HEART RATE VARIABILITY, NEGATIVE AFFECT, AND PERSONALITY DISORDER SYMPTOMOLOGY IN WOMEN RECEVING TREATMENT FOR ALCOHOL DEPENDENCE

by

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ABSTRACT OF THE THESIS

Heart Rate Variability, Negative Affect, and Personality Disorder Symptomology in Women Receiving Treatment for Alcohol Dependence

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Alcohol dependence (AD) is resistant to treatment and many patients relapse within the first year following care. There is a need to better understand specific factors that predict and moderate treatment response to help in the formulation of improved treatments for AD. One promising individual difference factor that is thought to influence AD treatment efficacy is the ability to regulate affect, that is, an individual's ability to understand or accept his or her emotional experience, engage in strategies to manage uncomfortable emotions in an adaptive manner, and respond appropriately to negative mood. To date, the psychophysiological components of affect regulation that occur outside of conscious awareness have not been well studied, although evidence suggests that individual differences in the ability to modulate arousal contribute to the development and maintenance of AD. The present study is an initial investigation of the relationship of psychophysiological indices of arousal modulation to levels of pre-treatment symptoms of anxiety and depression, as well as to changes in these symptoms over the course of treatment, in a sample of 50 women entering a 12-week clinical trial of CBT for alcohol

dependence. Indices of heart rate variability (HRV), electrocardiogram (ECG) derived measures of neurocardiac signaling, were used to operationalize modulation of psychophysiological arousal. Potential differences in the relationship of HRV to anxiety and depression in participants with symptoms of cluster-B personality disorders (PDs) was also explored. At pre-treatment baseline, depression and PD symptomology, but not anxiety, were inversely associated with measures of HRV. Measures of pre-treatment HRV failed to directly predict change in anxiety and depression through the course of treatment. However, HRV did moderate the relationship between baseline and post-treatment levels of anxiety. Specifically, greater reduction in anxiety through the course of AD treatment was predicted by higher basal anxiety, only when this high basal anxiety co-occurred with high HRV. The present results are discussed within the framework of Polyvagal Theory (Porges, 2003). It is hypothesized that HRV may be an indicator of a biological mechanism that contributes to affect dysregulation in individuals with co-occurring AD and PD symptomology. Clinical implications of this perspective are discussed, and future directions for research are suggested.

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Introduction

The etiology and course of alcohol dependence (AD) are complex and variable, involving dysfunction in psychological, biological and social domains (Marlatt, Baer, Donovan, & Kivlahan, 1988; McLellan, Lewis, O'Brien, & Kleber, 2000). Current diagnostic systems, such as that presented in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 2000), employ criteria from each of these domains that may contribute to, or result from, maladaptive patterns of drinking. They include, 1) tolerance, as defined by either a need for markedly increased amounts of alcohol to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount of alcohol, 2) withdrawal, as manifested by the characteristic withdrawal syndrome for alcohol, 3) alcohol being used in larger amounts or over a longer period than was intended, 4) presence of a persistent desire or unsuccessful efforts to cut down or control alcohol use, 5) a great deal of time spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects, 6) important social, occupational, or recreational activities being given up or reduced because of alcohol use, and 7) continued alcohol use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol. A diagnosis of AD is based upon meeting any three of these criteria within a one-year period. This polythetic classification system allows for an individual to qualify for diagnosis with any one of 35 different constellations of symptoms. Moreover, the path from initiation of use to development of AD appears to be highly variable across people (Chassin, Flora, & King, 2004; Sartor, Lynskey, Heath, Jacob, & True, 2007), and the combination of diagnostic criteria an individual meets is likely to transmute through the course of problem drinking (Sher, Grekin, & Williams, 2005).

This heterogeneity of development, course and diagnosis compounds the challenges associated with treating AD (Moos & Moos, 2006). AD treatment may also be complicated by comorbid factors (Modesto-Lowe & Kranzler, 1999) such as the presence of symptoms associated with personality disorders (PDs). Individuals expressing PD symptomology experience lower abstinence rates following AD treatment than people without such symptoms (Krampe et al., 2006). As such, there is a need to better understand specific factors that predict and moderate treatment response to help in the formulation of improved treatments for AD, as well as to enhance the efficacy of existing treatments (Allen, Babor, Mattson, & Kadden, 2003).

Affect Regulation

One promising individual difference factor that is thought to influence AD treatment efficacy is the ability to regulate affect (Berking et al., 2011). Affect regulation may be broadly defined as one's ability to understand or accept his or her emotional experience, engage in healthy strategies to manage uncomfortable emotions, and respond appropriately to negative mood and salient stimuli (Bradley, 2003; Morris & Reilly, 1987). Individuals with AD have difficulty regulating affect as evinced, for example, by the subjective experience of high emotional intensity (Gold, 2011), emotional lability (Simons, Carey, & Wills, 2009), and low distress tolerance (Gorka, Ali, & Daughters, 2011). Further, individuals with AD frequently cite difficulty regulating affect as a precursor to early use, as well as a major contributor to relapse (Berking et al., 2011). Although acute alcohol use may to a certain extent reduce negative affect in the moment (Cox & Klinger, 2011), chronic, heavy alcohol use exacerbates the problem by adding negative affect, while impairing neural control of affective states, leading to a vicious cycle that contributes to the escalating nature of AD (Koob & Le Moal, 2001). Thus, difficulty in

regulating affective states may both predispose an individual to use alcohol to cope emotionally (Bradley, 2003), and as a consequence of chronic, heavy alcohol use, affective regulation may become further impaired.

Affect regulation processes, and the specific influence of these processes on AD treatment outcome, have been attributed to the integrated brain-body systems that control them (Critchley, 2005, 2009; Porges, 2009). Affect regulation is believed to be a 'biobehavioral' phenomenon because it involves integrated psychological and physiological processes, some of which occur in conscious awareness, while others occur outside of conscious awareness (Diamond & Aspinwall, 2003; Forgas, 2008; Gross, 1998). Much previous research has focused on conscious, cognitive components of affect regulation, such as thought suppression and reappraisal (Gross, 2002), cognitive demand (Kellermann et al., 2011), cognitive restructuring (Andreotti et al., 2011), and rumination (Nolen-Hoeksema, 2012). These constructs have been applied to the problem of alcohol use disorders in various ways. For instance, suppression of alcohol related thoughts is paradoxically iatrogenic (Najmi & Wegner, 2008) in that attempts to suppress such thoughts can lead to their becoming hyper-accessible (Wenzlaff & Wegner, 2000), thereby promoting drinking behavior. Further, cognitive restructuring is an important component of cognitive behavioral therapy (CBT) based approaches for AD treatment (Marlatt, 2005), while rumination has been used to predict drinking behavior in problem drinkers (Caselli et al., 2010). The psychophysiological components of affect regulation that occur outside of conscious awareness have been less studied.

The present study extends the previous literature on conscious, cognitive regulation of affect by examining a dimension of affective regulation that operates largely outside of conscious

awareness and without volitional control. This dimension of affect regulation has to do with individual differences in the modulation of psychophysiological arousal while at rest and during emotional states, as well as during exposure to salient cues in the environment, and other psychological and physical challenges (Appelhans & Luecken, 2006; Damasio, 1998; Hagemann, Waldstein, & Thayer, 2003). The present study was designed as an initial investigation of at rest psychophysiological arousal modulation in a sample of women entering a 12-week clinical trial of CBT for alcohol dependence. Well-established measures of neurocardiac signaling (Berntson et al., 1997; Stauss, 2003) were used to operationalize modulation of psychophysiological arousal (Vaschillo, Lehrer, Rishe, & Konstantinov, 2002; Vaschillo, Vaschillo, Buckman, Bates, & Pandina, 2010), and examine their relationship to individual differences in symptoms of anxiety and depression at the start of treatment, as well as to changes in symptoms of anxiety and depression over the course of treatment. Potential differences in this relationship in women with personality disorder symptomology were also explored. The overarching hypothesis was that individual differences in the psychophysiological modulation of autonomic arousal would be linked to affective status at the start of treatment as well as changes in affect that occurred at the end of treatment.

Neurocardiac Signaling, Heart Rate Variability, and Affect Regulation

The experience of affect, usually driven by emotional states or environmental factors, is associated with moment-to-moment changes in physiological state (Levenson, 2003). These physiological changes usually serve a preparatory function. For instance, during psychological stress, the sympathetic nervous system may become dominant, producing physiological changes that aid adaptation to a challenge. A flexible autonomic nervous system allows for rapid

generation or modulation of physiological states in accordance with situational demands (Porges, 2009). In contrast, autonomic rigidity results in a lessened capacity to generate or alter physiological responses in synchrony with emotional changes or changes in the environment (Appelhans & Luecken, 2006). The term neurocardiac signaling refers to the bi-directional flow of information between the brain and the heart that continually occurs during rest and in response to such internal or environmental challenges (Napadow et al., 2008; Vaschillo et al., 2002). Neurocardiac communication can be assessed by measuring the psychophysiological function of heart rate variability (HRV), the subtle changes in the time-intervals between heartbeats. HRV is calculated by measuring the variance in the R-spike to R-spike intervals of the electrocardiogram (ECG) and reflects bidirectional communication between the cardiovascular and central nervous systems (Benarroch, 1997; Thayer & Brosschot, 2005).

The autonomic function of HRV has proven to be an informative indicator of brain-body integration that is relevant to affective regulation. Relatively higher levels of HRV have been linked consistently to emotional resilience and stress vulnerability (Appelhans & Luecken, 2006; Thayer, Hansen, & Johnsen, 2010), as well as to an individual's overall physical health (Britton et al., 2007; Lehrer et al., 2006; Vanderlei, Pastre, Hoshi, Carvalho, & Godoy, 2009). At rest, well-functioning systems generally exhibit a high degree of complexity and flexibility (i.e., high HRV), whereas somatic illness is characterized by lower HRV, which has been suggested to indicate a decoupling of autonomic nervous system components (Goldberger, Peng, & Lipsitz, 2002; Pincus & Goldberger, 1994). This is especially true in AD and affective disorders such as depression. Individuals with AD exhibit lower resting HRV than healthy controls (Ingjaldsson, Laberg, & Thayer, 2003; Weise, Müller, Krell, Kielstein, & Koch, 1986), possibly by dint of alcohol's neuro-

(Harper, 2007) and visceral-toxicity (Bode & Bode, 1997; Zakhari, 1997). Lower HRV in alcohol dependent individuals, however, may also represent a more pervasive pattern of autonomic dysregulation not directly attributable to the acute pharmacological effects of alcohol (Peterson, Pihl, Seguin, Finn, & Stewart, 1993). The fact that individuals with depressive disorders also exhibit lower resting HRV (Kemp et al., 2010), in the absence of neurotoxic substances, speaks to this postulate, and suggests that neurocardiac communication is an important component in the expression of these pathologies.

HRV involves a neural substrate referred to as the central autonomic network (Benarroch, 1997; Jellinger, 1998), working together with autonomic nervous system functions that feedback information to the brain (Card & Sved, 2011). The central autonomic network, comprises the prefrontal cortex, insular cortex, amygdala, hypothalamus, periaqueductal gray matter, parabrachial complex, nucleus of the tractus solitarius, and ventrolateral medulla (Benarroch, 1993). The central autonomic network serves to modulate biobehavioral resources in emotion by flexibly adjusting physiological arousal in accordance with changing situational demands (Friedman & Thayer, 1998), and may, therefore, serve a key role in alcohol craving (Verheul, van den Brink, & Geerlings, 1999) and goal-directed motor behaviors such as seeking out alcohol (Iversen, Kupfermann, & Kandel, 2000).

Efferent pathways, descending from the brain's central autonomic network include those that carry both sympathetic (i.e., thoracic visceral) and parasympathetic (i.e., vagus) signals that converge on the heart's central pacemakers, the sinoatrial, and atrioventricular nodes (Katz, 2010), serving to either increase or decrease heart rate (Bibevski & Dunlap, 2011). Thus, the amount of time, or period, between each pair of successive heartbeats is continually changing

depending on the balance of sympathetic and parasympathetic input being received by the heart. This constant flux in neural signaling to the heart contributes to HRV.

The body's feedback to the central autonomic network further contributes to HRV. This is accomplished through afferent processes (i.e., signaling from the heart to the brain) mediated by the baroreflex mechanism (Benarroch, 2008; Goldstein, Bentho, Park, & Sharabi, 2011). The baroreflex is a physiological reflex arc that controls heart-brain communication for the regulation of blood pressure, as well as integration of cognitive and physiological aspects of affect (Vaschillo, Vaschillo, Buckman, Pandina, & Bates, 2011). The central autonomic network communicates with the viscera via a series of feedforward and feedback loops contained within the autonomic nervous system (Pessoa, 2008), modulating autonomic nervous system functions, as needed, to adapt to physical and cognitive-emotional challenges (Benarroch, 1997). In turn, the autonomic nervous system, may serve a preparatory function in affect regulation, which involves general changes in arousal that prepare an organism as a whole for action (e.g., increase or decrease in heart rate) and specific changes in arousal that prepare the organism for goal-directed motor behaviors (e.g., drinking alcohol, distancing oneself from alcohol; Iversen et al., 2000).

Consistent with this model, the literature demonstrates an inverse relationship between HRV and disorders characterized by affective and behavioral dysfunction. For instance, lower background, or resting state levels of HRV are found in individuals with disorders such as posttraumatic stress disorder (Cohen et al., 2000), panic disorder (Klein, Cnaani, Harel, Braun, & Ben-Haim, 1995), and phobic anxiety (Kawachi, Sparrow, Vokonas, & Weiss, 1995). Individuals with major depression have lower HRV than non-depressed controls (Nahshoni et al., 2004), and HRV has been shown to be inversely related to severity of depression (Agelink,

Boz, Ullrich, & Andrich, 2002; Agelink et al., 2001). As such, HRV may serve as an overarching biobehavioral index of affective regulation that does not operate in conscious awareness, and thus may serve as an informative addendum to self reported information about affective regulation, in both affective and substance use disorders.

In addition to the information value of HRV in assessing difficulties in affective regulation, further understanding of psychophysiological modulation of arousal may have important treatment implications. Vagal withdrawal, associated with certain anxiety disorders and depression, causes decreased parasympathetic tone, i.e., reduced HRV resulting from dampened tonic activity in the vagus nerve (Carney et al., 1995; Gorman & Sloan, 2000). Treatments for these disorders, however, may reverse this effect. Chambers and Allen (2002) observed significantly increased vagal activity in individuals who had responded successfully to CBT for major depression, although they did not test whether increased HRV mediated the treatment effect. Further, they noted a linear relationship between Hamilton Rating Scale for Depression scores and vagal tone change. In addition to these spontaneous increases in HRV that have been observed following successful treatment for depression, other studies have attempted to directly modify HRV. Biofeedback techniques, which utilize rhythmic breathing to activate the baroreflex and concurrently increase HRV, have been shown to reduce depression (Karavidas et al., 2007; Siepmann, Aykac, Unterdorfer, Petrowski, & Mueck-Weymann, 2008), and symptoms associated with posttraumatic stress disorder (Zucker, Samuelson, Muench, Greenberg, & Gevirtz, 2009). This literature suggests that biofeedback techniques that increase vagal tone and baroreflex gain may be potentially useful components of treatment for alcohol use

disorders which also involve affective dysregulation (Cheetham, Allen, Yücel, & Lubman, 2010), and are associated with decreased levels of HRV.

Alcohol Use and Heart Rate Variability

Both acute (Bennett et al., 2001; Koskinen, Virolainen, & Kupari, 1994) and chronic alcohol use reduce basal HRV (Ingjaldsson et al., 2003; Malpas, Whiteside, & Maling, 1991), possibly through impairment of higher cortical and midbrain processes that affect cardio-dynamics, and through negative cardiovascular changes that compromise brain-heart communication. In parallel to the depression literature (Chambers & Allen, 2002), HRV has been shown to increase spontaneously with successful AD treatment (Minami et al., 2002; Weise et al., 1986). Low basal HRV is unfavorable in that it characterizes autonomic rigidity (Vanderlei et al., 2009) and usually co-occurs with higher HR and blood pressure (Britton et al., 2007; Parati, Saul, Di Rienzo, & Mancia, 1995). In addition, alcohol's impairment of HRV may have indirect adverse consequences. That is, it is possible that this combination of higher HR and blood pressure, and lower HRV, may actually exacerbate affective dysregulation in individuals with AD, which may serve to perpetuate emotion-focused coping drinking behavior, and ultimately interfere with AD treatment.

This deleterious relationship may be illustrated by the following example. A newly abstinent individual with AD is confronted by an alcohol cue in their environment. In response to this highly salient stimulus, the brain increases sympathetic outflow to the heart via the efferent nerves synapsing on the sinoatrial and atrioventricular nodes, thus increasing heart rate, and simultaneously, blood pressure, while decreasing HRV. In a well functioning system, this increase in blood pressure would be sensed by the baroreceptors in the aortic arch and carotid

sinuses, which would determine that a homeostatic perturbation has occurred. In response, they would increase their firing rate to signal this disruption to the brain, via the vagus and glossopharyngeal nerves, which conjointly synapse in the nucleus tractus solitarius in the medulla. The medulla would process this information as well as information received from the cerebral cortex, and determine whether the body has adapted appropriately to the nature and magnitude of the stressor. When the stressor is removed or its relevance diminished, the brain would again convey information via the efferent nerves, producing a reduction in heart rate. When working effectively, this closed loop circuit allows blood pressure and heart rate to appropriately return to resting levels in a rapid fashion. It also ensures that the heart and the brain react to stimuli in the environment in a coordinated fashion. However, problems concomitant with AD may stymie this process and interfere with the physiological component of affect regulation. For instance, diminished cortical functioning may lead to the cue being inaccurately magnified in significance, or to the cue being sustained in attention long after it has passed on in the environment. As such, a parasympathetic vagal response may not be initiated, resulting in the inappropriate maintenance of physiological arousal. The individual may thus seek out alcohol to cope with the discomfort and stress associated with this hyperaroused state.

Basal HRV and Changes in Affect during Treatment for Alcohol Dependence

The present study sought to characterize individual differences in neurocardiac functions that may contribute to affect regulation in women receiving treatment for AD. In addition to assessing self-reported differences in affect at the start of ministrations, prospective changes in affect were also assessed through the course of treatment. Certain self-reported psychological measures of affect are highly correlated with participant abstinence (S. A. Brown, Myers, Mott, &

Vik, 1994; Cornelius et al., 2004) and are thus useful predictors of treatment response. These correlated measures are particularly useful while individuals are actively engaged in treatment, a time through which one often sees ceiling effects in abstinence and floor effects in drinking. In particular, reduced symptoms of anxiety (Kushner, Abrams, & Borchardt, 2000) and depression (R. A. Brown et al., 1998) are associated with positive change during and after AD treatment. Furthermore, anxiety and depression may be easily measured throughout the treatment process to gauge an individual's response using well-validated questionnaires such as the Beck Anxiety Inventory (BAI; Beck & Steer, 1993a) and Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996). Further, the relationship between treatment effectiveness and negative affect may be particularly strong in women with AD, who experience higher rates of comorbid anxiety and depression than men (Burns & Teesson, 2002), and cite negative affect as their most important antecedent to drinking (Sell, 2001).

As such, the first goal of the present study was to characterize the relationship between basal levels of anxiety, depression and HRV. In addition, because AD treatment tends to reduce alcohol consumption, in part by reducing anxiety and depression (Morgenstern & Longabaugh, 2000), and levels of anxiety and depression have been associated with HRV (Chang et al., 2012; Watkins, Grossman, Krishnan, & Sherwood, 1998), the study sought to investigate the relationship between pre-treatment HRV and changes in negative affect from beginning to end of AD treatment.

Cluster-B Personality Disorders, Heart Rate Variability, and Alcohol Dependence

A second goal of the study was to explore whether an a priori defined subgroup of women with severe emotional disturbance would evince a different association between HRV

and change in symptoms of anxiety and depression during AD treatment. Thus, it was investigated how personality disorder symptomology, specifically that associated with the subgroup of dramatic, emotional, or erratic PDs known as cluster-B (which includes borderline, histrionic, narcissistic and antisocial PDs), may be associated with HRV, and how this symptomology may moderate the relationship between HRV and change in negative affect across treatment. Generally speaking, moderators are intra-personal or inter-personal difference factors that explain some of the variance in treatment response from person to person (Kraemer, Frank, & Kupfer, 2006; Kraemer, Wilson, Fairburn, & Agras, 2002).

Through the identification of moderators, researchers have begun to identify potential targets for behavioral interventions to bolster addiction treatment outcomes. For example, there is evidence that several client characteristics at the beginning of treatment, such as the patient's level of motivation to change (DiClemente, Bellino, & Neavins, 1999), positive expectancies about outcome (Jones & McMahon, 1996), readiness to change (DiClemente, Schlundt, & Gemmell, 2004), and severity of personal problems (McCrady & Barlow, 2007), consistently moderate treatment response (Haaga, McCrady, & Lebow, 2006). There is also preliminary evidence indicating other probable moderators, such as comorbid anxiety (Kushner et al., 2000), depression (Greenfield et al., 1998), antisocial tendencies (Rosenblum et al., 2005), and borderline personality disorder symptomology (Trull, Sher, Minks-Brown, Durbin, & Burr, 2000), suggesting that one's ability to regulate his or her affective state will also affect treatment outcome.

Borderline personality disorder is the most commonly diagnosed PD in cluster-B (Ekselius, Tillfors, Furmark, & Fredrikson, 2001; Samuels et al., 2002), and is characterized by

marked impulsivity accompanied by a pervasive pattern of instability of interpersonal relationships, self-image and affect (APA, 2000). AD is particularly prevalent in individuals expressing cluster-B PD symptomology (Grant et al., 2008; Regier et al., 1990), and is associated with poorer long-term treatment outcomes (Dawson et al., 2005; Hilsenroth, Holdwick Jr, Castlebury, & Blais, 1998). While Kreek and Koob (1998) posit that affective and emotional instability is a common precursor to substance use in all people, others argue that affective and emotional volatility characteristic of cluster-B PDs make this population particularly prone to "self-medication" (Trull et al., 2000). Healthy individuals tend to be better able to regulate emotional responses to environmental challenges, while recovering more quickly after emotional arousal (Gratz, Rosenthal, Tull, Lejuez, & Gunderson, 2010; Rosenthal et al., 2008). On the other hand, those exhibiting symptoms characteristic of cluster-B PD, often demonstrate hypersensitivity to perturbation by interoceptive or exteroceptive cues. One result is affective instability due to a marked reactivity of mood, resulting in emotional responses in individuals expressing high levels of cluster-B PD symptoms that are likely to be inappropriate in content, magnitude, and/or duration, which is ultimately indicative of a loss of behavioral flexibility. As such, emotional and affective hypo-stability associated with cluster-B PDs are thought to influence alcohol use behaviors (Gratz & Tull, 2010), and are hypothesized to be associated with impaired HRV.

Three empirical studies have compared basal levels of HRV in individuals with borderline personality disorder and healthy controls. These studies produced congruent findings for resting HRV, though their findings were somewhat divergent during cue exposure paradigms. Kuo and Linehan (2009) and Weinberg et al. (2009) both found basal HRV to be lower in study

participants with borderline personality disorder, while Austin and colleagues (Austin, Riniolo, & Porges, 2007) found a similar but non-significant effect in their study of a small sample (*n*= 20).

The present study sought to extend these findings by investigating differences in pre-treatment HRV in participants receiving treatment for AD, with and without a cluster-B PD diagnosis. Further, because prior work indicates that individuals with a cluster-B PD diagnosis have difficulty regulating autonomic arousal, it was hypothesized that basal state HRV may be a less sensitive predictor of within-treatment changes in anxiety and depression in this population.

Study Rationale & Predictions

A growing body of evidence suggests that physiological processes contribute to the regulation of emotional response (Buckman, White, & Bates, 2010; McGuire & Troisi, 1987; Porges, Doussard-Roosevelt, & Maiti, 1994; Thayer & Lane, 2000; Udo et al., 2009; Vaschillo et al., 2008), and that HRV is an accessible, non-invasive, and objective index of neurocardiac signaling that can increase our understanding of the processes that support or hinder behavior change (Appelhans & Luecken, 2006; Vanderlei et al., 2009). Yet, to our knowledge, no previous study has attempted to use HRV indices to predict how negative affect changes during the course of AD treatment.

The preset study utilized data from women who were participating in a clinical trial comparing individual to group treatment using a program of CBT developed specifically for women with AD (Epstein & McCrady, 2009). Volunteers' HRV was assessed prior to beginning treatment, and then again within a month of completing the course of CBT. PD symptomology was assessed at baseline using the Structured Clinical Interview for DSM Disorders (SCID-II; First & Gibbon, 1997), and psychosocial self-report surveys, including the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI), were completed weekly throughout the course of treatment.

Based on the prior research outlined above, it was hypothesized that, at the beginning of treatment, HRV would be inversely associated with BAI and BDI scores. Furthermore, because greater basal state HRV is indicative of more efficient integration of autonomic neural circuitry and baroreflex modulation of emotional arousal, it was hypothesized that higher baseline levels of HRV will predict greater amelioration of anxiety and depression symptoms through the course

of treatment, independently of any initial cross-sectional association. That is, individuals exhibiting higher HRV at treatment entry will be more likely to experience greater short-term benefits as a result of CBT, compared to those with lower baseline levels of HRV.

The relationship between HRV and cluster-B PD symptomology was also slated for investigation. Kuo and Linehan (2009) and Weinberg et al. found that basal HRV was lower in individuals with borderline personality disorder compared to healthy controls, while Austin and colleagues (2007) found a trend in the same direction. Therefore, participants with cluster-B PD diagnoses were predicted to have lower pre-treatment HRV than non-PD diagnosed participants. In addition, because of the emotional regulation challenges that people expressing cluster-B symptomology face, the possible moderating role of cluster-B PD diagnosis on the relationship between pre-treatment HRV, and total change in BAI and BDI scores over the course of twelve weeks of CBT was explored. Basal levels of anxiety and depression were statistically controlled for.

In summary, this study had the following aims and hypotheses:

Specific Aim 1

Determine the relationship between pre-treatment HRV and anxiety and depression symptoms among women in treatment for AD.

Rationale: Prior research has suggested that HRV is negatively associated with anxiety and depression, yet this relationship has not been examined in women with AD.

Hypothesis: Pre-treatment HRV will be negatively associated with pre-treatment BAI and BDI scores in women entering a program of CBT for the treatment of AD.

Specific Aim 2

Examine the relationship between pre-treatment measures of HRV and change in negative affect during a twelve-week course of CBT.

Rationale: HRV has not been investigated as a potential moderator of AD treatment response, however more adaptive regulation of autonomic arousal may facilitate clients' ability to benefit from therapeutic intervention.

Hypothesis: Pre-treatment HRV will predict amelioration of anxiety and depression symptoms, as measured by BAI and BDI scores, over the course of treatment. More specifically, greater baseline HRV will predict greater symptom reduction in negative affect.

Specific Aim 3

Investigate differences in pre-treatment HRV in participants with and without cluster-B PD diagnosis.

Rationale: Prior research has suggested that basal HRV is different in individuals diagnosed with cluster-B PD compared to individuals without PD diagnosis, although this relationship has not been examined in AD treatment populations.

Hypothesis: Pre-treatment HRV will be lower in participants diagnosed with cluster-B PD.

Specific Aim 4

Explore whether cluster-B PD moderates the relationship between pre-treatment HRV and the reduction of anxiety and depression symptoms over the course of treatment.

Rationale: Prior research indicates that individuals with cluster-B PD diagnosis have a pervasive difficulty in regulating autonomic arousal. Basal state HRV, therefore, may not be a sensitive predictor of affective changes in this population.

Tentative Hypothesis: Cluster-B PD will moderate the relationship between pre-treatment HRV and change in BAI and BDI scores. For participants with cluster-B PD diagnosis, higher levels of HRV will predict smaller reductions in negative affect, compared to participants with similar HRV, but without a PD diagnosis.

Methods

The current study was a component of ongoing research directed by Elizabeth Epstein Ph.D., and Marsha E. Bates Ph.D., Research Professors, Center of Alcohol Studies, Rutgers University. The parent project is an ongoing randomized clinical trial of individual and group CBT in a sample of women with AD (PI: Epstein). Additionally, an add-on study assesses changes in HRV from pre-treatment to post-treatment (PI: Bates).

Participants

The present investigation utilized data from participants who participated in both the 12-week study protocol of the parent study and the add-on study of physiology. From a total of 52 such participants, two were excluded because they were taking complex drug combinations (multiple blood pressure medications, benzodiazepines, an antipsychotic, and a selective-serotonin-reuptake-inhibitor), which would confound interpretation of HRV results. Thus, data from 50 participants were included.

Volunteers for the parent study were recruited through newspaper and online advertisements, the study's website (http://womenandalcohol.rutgers.edu/), information packets sent to community agencies, and pamphlets posted in physicians' offices and community centers. Potential participants were initially screened over the telephone to determine eligibility. To meet selection criteria, women needed to be 18 years of age or older, able to read English at a 6th grade level, show no evidence of psychotic symptoms or gross cognitive deficits in the six months prior to intake, and must had drunk alcohol in the previous 60 days. Furthermore, participants had to meet DSM-IV (APA, 2000) criteria for current alcohol dependence, as confirmed by the alcohol module of the SCID-I. Women were excluded if they had physiological drug dependence (except

caffeine and nicotine), or were currently receiving individual or group-modality treatment for their AD; however, they were allowed to participate if they were willing to suspend their current treatment during the three-month course of the study. Eligible participants were invited to take part in the HRV Study and were compensated with a $25 gift card for each of two completed physiology recording sessions (pre-treatment and post-treatment).

Intake

Potential participants were initially screened with a 10-minute brief telephone interview, which gauges basic alcohol use patterns, history of problem drinking and drug use, and determines their age and relationship status. Women meeting basic criteria for participation completed an in-person clinical screening at which they were administered 1) a clinical screen interview, 2) SCID-I (alcohol + drug modules; First, Spitzer, Gibbon, & Williams, 2002), 3) Clinical Institute Withdrawal Assessment of Alcohol Scale (Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989), 4) Drinking Goal Questionnaire, 5) Beck Anxiety Inventory (BAI; Beck & Steer, 1993a), 6) Beck Depression Inventory (BDI; Beck et al., 1996), and finally, if eligible, 7) written participation consent forms for both the clinical trial and Heart Rate Variability Study. Optional psychotic screen and mini-mental status exams (Folstein, Folstein, & McHugh, 1975) were administered if necessary.

Baseline & Psychological Measures

Participants deemed eligible after the screening interview were then scheduled for a comprehensive baseline interview to assess history and severity of alcohol use and alcohol related consequences, level of psychological functioning, and interpersonal resources. At the baseline interview participants were administered the SCID-I interview as well as other measures pertinent

to the parent study. The SCID-I assesses lifetime and current Axis I psychopathology. Good inter-rater reliabilities have been reported for the SCID-I, with kappas from .84 to 1.00 (Schneider et al., 2004). Overall inter-rater reliability for the alcohol modules of the SCID-I has been reported in the range of kappa = .65 to .75 (Lobbestael, Leurgans, & Arntz, 2011; Williams et al., 1992). Participants were also administered the SCID-II screener, which measures the presence of lifetime and current PD symptomology. In keeping with standard clinical practices, the complete SCID-II interview (First & Gibbon, 1997) for each personality disorder was administered only in the event that the screener suggested possible Axis II pathology. Good inter-rater reliabilities have been reported for the SCID-II personality disorder diagnoses, with kappas of .89 to .98 (Maffei et al., 1997; Schneider et al., 2004). The SCID-II screener is also well validated. It has high inter-rater reliabilities with kappas of .77 to .93 (Jane, Pagan, Turkheimer, Fiedler, & Oltmanns, 2006; Schneider et al., 2004) and good test-retest reliability (Zanarini & Frankenburg, 2001; Zanarini et al., 2000). The screener may be more effective than categorical diagnosis at predicting problem drinking behavior in the present sample (Hunter-Reel, Epstein, McCrady, & Eddie, 2012). Further, SCID-II screener results may be all the more relevant as DSM-5 is expected to move to a hybrid dimensional-categorical diagnostic approach for PD in 2013 (APA, 2012).

At the baseline interview, a reliable and valid timeline follow-back interview was used to measure drinking behavior over the past 90 days (Sobell & Sobell, 1992). The BAI (Beck & Steer, 1993a) and BDI (Beck et al., 1996) were administered during the clinical screen, and again before each weekly therapy session. The BAI is a 21-item self-report instrument, which measures symptoms of anxiety using a 4-point Likert-type scale. The BAI has high internal consistency (alpha = .92) and a test-retest reliability of .73 (Beck, Epstein, Brown, & Steer, 1988). The BDI is

a 21-item self-report instrument used to assess depression. Similarly, it uses a 4-point Likert-type scale, and has high internal consistency (alpha = .81) with test-retest reliability of .96 (Beck, Steer, & Carbin, 1988; Sprinkle et al., 2002). These measures are sensitive to change (Richter, Werner, Heerlein, Kraus, & Sauer, 2000), have high internal (Steer, Ranieri, Beck, & Clark, 1993; Storch, Roberti, & Roth, 2004), and content validity (de Beurs, Wilson, Chambless, Goldstein, & Feske, 1997; Osman, Kopper, Barrios, Gutierrez, & Bagge, 2004), and have been validated in both sexes (Richter et al., 2000).

Analysis of Heart Rate Variability

HRV is defined as changes in time interval from R-spike to R-spike (RR) in an ECG signal, where the R-spike represents a single contraction of the heart's ventricles. Changes in the RR interval captures moment-to-moment, fine-grained perturbations in the heart's rhythm that reflect subtle changes in the central and autonomic nervous systems. They may be analyzed in a number of different ways. For example, time domain indices are derived from direct measurement of RR intervals, also referred to as normal-to-normal (NN) intervals. Commonly estimated time domain indices include the standard deviation of all NN intervals (SDNN) and the root of the mean squared differences of successive NN intervals (Rmssd), which are useful for gauging general activity of autonomic regulation. In addition, the number of pairs of adjacent NN intervals differing by more than 50ms throughout a recording (NN50), and percentage of NN50 count divided by the total number of NN intervals (pNN50), closely reflect parasympathetic vagal activity (Task-Force, 1996).

Alternatively, HRV may be assessed in the frequency domain using power spectral density analysis, which provides information about how power distributes as a function of frequency

(Task-Force, 1996). By convention, frequency domain indices are divided into very low frequency (VLf: 0.005-0.04 Hz), low frequency (Lf: 0.04-0.15 Hz), and high frequency (Hf: 0.15-0.4 Hz) domains. Hf HRV activity is primarily parasympathetically mediated by vagal activity (Berntson et al., 1997; Task-Force, 1996). Hf HRV is the most widely studied aspect of HRV because it provides insight into respiratory sinus arrhythmia, that is, changes in heart rate driven by respiration, which conserves energy, minimizes cardiac workload, and is indicative of a well-functioning system. Lf HRV reflects both the parasympathetic and sympathetic influences, such that it captures the dual action of the baroreflex system as it affects both HRV, and vascular tone (Appelhans & Luecken, 2006; Cevese, Gulli, Polati, Gottin, & Grasso, 2001; Vaschillo et al., 2011). Finally, VLf HRV is thought to exclusively reflect fluctuations in the sympathetic nervous system (Berntson et al., 1997) that mediate baroreflex control of vascular tone (Vaschillo et al., 2011).

Treatment Group Randomization

Seven to eight participants were recruited at a time. They were administered the clinical screen and baseline interviews, and then randomized as a block to either group or individual therapy. This strategy afforded block randomization, and ensured all pre-treatment assessment was done prior to randomization.

Treatment

Both treatment conditions provided 12 weekly sessions of manualized CBT, tailored specifically to issues faced by female problem drinkers. Individual sessions were 60 minutes (except the first, which is 90 minutes) and group sessions were 90 minutes (except the first, which is 120 minutes), helping to maintain the ecological validity of each treatment. In community

clinic settings, individual therapy typically ranges from 45 to 60 minutes, and group therapy typically runs 90 minutes per session. The content of treatment, however, was similar for both groups. Individualized treatment utilized a female specific CBT manual developed for the parent study. The same material was presented to groups via a didactic presentation of the manual's contents, which was reinforced with group discussion, modeling of skills practice and interpersonal support.

In both conditions, each participant received a workbook of handouts and worksheets. Two core thematic women's issues were addressed, 1) A woman as an active agent in her own life, and 2) A woman's right to self-care versus other-care. These themes were integrated into the treatment, through discussion punctuated with examples, and female-specific illustrative material. Additionally, psycho-educational material was covered to elucidate the ways in which women are uniquely affected by heavy alcohol consumption. Core CBT elements were also covered, including motivational enhancement, self-recording, functional analysis, self-management planning, and relapse prevention. The manual specifically addressed high-risk situations deemed commonly challenging for women with AD, including, 1) dealing with heavy drinkers in the social network, 2) coping with anxiety, 3) coping with depression, 4) coping with stress and strong emotions, 5) improving positive social network support, 6) anger management, and 7) assertiveness. Other high-risk situations and drinking antecedents particularly pertinent to female alcoholics were used as examples of how to apply the various skills to specific problems (Epstein & McCrady, 2009).

Treatment was provided by master's and doctoral-level clinicians, who were crossed by treatment condition to avoid therapist condition confounds. In a recent study carried out at the

parent study's laboratory, there were no differences in therapy retention or outcome by gender of therapist (McCrady, Epstein, Cook, Jensen, & Hildebrandt, 2009). Therefore, to avoid potential gender by treatment condition interaction, male therapists were equally represented in each treatment condition. Because, in clinical settings, male therapists often treat females with AD, using both male and female therapists added further ecological validity to the study. Therapists met weekly to review cases, and to avoid therapist drift, digital audio-recordings of therapy sessions were systematically reviewed for each client. Sessions were reviewed by master's and doctoral-level clinicians using a therapy integrity rating scale modified from Morgenstern's 'Project Impact' (Morgenstern, Morgan, McCrady, Keller, & Carroll, 2001). The therapy integrity rating scale includes 58 items measuring various elements of CBT delivery, and treatment quality, including general and specific interventions, common factors in therapy, and coverage of female specific themes.

Psychophysiological Testing

At the end of the clinical screening intake, after signing informed consent for the parent study, each participant was invited to participate in the HRV study as an add-on to the parent study, and was given a consent form for the HRV study that describes the procedures, benefits and risks. Each volunteer was instructed to review the HRV consent form, and tell the clinical screener if she was interested in participating in the HRV study at the end of the baseline research interview, which was typically scheduled for a week hence. Women assenting to participate in the HRV study were then scheduled to complete a HRV session at the end of the baseline interview. Parent study participants who were undecided about doing the HRV study were allowed to take home the HRV consent form for further consideration. They were then

called during the week to see if they wish to take part in the HRV study. HRV sessions were completed directly after the baseline interview, or before the first treatment session. HRV sessions were never scheduled prior to the baseline interview, or after the participant began treatment (session 1).

Assenting participants were escorted to the Cognitive Neuroscience Laboratory where they signed the HRV Study informed consent. Participants were seated in a comfortable chair located 2.5m in front of a large computer screen in a sound attenuated, dimly lit room. Dermal ECG electrodes were placed ventrolaterally above the deltoid muscles on the right and left arms, as well as in a lateral position above the left ankle. Respiration belts were placed across the chest and stomach to capture thoracic and abdominal breathing, respectively. Participants then performed a standardized low-demand "plain vanilla" task (Jennings, Kamarck, Stewart, Eddy, & Johnson, 1992) for 5 minutes, wherein they viewed colored rectangles on a computer screen while silently counting the number of blue rectangles. This procedure provided the basal HRV measures for the study. Following this, participants engaged in a breathing exercise not related to the present study, wherein they breathed at a rate of six breathes per minute (0.1Hz) for 5 minutes, using a visual breathing pacer (Thought Technology). The entire HRV recording procedure took approximately 30 minutes, and was principally administered by a doctoral level physiologist and a doctor of medicine, both of whom have extensive experience recording human physiology. They received assistance from two doctoral students and a post-baccalaureate research assistant.

ECG and respiration data were continuously recorded at a rate of 2000-Hz by a Powerlab Acquisition system (ADInstruments, Colorado Springs, CO), while blood pressure was

continuously recorded using Finometer MIDI (Finapres, Amsterdam). Respiration sensors were calibrated pre-session by having subjects inflate and deflate an 800 ml breathing bag. Sequences of heart beat-to-beat intervals (RR) were recorded and exported to a WinCPRS software program (Absolute Aliens Oy, Turku, Finland) for analyses and calculation of HRV indices, as well as mean HR. After cubic interpolation of the non-equidistant waveform, the RRI sequence was checked for artifacts and irregular beats. Because respiration influences HR and HRV (Berntson et al., 1997), mean respiration frequency was calculated from the thoracic respiration record. All physiological measures were calculated separately for the 5-minute baseline task, and then analyzed using time and frequency domain methods. For frequency domain HRV indices, RRI spectra were calculated through Fourier analysis (Cooke et al., 1999; Taylor, Carr, Myers, & Eckberg, 1998). HR, expressed as beats per minute, was derived by calculating the average number of R-spikes in the ECG signal occurring each minute during the 5-minute recording period. HRV was calculated from sequential RR intervals derived from the ECG signal with corrections for artifacts and irregular beats:

$$\overline{RR} = \frac{RR_1 + RR_2 ... R_N}{N} = \frac{1}{N}\sum_{i=1}^{N} RR_i[ms; -, ms]$$

The following time domain measures of HRV were calculated:

1) Standard deviation of normal-to-normal R-spike intervals (SDNN):

$$SDNN = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(RR_i - \overline{RR})}[ms; -, ms, ms]$$

2) Square root of the mean squared differences of successive NN intervals (RMSSD):

$$RMSSD = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N-1}(RR_{i+1} - RR_i)^2}[ms; -, ms, ms]$$

3) Number of pairs of adjacent NN intervals differing by more than 50ms throughout a recording (NN50):

$$NN50 = \sum_{i=1}^{N}\{|RR_{i+1} - RR_i| > 50ms\}[count; -]$$

4) Percentage of NN50 count divided by the total number of NN intervals (pNN50):

$$pNN50 = \frac{NN50}{N} \cdot 100[\%; -]$$

Frequency domain analysis was performed by discrete Fourier transform, to determine the spectral power of HRV. By convention, HRV components are divided into high frequency (Hf: 0.15–0.4 Hz), low frequency (Lf: 0.04–0.15 Hz), and very low frequency (VLf: 0.005–0.04 Hz) domains. Total spectral power of each frequency component was estimated by a power spectral density analysis, calculated from the variance of each component divided by the frequency range.

Results

Preliminary Analysis

There were no significant differences between women randomized to the individual and group treatment conditions in the parent study on measures of age, baseline BAI and BDI scores, total change in BAI or BDI scores over treatment, drinking measures, or baseline physiology measures (all $p > .05$). Therefore, data from participants in the two treatment conditions were combined for all subsequent analyses. The combined sample ($n = 50$) was 88% European American, 6% African American, and 6% of more than one race, was on average 49.1 ($SD = 8.5$) years of age, and had 15.9 ($SD = 3.1$) years education. Total household income ranged from $0 – $1,000,000, with a mean household income of $106,278 ($SD = $140,901).

At the baseline interview, 8 women met current DSM-IV criteria (APA, 2000) for generalized anxiety disorder, 2 of whom also qualified for panic disorder, and 7 women met current criteria for a major depressive episode. Two women qualified for a PRISM (Hasin, Trautman, Miele, Endicott, & Glick, 1999) post-traumatic stress disorder diagnosis, though neither was currently symptomatic. On average, participants scored 13.0 ($SD = 11.1$, range 0–63) on the BAI at baseline, which falls in the mild range of anxiety (Beck & Steer, 1993b). They improved, showing a mean reduction of 7.2 ($SD = 9.9$) points through the course of treatment. On the BDI, participants scored a baseline average of 19.4 ($SD = 10.4$, range 0–63), which falls in the mildly depressed range (Beck, 1996), and demonstrated an average reduction of 11.9 ($SD = 10.3$) points through treatment. 4% of the sample was taking medication for anxiety, 16% were taking medication for depression, and 12% were taking medication for both anxiety and depression. On average, participants drank alcohol 69.0% ($SD = 30.9\%$) of the 90 days in the

timeline follow back period before commencing treatment, and on drinking days drank an average of 6.3 (*SD* = 2.7) standard drinks per day.

Only three women met full DSM-IV criteria for PD diagnosis (one avoidant, one narcissistic, and one borderline), so that it was not possible to perform the planned moderation analysis. Thus, exploratory analyses were used to probe more general personality disorder symptoms in the sample. Total SCID-II screener scores were used to quantify total personality disorder symptomatology (First, 1997; Grover et al., 2007; Nakao et al., 1992). In addition, the cluster-B component of the screener was used to gauge symptomology for the cluster-B PDs. The mean total SCID-II screener score was 19.9 (*SD* = 9.1, range 0–103) and participants' mean score on the cluster-B component of the screener was 7.1 (*SD* = 5.0, range 0–54).

All questionnaire (BAI, BDI & SCID-II screener) and physiological indices (Mean HR, SDNN, pNN50, Rmssd, Hf, Lf & Vlf HRV) were checked for skewness and kurtosis and normalized using logarithmic transformation. Logarithmic transformation was found to normalize the distribution of each measure. Testing for multivariate outliers in the baseline sample was conducted using Mahalanobis distance [D^2] (de Maesschalck, Jouan-Rimbaud, & Massart, 2000). Mean HR, SDNN, Rmssd, pNN50, Hf HRV, Lf HRV and Vlf HRV, as well as baseline BAI and BDI scores were entered into the model. With criterion set at $p < .001$, three outliers were identified and removed from the baseline sample ($n = 47$). Pearson product correlations were used to examine associations between physiological indices, age, and drinking severity during the timeline follow-back period. HR and HRV indices were all highly correlated ($r = .71$ - $.91$; all $p < .0001$), therefore, only three frequently used and widely validated time-series measures (SDNN, Rmssd and pNN50), and the three spectral indices (Hf HRV, Lf HRV and Vlf

HRV) were used in the subsequent analyses. Together these indices cover the breadth of HRV complexity. Specifically, SDNN captures overall HRV, Rmssd is an excellent estimate of short-term components of HRV, and pNN50 is a particularly sensitive measure of fine-grained changes in parasympathetic vagal tone (Task-Force, 1996). In addition, Hf HRV captures parasympathetically mediated HRV, while Lf HRV captures the combined effects of parasympathetically mediated baroreflex regulation of HRV and sympathetically mediated baroreflex regulation of vascular tone (Task-Force, 1996). Vlf HRV is thought to capture the sympathetically mediated effects of baroreflex control of vascular tone exclusively (Vaschillo et al., 2011).

Age, percent drinking days, and drinks per drinking day were not significantly associated with either HR or any measure of HRV in this sample (all $p > .05$), therefore, these variables were not controlled in subsequent analyses.

Relationship Between Pre-treatment BAI and BDI Scores, and HRV

Hypothesis 1, that pre-treatment HRV will be inversely associated with pre-treatment BAI and BDI scores, was tested using Pearson's *r* coefficients (2-tailed). Results are presented in Table 1. As predicted, BDI scores were negatively associated with two indices of HRV, Rmssd ($r = -.36$, $p = .01$) and pNN50 ($r = -.32$, $p = .02$), and were marginally associated with Hf HRV ($r = -.28$, $p = .05$). In addition, there was a trend toward a positive association between HR and BDI scores ($r = .28$, $p = .05$). Contrary to the hypothesis, baseline BAI scores were not associated with HR or any indices of HRV.

Because only three women in the sample met full diagnostic criteria for a personality disorder, hypothesis 3, that pre-treatment HRV will be lower in participants diagnosed with a

cluster-B PD diagnosis, was modified and tested using cluster-B SCID-II screener scores (First, 1997) in the correlational analysis. Women with greater cluster-B symptomology had lower HRV, as evinced by SDNN (r = –.35, p = .01), Lf HRV (r = –.38, p = .01), and Vlf HRV (r = –.32, p = .02), as well as marginally higher HR (r = .28, p = .05). Total SCID-II screener scores were positively associated with HR (r = .30, p = .03) and negatively associated with SDNN (r = –.31, p = .03), Rmssd (r = –.30, p = .04), pNN50 (r = –.30, p = .04), and Lf HRV (r = –.34, p = .01), with a marginal negative association found for Hf HRV (r = –.28, p = .05).

Relationship between Change in BAI and BDI Scores During Treatment and Baseline HRV

Fourteen women failed to complete treatment, or the end-of-treatment assessment, and were therefore excluded from analyses of change from pre- to post-treatment. Women attending 7 or less treatment sessions were considered non-completers (1 participant attended 1 session, 4 participants attended 2 sessions, 3 participants attended 3 sessions, 3 participants attended 4 sessions, 1 participant attended 5 sessions, 1 participants attended 6 sessions, and 1 participant attended 7 sessions). The non-completers were not significantly different from women who did complete treatment in terms of age, alcohol use variables, baseline anxiety or depression, change in anxiety or depression, SCID-II screener scores, cluster-B symptomology, or HRV (all p >.05). One outlier in the analysis of change scores was detected using Mahalanobis distance and removed; the final sample size for these analyses was 35.

Hierarchical regression analysis was performed separately for each HRV index to examine the association between baseline HRV and change in anxiety and depression during treatment. The dependent variables were BAI change scores and BDI change scores, respectively (Δ score = baseline score – end of treatment score). Baseline BAI or BDI score was entered at step 1, HRV

was entered at step 2, and the interaction between baseline BAI or BDI score and HRV was entered at step 3. Results from the hierarchical analysis are presented in Tables 2 and 3. Contrary to the hypothesis that pre-treatment HRV would predict amelioration of anxiety and depression symptoms over the course of treatment, basal levels of HRV were not associated with change in either anxiety or depression through the course of treatment (all $p > .05$). However, the interactions between basal BAI scores and HRV indices were significant. Plots of the slopes of these interactions revealed that women with higher baseline HRV and greater anxiety showed greater reductions in anxiety through the course of treatment compared to women with lower baseline HRV and higher pre-treatment BAI scores (Figures 1-3). Because of an insufficient sample size to test a three-way interaction, resulting from participant attrition, hypothesis 4 (cluster-B PD [cluster-B SCID-II screener scores] will moderate the relationship between pre-treatment HRV and change in BAI and BDI scores) was not tested.

Discussion

The present study investigated the relationship between measures of HRV hypothesized to reflect neurocardiac communication processes that influence affect regulation, and AD treatment outcome. Specifically, it investigated the utility of baseline HRV for predicting AD treatment response, while also seeking to characterize the relationship between pretreatment anxiety, depression, personality disorder symptomology, and HRV in a sample of women engaged in a 12-week clinical trial of CBT tailored for women with AD. Pretreatment HRV was associated with depression, and PD symptomology, as evinced by moderate to strong correlations between indices of HRV, BDI scores, and SCID-II screener scores. Pretreatment HRV was not significantly associated with baseline anxiety, nor did HRV directly predict treatment response, however, pre-treatment HRV appeared to be an important moderator of total change in anxiety through the course of AD treatment.

Given that affect dysregulation is an important concomitant factor attributing to AD pathology (Cheetham et al., 2010), this investigation first sought to characterize the relationships of anxiety and depression with HRV. To date, the relationship between HRV and depression has been better elucidated than the relationship between HRV and anxiety. Depression tends to be positively associated with HR and negatively associated with HRV. This relationship is generally ascribed to impaired vagal tone in individuals with depression, as evinced by indices that capture parasympathetic vagal activity such as pNN50, and Hf HRV (Agelink et al., 2002; Udupa et al., 2007). The present results are generally concordant with previous work, indicating women with co-occurring AD and depressive symptomology present similarly, in this respect, to individuals with depression alone. In the present sample, pNN50 which primarily captures parasympathetic

autonomic cardiac modulation mediated by the vagus nerve (Hedman, Hartikainen, Tahvanainen, & Hakumaki, 1995) was negatively associated with BDI scores, while Hf HRV trended in the same direction. On the other hand, Lf HRV, which captures both parasympathetic and sympathetic baroreflex activity (Lombardi, Malliani, Pagani, & Cerutti, 1996; Task-Force, 1996) evinced no association whatsoever. Further, BDI scores were negatively associated with Rmssd, a measure thought to gauge general neurocardiac activity associated with autonomic regulation. These findings are consistent with Porges' polyvagal theory (Porges, 2001), which posits that individuals' ability to regulate affect is determined in part by psychophysiological processes, in particular, their vagally mediated capacity to suppress sympathetic influence on the heart.

There are two sources of vagal efference on the heart, one emanating from the nucleus ambiguus, which also regulates cranial and facial muscles related to social engagement and non-verbal communication, and the other originating from the dorsal motor nucleus at the floor of the fourth ventricle (Simon & Mertens, 2009). Polyvagal theory provides an explicit neurobiological model of how difficulties in affect regulation, such as those experienced during depressive states, are linked to regulation of the heart and, reciprocally, how poor affect regulation may in turn serve as a regulator of physiological activity (Porges, 2003; Reed, Porges, & Newlin, 1999). As such, polyvagal theory offers a neurobiological explanation of many of the symptoms associated with depression including social withdrawal, blunted facial affect, digestive problems and reduced HRV.

Counter to our findings for depression and HRV, pre-treatment levels of anxiety, measured by total BAI score, were not associated significantly with any index of HRV. This result

may be related to sample characteristics. That is, the majority of women in the present sample exhibited sub-clinical levels of anxiety, as measured by the BAI. In addition, the literature on anxiety and HRV is somewhat mixed. In some instances, specific types of anxiety symptoms have been shown to be negatively associated with HRV (McCraty, Atkinson, Tomasino, & Stuppy, 2001; Miu, Heilman, & Miclea, 2009), while no relationship was found in another study that used a very broad anxiety criteria (Licht, de Geus, van Dyck, & Penninx, 2009). This disparity, thus, may be due to differences in sample characteristics between studies, representing a range of anxiety disorder subtypes, which the BAI is not able to characterize. It is, therefore, possible that in the present study, any association between anxiety and HRV was washed out by the heterogeneity of anxiety subtypes in the sample.

This investigation also hypothesized that pre-treatment HRV would predict AD treatment response, as gauged by total change in anxiety and depression over the course of treatment. There was, however, no direct relationship between these measures, although pre-treatment BAI and BDI scores were highly correlated with BAI and BDI change scores, respectively. With this in mind, the extent to which HRV might moderate this relationship was examined. While HRV did not moderate the relationship on indices of depression, it did moderate the relationship for anxiety. More specifically, greater reduction in anxiety through the course of AD treatment was predicted by higher basal anxiety, only when this high basal anxiety co-occurred with high SDNN, Hf HRV and Lf HRV.

It is possible that these measurements of HRV may be detecting distinct anxiety subtypes not captured by the BAI instrument. More specifically, among participants in the sample who reported higher levels of anxiety, there may be a subset who are experiencing primarily

physiologically mediated anxiety, which is co-occurring with poorer HRV. It is also possible that the indices of HRV are reflecting greater anxiety severity that is not being captured by the BAI instrument. As a result these women may be slower, or less likely to respond to AD treatment. As such, it could be speculated that high anxiety concomitant with low HRV may be an indicator for a higher level, or alternative kind of care, for individuals seeking treatment for alcohol use disorders.

Due to the high incidence of AD in individuals with cluster-B PDs (Grant et al., 2004), we also sought to characterize the relationship between cluster-B PD and basal levels of HRV. However, because of the low number of PD diagnoses in the sample, this association could not be directly tested. As an alternative, the total number of cluster-B items endorsed was used in lieu of categorical PD diagnoses. This approach was supported by previous research demonstrating that SCID-II screener scores offer a reliable and well-validated measure of PD symptomology and concomitant problems (Jane et al., 2006; Zanarini et al., 2000). Further, this symptom-based approach may be informative to future research because it is consistent with the pending DSM-5's shift to a hybrid dimensional-categorical diagnostic approach (APA, 2012). Though cluster-B PDs, which represent the dramatic, emotional and erratic PDs, are frequently associated with depression (Grant et al., 2005), they most often co-occur with anxiety (Coid, Yang, Tyrer, Roberts, & Ullrich, 2006). Cluster-B screener scores in the present sample of women with AD were associated with anxiety, but not depression.

It was anticipated that cluster-B SCID-II screener scores would be positively associated with HR, and negatively associated with measures of HRV, given that emotional instability and dysregulation represent a core feature of cluster-B PDs. In line with this prediction, higher

cluster-B screener scores predicted lower HRV, specifically on the measures SDNN, Lf HRV and Vlf HRV, while HR trended toward a positive association. This is believed to be the first study to assess the relationship between dimensionally measured PD symptomology and HRV in a clinical population. Several previous investigations, however, have investigated the relationship between cluster-B PD diagnosis and HRV. For instance, both Kuo and Linehan (2009) and Weinberg et al. (2009) found that, compared to healthy controls, participants with borderline personality disorder exhibited significantly lower basal levels of respiratory sinus arrhythmia (as measured by Hf HRV), while Austin and colleagues (2007) found a similar but non-significant effect.

The present results are generally concordant with Kuo and Linehan (2009), and Weinberg et al.'s (2009) findings. From the perspective of polyvagal theory, emotional impairment in cluster-B PD may be explained by an increased sensitivity to perceived threat (Porges, 2004). This increased sensitivity is reflected in decreased vagal tone and results in an inability to appropriately engage or disengage defense systems (Weinberg et al., 2009), potentially resulting in heightened anxiety, adoption of aberrant affective coping behaviors such as alcohol use, and thus heightened risk for AD. The aforementioned studies, however, did not consider Lf HRV, which captures both parasympathetic and sympathetic autonomic activity, and to a large degree reflects the action of the baroreflex (Rahman, Pechnik, Gross, Sewell, & Goldstein, 2011; Task-Force, 1996). The robust inverse association between cluster-B screener scores and Lf and Vlf HRV in this investigation is, therefore, of particular interest.

The negative relationship between Lf HRV, Vlf HRV and cluster-B symptomology suggests poor baroreflex sensitivity in participants with greater cluster-B symptomology. Although causality cannot be established in the context of this study, it is possible that poor baroreflex

sensitivity is contributing to affective and emotional dysregulation in these women, by impairing their ability to effect fine grained, moment-to-moment changes in brain blood perfusion, a biological function largely mediated by blood pressure that is critical for effective cognitive functioning (Duschek & Schandry, 2007; Waldstein, Giggey, Thayer, & Zonderman, 2005). It is possible that individuals expressing cluster-B symptomology are experiencing physiological dysregulation that goes beyond vagal withdrawal, and extends to systems such as the baroreflex, which helps regulate heart rate and blood pressure, and thus blood perfusion in the brain. This postulate is supported by the observation that poor blood pressure regulation adversely affects cognition (Duschek & Schandry, 2007; Glynn et al., 1999), and is associated with negative affect (Jorgensen, Johnson, Kolodziej, & Schreer, 1996) and dementias characterized by affective and emotional instability (Skoog et al., 1996). As such, it is possible that in individuals suffering from cluster-B PDs, challenges regulating affect may at least be partly explained by an impaired ability to finely modulate brain hemodynamics. If this is the case, it may represent a long sought after biological mediator of cluster-B PD pathology, and could provide preliminary physiological evidence for a biological component of cluster-B PD etiology.

The association between HRV and total SCID-II screener scores was also investigated in order to more fully characterize the relationship between HRV and PD symptomology in women with alcohol use disorders. At their core, all PDs are characterized by some degree of emotional and behavioral dysregulation (Livesley, Jang, & Vernon, 1998), even though they may be outwardly expressed in divergent phenotypes. It was, therefore, anticipated that total SCID-II screener scores would be correlated with general dysregulation in the autonomic nervous system, and thus indices of HRV, though no a priori hypothesis was put forward. Results support this

postulate. Total SCID-II screener scores were positively associated with HR and negatively associated with SDNN, Rmssd, pNN50, and Lf HRV, while Hf HRV trended in the same direction. As with cluster-B scores, the association for Lf HRV was particularly robust. It is possible that the low-frequency band is capturing autonomic dysregulation that is pervasive across PDs, a phenomenon that may be a symptom of, or a mediator of the neurobiological component of PD pathology. There was, however, no relationship between Vlf HRV and total SCID-II screener scores. It could be speculated that impaired sympathetically mediated baroreflex control of vascular tone may be a characteristic of the dramatic, emotional and erratic PDs in cluster-B, but not cluster-A (odd or eccentric disorders) or cluster-C (anxious or fearful disorders) PDs.

There were several limitations in the present study that should be considered in interpreting the results. Because participants in the parent study self-selected to participate in the psychophysiological testing as an additional research component, they may have differed in unknown ways from the treatment sample at large. Due to its longitudinal design, patient attrition, which is typical in AD treatment studies, resulted in a reduced sample size in the prospective tests of the relationship between pre-treatment HRV, and the amelioration of anxiety and depressive symptoms through the course of treatment. The resulting loss of power may have contributed to the null findings for main effects in hierarchical regression models, and may have limited our ability to detect interactions. In addition, this study was not sufficiently powered to take into account the variety of co-occurring physical and psychological disorders of women in the sample, and their medication status. Thus, while the results may generalize to real-world samples of women in treatment for AD, the influence of hypertensive and other medications on the relations found in this study is unknown. Further, due to the relative absence of women

meeting full diagnostic criteria for PD in the sample, SCID-II screener scores were used to characterize PD symptomology, therefore, the findings herein may not generalize to women meeting full diagnostic criteria for PDs. Future research should investigate the present findings in individuals with more severe PD pathology, as well as in larger samples representing both sexes. Finally, although anxiety and depression symptoms were assessed weekly during 12 weeks of treatment, the current sample was too small to model trajectories of intra-individual change in affect across the course of treatment. Future studies with larger sample sizes will be useful in quantifying person-centered change trajectories that may be more informative than the pre-treatment to post-treatment change scores used in this study.

Despite these caveats, this investigation was useful in representing a novel foray into the search for AD treatment moderators in the autonomic nervous system, while investigating the association between HRV and a subset of psychopathologies associated with poor affect regulation. The dearth of research into autonomic processes associated with such pathologies may be due, in part, to the perceived complexity and cost of measuring these phenomena. Self-reported psychosocial measures are efficient to deploy in large samples and diverse environments, are cost-efficient, and typically do not require specialized skills or equipment to administer, while studying non-conscious processes can require sophisticated technology such as fMRI. Such methods must be implemented in relatively small samples, are constrained to high-technology environments, are costly, and involve substantial participant and investigator burden. These considerations highlight the need for innovative methods that bridge the neurobiological and behavioral levels of response, yet may be employed broadly in psychosocial and behavioral research and treatment to capture regulatory systems that are not cognitively accessible. As well as

lending itself to such considerations, the cardiovascular system is a central component of autonomic regulation (Thayer & Lane, 2009).

Further, the cardiovascular system can be studied non-invasively and its activity may be quantified using well-established standardized indices. These measures do not require self-report and can, therefore, provide an unbiased assessment of an important substrate that gives rise to a biobehavioral process known to be involved in the regulation of affect. Not only is the assessment procedure relatively straightforward and inexpensive, HRV is measured using electrocardiogram (ECG) equipment ubiquitous to health care settings, from hospitals to doctors' offices. Moreover, handheld HRV monitoring equipment is widely available and simple to use, making it accessible to clinical psychologists and psychiatrists in private practices and small clinics. The relative ease of recording HRV, and the potential insights it may add to patient assessment, as suggested by the present findings, indicate this measure is ripe for further investigation, and ultimately may have broad clinical utility.

Should future research replicate and extend the present findings, it may provide the impetus for the investigation of interventions directed at improving HRV, as an adjunct to traditional CBT, such as heart rate variability biofeedback, which uses paced breathing to increase baroreflex gain and effect chronic increases in HRV. Such interventions may be particularly useful in populations suffering from high anxiety and low HRV, who have been shown here to be poorer responders to conventional AD CBT based treatment. In addition, such interventions may also be effective for people suffering symptomology characteristic of disorders of affect regulation, such as cluster-B pathology, who have been shown here to have lower HRV than individuals without such symptomology. Rather than attempting to ameliorate these

conditions solely by effecting cognitive change, we may attempt to concurrently treat these disorders physiologically, that is, by effecting change in the autonomic nervous system.

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Tables

Table 1. Pearson's correlation coefficients between Beck Anxiety and Depression Inventory scores, SCID-II screener scores and indices of heart rate variability (2-tailed).

	Baseline BAI	Baseline BDI	Total SCID-II	Total Cluster-B	HR Mean	SDNN	Rmssd	pNN50	Hf HRV	Lf HRV
Baseline BAI										
Baseline BDI	.67**									
Total SCID-II	.32*	.39**								
Total Cluster-B	.33*	.24	.83**							
HR Mean	.13	.28*	.30*	.28*						
SDNN	–.09	–.21	–.31*	–.35**	–.79**					
Rmssd	–.16	–.36**	–.30*	–.26	–.76**	.90**				
pNN50	–.09	–.32*	–.30*	–.26	–.66**	.75**	.86**			
Hf HRV	–.12	–.28*	–.28*	–.27	–.80**	.91**	.92**	.80**		
Lf HRV	–.01	–.20	–.34**	–.38**	–.66**	.85**	.69**	.59**	.75**	
VLf HRV	.01	–.06	–.19	–.32**	–.70**	.80**	.65**	.50**	.71**	.76**

Notes. All data log transformed (n= 47), ** $p \leq .01$, * $p \leq .05$

BAI= Beck Anxiety Inventory, BDI= Beck Depression Inventory, HR= heart rate, SDNN= standard deviation of normal-to-normal intervals, Rmssd= square root of the mean squared difference of successive normal-to-normal intervals, pNN50= percent of normal-to-normal intervals greater than 50ms, Hf HRV= high frequency range of the power spectral analysis, Lf HRV= low frequency range of the power spectral analysis, Vlf HRV= very low frequency range of the power spectral analysis

Table 2. Hierarchical regression analysis of the effect of baseline BAI, neurocardiac function, and their interaction on BAI change score during treatment (*n*= 35).

Beck Anxiety Inventory Change Scores		β	ΔR^2	*P*
Mean Heart Rate				
Step 1	Baseline BAI	.594	.353	<.001
Step 2	Heart Rate	–.010	.000	.946
Step 3	Baseline BAI x Heart Rate	1.27	.001	.801
SDNN				
Step 1	Baseline BAI	.594	.353	<.001
Step 2	SDNN	.178	.030	.232
Step 3	**Baseline BAI x SDNN**	**2.06**	**.086**	**.036**
Rmssd				
Step 1	Baseline BAI	.594	.353	<.001
Step 2	Rmssd	.161	.025	.269
Step 3	Baseline BAI x Rmssd	1.02	.041	.154
pNN50				
Step 1	Baseline BAI	.594	.353	<.001
Step 2	pNN50	.039	.001	.791
Step 3	Baseline BAI x pNN50	.578	.036	.196
Hf HRV				
Step 1	Baseline BAI	.594	.353	<.001
Step 2	Hf HRV	.213	.045	.140
Step 3	**Baseline BAI x Hf HRV**	**1.55**	**.091**	**.028**
Lf HRV				
Step 1	Baseline BAI	.594	.353	<.001
Step 2	Lf HRV	.150	.021	.319
Step 3	**Baseline BAI x Lf HRV**	**.706**	**.115**	**.015**

Vlf HRV				
Step 1	Baseline BAI	.594	.353	<.001
Step 2	Vlf HRV	.171	.028	.243
Step 3	Baseline BAI x Vlf HRV	1.24	.034	.196

BAI= Beck Anxiety Inventory, HR= heart rate, SDNN= standard deviation of normal-to-normal intervals, Rmssd= square root of the mean squared difference of successive normal-to-normal intervals, pNN50= percent of normal-to-normal intervals greater than 50ms, Hf HRV= high frequency range of the power spectral analysis, Lf HRV= low frequency range of the power spectral analysis, Vlf HRV= very low frequency range of the power spectral analysis

Table 3. Hierarchical regression analysis of the effect of baseline BDI, HRV, and their interaction on BDI change score during treatment (*n*= 35).

Beck Depression Inventory Change Scores		β	ΔR^2	*P*
Mean Heart Rate				
Step 1	Baseline BDI	.613	.376	<.001
Step 2	Heart Rate	.081	.006	.583
Step 3	Baseline BDI x Heart Rate	3.48	.019	.338
SDNN				
Step 1	Baseline BDI	.613	.376	<.001
Step 2	SDNN	.048	.002	.740
Step 3	Baseline BDI x SDNN	.210	.001	.844
Rmssd				
Step 1	Baseline BDI	.613	.376	<.001
Step 2	Rmssd	–.019	.000	.898
Step 3	Baseline BDI x Rmssd	–.347	.005	.626
pNN50				
Step 1	Baseline BDI	.613	.376	<.001
Step 2	pNN50	.003	.000	.982
Step 3	Baseline BDI x pNN50	–.380	.011	.478
Hf HRV				
Step 1	Baseline BDI	.613	.376	<.001
Step 2	Hf HRV	.132	.017	.363
Step 3	Baseline BDI x Hf HRV	.155	.001	.827
Lf HRV				
Step 1	Baseline BDI	.613	.376	<.001
Step 2	Lf HRV	.104	.011	.466
Step 3	Baseline BDI x Lf HRV	.601	.011	.464

Vlf HRV				
Step 1	Baseline BDI	.613	.376	<.001
Step 2	Vlf HRV	.074	.005	.606
Step 3	Baseline BDI x Vlf HRV	.377	.003	.464

BDI= Beck Depression Inventory, HR= heart rate, SDNN= standard deviation of normal-to-normal intervals, Rmssd= square root of the mean squared difference of successive normal-to-normal intervals, pNN50= percent of normal-to-normal intervals greater than 50ms, Hf HRV= high frequency range of the power spectral analysis, Lf HRV= low frequency range of the power spectral analysis, Vlf HRV= very low frequency range of the power spectral analysis

Figures

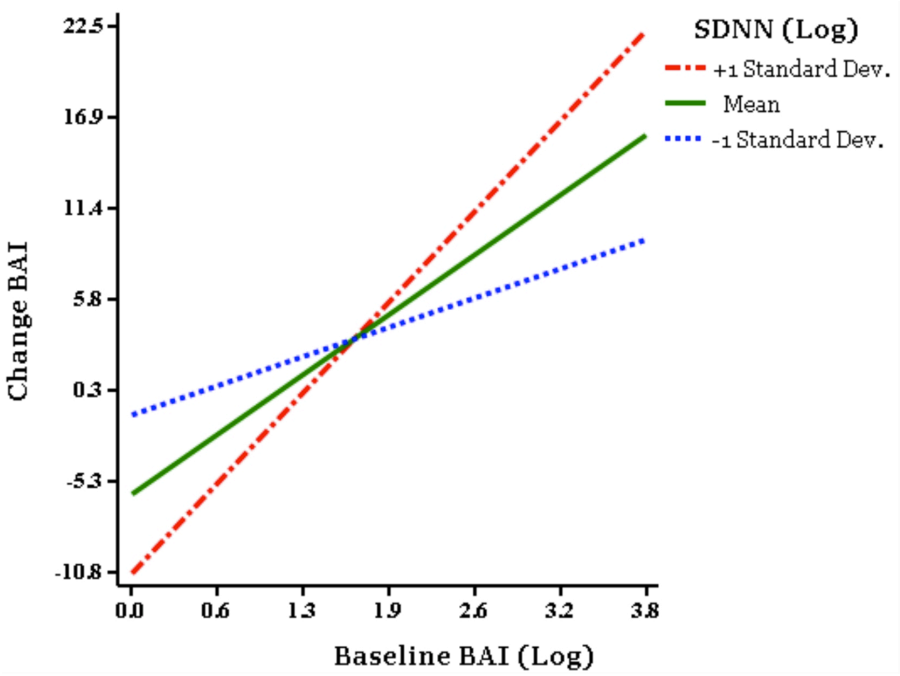

Figure 1. Basal SDNN (standard deviation of normal-to-normal intervals) moderated change in BAI (Beck Anxiety Inventory) scores over the course of treatment. BAI change score is plotted as a function of baseline BAA score separately for mean level of SDNN, compared to +1 and –1 standard deviation from the mean SDNN score.

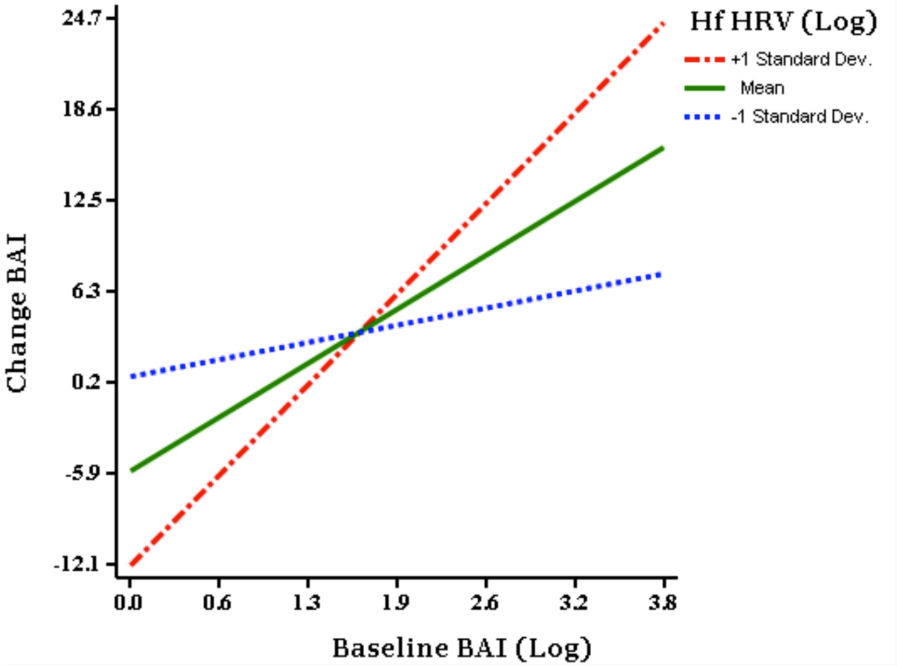

Figure 2. Basal Hf HRV (high frequency heart rate variability) moderated change in BAI (Beck Anxiety Inventory) scores over the course of treatment. BAI change score is plotted as a function of baseline BAA score separately for mean level of Hf HRV, compared to +1 and –1 standard deviation from the mean Hf HRV score.

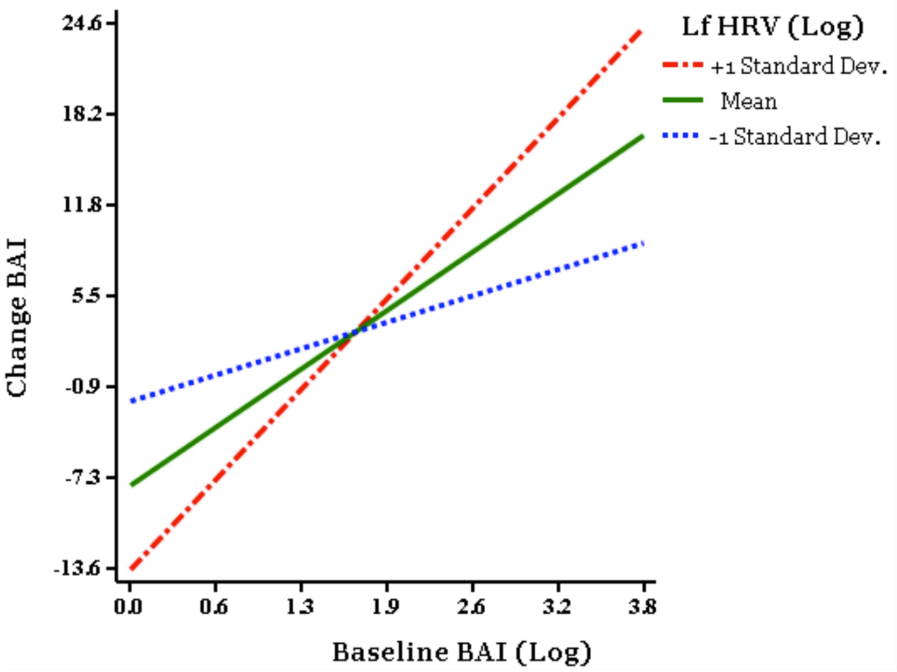

Figure 3. Basal Lf HRV (low frequency heart rate variability) moderated change in BAI (Beck Anxiety Inventory) scores over the course of treatment. BAI change score is plotted as a function of baseline BAA score separately for mean level of Lf HRV, compared to +1 and –1 standard deviation from the mean Lf HRV score.