random Effects.** Mixed models have two sides: the model for the means and the model for the variance. The model for the means states the fixed effects of predictors on the outcome showing how the outcome varies as a function of predictor values on average. On the other hand, the model for the variance describes the pattern of variance and covariance for the *residuals* of the outcome showing the random effects of the predictor. In this context, “the term fixed means that everyone gets the same effect (i.e. a single slope estimated for the predictor’s effect in the model for the means), whereas the term random means that everyone gets his or her own effect (i.e., achieved by estimating variance across persons for the slope of the predictor)” (Hoffman, 2015, p. 11).

Time is a primary predictor in longitudinal models of change. It is therefore crucial to consider both fixed and random effects of time in such models. Figure 1 displays four possible combinations of fixed and random effects of time in any given longitudinal study. In each panel, the x-axis is time and the y-axis is any given outcome, with thin lines showing time slopes for hypothetical individuals in the sample (i.e., random effects) and a heavy line depicting the fixed slope for mean change over time in
the overall sample (i.e., fixed effect). There are instances where no effects of time are
evident, neither fixed nor random, indicating no significant change over time on average
and for everyone in the sample (Panel a). Sometimes, change is the same across all units
in a sample (Panel b) showing a fixed but no random effect of time (i.e., the average
slope is a sufficient descriptor of individual slopes). Panel (c) illustrates a scenario where
units in a sample change in opposite directions leading to a zero fixed effect of time.
However, this zero average slope does not describe individual slopes indicating a random
effect of time despite the lack of a fixed effect of time. Finally, panel (d) depicts the most
common pattern where both fixed and random effects of time are evident. Although
average and individual slopes are in the same direction, the average slope does not
accurately describe every individual in the sample. There is a random effect of time
because individuals in this sample change at different rates over time and each person
needs his or her own slope for time beyond the average fixed slope. The individual
differences in patterns of change are therefore depicted through random effects by
estimating random variance across persons (i.e. individual deviations from the fixed time
slope) in the model for the variance rather than estimating different fixed slopes for each
person in the model for the means.

**Summary of Rationale for MLM.** The primary advantage of a longitudinal
study lies in its capacity to inform about within-person in addition to between-person
relationships. The use of MLM in analyzing longitudinal data allows the examination of
both between- and within-person relationships at different levels of analysis
simultaneously. Many benefits have been reported of the use of MLM over traditional
general linear models in analyzing longitudinal data.
With repeated measurements, strong correlations (or dependency) are expected between the individual’s responses over time, which violates the assumption of independence of data that is required for repeated measures analyses of variance and regression analyses. Multilevel models overcome this shortcoming by partitioning the outcome’s residual variance into a within-person component (the variance of the time-level or level 1 residuals) and a between-person component (the variance of the person-level or level 2 residuals). The covariance between residual components at each level in the hierarchy and between hierarchies is therefore explored to identify sources of dependency and accurately distinguish individual and time-specific differences (Hoffman, 2015; Hox,
Furthermore, MLM handles missing and unbalanced data while preserving statistical power and the generalizability of results, which overcomes the problem of listwise deletion with general linear models.

**Steps for MLM.** The assumptions of MLM was evaluated, including linear relations between variables, normal distribution of error terms at levels 1 and 2, homoscedasticity, and the absence of correlations between residuals at levels 1 and 2. Since the actual time intervals between measurement occasions differed per participant in this study, time was entered as a covariate in the models and was centered such that 0 indicated the first observation. Time observations were balanced across persons by using the actual number of weeks in the study corresponding to each measurement occasion for each participant, starting with week one after the first control session (session 1) and week 35 before the last experimental session (session 12). The 95% confidence interval (CI) for the random variation around each fixed effect was calculated as +/- 1.96. The MIXED function was used in SPSS to estimate the mixed effects random coefficient models. Time models were estimated using restricted maximum likelihood (REML) whereas Maximum Likelihood (ML) was used when fixed predictors were added to the models (Hoffman, 2015). The significance of individual fixed effects was evaluated using their Wald test p values. The significance of multiple fixed effects and random effects variances and covariances was evaluated using likelihood ratio tests including -2 Log Likelihood (-2LL), Akaike Information Criterion (AIC), and Bayesian Information Criterion (BIC). Given that standardized coefficients do not exist for two-level models, pseudo-$R^2$ were calculated to determine the proportion of variance reduction accounted for by the predictors at each level of analysis. In addition, the proportion of explained
total outcome variance ($R^2$) was determined by calculating the square of the Pearson correlation between the predicted outcome and the actual outcome. This method generates a true $R^2$ since it is based on the total original outcome variance (Hoffman, 2015).

The below steps were based on the MLM methodology by Hoffman (2015):

**Step 1: Estimating the empty means random intercept model (or null model).** A series of unconditional models were estimated to describe the variance and covariance of craving over time using REML. An unstructured model was first examined to provide a baseline for comparison. Alternative covariance structure models were then evaluated using -2 Log Likelihood (-2LL), the Akaike Information Criteria (AIC), and the Bayesian Information Criteria (BIC). The covariance structure with compound symmetry provided the best model fit and was therefore selected. Preliminary analyses were conducted to confirm whether a two-level model is indicated for the present data. To determine sources of variation in substance craving, the intraclass correlation (ICC) statistic was calculated based on covariance parameters from the null model with craving as the outcome variable and no predictors. The ICC value reflects the ratio of between-person (BP) to within-person (WP) variation in the outcome. ICC was calculated using this formula: $ICC = \frac{BP \text{ variation}}{BP + WP \text{ variation}}$. ICC values range from 0 to 1. The higher the ICC the higher the correlation between outcome residuals, which violates the assumption of independence. Thus the use of multiple linear regression is not appropriate given the dependence in the data. In addition, the higher the ICC the higher the variability between-persons (level-2) and consequently the lower the variability within-persons (level-1).
Therefore, a low to moderate ICC value in the null model indicates the need for random coefficients models (Hoffman, 2015; Hox, 2010).

**Step 2: Developing the fixed linear time random intercept model (level 1).** This model was developed by adding a fixed linear effect of time to the null model. This model determined the basic longitudinal trajectory of craving changes over time and included a random intercept and fixed linear slope of time as an explanatory variable in the level 1 model. This model predicted an average linear trajectory of time and parallel individual trajectories of craving, as represented in panel (b) of Figure 1.

This step tested the following hypothesis:

*Hypothesis 1.* Craving levels decline on average over time.

**Step 3: Developing the random linear time model (level 2).** The random model was constructed by adding a random linear time slope variance to the level 1 model to examine within-person in addition to between-person variation in craving over time. This model predicted an average linear trajectory of time and non-parallel individual trajectories of craving, as represented in panel (d) of Figure 1. This step tested the following hypotheses:

*Hypothesis 2.* Craving reductions occur at different rates over time.

**Step 4: Adding intra-individual predictor variables.** Before adding predictors, continuous variables were centered to have a meaningful zero, which facilitates interpretation since intercept values represent the mean when predictors have a value of zero. Age was centered at the median, such that 0=23 years. These models were estimated to examine the relationships among craving changes over time and intra-
individual or time-invariant predictors (age, sex, length of abstinence, and daily HRVB practice). This step tested the following hypotheses:

_Hypothesis 3._ Age is related to craving changes over time.

_Hypothesis 4._ Sex is related to craving changes over time.

_Hypothesis 5._ Length of abstinence is related to craving changes over time.

_Hypothesis 6._ The dose of daily HRVB practice predicts craving changes over time.

**Step 5:** Adding inter-individual predictor variables. These models were estimated to examine the relationships among craving changes over time and inter-individual or time-varying predictors (depression, anxiety, and perceived stress). BDI, BAI, and PSS were centered at their respective mean values, such that 0=8 for BDI, 0=10 for BAI, and 0=13 for PSS. For inclusion as predictors of craving, BDI, BAI, and PSS were person-mean-centered by creating two separate predictor variables for each. The within-person variable represented the deviation from each person’s mean score across all his or her occasions (level-1 effect) and the level-2 between-person variable represented the person’s mean score across weeks centered at the grand mean. Main effects of BDI, BAI, and PSS were examined at each level of analysis. This step tested the below hypothesis:

_Hypothesis 7._ Variations in depression, anxiety, and perceived stress are associated with craving changes over time.

**Step 6:** Piecewise mixed model of change. To determine the effect of the HRVB protocol on craving changes over time, a piecewise random coefficient model of craving changes over time was examined. The first HRVB training session (session 5) was
identified as the breakpoint in the craving trajectory. A piecewise model of change was estimated, in which slope15 was created to describe change from session 1 to 5 and slope512 described the change from session 5 to 12. This step tested the below hypothesis:

Hypothesis 8. Craving reductions in the experimental condition are greater than craving reductions in the control condition.

**Conclusion**

This study proposed a longitudinal analysis of craving changes in college students receiving HRVB during recovery from SUD. A series of mixed effects random coefficient models will be analyzed with observations at level-1 nested within persons at level-2. By estimating these models, the study addressed current gaps in the literature by (1) providing a longitudinal examination of craving changes during prolonged HRVB training, (2) examining dose-related effects of HRVB on craving reductions, and (3) employing multilevel modeling to distinguish between- and within-person variation in substance craving changes.
MANUSCRIPT 2: A REVIEW OF PSYCHOMETRIC PROPERTIES OF THE PENN ALCOHOL CRAVING SCALE

Background Information

Alcohol craving is a key feature of alcohol addiction and recovery and was added as a criterion for Alcohol Use Disorder in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (Kavanagh et al., 2013). Craving is a subjective experience that varies from a person to another and has virtually no universal definition. The Penn Alcohol Craving Scale (PACS; Flannery, Volpicelli, & Pettinati, 1999) is considered to be among the better performing measures of craving. The purpose of this paper is to evaluate the psychometric properties of PACS discussing its development, measurement validity, and reliability.

Definitions and Theories of Craving

Advances in the neural understanding of craving and pharmacotherapies targeting craving have stimulated research in the area and resulted in various views of craving as a phenomenon of both psychological and physiological origins (Kavanagh et al., 2013). Other theories present craving in the context of classical conditioning and identify three types of craving (cue-, withdrawal-, and drug-induced) depending on the precursor of craving (Bruehl, Lende, Schwartz, Sterk, & Elifson, 2006; Drummond, 2001). As a result of the conceptual confusion around craving, various craving measures have emerged ranging from single-item (such as the Visual Analog Scale, VAS) to multi-dimensional instruments (such as the Obsessive-Compulsive Drinking Scale) depending on the underlying theoretical assumptions (Kavanagh et al., 2013).

General Characteristics of PACS
The PACS is a five-item single-factor scale that measures characteristics of craving without asking about factors associated with craving, such as emotional states or incentives. PACS is self-administered requiring one to two minutes for completion. The first three questions ask about the frequency, intensity, and duration of thoughts about craving. The fourth question asks about the ability to resist drinking and the final question asks for an average rating of alcohol craving. All questions specify a time frame of “during the past week”, which may introduce retrospective memory biases (Kavanagh et al., 2013). Response items range on a numerical scale of zero to six coupled with descriptors relevant to the question.

**Development of the PACS**

The PACS was initially developed by Flannery et al. (1999) for an alcohol dependence treatment study comparing the effectiveness of naltrexone/placebo and nurse-delivered behavioral intervention between 1995 and 1997. The sample included 147 adult patients, who met diagnostic criteria for alcohol dependence, after successfully completing a one-week detoxification program. There is no information on how the PACS items were developed yet the authors assumed an atheoretical approach. Unfortunately, the original article by Flannery et al. (1999) does not include any information about the method used to develop PACS and communications with the authors have yielded no response. The authors identified that their goal for developing PACS was to create an instrument that defeats the “inherent disadvantages of single-item and multiple-item scales” (p. 1290). In their argument, they stated that single-item scales are limited in terms of predictive validity and multi-item scales are bound by specific theoretical frameworks. Nonetheless, the proper steps of scale development would
include: concept definition, item pool generation, response scale decision, expert review, item validation, scale administration, and final item evaluation (DeVellis, 2011).

**Validity of the PACS**

**Content Validity**

Content validity is the extent to which the items adequately sample the universe of items measuring the construct (DeVellis, 2011). In this case, the PACS’s content validity is difficult to assess due to the lack of information on the methods used for item generation. If expert review is used to validate the items, a Content Validity Index of 0.8 or larger is usually recommended (Grant & Davis, 1997). This information is however unavailable.

**Construct Validity**

**Convergent and Discriminant Validity.** Convergent validity is supported when the measure strongly correlates with a measure of the same or similar construct (Waltz et al., 2010). In the initial study by Flannery et al. (1999), convergent validity of the PACS was established as evidenced by the significant ($p<0.001$) moderate correlation of PACS with total OCDS scores ($r = 0.55$) and the Alcohol Urge Questionnaire (AUQ) scores ($r = 0.39$), both of which are instruments used to assess craving. In subsequent studies, higher correlations were reported between PACS and OCDS and PACS and the craving VAS in a study of college binge drinkers (Rosenberg & Mazzola, 2007) and a study using the Korean version of PACS (Kim et al., 2008). Discriminant validity is supported when the measure does not correlate with measures of dissimilar constructs (Waltz et al., 2010). The lack of significant relationships ($p>0.05$) between PACS and Addiction Severity Index (ASI) psychiatric severity scores ($r = 0.11$), ASI interpersonal relationships scores
Hypothesis Testing. Findings of subsequent studies were consistent with hypothesized expectations thus supporting PACS’s construct validity (DeVellis, 2011). For example, naltrexone trials using PACS showed evidence of reduced craving in the naltrexone experimental groups compared to placebo (Garbutt, 2009; Monterosso et al., 2001; Richardson et al., 2008).

Statistical Testing. In a Rasch Analysis study of alcohol craving in Veterans with mental health disorders and mild traumatic brain injury, infit mean square (MNSQ) standardized residuals indicated that four of the five PACS items fit the measurement model. The item on ‘resisting to drink’ showed the only misfit. However, removing this item did not improve model fit. Also, data of 14% of the Veterans showed model misfit which was attributed to the heterogeneous nature of the sample but may also suggest room for scale improvement. Overall, psychometric analyses showed that PACS functioned as expected supporting construct validity in this sample of Veterans (Herrold et al., 2014). Furthermore, a confirmatory factor analysis showed the unidimensionality of PACS in a study of 147 opioid-dependent outpatients. All items loaded on a common factor but loadings ranged from 0.58 to 0.93, suggesting that a rotated solution may provide different results. Also, the authors did not report on indicators of the factor analysis appropriateness, such as sampling adequacy or eigenvalues (Kaiser, 1960). However, the single-factor model provided a Comparative Fit Index (CFI) of 0.991 (Tsui,
Anderson, Stron, & Stein, 2014). CFI values of $\geq 0.95$ indicate good model fit (Hue & Bentler, 1999).

**Criterion Validity**

**Concurrent Validity.** This type of criterion validity is supported with evidence of correlation between a scale and a criterion measure when administered concurrently (DeVellis, 2011). Flannery et al. (1999) claimed that the correlations of PACS, OCDS, and AUQ scores provide evidence for concurrent validity of PACS. Although the three measures were administered concurrently, there is no evidence that either the OCDS or the AUQ instrument is the “gold standard” for craving measurement. The authors’ claim is therefore questionable.

**Predictive Validity.** Evidence of predictive validity is considered adequate when scores on one test predict the outcome of a future test (DeVellis, 2011). A multitude of studies investigated the ability of PACS to predict treatment outcomes in terms of alcohol relapse. In the initial PACS study, logistic regression analyses showed that week 2 craving scores significantly predicted relapse during weeks 3 to 12 ($Wald = 6.46, df = 1, p = 0.01$). However, when the total number of standard drinks was added as a covariate in the model, drinking rather than craving, was a stronger predictor of subsequent relapse. Subsequent alternative analyses of the same data using Generalized Estimating Equations showed that PACS was the strongest predictor of subsequent drinking while controlling for current drinking (Flannery, Poole, Gallop, & Volpicelli, 2003). Similar findings were reported in a longitudinal study of 102 Turkish male alcohol dependents where PACS scores predicted relapse 1 year following inpatient treatment ($OR=1.293, p<0.001$) (Evren, Durkaya, Dalbudak, & Cetin, 2012). In studies of craving in patients in
residential alcoholism treatments, higher PACS scores predicted higher rates of relapse at discharge (Schneekloth, 2012) and 12-month follow-up (Hitschfeld et al., 2015).

Contrarily, in a treatment trial by Garbutt (2009), PACS scores before the intervention did not predict relapse in terms of percent heavy drinking and abstinent days. These mixed findings suggest a stronger predictive validity of PACS in treated patients compared to alcohol dependents before treatment. Overall, the majority of studies provide adequate evidence that support the predictive validity of PACS. Additional evidence is needed to elucidate whether PACS’ predictive validity holds up in different treatment settings and patient populations.

**Samples**

PACS’s psychometric characteristics have been tested in various large samples of substance-dependents in outpatient and residential treatment settings. Table 5 provides further details on sample characteristics of a number of studies, showing that the majority of samples engaged Caucasian male patients. PACS was also adapted for use in a population of gamblers; however no evidence of validity or reliability were reported (de Castro, Fong, Rosenthal, & Tavares, 2007).

**Table 5 - Sample Characteristics of Studies Testing PACS**

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Population/site</th>
<th>Demographics</th>
<th>Mean (SD) / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flannery et al. (1999)</td>
<td>147</td>
<td>Alcohol dependents after 1 week detoxification</td>
<td>Age</td>
<td>47 (12.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caucasian</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Married</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mid-upper SES</td>
<td>53%</td>
</tr>
<tr>
<td>Yoon et al. (2006)</td>
<td>101</td>
<td>Outpatient alcohol dependent Veterans</td>
<td>Age</td>
<td>51.6 (7.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caucasian</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Married</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>45.5%</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Sample Description</td>
<td>Age</td>
<td>Gender</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>Rosenberg et al. (2007)</td>
<td>112</td>
<td>College students with binge-drinking issues</td>
<td>19.85 (1.5)</td>
<td>Male</td>
</tr>
<tr>
<td>Kim et al. (2008)</td>
<td>80</td>
<td>Alcohol-dependent inpatients in Korea</td>
<td>46.6 (7.4)</td>
<td>Male</td>
</tr>
<tr>
<td>Witkiewitz &amp; Bowen (2010)</td>
<td>168</td>
<td>General substance use disorders; after inpatient treatment</td>
<td>40.45 (10.28)</td>
<td>Male</td>
</tr>
<tr>
<td>Evren et al. (2012)</td>
<td>102</td>
<td>Alcohol-dependent inpatients in Turkey</td>
<td>44.97 (9.07)</td>
<td>Male</td>
</tr>
<tr>
<td>Tsui et al. (2014)</td>
<td>147</td>
<td>Opioid-dependent inpatients</td>
<td>37.5 (9.9)</td>
<td>Male</td>
</tr>
</tbody>
</table>

SD = Standard deviation; SES = Socioeconomic status

Reliability of the PACS

A perfectly reliable instrument reflects the ‘true’ state of the variable measured and produces a consistent score which does not change unless there is an actual change in the variable (Carmines & Zeller, 1979; DeVellis, 2011).

Test-Retest Reliability

The psychometric study of the Korean version of PACS by Kim et al. (2008) reported a high correlation between PACS scores performed at 1-day intervals (r = 0.769, p < 0.01), indicating adequate test-retest reliability. Knowing that craving is an unstable subjective experience that may differ on the same day, alternative tests such as parallel forms reliability may provide more robust evidence (Carmines & Zeller, 1979).

Internal Consistency
Internal consistency is a measure of reliability that is statistically tested using Cronbach’s coefficient alpha when continuous variables are studied. According to Nunnally (1978), a Cronbach’s coefficient alpha of 0.7 is acceptable, 0.8 is optimal, and alphas larger than 0.8 are not necessarily needed and may indicate redundancy. The original study on PACS reported a Cronbach’s alpha of 0.92. High item-total correlations, ranging from 0.8 to 0.92, were also reported further illustrating the scale’s adequate internal consistency with potential redundancy (Flannery et al., 1999). Cronbach’s alphas in subsequent studies ranged from 0.87 to 0.96 showing consistently appropriate reliability across substance-dependent populations, such as 0.87 in a general sample of inpatients with substance use disorders (Witkiewitz & Bowen, 2010), 0.88 in a sample of adult opioid-dependents (Tsui et al., 2014), 0.90 in a study of college students binge drinking, and 0.96 in a population of Turkish alcohol-dependent inpatients (Evren et al., 2012).

Conclusions and Recommendations

PACS has been extensively used in alcohol dependence treatment trials and in clinical practice. It is a well-tested instrument with established convergent and discriminant validity and reliability in various populations with substance use disorders and treatment settings. Some weaknesses have been identified in this review including: (1) Unknown content validity due to the lack of information on the scale’s development and the atheoretical background; (2) Craving is assumed to be a unidimensional phenomenon with little supportive research evidence; (3) Mixed evidence on the scale’s predictive validity in samples from different treatment settings; and (4) Lack of psychometric testing in adolescent populations. It would be therefore recommended that
future research addresses these issues by: (1) Clarifying the underlying conceptual definition of craving; (2) Considering a “daily” timeframe for the scale’s items to minimize retrospective memory bias; (3) Revising PACS items using focus groups or a qualitative approach to enhance or confirm the scale’s content validity; (4) Conducting an accurate confirmatory factor analysis of the revised scale to provide evidence on the dimensionality of craving; (5) Providing robust evidence on the scale’s predictive validity in different treatment settings taking into consideration plausible confounding variables; and (6) Conducting psychometric testing of the scale’s use in adolescents. It would also be valuable to identify normed values and cutoff scores to enhance score interpretation.
CHAPTER FIVE. MANUSCRIPT 3: A LONGITUDINAL ANALYSIS OF CRAVING CHANGES IN RECOVERING COLLEGE STUDENTS RECEIVING HEART RATE VARIABILITY BIOFEEDBACK

Background

Substance Use Disorder in College Students

In 2016, the prevalence of substance use in college students (47%) was more than four times the prevalence in the general population of Americans aged 12 years and older (9.4%) (Johnston, O’Malley, Bachman, Schulenberg, & Miech, 2016; NIDA, 2015). Almost one in four college students were found to meet the criteria for substance use disorder (SUD), 2.5 times the prevalence in the overall population, in a Columbia University report of their 1993-2005 national study on substance use among college students (Califano, 2007). Although more recent studies of college-specific SUD prevalence are not available, current statistics of substance use trends among college students point to a significant SUD prevalence in this population (Johnston et al., 2016).

Craving and Recovery from Substance Use Disorder

Recovery from SUD is difficult to maintain. On average, 50% to 70% of persons recovering from SUD relapse within the first year of treatment (NIDA, 2012; SAMHSA, 2009). While many factors may be associated with relapse, craving is one of its strongest and most distressing predictors (Fatseas et al., 2015; Paliwal, Hyman, & Sinha, 2008; Sinha, 2011). Research showed that persons recovering from SUD can still experience cravings years after abstinence, long after their withdrawal symptoms disappear (Addolorato, Leggio, Abenavoli, & Gasbarrini, 2005). Craving is therefore a key feature of addiction and recovery and a criterion of SUD in the fifth edition of the Diagnostic and
Statistical Manual of Mental Disorders (APA, 2013). Treatment of substance craving is now considered an essential component of recovery maintenance and relapse prevention (NIDA, 2016; Tiffany & Wray, 2012). However, patient outcomes have not changed much despite treatment advancements and maintaining recovery is still a major challenge (Behere, Muralidharan, & Benegal, 2009; Miller, Walters, & Bennett, 2001; NIDA, 2012; O'Brien, 2005). The impact of craving as a frequently experienced and strong predictor of relapse underscores the need for investigating innovative anti-craving interventions.

**The Psychophysiology of Craving**

Simply stated, craving is an overwhelming involuntary desire to use a drug that “if unfulfilled produces a powerful physical and mental suffering” (Manejwala, 2013, p. 2). From a psychological standpoint, craving is thought to be an automatic drive resulting from dysfunctional reward-related processes (Drummond, 2001) or higher order cognitive functions (Skinner & Aubin, 2010). On the other hand, psychobiological models attribute craving to neurobiological adaptations of various brain circuits resulting in pathological motivation towards the drug and alterations in behavioral control (Robinson & Berridge, 2008). Autonomic imbalances in sympathetic and parasympathetic systems have been reported with increased craving (Sinha, 2013). Experiences of craving are often associated with physiological responses such as increased salivation, heart rate, and blood pressure, as well as psychological responses such as depression and anxiety (Eddie, Vaschillo, Vaschillo, & Lehrer, 2015; Haass-Koffler, Leggio, & Kenna, 2014). The experience of craving is therefore associated with moment-to-moment changes in physiological states which contribute to the person’s behavior (Eddie et al., 2015; Kemp & Quintana, 2013; Quintana, Kemp, Guastella,
Hickie, & McGregor, 2013). A flexible autonomic system provides the ability for rapid modulation of physiological states in accordance with situational demands resulting in improved behavioral flexibility (Lehrer & Eddie, 2013; Porges, 2007). Neurocardiac dynamics, such as heart rate variability (HRV), underlie the heart-brain feedback loop that contributes to behavioral flexibility (Bates & Buckman, 2013). The integrated psychophysiological processes of craving underpin this study’s conceptualization of craving as a biobehavioral phenomenon. Biobehavioral interventions, such as HRV biofeedback (HRVB), may offer the advantage of addressing psychophysiological processes of craving to increase the efficacy of conventional anti-craving treatments.

**Heart Rate Variability Biofeedback and Craving**

HRVB is a form of cardiorespiratory feedback training that increases HRV and enhances vagal heart rate control (Lehrer & Gevirtz, 2014; Lehrer, Vaschillo, & Vaschillo, 2000; Nolan et al., 2005). In HRVB, users are trained to breathe at their own resonance frequency to maximize HRV. The goal is to improve autonomic regulation by engaging the parasympathetic nervous system and recovering from stress-induced sympathetic responses (Gevirtz, 2013). To date, four controlled studies investigated the relationship between HRVB and craving in different populations. A controlled pilot study of 38 patients in a SUD residential program showed no substance craving differences between the biofeedback group and the control group (Zucker, Samuelsion, Muench, Greenberg, & Gevirtz, 2009). However, the biofeedback group showed a trend of craving reductions following a four-week daily practice of slowed breathing. Also, in a study of young men (N=41) receiving inpatient SUD treatment, a larger craving reduction trend was found in the HRVB group compared to the control group. This finding was not
statistically significant despite a medium effect size (Cohen’s d = .35). In both studies, the intensity of HRVB training may have been an insufficient dose to produce clinically significant craving reductions. On the other hand, in a study of high food cravers, assignment to a 12-session HRVB intervention was associated with decreased food cravings suggesting that more intensive training may be necessary (Meule, Freund, Skirde, Kübler, & Vögele, 2012). A recent randomized controlled trial showed similar results in a sample of alcohol dependents from an inpatient rehabilitation center in Germany (Penzlin, Siepmann, Illigens, Weidner, & Siepmann, 2015). Craving reductions occurred immediately following six 20-minute HRVB training sessions given over two weeks in addition to standard rehabilitation treatment, compared to no craving changes in the control group. However, participants in the control group showed larger craving reductions, than the experimental group, at three and six weeks after the intervention. These findings suggest that HRVB contributed to earlier craving reduction than standard treatment alone but did not sustain long-term effects in terms of craving control (Penzlin et al., 2015). Although HRVB was shown to be of significant therapeutic potential, previous findings suggest an important gap in our current knowledge of craving changes over time with and without HRVB and the dose of HRVB practice that is necessary to produce craving reductions. The current study presents a longitudinal analysis of craving changes in recovering college students receiving intensive HRVB training over a prolonged duration of 12 weeks.

**HRVB, Psychosocial Factors, and Craving**

Stress, anxiety and depression predict relapse (Sinha, 2011) and are associated with craving (Porges, 2007; Thayer & Lane, 2000). Stress and anxiety are positively
correlated with craving across different substances (Eddie, Kim, Bates, Lehrer, & Deneke, 2014b; Fox, Tuit, & Sinha, 2013). Controlled studies suggest that HRVB was a useful intervention for stress and anxiety in non-clinical samples (Thurber, Bodenhamer-Davis, Johnson, Chesky, & Chandler, 2010; Wells, Outhred, Heathers, Kemp, & Fontenelle, 2012), and a clinical sample of persons with major depression (Karavidas et al., 2007). Despite some evidence for the usefulness of HRVB in decreasing anxiety, depression, perceived stress, and craving, the relationships among these factors have not been previously evaluated. Investigating the associations among trajectories of perceived stress, anxiety, depression, and substance craving changes may provide more insight into the mechanisms underlying the relationship between HRVB and craving. It is especially important to evaluate these relationships in the SUD population in which anxiety, depression, and stress disorders are commonly co-occurring (Garland, Roberts-Lewis, Tronnier, Graves, & Kelley, 2016); roughly 45% of persons with SUD have at least one serious mental illness (SAMHSA, 2012).

**HRVB, Length of Abstinence, and Craving**

The length of abstinence from alcohol and drug use appears to be an important factor of craving. While baseline substance craving decreases with length of abstinence, cue-induced craving shows time-dependent increases in both animal and laboratory studies (Li, Caprioli, & Marchant, 2015b). For example, methamphetamine users showed increases in cue-induced craving for up to three months of abstinence followed by reductions in cue-induced craving at 6 and 12 months of abstinence (Wang et al., 2013). Similarly, increases in cue-induced craving were shown in alcohol dependents until two months of abstinence (Li et al., 2015a) and heroin dependents during the first month of
abstinence (Shi et al., 2009). The existing literature lacks evidence on whether length of abstinence is related to HRVB craving outcomes.

Significance to Nursing

Whether in inpatient or outpatient settings, nurses represent the largest number of mental health providers (Edward & Munro, 2009) and are key stakeholders in the treatment of patients with SUDs. While current empirically supported SUD treatments are primarily focused on pharmacological and psychosocial interventions, nurses provide a unique holistic perspective of symptom management which can integrate psychophysiological processes. Slow abdominal breathing as a therapeutic intervention has been widely used in nursing to facilitate post-operative recovery (Cassidy, Rosenkranz, McCabe, Rosen, & McAneny, 2013; Cronin et al., 2015), pain management (Friesner, Curry, & Moddeman, 2006; Kwekkeboom & Gretarsdottir, 2006), and stress and anxiety reduction (Hayama & Inoue, 2012; Kim et al., 2013). Furthermore, breathing techniques that improve HRV and autonomic balance have been used by nurses to improve quality of life in hemodialysis patients (Stanley, Leither, & Sindelir, 2011), enhance sleep quality in patients with depression (Chien, Chung, Yeh, & Lee, 2015), decrease depressive symptoms in patients with coronary heart disease (Chung et al., 2010), and reduce pre-procedural distress in pediatric cancer patients (Shockey et al., 2013). Therefore, HRVB training that is based on a paced breathing technique could be easily integrated within non-pharmacological mental health nursing interventions.

Current Hypotheses and Study Questions

The main objective in the current study was to model craving changes at 12 time points over the course of 35 weeks. Participants were assessed at four occasions in the control condition over the first 12 weeks followed by an 11-week rest period (semester
break) and 12 weeks in the experimental condition (8 occasions). Our initial guiding hypotheses were: (1) Craving levels decline over time; (2) Craving reductions occur at different rates over time; (3) Age is related to craving changes over time; (4) Sex is related to craving changes over time; (5) Length of abstinence is related to craving reductions over time; (6) The dose of daily HRVB practice predicts craving reductions over time; (7) Craving reductions in the experimental condition would be greater than reductions in the control condition, if any; and (8) Variations in depression, anxiety, and perceived stress are associated with craving changes over time. The following research questions were addressed:

1. What are the substance craving trajectories over 12 weeks in the control condition followed by 12 weeks in the experimental condition?

2. Do craving changes over time differ by intra-individual predictors including age, sex, length of abstinence, and dose of daily HRVB practice?

3. Do craving changes over time differ by inter-individual predictors including depression, anxiety, and perceived stress?

4. Are craving reductions during the HRVB intervention greater than craving reductions in the control condition?

**Participants**

Data for this study were collected at the Rutgers Center of Alcohol Studies. Participants were recruited between the spring semesters of 2011 and 2015 through the recovery housing program of a public northeastern United States university. Recovery housing is available for students voluntarily recovering from SUD. Information flyers were made available to the students affiliated with the recovery house. Interested students
were directed to contact the research staff at the Center of Alcohol Studies. Participation in this study was strictly voluntary and participants were neither charged nor paid to participate in the study. A total of 46 college students were enrolled in the study.

Inclusion criteria were as follows: (1) current student in voluntary recovery from a SUD who currently or previously resided in Recovery Housing, (2) fluency in the English language, and (3) 20/20 or corrected vision. Exclusion criteria included conditions that may contraindicate physiological assessment or confound interpretation of HRV including: (1) cardiovascular disease (CVD) (e.g. pacemaker, cardiac arrhythmia, and hypertension) or other medical condition which increases CVD risk (e.g. diabetes) or pregnancy, (2) psychiatric condition (e.g., psychosis), or neurological condition (e.g., Parkinson’s disease), (3) medications such as MAOIs, Alpha or Beta Blockers, antipsychotics, or benzodiazepines, and (4) previous experience with HRVB.

Power Analysis

The Repeated Measures and Sample Size (RMASS) (Roy, Bhaumik, Aryal, & Gibbons, 2015) web application was used to compute sample size for the planned multilevel mixed-effects linear regression models for the analysis of longitudinal data. The sample size determinations in this program are based on the requirements for a test of treatment by time interactions. The two-level model allows for random-effects of the time trends at subject-level. This approach allows for differential attrition rates over time (Roy, Bhaumik, Subhash, & Gibbons, 2007). In our calculation, we accounted for four time points and the actual attrition rate of 13%. Using a two-tailed significance level of 0.05 and a power of 0.8, RMASS calculated a sample size of 35 participants. Our sample size (N=46) met the criteria.
Psychological Measures

**Penn Alcohol Craving Questionnaire (PACS).** The PACS is a unidimensional 5-item questionnaire that assesses the severity of an individual’s alcohol craving. Items are coded on a 7-point scale from “0” (Not present) to “6” (Severe). A total PACS score range of 0 to 30 is possible with higher scores indicating greater substance craving. The scale has high internal consistency (α = .92) and has been validated in various clinical samples (Flannery, Volpicelli, & Pettinati, 1999; Hitschfeld et al., 2015; Kim et al., 2008). A modified version of PACS that captures both drug and alcohol craving was used in this study. This amended version of PACS had similar internal consistency to the original scale, and convergent and discriminant validity (Eddie, Kim, Bates, Lehrer, & Deneke, 2014a). In the current sample of recovering college students, Cronbach’s alpha ranged from .72 to .94 depending on the occasion of measurement.

**Beck Anxiety Inventory (BAI).** The BAI is a 21-item questionnaire that assesses the severity of an individual’s anxiety in the past week. Items are coded on a 4-point scale ranging from “0=Not at all” to “3=Severely”. A total BAI score range of 0 to 63 is possible with higher scores indicating greater anxiety symptoms (Beck, 1993). The BAI has been validated in studies involving populations with SUD showing adequate validity and reliability (Ali, Seitz-Brown, & Daughters, 2015; Thekiso et al., 2015). Cronbach’s alpha ranged from .86 to .91 in the current sample depending on occasion of measurement.

**Beck Depression Inventory – II (BDI-II).** The BDI-II is a 21-item questionnaire that assesses the severity of an individual’s depression in the past week. Items are coded on a 4-point scale from “0=Not at all” to “3=Severely”. A total BAI score range of 0 to
63 is possible with higher scores indicating greater depression symptoms (Beck, 1996). The BDI-II has been validated in various studies involving populations with SUD showing adequate validity, good internal consistency, and test-retest reliability (Ali et al., 2015; Buckley, Parker, & Heggie, 2001; McPherson & Martin, 2010). The BDI-II was also found to discriminate between depression and other psychiatric disorders in substance-dependent patients with dual diagnosis (Lykke, Hesse, Austin, & Oestrich, 2008). Cronbach’s alpha ranged from .79 to .90 in the current sample depending on occasion of measurement.

**Perceived Stress Scale (PSS).** The PSS is a 10-item questionnaire that assesses stress frequency in the past month. Items are measured on a 5-point, Likert-type scale ("0=Never" to "4=Very often"). A total PSS score range of 0 to 40 is possible with higher scores indicating greater perceived stress (Cohen, Kamarck, & Mermelstein, 1983). The PSS has well-established validity and reliability in various populations such as persons with chronic diseases (Lee, Chung, Suh, & Jung, 2015) and college students (Smith, Rosenberg, & Timothy Haight, 2014). It was used in two studies involving persons with SUD and showed adequate hypothesis testing validity (Pedrero-Perez et al., 2015; Tavolacci et al., 2013). Cronbach’s alpha ranged from .81 to .87 in the current sample depending on occasion of measurement.

**Procedure**

Psychological measures were collected at 12 occasions over 35 weeks. There were four occasions of measurement for the control condition and eight occasions of measurement for the experimental condition, each over the course of one semester (12 weeks), separated by a semester break (11 weeks). In the first semester of data collection
(Spring 2012), participants were randomly assigned to either the HRVB condition (8 participants) or the waitlisted control condition with treatment as usual (TAU) (4 participants). From the second semester on, participants were enrolled in a control condition of TAU followed by an experimental condition of HRVB. All research measurements were conducted in a private area at the recovery house following a specific data collection protocol. Participants in the HRVB condition engaged in a total of 7-8 hours of physiological monitoring and breathing training and responded to the PACS and PSS at each occasion and to the BDI and BAI on occasions 5, 8, 11, and 12 only. Measures of ECG and respiration were also obtained during occasions 5, 8, 11, and 12 to ensure appropriateness of the HRVB intervention. Occasions 6, 7, 9, and 10 included HRVB training with no physiological recording. In addition, participants were asked to practice resonance frequency breathing for 15-minute periods twice daily on their own, using portable biofeedback devices that were provided to them while in the study. Daily HRVB practice was logged on weekly basis based on participant self-report. Participants in the control condition did not engage in any physiological recording but responded to the PACS, BAI, BDI, and PSS at the first four occasions.

**The HRVB Intervention.** Participants were trained to breathe at their own resonance frequency, to maximize HRV by eliciting high-amplitude heart rate oscillations. They were asked to breath at five specific frequencies ranging from 4.5 to 6.5 breaths per minute (i.e., 0.075 to 0.108 Hz). Resonance frequency was identified when respirations and heart rate oscillations occurred in phase (i.e. heart rate rises simultaneously with inhalation and decreases simultaneously with exhalation) (Eddie et al., 2015; Vaschillo, Vaschillo, & Lehrer, 2006). Users were then trained to practice
breathing at their own resonance frequency with the help of visual pacers and electronic monitoring of the heart rate. The HRVB intervention was based on the protocol developed by Lehrer et al. (2000).

**Treatment As Usual (or Control) Condition.** Participants who lived at the recovery housing during the study were provided conventional recovery services offered by the recovery house including as-needed therapy, regular peer support meetings, psychoeducation seminars, and organized social and sports activities. Other participants were previous recovery house residents who lived outside campus during the study period. These participants continued to attend peer support meetings and any therapies they needed. However, none of the participants in the TAU condition received biobehavioral interventions before taking part of the HRVB condition.

**Analyses**

All data analyses were conducted with the Statistical Package for the Social Sciences (SPSS) version 23.0. Measures of central tendency were computed to describe sample characteristics including demographics and symptom severity scores. The data were examined for distribution, skewness, outliers, and linearity using histograms, scatterplots, and skewness and kurtosis statistics. All variables met assumptions of normal data distribution. In addition, the variables were carefully examined for missing data points. A minimum of three observations was required to differentiate fluctuation from real change. Two participants had less than three time points on the outcome variable and were thus excluded from the sample (Hoffman, 2015). Of the 44 remaining participants, four dropped out from the experimental condition because they felt too busy with school work.
A multilevel modeling (MLM) approach was used to perform a longitudinal analysis of substance craving changes over time and across conditions. The purpose of these analyses was to (1) describe the average pattern of craving changes over time, (2) describe the individual differences within these changes, and (3) predict between-person differences and the remaining within-person variation over time. A series of mixed effects random coefficient models were analyzed with observations at level-1 nested within persons at level-2. These analyses modeled within-person and between-person craving variations simultaneously. The effects of craving predictors including perceived stress, depression, anxiety, length of abstinence, and daily breathing practice time were also modeled at both levels. Since the actual time intervals between measurement occasions differed per participant, time was entered as a covariate in the models and was centered such that 0 indicated the first observation. Time observations were balanced across persons by using the actual number of weeks in the study corresponding to each measurement occasion for each participant, starting with week one after the first control session (session 1) and week 35 before the last experimental session (session 12). The 95% confidence interval (CI) for the random variation around each fixed effect was calculated as +/- 1.96. Time models were estimated using restricted maximum likelihood (REML) whereas Maximum Likelihood (ML) was used when fixed predictors were added to the models (Hoffman, 2015). The significance of individual fixed effects was evaluated using their Wald test $p$ values. The significance of multiple fixed effects and random effects variances and covariances was evaluated using likelihood ratio tests including -2 Log Likelihood (-2LL), Akaike Information Criterion (AIC), and Bayesian Information Criterion (BIC). Given that standardized coefficients do not exist for two-
level models, pseudo-R² were calculated to determine the proportion of variance reduction accounted for by the predictors at each level of analysis. In addition, the proportion of explained total outcome variance (R²) was determined by calculating the square of the Pearson correlation between the predicted outcome and the actual outcome. This method generates a true R² since it is based on the total original outcome variance (Hoffman, 2015).

The steps for MLM included:

1. Determining sources of variation in substance craving by calculating the Intraclass Correlation (ICC) statistic based on covariance parameters from the null model with craving as the outcome variable and no predictors. The ICC is the proportion of the variance explained by the grouping structure in the population, also reflecting the correlation of the outcome residuals over time (Hoffman, 2015; Hox, 2010). In this study, the ICC represents the proportion of variance explained by the repeated measures of PACS within individuals. ICC values range from 0 to 1. The higher the ICC the higher the correlation between outcome residuals, which violates the assumption of independence. Thus the use of multiple linear regression is not appropriate given the dependence in the data. In addition, the higher the ICC the higher the variability between-persons (level-2) and consequently the lower the variability within-persons (level-1). Therefore, a low to moderate ICC value in the null model indicates the need for random coefficients models (Hoffman, 2015; Hox, 2010).

2. Estimating the baseline time model to determine a trajectory of substance craving changes over time (35 weeks).
3. Centering continuous predictors to have a meaningful zero, which facilitates interpretation since intercept values represent the mean when predictors have a value of zero. Age was centered at the median, such that 0=23 years. BDI, BAI, and PSS were centered at their respective mean values, such that 0=8 for BDI, 0=10 for BAI, and 0=13 for PSS.

4. Estimating the practice and final models by adding intra-individual (age, sex, length of abstinence, daily breathing practice) and inter-individual (depression, anxiety, perceived stress) predictors incrementally.

**Results**

Data in these analyses consisted of 44 participants x 12 sessions = 528 observations. There were 128 missing observations in the outcome due to the lack of control condition for 16 of the participants in addition to the 6 dropouts and other randomly missing responses, amounting to 24.24% of the expected observations.

**Sample Characteristics**

Sample characteristics are reported in Table 6. In general, the majority of the sample consisted of White young male college students with a relatively long abstinence time (M = 2.62 years, SD = 1.93 years). Approximately, half of the participants (52.10%) reported taking prescribed antidepressant or mood stabilizing medications and none reported changing medications during their study participation. Most participants were single (97.6%) and 50% were living outside recovery housing during the study period.

**Craving and other Psychological Measures per Session**

Psychological measures across time-points, including craving (PACS), perceived stress (PSS), anxiety (BAI), and depression (BDI) are reported in Table 7. Participants
reported relatively low levels of craving, perceived stress, anxiety, and depression at baseline and throughout the study.

Table 6 - Sample Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N= 44 (mean / %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>23.6 (5.1)</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>29.5%</td>
</tr>
<tr>
<td>Ethnicity (% Hispanic)</td>
<td>11.4%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>American Indian/Alaskan Native</td>
<td>0%</td>
</tr>
<tr>
<td>Asian</td>
<td>2.3%</td>
</tr>
<tr>
<td>Black/African American</td>
<td>0%</td>
</tr>
<tr>
<td>Native Hawaiian/Other Pacific Islander</td>
<td>0%</td>
</tr>
<tr>
<td>White/European</td>
<td>93.2%</td>
</tr>
<tr>
<td>Other</td>
<td>4.5%</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
</tr>
<tr>
<td>Full–time</td>
<td>3.4%</td>
</tr>
<tr>
<td>Part-time</td>
<td>43.3%</td>
</tr>
<tr>
<td>Unemployed</td>
<td>53.3%</td>
</tr>
<tr>
<td>Other Variables</td>
<td></td>
</tr>
<tr>
<td>University standing</td>
<td></td>
</tr>
<tr>
<td>Freshman</td>
<td>10%</td>
</tr>
<tr>
<td>Sophomore</td>
<td>26.7%</td>
</tr>
<tr>
<td>Junior</td>
<td>33.3%</td>
</tr>
<tr>
<td>Senior</td>
<td>20%</td>
</tr>
<tr>
<td>Graduate</td>
<td>10%</td>
</tr>
<tr>
<td>Current recovery house residence</td>
<td>50%</td>
</tr>
<tr>
<td>Smoker</td>
<td>36.4%</td>
</tr>
<tr>
<td>GPA</td>
<td>3.2 (0.9)</td>
</tr>
<tr>
<td>Length of abstinence (years)</td>
<td>2.6 (1.9)</td>
</tr>
</tbody>
</table>

Notes. Standard deviations in parentheses

Remarkably, no participants reported relapse to substance use during study participation in either the control or experimental conditions. Baseline PACS scores at Time 0 were neither significantly correlated with age ($r = -0.266, p > 0.05$) nor with length
of abstinence ($r = -0.351, p > 0.05$). Length of abstinence and age were highly correlated ($r = 0.626, p < 0.01$). Baseline PACS scores were not significantly correlated with any of the baseline PSS, BAI, and BDI scores ($p > 0.05$). However, PSS and BDI ($r = .56, p < .01$) and BAI and BDI ($r = .60, p < .01$) were positively correlated at baseline. PSS and BAI were not significantly correlated ($p > 0.05$). There were observed differences in PACS levels by age despite the lack of a statistically significant correlation between baseline PACS and age. Participants younger than 23 years reported higher PACS scores ($M=5.64$, $SD=1.17$) than participants who were 23 years and older ($M=3.93$, $SD=1.12$).

Table 7 - Mean PACS, PSS, BAI, and BDI Scores over Time

<table>
<thead>
<tr>
<th></th>
<th>PACS</th>
<th>PSS</th>
<th>BAI*</th>
<th>BDI - II*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>0–30</td>
<td>0–40</td>
<td>0–63</td>
<td>0–63</td>
</tr>
<tr>
<td>Time 1</td>
<td>5.0 (4.1)</td>
<td>18.1 (6.5)</td>
<td>12.8 (9.5)</td>
<td>9.5 (6.0)</td>
</tr>
<tr>
<td>Time 2</td>
<td>5.8 (4.6)</td>
<td>19.7 (6.6)</td>
<td>11.7 (9.0)</td>
<td>8.8 (6.6)</td>
</tr>
<tr>
<td>Time 3</td>
<td>5.1 (4.7)</td>
<td>20.4 (6.9)</td>
<td>12.1 (9.8)</td>
<td>12.4 (10.2)</td>
</tr>
<tr>
<td>Time 4</td>
<td>4.4 (3.0)</td>
<td>17.9 (5.5)</td>
<td>8.0 (7.3)</td>
<td>7.9 (6.6)</td>
</tr>
<tr>
<td>Time 5</td>
<td>4.5 (4.9)</td>
<td>18.4 (7.2)</td>
<td>9.4 (7.4)</td>
<td>7.1 (5.7)</td>
</tr>
<tr>
<td>Time 6</td>
<td>3.5 (4.4)</td>
<td>16.4 (7.6)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Time 7</td>
<td>3.3 (3.7)</td>
<td>17.4 (6.4)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Time 8</td>
<td>3.4 (4.0)</td>
<td>17.3 (7.0)</td>
<td>9.9 (9.0)</td>
<td>8.1 (7.4)</td>
</tr>
<tr>
<td>Time 9</td>
<td>3.3 (3.6)</td>
<td>16.6 (5.8)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Time 10</td>
<td>2.6 (3.3)</td>
<td>16.4 (7.3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Time 11</td>
<td>2.8 (3.1)</td>
<td>16.6 (7.3)</td>
<td>7.8 (7.7)</td>
<td>6.6 (7.1)</td>
</tr>
<tr>
<td>Time 12</td>
<td>3.5 (3.7)</td>
<td>17.4 (6.8)</td>
<td>8.8 (7.9)</td>
<td>6.5 (6.6)</td>
</tr>
</tbody>
</table>

PACS=Penn Alcohol Craving Scale; PSS=Perceived Stress Scale; BAI=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory-II; *BAI and BDI were not measured at times 6, 7, 9, and 10

Daily HRVB Breathing Practice

During the experimental phase, participants reported practicing HRVB paced breathing for an average of 11.46 minutes per day in the study ($SD=7.88$) on 3.93 days per week ($SD=2.03$). The mean experimental weeks was 11.63 ($SD=3.17$) during which
participants practiced HRVB breathing for a total of 14.47 hours (SD=10.19) outside experimental sessions over 79.17 days (SD=20.25) on average. On the days they practiced HRVB breathing, participants practiced for 19.09 minutes (SD=6.74) on average. Notably, the amount of daily HRVB practice differed by age. Using a median split of age, we found that participants younger than 23 years practiced more than participants who were 23 years and older. The mean daily HRVB practice time was 14.32 minutes (SD=7.84) for age < 23 versus 9.23 minutes (SD=7.16) for age 23 and older. Figure 2 depicts a boxplot presentation of the distribution of HRVB practice by age group.

**Figure 2 - Mean Daily HRVB Practice by Age Group**

Multilevel Modeling Results
Multilevel models were estimated to examine the overall pattern and individual differences in substance craving changes over time. In these models, time at level 1 was nested within persons at level-2.

**Question 1: Unconditional and Time Models of Craving Changes**

Three empty models were first estimated to test for random effects of time before adding any fixed effects. An empty random intercept model was estimated to describe the variation in craving across levels of analysis. The fixed intercept for the grand mean craving over time was estimated as 3.95 (SE=.464). The variance due to repeated measures was 8.683 and the variance due to participant differences was 8.400. Therefore, the intraclass correlation (ICC) was calculated using this formula: ICC = BP variation / (BP + WP variation) = (8.40/ 8.68 + 8.40) = 0.49. Of the total variation in craving over time, 49% was between persons (Level 2) and thus 51% was within persons (Level 1), indicating the need for a two-level model for time within persons in modeling craving changes over time. Individual craving trajectories are shown in Figure 3, with the red line representing the sample average. Second, an empty random slope model was assessed by adding a random slope of time. This addition significantly improved model fit (-2ΔLL(2) = 54, p<.001) and caused a 47.03% increase in intercept variance. Third, an empty quadratic model was estimated by adding a quadratic slope of time to assess for non-linear change. The empty quadratic model significantly improved fit (-2ΔLL(3) = 10.6, p<.05) and positive quadratic intercept and slope were found indicating an accelerating rate of craving reduction over time. The fixed effect of quadratic time was not significant indicating there was no acceleration of craving reduction on average but the significant random quadratic time signifies that some participants showed minimal
acceleration of craving reduction over time. The empty random intercept and empty random quadratic model parameters are presented in Table 8. To create a baseline model of craving over time, a fixed quadratic effect of time was added to the empty random quadratic model. The fixed quadratic effect of time was not significant as specified by its Wald test ($p > .05$) and was therefore removed from the model.

**Table 8 - Empty random Intercept and Quadratic Time Models (N=44)**

<table>
<thead>
<tr>
<th>Model Parameters</th>
<th>Empty Random Intercept Model</th>
<th>Empty Random Quadratic Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed Effects:</td>
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<tr>
<td>Intercept</td>
<td>3.95</td>
<td>3.87</td>
</tr>
<tr>
<td>Variance Components:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept Variance</td>
<td>8.40</td>
<td>14.38</td>
</tr>
<tr>
<td>Residual Variance</td>
<td>8.68</td>
<td>6.74</td>
</tr>
<tr>
<td>Intercept-Linear Covariance</td>
<td>-</td>
<td>-0.52</td>
</tr>
<tr>
<td>Linear Slope Variance</td>
<td>-</td>
<td>0.11</td>
</tr>
<tr>
<td>Quadratic Intercept Variance</td>
<td>-</td>
<td>0.006</td>
</tr>
<tr>
<td>Intercept-Quadratic Covariance</td>
<td>-</td>
<td>-0.002</td>
</tr>
<tr>
<td>Quadratic Slope Variance</td>
<td>-</td>
<td>0.004</td>
</tr>
<tr>
<td>Intraclass Correlation (ICC)</td>
<td>0.49</td>
<td></td>
</tr>
</tbody>
</table>

**REML Model Fit:**

- $-2LL$: 2096.7, 2032.1
- AIC: 2100.7, 2046.1
- BIC: 2108.7, 2073.9
- Number of Parameters: 3, 8

Next, the assumption of no residual covariance across time after accounting for the random intercept and random time slope was tested by comparing the fit of a random quadratic time model without within-person residual correlations to that of a random quadratic time model with within-residual correlations. Neither a first-auto-regressive correlation nor a lag-1 Toeplitz residual covariance resulted in significant improvement.
in model fit \( (p > .05) \). The random quadratic time model without within-person residual correlation over time was thus retained. The final baseline model included a fixed effect of time and random effects of linear and quadratic time, indicating that the acceleration of craving reductions over time was due to individual differences and did not occur for all participants on average. The final baseline model predicted that PACS scores decreased by -0.074 point per week, i.e. -2.59 points by week 35, from a predicted value of 5.40 at Time 0 (Table 9). The 95% random effects confidence intervals for the intercept and linear time slope indicated that 95% of the sample was expected to have individual intercepts ranging from 4.10 to 6.70 and individual linear time slopes ranging from -0.12 to -0.03. There was therefore a significant rate of linear reduction in craving on average. However, the random variation around the linear slope indicated that craving reductions were expected to occur at different rates over time. The \( R^2 \) for the baseline model was determined by calculating the square of the correlation between predicted PACS and actual PACS, yielding an \( R^2 \) of .018.

**Question 2: Conditional Model of Intra-Individual Predictors of Craving Changes**

The addition of mean daily practice to the baseline model did not show any statistically significant practice effects \( (p > .05) \). A dichotomous variable of low and high practice was then created to differentiate the effects of low versus high amounts of HRVB practice outside experimental sessions. High practice was coded as 1 indicating more than 12 minutes of daily HRVB breathing, which is more than the sample mean daily practice. A mean cutoff for low and high practice was chosen because the median of 9.76 minutes per day was much lower than the recommended practice of 15 minutes twice daily.
Controlling for age, sex, and length of abstinence (intra-individual covariates), a fixed effect of high practice was added to the baseline model. Sex and length of abstinence did not show any significant effects on craving changes as indicated by their Wald test ($p>.05$). Age was found to be a significant covariate (-0.28, $p<.05$) of craving, such that every one year increase in age>23 was expected to contribute to an additional -0.28 point reduction in PACS scores. A significant effect of high practice ($\beta = -2.26, p<.05$) was found indicating that participants who practiced HRVB breathing for more than 12 minutes per day were predicted to have an additional -2.26 point reduction on PACS. This model significantly improved fit ($-2\Delta L(2) = 205.9, p<.001$) and accounted for 57.63% of the total level-2 craving variance. The interaction between age and high practice was not statistically significant ($p>.05$). The true $R^2$ for the practice model was
determined by calculating the square of the correlation between predicted PACS and actual PACS, yielding an $R^2$ of .140.

Table 9 - Baseline and Final Model Parameters (N=44)

<table>
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<tr>
<th>Model Parameters</th>
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<th>Final Model</th>
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<tr>
<td>Daily Practice &gt; 12 min</td>
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<td>-</td>
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<tr>
<td>Within-person BDI</td>
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<tr>
<td>Between-person BDI centered at mean (0=8)</td>
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<td>AIC</td>
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<td>BIC</td>
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<td>Number of Parameters</td>
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Question 3: Conditional Models of Inter-Individual Predictors of Craving Changes

Potential inter-individual predictors of craving changes included depression (BDI), anxiety (BAI), and perceived stress (PSS). Because longitudinal variables usually contain both between-person and within-person effects, the ICC for each of the variables was obtained. The ICC for BDI, as calculated from an empty means random intercept model with BDI as the outcome, was ICC=0.50, indicating that 50% of the BDI variance
was due to between-person mean differences and 50% was due to within-person variation around the person mean across weeks. For inclusion as a predictor of craving, BDI was person-mean-centered by creating two separate predictor variables of BDI. The within-person BDI represents the deviation from each person’s mean BDI across all his or her occasions (level-1 effect) and the level-2 between-person BDI represents the person’s mean BDI across weeks centered at the grand mean BDI (M=7.88, SD=5.59). Main effects of BDI at each level were then examined. Controlling for age and high practice, the two new main effects significantly improved model fit over the practice model ($-2\Delta LL(1) = 663.0, p<.001$) with concurring smaller AIC and BIC. However, only the level-1 effect of BDI (within-person) was statistically significant indicating that reporting greater depression than usual was related to less craving reduction on that week, such that for every one-point higher BDI than usual (i.e. relative to the person’s mean) that specific week’s PACS is expected to be significantly higher by 0.27 (95% CI: 0.182-0.349, $p<.05$). The level-2 effect of BDI (between-person) was not statistically significant and indicated that for every one-unit higher person mean BDI, mean PACS was expected to be non-significantly higher by 0.087 per week. The same person-mean-centering method was followed to add BAI and PSS as predictors but yielded no significant effects. Interactions could not be assessed due to lack of power.

The final model (Table 9) included age, high practice, and within-person BDI as significant predictors of craving, such that for a 23 year old male with a person mean BDI of 8, PACS score was expected to be 6.08 (95% CI: 4.59-7.58, $p<.05$) at Time 0 and to decrease by -0.05 point per week. At level-2, the significant effects of age and high practice indicates that with every year increase in age PACS is predicted to decrease by
an additional -0.26 point and persons who practice daily breathing more than 12 minutes daily are expected to have an additional reduction of -1.83 points. At level-1, the significant effect of within-person BDI predicts less PACS reduction. The true $R^2$ for the final model was determined by calculating the square of the correlation between predicted PACS and actual PACS, yielding an $R^2$ of .205. Therefore, the final model with age, high practice, and within-person depression explained 20.5% of the total variance in craving over time.

**Question 4: The effect of HRVB on craving reductions**

To determine the effect of the HRVB protocol on craving reductions over time, a piecewise random coefficient model of craving changes over time was examined. The first HRVB training session (session 5) was identified as the breakpoint in the craving trajectory. A piecewise model of change was estimated, in which slope15 was created to describe change from session 1 to 5 and slope512 described the change from session 5 to 12. Both slopes were significant ($p<.05$). Adding random variances and covariances for the random slope before session 5 and the random slope after session 5 improved model fit ($-2\Delta LL(5) = 32.3$, $p<.001$) with a smaller AIC and BIC (Table 10). However, only slope512 remained significant indicating that the decline in craving scores before session 5 (control condition) was not statistically significant whereas craving reductions after session 5 (experimental condition) were statistically significant. The addition of a fixed quadratic slope512 did not improve model fit ($p>.05$), suggesting that a linear slope after session 5 was sufficient. The parameters of the best-fitting piecewise model suggest that after a predicted PACS score of 5.35 at session 1, PACS declined with a fixed linear change -0.21 per session after session 5. The 95% random effects confidence intervals
indicate that 95% of the sample was expected to have individual linear intercepts for the predicted PACS score at session 1 of 3.93 to 6.77 and individual linear rates of change after session 5 of -0.404 to -0.006 per session. Thus, 95% of the sample was predicted to have craving reductions over time on average during the HRVB intervention although rates of change differed between persons.

Table 10 - Piecewise Model Parameters (N=44)

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<th>Random Slope15, Random Slope512, Model (Time 0 = Session 1)</th>
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Discussion

This study is the first longitudinal investigation to model substance craving changes in college students recovering from SUD, before (12 weeks) and during HRVB treatment (another 12 weeks). The total study time was 35 weeks due to a semester break
between the two conditions. Our longitudinal design allowed the examination of within-
persons sources of variance in addition to between-persons variance. In our sample, there
were more within-persons (51%) than between-persons (49%) variations in craving
indicating the importance of addressing individual differences in explaining craving
changes over time. The first research question addressed substance craving trajectories
across the 35 weeks. Our results showed a quadratic pattern of craving reductions
indicating that craving reduced over time and that the rate of craving reductions showed
greater acceleration with time. In addition, the random variation around the linear time
slope indicated that craving reductions were expected to occur at different rates over
time. Our hypotheses that craving levels decline over time and that reductions occur at
different rates were thus supported. The piecewise model, creating a slope for the first 4
sessions before HRVB and the 8 sessions after HRVB, showed that substance craving
reductions before HRVB were not statistically significant confirming that participation in
the eight-session HRVB protocol (total of 7-8 hours of laboratory-based training over 12
weeks) explained craving reductions over time. In previous studies using SUD samples,
less intensive HRVB protocols of 3-3.75 hours of laboratory-based training over 3 weeks
(Eddie et al., 2014) and one 30-minute formal laboratory training (Zucker et al., 2009)
found non-statistically significant craving reduction trends. Our study’s outcome is
however consistent with previous findings of food craving reductions after 4 hours
laboratory-based training over 4 weeks (Meule et al., 2012), although the two populations
may not be comparable in terms of craving type and intensity. Previous clinical trials of
intensive HRVB protocols offered over 8 to 10 weeks have produced similar clinically
significant changes in fibromyalgia, depression, and PTSD symptoms (Hassett et al.,
Our results suggest that an eight-session HRVB protocol can be an effective complementary anti-craving intervention for college students recovering from SUD. HRVB may be an especially promising intervention because it offers the advantage of addressing psychophysiological processes of craving. In fact, in our study HRVB seemed to enhance the efficacy of conventional therapies by producing craving reductions that were not evident prior to the HRVB intervention despite usual treatment.

The second research question addressed the effects of time-invariant predictors of craving changes including age, sex, length of abstinence, and average daily HRVB practice. Craving changes did not differ by sex or length of abstinence time. Yet, of the between-persons mean differences found in the empty model (49% of the total craving variance), more than half (58%) was due to continued high daily HRVB practice (>12 minutes) and age, such that older age was associated with greater craving reductions over time. Our hypothesis that the dose of daily HRVB practice predicts craving changes over time was thus supported. Previous studies have not found such dose-dependent effects (Eddie et al., 2014; Zucker et al., 2009). The lack of practice effects in the literature may have been due to various challenges associated with craving research. The measurement of craving itself is challenging because of its temporal and very subjective nature. Only a longitudinal study with three or more observations has the ability to differentiate real change from undirected fluctuations. Also, HRVB studies, although limited in number, employed a variety of training protocols using different session allocations, treatment durations, and home practice requirements, which makes comparison among studies difficult. Two important factors are the adherence to recommended daily practice and the
reliability of practice reporting. Our sample showed age differences in terms of adherence to daily HRVB practice. Younger participants seemed to be more committed to daily HRVB practice, although many did not achieve the recommended daily practice of 15 minutes twice daily. This may be partly explained by the fact that participants younger than 23 years reported higher craving scores than older participants. It may be that participants with more severe cravings felt a higher need to practice HRVB more consistently. The more than 12 minutes daily practice dose-effect relationship found in this study should be confirmed in future SUD studies of persons with clinical craving levels and at earlier stages in their recovery. In addition, it would be useful to assess determinants of adherence to recommended daily HRVB practice and practice effects in relation to triggering events, possibly using real-time momentary assessment tools that could accurately characterize when and why an individual practices.

Although previous studies showed sex differences in experiences of craving (Hitschfeld et al., 2015; Kennedy, Epstein, Phillips, & Preston, 2013), our sample did not have enough variability in terms of sex distribution which may have contributed to a Type II error. We hypothesized that length of abstinence is related to craving reductions over time, however given the long abstinence time found in our sample there was not enough variability to allow for any significant differences. Since craving is expected to decline with prolonged abstinence (Li et al., 2015b; Wang et al., 2013), exploring this relationship in persons early in recovery may show differences in HRVB dose requirements that are dependent on length of abstinence.

The third research question addressed the effects of inter-individual predictors of craving changes including depression, anxiety, and perceived stress. Our hypothesis that
variations in depression, anxiety, and perceived stress are associated with craving changes over time was partly supported. The within-person aspect of depression had the only statistically significant effect among the three intra-individual predictors of craving changes over time. This finding indicated that persons who had depressive symptoms more than usual (relative to their mean depression score) were expected to have less craving reduction during that period. There was, however, no significant between-person effect of depression on craving changes. Fluctuation in anxiety and perceived stress did not have any significant effects on craving. It seemed that depression effects surpassed anxiety and perceived stress effects on craving during HRVB, which may have important treatment implications. Given the lack of previous evidence in this regard, it is important to confirm these results during recovery in samples with clinical levels of psychological symptoms.

Collectively, our study outcomes provided evidence that HRVB may be a valuable addition to existing anti-craving interventions and relapse prevention treatment. HRVB is especially promising because it supports physiological health, has no side effects, and can be easily accessible through smart phone applications. HRVB can therefore be used strategically whenever persons experience triggers or acute craving episodes and on a regular basis during their free time. Nevertheless, our findings should be confirmed in larger samples with participants in various stages of recovery and with higher baseline craving levels. Future studies should attempt to determine the long-term effects of HRVB, whether the craving reductions achieved during HRVB are sustained after the intervention ends, and whether continued daily practice is needed to keep craving at bay.
**Strengths and Limitations**

This study had limitations related to study design, sampling, and practice measurement. First, the use of a non-random convenience and rather homogenous (mostly male) sample may have increased selection bias affecting both internal and external validity (Fain, 2014). Second, participants in this study reported subclinical craving levels and were in advanced SUD recovery stages given their long abstinence time. Third, our relatively small sample size (n=44) increased the likelihood of Type II error and did not provide enough power for building a more comprehensive model of craving changes that includes the effects and interactions among the assessed predictors. Thus, our findings may not be generalizable to all college students recovering from SUD. A population-based sample of a larger number of participants would yield results generalizable to a broader population of recovering college students and greater power for detection of potential interactions over time. Fourth, practice data were measured using weekly recall methods and the reliability of practice reports may be questionable.

Nevertheless, this study was the first to investigate longitudinal craving changes in recovering college students before and during an intensive (eight-session) HRVB intervention. The primary advantage of a longitudinal study lies in its capacity to inform about within-person in addition to between-person relationships (Hoffman, 2015). The discrepancies found in the literature highlight the predominance of individual differences in craving assessments and the necessity of interpreting craving changes as a function of intra- and inter-individual sources of variance. General linear models, such as the analyses of variance and regression analyses employed by previous studies, failed to distinguish intra- and inter-individual differences because they do not examine sources of...
dependency (Hoffman, 2015; Holden, Kelley, & Agarwal, 2008). The use of MLM in this study allowed the simultaneous examination of between- and within-person relationships and permitted us to identify individual differences that relate to craving reductions during the HRVB intervention. In addition, this study was the first to provide longitudinal evidence supporting the theoretical assumption that daily HRVB practice produces craving reductions.
CHAPTER SIX: SUMMARY, CONCLUSIONS, AND IMPLICATIONS

Summary

Research investigating heart rate variability (HRVB) as an anti-craving intervention is limited. The principal goal of this dissertation was to evaluate the effectiveness of HRVB in reducing substance craving in college students recovering from substance use disorder. It was hypothesized that HRVB may lead to greater substance craving reductions over time, compared to treatment as usual alone. Additionally, this research sought to determine the relationship between HRVB home practice and substance craving, specifically the dose of daily HRVB practice that is required to reduce cravings. The roles of other intra-individual (age and length of abstinence) and inter-individual (depression, anxiety, and perceived stress) predictors of craving were also explored in relation to HRVB.

Substance craving is a highly subjective and temporal phenomenon that is difficult to define. In this study, craving was conceptualized as a psychophysiological phenomenon based on the incentive-sensitization theory of addiction that defines craving as the intense ‘wanting’ of a substance which leads to drug seeking (Robinson & Berridge, 1993, 2008). Repeated drug exposure results in pathological motivation towards the drug (or sensitized incentive salience) that is accompanied by implicit and/or explicit affective and cognitive changes. Such changes may affect the person’s ability to flexibly regulate behavior resulting in drug seeking (Robinson & Berridge, 1993, 2008).

HRVB is thought to increase behavioral flexibility resulting in better craving control. The objectives of HRVB are to (1) help persons acquire awareness of the interaction between thoughts and automatic physiological responses; (2) acquire methods
to control maladaptive physiological responses with the help of heart rate and respiration monitoring; and (3) learn to regulate their thoughts and physiology in everyday life (Calderon & Thompson, 2004; Lehrer & Eddie, 2013). The overarching goal is to improve autonomic regulation by engaging the parasympathetic nervous system and recovering from stress-induced sympathetic responses (Gevirtz, 2013). Autonomic imbalances have been reported with experiences of craving (Sinha, 2013) that are often associated with moment-to-moment changes in physiological states contributing to the person’s behavior (Eddie et al., 2015; Kemp & Quintana, 2013; Quintana et al., 2013). A flexible autonomic system provides the ability to rapidly modulate physiological states in accordance with situational demands (Lehrer & Eddie, 2013; Porges, 2007).

Manuscript 1 of this dissertation discussed current evidence on the effectiveness of HRVB in reducing craving and the challenges of research in this area. The review was expanded to include additional evidence from controlled breathing studies due to the limited amount of HRVB studies investigating its effects on craving. Our review of the existing literature yielded four HRVB studies (Table 1) and four controlled breathing studies (Table 2) targeting substance craving as an outcome. HRVB was shown to be of significant therapeutic potential. Most reviewed studies showed positive results and a relatively moderate effect size across SUD populations (Table 3). However, due to the scarcity and limitations of the studies available, further study of HRVB as an anti-craving intervention for persons recovering from SUD was recommended, using improved methodology. Suggested improvements included: (1) the use of reproducible HRVB protocols and treatment durations of 8 to 10 weeks at a minimum, (2) the longitudinal examination of craving changes over time to differentiate undirected fluctuation from real
change, (3) the examination of the effects of personal practice outside laboratory-based HRVB training using accurate measurements of practice time and treatment fidelity, (4) further examination of confounding variables (such as substance type, co-morbidity, length of abstinence, treatment setting) and other predictors of craving in relationship to HRVB, (5) the use of multiple craving instruments to ensure measurement validity of the currently debatable craving phenomenon, and (6) the use of advanced statistical analyses that differentiate between- and within-person variations, such as multilevel modeling.

In Manuscript 2, we reviewed the psychometric properties of the Penn Alcohol Craving Scale (PACS) that was used to measure the outcome of substance craving for this dissertation. PACS was found to be is a well-tested instrument with established convergent and discriminant validity and reliability in various populations with SUD. However, some weaknesses were identified that are mainly related to the instrument’s unknown content validity and its atheoretical background. Our main recommendations for improvement included: (1) Revising PACS items using focus groups or a qualitative approach to enhance or confirm the scale’s content validity; (2) Conducting an accurate confirmatory factor analysis of the revised scale to provide evidence on the dimensionality of craving; (3) Considering a “daily” timeframe for the scale’s item to minimize retrospective memory bias; (4) Conducting psychometric testing of the scale’s use in adolescents; and (5) Identifying normed values and cutoff scores to enhance score interpretation.

In Manuscript 3, we reported study findings. Our hypotheses included: (1) Craving levels decline over time; (2) Craving reductions occur at different rates over time; (3) Age is related to craving changes over time; (4) Sex is related to craving
changes over time; (5) Length of abstinence is related to craving reductions over time; (6) The dose of daily HRVB practice predicts craving reductions over time; (7) Craving reductions in the experimental condition would be greater than reductions in the control condition, if any; and (8) Variations in depression, anxiety, and perceived stress are associated with craving changes over time. The sample consisted of 44 college students recovering from SUD, recruited through recovery housing of a public northeastern United States university. Participants were assessed at four occasions in the control condition over the first 12 weeks followed by an 11-week rest period (semester break) and 12 weeks in the experimental condition (8 occasions). The majority of the sample consisted of single (97.6%) White (93.2%) young male (70.5%) college students with a relatively long abstinence time (Table 6). A longitudinal multilevel modeling approach was used to analyze data in SPSS. The level of significance for hypothesis testing was calculated at the .05 level. Data in these analyses consisted of 400 observations; 24.24% of the expected observations were missing due to the lack of control condition for 16 of the participants, 6 dropouts, and other randomly missing responses. Hypothesis 1 was supported by our finding of craving reductions over time, with an expected -2.59 points reduction by week 35. Hypothesis 2 was supported by the significant random quadratic time signifying that some participants showed acceleration of craving reduction over time (Table 7). Hypothesis 3 was supported by the significant fixed effect of age ($\beta = -0.28$, $p<.05$) on craving. Neither hypothesis 4 nor hypothesis 5 were supported through this research, with non-significant effects of sex and length of abstinence on craving. However, the results could possibly have been confounded by a Type II error and may prove different in a larger sample or in a sample of persons early in the recovery
continuum. Hypothesis 6 was supported through this research. Of the between-persons mean differences found in the empty model (49% of the total craving variance), more than half (58%) was due to continued high daily HRVB practice (>12 minutes) and age, such that older age and high practice were associated with greater craving reductions over time. Hypothesis 7 was partly supported in this study. Our findings indicated that persons who had depressive symptoms more than usual (relative to their mean depression score) were expected to have less craving reduction during that period. There was, however, no significant between-person effect of depression on craving changes. Fluctuation in anxiety and perceived stress did not have any significant effects on craving either. Hypothesis 8 was supported by the piecewise model confirming that participation in the eight-session HRVB protocol (total of 7-8 hours of laboratory-based training over 12 weeks) explained craving reductions over time. The true $R^2$ for the final model was determined by calculating the square of the correlation between predicted PACS and actual PACS, yielding an $R^2$ of .205. All model parameters are presented in Tables 7, 8, and 9 of this dissertation.

**Conclusions and Recommendations**

This dissertation filled several gaps in the literature, as identified in Manuscript 1, by providing longitudinal evidence on the effectiveness of an intensive and reproducible HRVB intervention using multilevel modeling that differentiated between- and within-person variations in craving over time. The discrepancies found in the literature highlight the predominance of individual differences in craving assessments and the necessity of interpreting craving changes as a function of intra- and inter-individual sources of variance. In our sample, there were more within-persons (51%) than between-persons
(49%) variations in craving indicating the importance of addressing individual differences in explaining craving changes over time. Our results suggested that an eight-session HRVB protocol can be an effective complementary anti-craving intervention for college students recovering from SUD. In fact, HRVB seemed to enhance the efficacy of conventional therapies by producing craving reductions that were not evident prior to the HRVB intervention despite usual treatment.

In addition, we examined the usefulness of personal practice outside laboratory-based HRVB training. A continued daily HRVB practice of more than 12 minutes was found to enhance treatment as usual outcomes and contribute to greater craving reductions over time. Notably, our sample showed age differences in terms of adherence to daily HRVB practice. Younger participants seemed to be more committed to daily HRVB practice, although many did not achieve the recommended daily practice of 15 minutes twice daily. This may be partly explained by the fact that participants younger than 23 years reported higher craving scores than older participants. It may be that participants with more severe cravings felt a higher need to practice HRVB more consistently. Furthermore, the effects of depression, anxiety, and perceived stress were examined as inter-individual predictors of craving. Increases in depressive symptoms were found to attenuate the effects of HRVB on craving. Anxiety and perceived stress were not found to be significantly associated with craving in this study.

Nevertheless, our findings should be confirmed in larger samples with participants in early recovery and with higher baseline craving and other co-occurring symptomatology. Future studies should attempt to determine the long-term effects of HRVB, whether the craving reductions achieved during HRVB are sustained after the
intervention ends, and whether continued daily practice is needed to keep craving at bay. As noted in Manuscript 2, one of the weaknesses of PACS, which was used to measure this study’s outcome, is the lack of information about its content validity. Our results may therefore be applicable to one dimension of craving and other aspects of craving may have not been revealed. Due to craving’s subjective and temporal nature, future studies should attempt at using more than one measure of craving in order to ensure appropriate and comprehensive measurement of the phenomenon. We also recommend the use of accurate measurements of practice time and treatment fidelity in order to identify determinants of adherence to recommended daily HRVB practice.

**Implications to Nursing**

The high prevalence of SUDs among college students (Califano, 2007) is a significant healthcare and public concern. Despite conventional treatments, high relapse rates are evident in persons recovering from SUD (SAMHSA, 2014) and substance craving is one of its strongest predictors (Paliwal et al., 2008; Sinha, 2011). Nurses are key stakeholders in the treatment of patients with SUDs and are therefore strategically positioned to address the symptom of substance craving. Novel anti-craving interventions that can be used by nurses are therefore warranted. As explained earlier, slow abdominal breathing as a therapeutic intervention has been widely used in nursing. HRVB training is consistent with nursing’s holistic approach to patient care and may be effectively incorporated within non-pharmacological interventions nurses provide to help patients with SUD control the symptom of craving. This study provided longitudinal evidence that HRVB can help recovering college students better manage substance craving and maintain recovery by improving their ability to control physiological arousal. HRVB is
an especially promising addition to nursing care because it supports physiological health, has no side effects, and can be easily accessible through smartphone applications. Nurses can teach patients how use HRVB strategically whenever they experience triggers or acute craving episodes. The integration of HRVB may enhance nursing care of recovering SUD patients, which may in turn promote better clinical outcomes and have broader implications for the development of contemporary mental health nursing practices.
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Appendix A

HRV BFB Recording and Training Protocol

Calibration: Prior to each of the recording sessions, participants are asked to take five complete breaths into a tube attached to an 800cc capacity plastic bag so that a calibration of their respiration volume can be conducted.

Pre-test baseline: Participants perform a standardized low-cognitive-demand baseline task, the “plain vanilla” task32 for 5 minutes. Physiological reactivity during this period serves as a pre-test baseline.

Post-test baseline: Participants perform the “plain vanilla” task32 for 5 minutes after the paced breathing activity. Physiological reactivity during this period serves as a post-test baseline.

Session 1: Obtaining Initial Estimates of Resonance Frequency (45 to 75-min Recording and Training)

- Calibration and pre-test baseline data are recorded followed by 5-min breathing along with a computerized visual breathing pacer, at a speed of 6 breaths per minute (BPM).
- Defining resonance frequency (RF) – HR oscillation amplitude is measured while participants breathe for 2 min each at five specific frequencies ranging from 4.5 to 6.5 BPM. A visual pacing stimulus (line-and-ball pacer) is provided to keep constant RR. Trainees are instructed to inhale as the ball rises and exhale as the ball descends along the line. RF is identified based on the participants’ physiological data and verbal feedback. Participants are then asked to breathe at this rate for an additional 5 min, using the visual breathing pacer. This aspect of training lasts approximately 45-75 minutes.
- Post-test baseline data using the plain vanilla task.
- Homework training – Trainees are instructed to practice breathing easily and comfortably at their RF, with longer exhalations than inhalations, for two 15-minute periods on their own each day. Trainees are told how long (in seconds) each breath should be (60 divided by the RF in breaths per minute), and are instructed to time their practice breathing cycles using the second hand of a clock.

Session 2: Learning Abdominal and Pursed Lips Breathing Techniques (30-45min Training only)

The trainer reviews the trainees’ understanding and practices of breathing at RF with longer exhalations than inhalations without breathing too deeply to avoid
hyperventilation. Pursed lips and abdominal breathing techniques are introduced to make RF breathing less effortful. Training session 2 lasts approximately 30-45 minutes.

**Session 3: Review of Pursed-lips, Abdominal Breathing, HRV BFB Training, and Learning How to Breath with Cardiotachometer Feedback (30 to 45-min Training only)**

The trainer reviews the trainees’ understanding and practices of breathing at RF with pursed lips and abdominal breathing techniques. Trainees are then instructed to maximize the peak amplitude of HR oscillations using the cardiotachometer and respiration rate displays on the computer screen as biofeedback for 5 min. The phase shift between the HR and respiration curves is evaluated with the trainee on the computer screen. The pacer’s frequency is adjusted until the phase between HR and respiration is approximately zero degrees. Finally, the Stress Eraser device will be introduced and participants will be instructed to use it for 15 minutes while they observe their own heart rate and respiration rate on the computer screen. Training session 3 lasts approximately 30-45 minutes.

**Session 4, 7 & 8: Continued RFB BFB Practice and Assessment (35 to 50-min Recording and Training)**

- Calibration and pre-test baseline data are recorded followed by 5-min breathing along with a computerized visual breathing pacer, at a speed of 6 breaths per minute (BPM).
- Participants are also asked to breathe for 5 min at their RF using the Stress Eraser device and for 5 min using the cardiotachometer line display as their pacer.
- Post-test baseline data using the plain vanilla task.

These recording sessions allow us to collect physiology data to gauge participant progress. Recording sessions 4, 7 & 8 last approximately 35-50 minutes.

**Session 5 & 6: Maximizing Heart Rate Variability (30 to 45-min Training only)**

Participants are asked to breathe at their resonance frequency for 5 min using the computerized visual breathing pacer, followed by 5 min breathing with the cardiotachometer line. Participants are asked to notice their physiological and psychological responses to the resonance frequency breathing. Finally, trainees do 10 min of breathing with the cardiotachometer line. Training sessions 5 & 6 last approximately 30-45 minutes.