HEART RATE VARIABILITY BIOFEEDBACK IN THE TREATMENT OF MAJOR DEPRESSION

A DISSERTATION

SUBMITTED TO THE FACULTY

OF

THE GRADUATE SCHOOL OF APPLIED AND PROFESSIONAL PSYCHOLOGY

OF

RUTGERS,

THE STATE UNIVERSITY OF NEW JERSEY

BY

NASYA BRENDA BREACH

IN PARTIAL FULFILLMENT OF THE

REQUIREMENTS FOR THE DEGREE

OF

DOCTOR OF PSYCHOLOGY

NEW BRUNSWICK, NEW JERSEY OCTOBER 2012

APPROVED: _____
Maria Katsamanis, Psy.D.

_____
Donald Morgan, Psy.D.

DEAN: _____
Stanley Messer, Ph.D.

Copyright 2012 by Nasya Breach

ABSTRACT

Major depressive disorder is the most common mood disorder and is one of the most burdensome and disabling diseases in the world. Prevailing approaches to treating depression have a number of significant limitations and drawbacks. Consequently, alternative and adjunctive treatments for depression are being increasingly explored. The role of autonomic nervous system functioning in the etiology of depression has been examined, and depression has been found to be associated with sympathetic predominance and parasympathetic impairment. This decreased parasympathetic modulation has been attributed to impaired activity of the vagus nerve, as indexed by attenuated heart rate variability (HRV) at the respiratory frequency. Areas of the brain that are involved in emotion regulation influence vagus nerve functioning. HRV biofeedback has been shown to be a modality through which individuals can learn to increase the amplitude of their HRV oscillations by breathing at specific rates. Through HRV biofeedback, the vagus nerve is thought to be stimulated in such a way that promotes autonomic balance and improved emotion regulation. Previous research suggests that HRV biofeedback may significantly reduce depression symptoms. The current study was a preliminary efficacy, randomized controlled trial that intended to follow-up an open label pilot study previously conducted by this lab, which found HRV biofeedback to be effective at significantly reducing depressive symptoms. The primary goal was to evaluate the efficacy of a HRV biofeedback protocol by comparing it to a sham control protocol with similar demand characteristics. The study also sought to evaluate the feasibility, tolerability and effectiveness of this placebo. Eleven participants were recruited from the UMDNJ-University Behavioral Health Care population and

surrounding communities, and were randomized to a treatment group, receiving ten weeks of HRV biofeedback training and home practice, or a control group, receiving ten weeks of sham respiratory biofeedback training and home practice. Primary outcome measures were the HAMD and the BDI-II—assessed at baseline, week four, week seven, and week ten. Results indicated no significant differences in depression symptom improvement between groups, although significant main effects for time were observed for both groups ($p<.05$). Results did, however, support the utility, feasibility, and tolerability of the credible sham respiratory control protocol.

ACKNOWLEDGMENTS

First and foremost I would like to thank my beautiful mother, Camilla, my dear brother, Jeshurun, my grandfather, Cabell Turner, my late grandmothers, Shirley Turner and Eunice Breach, and the rest of my family for their undying and unconditional love, support, encouragement, and sacrifice, as well as their continual inspiration. Through all of my endeavors and accomplishments, I stand humbly upon their shoulders. I am ever grateful for Dr. Maria Katsamanis having guided me over the past 6 years with her generous spirit, knowledge, passion and compassion. The completion of the data analysis portion of my dissertation would not have been possible without the generous contributions of Dr. Michael Gara. I must also thank Dr. Paul Lehrer and Dr. Donald Morgan for having accommodated and encouraged my interest in mind-body modalities as a wide-eyed first-year graduate student. Finally, I would like to thank all of my awesome childhood, college, Rutgers, internship, and GSAPP friends for all of the levity and laughter they shared that helped sustain me throughout my graduate career.

TABLE OF CONTENTS

PAGE

ABSTRACT....ii

ACKNOWLEDGEMENTS....iv

LIST OF TABLES....viii

CHAPTER

I. INTRODUCTION AND REVIEW OF THE LITERATURE....1

Statement of the Problem....1

Depression Classification and Symptoms....2

Prevailing Theories of Depression Etiology....4

Negative Self Complexity: A Proposed Moderator of Depression....5

Current Treatments for Depression....7

Limitations of Current Treatments....9

Autonomic Functioning and Emotion Regulation....11

Autonomic Dysregulation and Depression....13

Cardiac Morbidity and Depression....14

HRV Anatomy and Phyisology....15

RSA: Origins and Biobehavioral Functions....17

HRV/RSA and Depression: Studies....20

HRV Biofeedback: General Applications....21

HRV Biofeedback and Depression: Extant Research....25

Current Study: Goals and Hypotheses....28

II. METHODS 31
Participants 31
Location 31
Recruitment Procedures 31
Inclusion and Exclusion Criteria 32
Demographic Characteristics of the Sample 33
Protection of Human Participation 33
Documentation 37
Telephone Screening 37
In-Person Screening and Baseline Assessment 38
Group Assignment 39
HRV Biofeedback Condition 40
Control Condition 42
Follow-up Session 43
Biofeedback Data Collection Procedure 44
Equipment 44
Primary Outcome Measures 45
Exploratory Outcome Measures 45
Statistical Analysis 47
III. RESULTS 49
Sample Characteristics 49

Group Equivalence at Baseline 49
Baseline Analysis 52
Negative Self Complexity: A Proposed Moderator of Depression 57
Main Analysis of Outcome Measures 57
Exploratory Analyses 60
IV. DISCUSSION 62
Biofeedback and Depression 62
Biofeedback and Anxiety, and Functional Health and Wellbeing 65
Negative Self-Complexity and Depression 65
Credibility, Expectancy & the Feasibility of the Sham Control 66
Limitations of Current Study 68
Recommendations for Future Directions 70
Summary/Conclusions 71
REFERENCES 72
APPENDICES 95

LIST OF TABLES

Table 1 Summary of Demographic Variables at Baseline 33

Table 2 Timeline for Measures and Procedures 39

Table 3 Group Equivalence at Baseline for Outcome Measures 49

Table 3.A Group Equivalence at Baseline for Demographic Variables 51

Table 4 Means and Standard Deviations of Outcome Measures 53

Table 5 2x4 Repeated Measures ANOVA for Outcome Measures 57

CHAPTER I

Introduction and Review of Literature

Burden and Cost of Depression/Statement of the Problem

Depression, which has been with humanity since ancient times, is currently ranked as one of the world's most burdensome and disabling diseases (Luppa, et al., 2007; Regler, et al., 1998). The profound emotional, and often physical, discomfort experienced by those suffering with depression causes functional impairment that has significant consequences (Donohue and Pincus, 2007). In fact, those with major depressive disorder (MDD) often experience as much or more limitations in multiple aspects of their well-being and daily functioning as is associated with most medical conditions- including hypertension and diabetes (Berto, et al., 2000). This is because depressed individuals often experience significantly more pain, physical illness and impairment in social and role functioning than most individuals seen in the general medical setting (APA, 2000).

Depression affects physical health by negatively impacting health behaviors and medical compliance, and can lead to changes in the functioning of the central nervous, immune, endocrine, and cardiovascular systems (Kiecolt-Glaser and Glaser, 2002). It is projected that by the year 2020 depressive disorders will rank second in terms of disability-adjusted-life years (Murray and Lopez ,1996). Social and role functioning is impaired as a result of the loss of interest in normal activities and diminished motivation to engage in work and social activities typically experienced by those with MDD (APA, 1994).

Yet the gravest consequence of depression is suicide. The high incidence of mortality associated with MDD is due to a suicide rate that is estimated to be as much as 15%, or about one out of seven people (Fawcett, 1987). Suicides attributable to depression are believed to account for approximately 60% of the total suicide rate (about 16,111 suicides per year) (Berto, et al., 2000).

Depression has a profound and wide-reaching impact on society as well, as it imposes a significant burden on industrialized countries both with regards to the medical resources used to treat it and in terms of production losses (Berto, et al., 2000; Donohue and Pincus, 2007). Due to work absenteeism, early retirement and premature mortality, depression is the leading cause of reduced productivity (Berto, et al., 2000; Donohue and Pincus, 2007). Productivity losses can exceed a thousand dollars in cost per individual and the total economic cost of depression in the United States was measured at $US82.1 billion in 2000- 62% of which being workplace costs (Donohue and Pincus, 2007; Luppa et al., 2007). Depression also leads to higher healthcare utilization and spending, most of which is not the result of depression treatment costs (Donohue and Pincus, 2007).

Thus, the individual and societal burden of depression cannot be overstated, and for this reason the development of effective treatments for the condition is of the utmost relevance.

Depression Classification and Symptoms

Major depression is the most common mood disorder, and the clinical course of MDD is generally characterized by one or more major depressive episodes (MDE) (APA, 2000). The essential features of an MDE are depressed mood and/or loss of pleasure, experienced for at least a two-week period (APA, 2000). Other associated features

include neuro-vegetative (i.e. psychomotor agitation or retardation, sleep disturbances, and significant weight changes), somatic (i.e. fatigue, muscle aches) and psychological (i.e difficulty concentrating, feelings of worthlessness and guilt, hopelessness, and thoughts of death) signs and symptoms (APA, 2000). A diagnosis of MDD is made when the above symptoms result in clinically significant levels of distress and/or interference in social, occupational, or other meaningful areas of functioning (APA, 2000).

MDD has the highest lifetime prevalence among all psychiatric disorders (Kessler, et al., 2005), and often presents comorbidly with a variety of other mental disorders, including anxiety disorders, eating disorders, borderline personality disorder, and substance-related disorders (APA, 2000). It usually appears over days or weeks, but it can erupt in a day or evolve over months or years. While some depressive episodes arise 'out of the blue', others emerge after a precipitant (i.e. negative life event) (Maxmen & Ward, 1995). If left untreated, MDD usually persists for three to nine months (Maxmen & Ward, 1995). Although roughly half of all patients with MDD never have another episode, recurrence is a major problem for many individuals suffering from depression (Barlow, 2007; Ramana, et al., 1995). Recurrent rates are greatest during the first four to six months after recovery; thereafter, the further away from the episode, the lower the chance of a recurrence (Maxmen & Ward, 1995). Of those having a recurrence, 22% are depressed for over a year, especially if they delay getting treatment, are elderly, poor, or experienced a longer prior depressive episode (Maxmen & Ward, 1995).

Prevailing Theories of Depression Etiology

Psychodynamic Theory of Depression Etiology. In the classic psychoanalytic tradition, it is thought that depression arises from early childhood experiences of object (i.e., caregiver) loss, wherein the individual directs her rage and disappointment felt towards the lost object inward onto the self (Freud, 1957). Contemporary psychodynamic theory integrates elements from this perspective with ego, object relations, and self psychology traditions, and views depression as potentially arising from, among other things: damaged self esteem, dysfunction in patient's sense of self originating from lack of meaningful self-object experiences (i.e., experiences with caregivers that are crucial to normal functioning), early attachment experiences that were lacking or traumatizing, and early childhood experiences or perceptions of rejection and inadequacy (Strupp, et al., 1982).

Cognitive-Behavior Theory of Depression Etiology. In the cognitive-behavioral theory of depression set forth by Beck (1967), depression develops from maladaptive cognitive schemas—which are stable, enduring, dysfunctional, and negatively biased thought patterns that develop in early childhood (Beck, 1967; Beck, et al., 1979). For depressed individuals, these schemas become reactivated by life events that are similar to the contexts under which the negative thought patterns originally developed. This results in the narrowing of the individual's field of awareness, wherein negative aspects of the self and negative experiences are most salient (Beck, 1967; Beck, et al., 1979; Fennell, 2004). The CBT perspective on depression emphasizes the cognitive triad: depressed people are prone to maintaining negatively distorted views of themselves, their environment, and the future (Beck, 1967; Beck, et al., 1979; Fennell, 2004).

The other prominent cognitive theory of depression is the, now reformulated, learned helplessness theory--which states that individuals who maintain a negative cognitive attributional style (or manner of attributing negative experiences) characterized by the tendency to view the cause of negative events as stable, internal and global, are predisposed to depression (Abramson, et al., 1978; Abramson, et al., 1995).

Interpersonal Theory of Depression Etiology. In the interpersonal psychology school of thought, impoverished social and interpersonal relationships (especially the absence or loss of significant others) in childhood as well as adulthood are believed to predisposed one to developing depression, as adaptability and susceptibility to depression is inextricably related to the quality of one's social bonds, (Weissman, 2007).

Monoamine Theory of Depression Etiology. Research in the field of neuropsychopharmocology suggests that, irrespective of specific psychosocial triggers, it is ultimately deficiencies in cortical monoamine neurotransmitters that lead to depression (Pineyro and Blier, 1999; Schildkraut, 1965). The monoamine theory considers the symptoms clusters of depression to be caused by several different dysfunctional neurobiological pathways, most of which respond to increases in either noradrenaline or serotonin in the brain (Elhwuegi, 2004).

Negative Self-Complexity: A Proposed Moderator/Predictor of Depressive Symptomology

A variety of theories have been proposed about the various biopsychosocial factors thought to contribute to the development of depression. Factors pertaining to the cognitive components of depressive etiology (i.e., namely, the *content* of depression-related thoughts about self, other, and the world at large) have been systematically

explored. Relatively fewer attempts, however, have been made to examine the *structural* characteristics of depression (i.e., the quality of organization and interconnectedness between the self constructs that underlie depressogenic thoughts) (Kendall, 1992; Segal, 1988). Efforts to examine these structural properties have focused mainly on the "complexity" of self-appraisal, or self-complexity (Woolfolk, et al., 2004). The concept of self-complexity arises from social-cognitive paradigms that conceptualize the self as "a manifold, dynamic system of constructs—a constellation of cognitive schemas," (Kihlstrom & Cantor, 1984; Salovey & Rodin, 1985; Segal, 1988). Though self-complexity has been conceptualized in a variety of ways (Woolfolk, et al., 2004), Gara et al. (1993) operationalized it as, "the number of distinct classes of self-generated attributes that [are] linked to the self in a hierarchical classes analysis," (Woolfolk, et al., 2004). This definition refers to one of the methods that has been used in self-complexity research to represent an individual's view of herself; responses from structured inventories of a person's self identities are transformed into a matrix which is then analyzed using a statistical procedure termed 'hierarchical classification'—the results of which index the individual's multidimensional 'selves' (Robey, et al., 1989). Self-complexity is comprised of two main independent components: positive self-complexity and negative self-complexity (Woolfolk, et al., 1995)—as negative and positive appraisals of the self have been shown to reflect distinct aspects of self-evaluation (Woolfolk et al., 1995). Various studies have found higher measures of negative self-complexity to be associated with depressive symptoms, and to be predictive of their persistence post-treatment (Gara et al., 1993; Woolfolk et al., 1995; Woolfolk, et al., 1999). As such, negative self-complexity is thought to be a potential hindrance to

optimal recovery from depression (Woolfolk, et al., 1999), and, therefore, a possible moderating factor of major depression treatment outcomes.

Current Treatments for Depression

The past several decades have seen the development of numerous treatment paradigms for depression. For the purposes of this review, however, the sections below will focus on the current prevailing consensual treatment modalities, which are antidepressant medications, cognitive behavioral psychotherapy, interpersonal psychotherapy, and psychodynamic psychotherapy.

Antidepressant Medications. Antidepressant medications (ADM) are the most widely used form of depression treatment in the United States and are the current treatment standard, as recommended by the American Psychiatric Association (APA, 1993; Hollon, et al., 2002). There are several different drug classes used in the treatment of depression, including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), monoamine reuptake inhibitors (MARI's), triiodothyronin (T3), selective seratonin reuptake inhibitors (SSRIs), serotonin-norepinephrnine reuptake inhibitors, and other second-generation antidepressants such as bupropion, nefazodone, and mirtazapine (Little, 2009). Over the past several decades, numerous randomized-controlled trials have evidenced ADM's superior efficacy as compared to placebo in the treatment of depression symptoms (Imel, et al., 2008; Mulrow et al., 1999; U.S. Dept. of Health and Human Services, 1993).

*Cognitive-Behavioral Psychotherapy***.** Of all the many psychotherapeutic paradigms that have been developed and implemented in the treatment of depression, cognitive-behavioral therapy (CBT) has been subject to the most empirical study and, as a result, has garnered the most evidence-based support and clinical application (Barlow,

2007). The literature on the efficacy and effectiveness of CBT suggests that it is often just as effective as ADMs in treating depression, and may, in certain instances be more effective (DeRubeius, et al., 2005; Hollon, et al., 2002). CBT is typically time-limited and structured, with the therapist assuming an active and collaborative role in the therapeutic process. The goals of the CBT approach are to locate and correct negative automatic thoughts and cognitive biases, and to change maladaptive schemas--which, in turn, alleviate the depressive symptoms (Cuijpers, et al., 2007). CBT also incorporates behavioral techniques--such as the scheduling of pleasurable activities--that are meant to target the social withdrawal and anhedonia associated with depression (Barlow, 2007).

Psychodynamic/analytic Psychotherapy. Although there have been limited controlled trials examining its efficacy, psychodynamic therapy is rated as "probably efficacious," with a number of studies having demonstrated its effectiveness, and has been widely applied in clinical practice for decades, (Abbass, et al., 2006; Chambless & Ollendick, 2001; Driessen, et al., 2010). What is thought to be curative in the psychodynamic approach is the emphasis on enhancing the patient's level of insight about repetitive conflicts (interpersonal and intrapsychic) and negative experiences that underlie and sustain the patient's depression symptoms (Maina, 2009). The primary objective of brief dynamic therapy (BDT) is to enhance the patient's insight about repetitive conflicts (intrapsychic and interpersonal) and trauma that underlies and sustain the patient's problems. The principal strategies of psychodynamic psychotherapy for depression include clarification, interpretation, confrontation, and working through (Busch, 2005; Maina, 2009; Karasu, 1990). The therapist also uses the actual relationship with the patient to further the aims of therapy. Therapy may last for years,

or, as is the case with BDT paradigms, can be limited to as few as 16 sessions (Leichsenring, 2001; de Maat, 2008).

Interpersonal Psychotherapy. Interpersonal psychotherapy (IPT) for depression is a brief, manualized psychotherapy approach which focuses on intervening around the interpersonal factors (i.e., abnormal grief, role disputes, interpersonal deficits, role transitions) that cause and maintain the symptoms of depression (Cornes and Frank, 1994). The process of IPT for depression involves rectifying these interpersonal challenges through the learning of new social and communication skills--which is facilitated by the active here-and-now exploration and resolution of maladaptive communication patterns, feelings around loss, and dysfunctional coping strategies (Klerman, et al., 1984). IPT has been found to be equally, if not slightly more, efficacious in treating depression as compared to CBT and psychodynamic psychotherapy (Cuijpers, et al., 2008).

Limitations of Current Treatments

Despite their wide clinical application and the evidence that supports their effectiveness, there are, in fact, several significant limitations and drawbacks to the current treatment paradigms for depression—the most important of which being the existence of significant residual symptoms of depression that persist both during and after depression treatment.

Residual symptoms of depression are symptoms that persist, "despite apparent response or remission," (Fava, 1999). There is a sizable body of literature demonstrating that, even after both psychotherapy and/or pharmacotherapy, most patients still experience a clinically significant degree of depression symptoms (APA, 2000; Berlim, et

al., 2008; Cain, 2007). For example, Ogrodniczuck, et al. (2004), found that 82% of patients who responded successfully to psychotherapy experienced residual symptoms. It has also been estimated that between 50-60% of patients experience residual symptoms following antidepressant treatment (Fava, 2003). Residual symptoms have been associated with relapse and poorer long-term outcomes (Fava, et al., 2002).

Dysfunctional cognitions, irritability, anxiety, and interpersonal friction were all symptoms found to persist after 'recovery' (Brown, 1990; Fava, et al., 1986). Additionally, somatic symptoms, which are a common core feature of MDD (APA, 1995; Vaccarino, 2008), have been associated with response without remission following depression treatment (Vieta, 2008). This is significant because somatic symptoms within the context of depression have been found to be predictive of poorer treatment outcomes (Katona, et al., 2005). This is of particular importance when considering depression treatment in patients from non-Western cultures, where somatization is often the "idiom of distress" as a result of the stigma attached to psychiatric diagnoses and treatment (Kleinman, 1977).

Another limiting aspect of the prevailing depression treatments is the fact that it appears the efficacy of a particular paradigm may be constrained by specific patient characteristics. For example, studies demonstrate that ADMs are often only optimally effective for individuals suffering from very severe depression, whereas individuals with mild to moderate symptoms often experience little symptom relief (Fournier, et al., 2010). With regards to psychotherapy, it has been posited that psychodynamic treatment may tend to be inherently biased to exclude less "verbal, psychological-minded populations", CBT to exclude individuals with cognitive limitations and/or who are less

"sophisticated and introspective", and, in the case of IPT, unmarried, male patients (Karasu, 1990).

Even when effective, a major drawback of ADMs are the unpleasant, and, at times, deleterious side effects, which can include dry mouth, urinary retention, constipation, diarrhea, nausea, vomiting, weight gain, sedation, hypotension, hypertension, and cardiac arrhythmias (Little, 2009). Moreover, certain classes of ADMs have been associated with decreased heart rate variability, which has been shown to be related to cardiac morbidity and mortality (van Zyl, et al., 2008). Heart rate variability and its implications with respect to cardiac health and depression will be discussed at greater length in a subsequent section of the literature review.

An additional disadvantage of both psychotherapy and pharmacotherapy is the cost. Particularly when considering the current recommendation that treatments be combined for optimal effect (Cuijpers, et al., 2010), the cost of traditional depression treatment can become especially prohibitive (Lam, et al., 2002).

Because of the aforementioned shortcomings of the prevailing treatments for depression, the need for and utility of alternative and/or adjunctive depression treatments has been increasingly emphasized and explored in the literature (Manber, et al., 2001; Nemeroff, 2007; Rush, et al., 2004).

Autonomic Functioning and Emotion Regulation

A key factor in biological, emotional, and behavioral functioning is the mutual influence of psychological and physiological processes (Lacey & Lacey, 1978; Oatley & Jenkins, 1992; Porges, 1994). Emotional and behavioral processes often involve a complex system of interacting between nervous, endocrine, immune, respiratory, and

circulatory systems (Grossman, 1992; Krantz & McCeney, 2001; Mandel, 2003). Accordingly, shifts in cognitive, behavioral, and affective responding are often accompanied by corresponding changes is physiology (Grossman, 1992; Oatley & Jenkins, 1992). For example, specific respiratory parameters (i.e. respiratory rate and end tidal CO2) have been shown to reflect alterations in affective states and behavioral demands, such as in the experience of pain, anxiety, and increased mental activity (Bass & Gardner, 1985; Grossman, 1983; Grossman & Sveback, 1987).

The ability of a system to fluidly modulate itself towards balance and homeostasis is considered indicative of physiological and psychological health and resilience (Cox, 1978). One such system is the autonomic nervous system (ANS), which is divided into two branches: the sympathetic nervous systems (SNS) and the parasympathetic nervous system (PNS). The SNS, along with the adrenal glands, control arousal, catabolism (i.e., the breakdown of molecules for energy use), and prepare the body for "flight-or-fight" responding (Sheridan & Radmacher, 1992), whereas the PNS is responsible for anabolism (i.e, the synthesis of molecules for energy storage) and restorative processes (Sheridan & Radmacher, 1992). When dyregulation occurs in the ANS (i.e. immobilization and/or dominance in one branch over the other), homeostatic and adaptive functioning becomes significantly hindered (McEwen, 1998), and can give rise to not only physical, but also psychological dysfunction (Mandel, 2003).

With increased emotional display and impaired ability to regulate affect characterizing many Axis I and Axis II disorder (APA, 2000), mental illnesses, including MDD, are being conceptualized as disorders of emotion regulation (Gross, 1998; Rottenberg, 2007). Indeed, ANS functioning is increasingly being implicated in

psychopathology, and vice versa. There is evidence to support the notion that prenatal and infant social and emotional stressors contribute to the development of life-long ANS response patterns (Cozolino, 2006; Mandel, 2003). Moreover, a number of studies have linked externalizing and internalizing problems (Dietrich, et al., 2007), negative affect, worry (Hoffmann et al., 2005), and disorders such as PTSD (Blechert, et al., 2007), PD (Middleton & Ashby, 1995), and MDD with various physiological indices reflecting reduced autonomic flexibility and ANS dysregulation.

Autonomic Dysregulation and Depression

Depression can impact and be influenced by physical health through multiple physiological pathways (i.e. dysfunction in endocrine, immune, CNS, and cardiovascular systems) (Carney, et al., 1995; Davidson, et al., 2000; Krantz & McCeney, 2001; Miller, 1998). For example, depression has been shown to promote the production of cytokines, which are major immunological factors that can precipitate a cascade of detrimental physiological responses/symptoms (Dantzer, et al., 1999; Leventhal, et al., 1998; Miller, 1998). As the presence of depressive disorders is often accompanied by significant alterations in ANS functioning (Dawson, et al., 1977), it has been hypothesized that these alterations, at least in part, underlie the numerous unfavorable health outcomes among persons suffering from depression (Guinjoan, et al., 1995; Lehofer, et al., 1997; Moser, et al., 1998; Rechlin, et al., 1994; Veith, et al., 1994).

Some of the earliest studies that gave support to the role of ANS dysregulation in depression were those done with medically well patients with MDD (Barnes, et al., 1983; Siever, et al., 1985; Veith, et al., 1994; Wyatt, et al., 1971). Depression has been shown to be associated with sympathetic/adrenergic predominance, parasympathetic

impairment, or both (Guinjoan et al., 1995). This sympathetic hyperarousal has been evidenced to manifest in lower tonic and phasic skin conductance levels (Dawson, et al., 1985), elevated levels of plasma and urinary catecholamines (i.e. norepinephrine, a stress hormone), (Barnes, et al., 1983; Wyatt, et al., 1971;Veith, et al., 1994), exaggerated heart rate responses to stressors (Dawson, et al., 1985; Guinjoan, et al., 1995; Lehofer, et al., 1997), and decreased heart rate variability (HRV) (Carney, et al., 1995; De Guevara, et al., 2004; Horsten, et al., 1999; Kim, et al., 2005; Lahmeyer & Bellur, 1987; Stein, et al., 2000; Van der Kooy, et al., 2006).

Cardiac Morbidity and Depression

The burgeoning level of attention to and illumination of the relationship between depression and autonomic dysfunction has been particularly spurred by the line of research exploring the link between depression and cardiac morbidity and mortality (Grippo and Johnson, 2002; Rabins, et al., 1985).

MDD has been found to be associated with increased risk of cardiac morbidity and mortality in persons both with and without other cardiac risk factors (Carney, et al., 2005; Frasure-Smith, et al., 1993; Frasure-Smith, et al., 1995; Ladwig, et al., 1991; Penninx, et al., 2001). For example, about 20% of individuals that suffer from an acute myocardial infarction (MI) will be prone to developing either depression and/or a related mood disorder (Glassman & Shapiro, 1998). Moreover, such patients are significantly more likely to die 6 months after the event (Frasure-Smith, et al., 1993; Frasure-Smith, et al., 1995; Ladwig, et al., 1991). Furthermore, patients who are medically well have been shown to exhibit cardiac autonomic dysfunction as manifested by lower heart rate variability (HRV) (Carney et al, 2005).

Although the pathophysiology of the bi-directional relationship between cardiovascular disease (CVD) and depression is likely multi-determined (Glassman and Shapiro, 1998), one of several mechanisms that have been proposed to account for this association is autonomic dysregulation in the form of decreased parasympathetic modulation and heightened sympathetic activity (Carney, et al., 2005a; Carney, et al., 1995; Carney, et al., 1988; Careney, et al., 2001; Carney, et al., 2005b).

HRV Anatomy and Physiology

Heart rate variability (HRV) indexes the beat-to-beat changes in heart rate that are normally controlled by membrane activity of the cardiac sinoatrial (SA) node (Burkholder, et al., 1992; Levy & Warner, 1994; Randall, 1994). This activity is modulated by neuronal input from both branches of the ANS: the parasympathetic terminals slow the rate of SA node depolarization (i.e., cell firing) via acetylcholine release onto muscarinic receptors, and sympathetic terminals accelerating the rate of SA node depolarization through the action of norepinephrine binding onto receptors which mediate a second messenger cascade of intercellular signaling (Burkholder, et al., 1992; Levy & Warner, 1994; Randall, 1994).

Normal HRV manifests as a complex pattern of several aggregated frequency components that are usually superimposed upon each other (Berntson, et al., 1997; Vaschillo, et al., 2002). The slowest fluctuations, referred to as ultra-low frequency (ULF), are thought to reflect circadian rhythms; very low frequency oscillations (VLF), occurring between .003 Hz-0.05 Hz (Berntson, et al., 1997; Lehrer, et al., 2000), are sympathetically mediated (Lehrer, et al., 2000), and are thought to reflect regulation of temperature and vascular tone, as well as hormonal and metabolic processes (Cohen, et

al., 1999; Lehrer, et al., 2000); low frequency patterns (LF) occur between .05-.15 Hz (Penaz, 1978; Vaschillo, et al., 2002) and are generally thought to be influenced by both sympathetic and parasympathetic input (Berntson, et al, 1997; Lehrer, et al., 2000), via baroreceptor (blood pressure receptor)-mediated regulation (Pellizzer, et al., 1996); a still higher oscillation band--the most conspicuous of the pattern complex--is referred to as high frequency (HF), occurring approximately between 0.15-0.4 Hz (Berntson, et al., 1997). It is strongly linked to the respiratory cycle through fluctuations in vagal (parasympathetic) innervation (Berntson et al., 1997; Lehrer, et al., 2000). Accordingly, the changes in heart rate that occur within this particular frequency domain are often referred to as "respiratory sinus arrhythmia" (RSA) (Vaschillo, et al., 2002).

Many physiological processes manifest in rhythmic cycles, or oscillatory rhythms--including vascular tone (VT), respiration, and heart rate (HR) (Vaschillo, et al., 2002). It has been suggested that complexity and amplitude of physiological oscillations reflect optimal regulatory and homeostatic capacity of a system in general (Giardino, Lehrer & Feldman, 2000), and that in the cardiovascular system in particular they are indicative of the health and adaptability of autonomic regulation (Bernardi, et al., 1997; Task Force of the European Society of Cardiology and the North American Society of Racing and Electrophysiolog, 1996). As such, HRV measures are often used as prognostic indicators of cardiovascular disease (Bernardi et al., 1997; Task Force of the European Society of Cardiology and the North American Society of Racing and Electrophysiolog., 1996). In the realm of psychophysiology, HRV is increasingly being examined in relation to processes that presently do not lend themselves to direct measurement (i.e. mental effort, attention, and affect regulation) (Kobele, et al., 2010;

Mulder, 1985; Mulder, 1992; Richards & Casey, 1991; Weber, van der Molen, & Molenaar, 1994).

RSA: Origins and Biobehavioral Functions

With compromised PNS activity being one of the primary pathways implicated in cardiac ANS dysfunction and its relation to depression, the role of the vagus nerve—which is a major peripheral afferent and efferent of parasympathetic modulation to the heart-- is of much relevance to these processes.

The vagus nerve is the 10th cranial nerve and its innervations contribute to the regulation of the visceral organs, including the heart (Porges, 1995b). There are two distinct populations of vagal source nuclei that are located in the brainstem (specifically, the medulla)—the ventrally situated nuclei ambiguous (NA) and the dorsal motor nucleus (DMN) (Grossman & Taylor, 2007; Porges, 1995b); thus leading to two different vagus nerve branches (Porges, 1995b, 2001, 2003a, 2007). The Polyvagal Theory, set forth by Porges (Porges, 1995b, 2003a), posits that while the DMN branch, deemed phylogenetically older (Porges, 1995b), is primarily responsible for the innervation of visceral organs that are subdiaphragmatic (Porges, 2003b), the fibers originating from the NA branch—sometimes referred to as the mylenated "smart vagus" (Beauchaine, et al., 2007), which is thought to be unique to mammalian vertebrates (Porges, 2003b)—are uniquely responsible for respiratory sinus arthymia (RSA) (Porges, 2007). The NA fibers also terminate on structures related to communication and emotion (e.g., the facial muscles and the larynx) (Porges, 1995b, 2001, 2003a, 2007).

As previously described, respiratory sinus arrhythmia (RSA) is a cardio-respiratory phenomenon characterized by the rhythmical variation in heart period at the

respiratory frequency (Berntson, et al., 1997; Grossman & Taylor, 2007). RSA is characterized by the shortening of heart period during inspiration and the lengthening of heart period with exhalation (Berntson, et al., 1997; Grossman & Taylor, 2007). Because the neurochemical dynamics of sympathetic innnervation at the SA node are slower than parasympathetic cardiac nerve traffic, RSA is thought to mainly index parasympathetic (vagal) tone (Berntson, et al., 1993; Saul et al., 1991, 1992).

Although other physiological mechanisms can influence RSA (i.e. chemoreceptor and baroreceptor reflexes; local metabolic and mechanical factors), vagal cardiac neural input is the predominant determinant of RSA (Berntson, 1993: Daly, 1985; Davies & Neilson, 1967a, 1967b; Feldman & Ellenberger, 1988; Grossman, 1983; Richter & Spyer, 1990; Saul, et al., 1990; Syper, 1990). RSA oscillations are the result of complex interaction between several central and peripheral (parasympathetic) nervous system parameters, including two functionally-linked, respiratory-driven mechanisms (Daly, 1985): (a) The central respiratory rhythm generator—which derives from dorsal medullary, periambigual medullary and nucleus tractus solitarus structures of the brain stem (Richter & Spyer, 1990)—is capable of maintaining respiratory heart period fluctuations even in the absence of peripheral input (Davies & Nielson, 1967a; Hirsh & Bishop, 1981; Kollai & Mizsei, 1990), and is responsible for phasic excitatory and inhibitory modulation of cardiac vagal motor neurons at the SA node (Richter & Spyer, 1990); (b) Thoracic pulmonary stretch receptor afferents phasically gate vagoexcitatory input to the SA node (Berntson, Cacioppo, & Quigley, 1993) in a manner such that inspiration inhibits vagal motor outflow and exhalation activates vagal motor innervation,

--resulting in increases and decreases in heart rate, respectively (Movius and Allen, 2005).

As RSA thus coordinates breathing and blood flow, it has been theorized that it may function to optimize oxygen/carbon dioxide gas exchange in response to a variety of behavioral demands (Grossman & Taylor, 2007). Porges has hypothesized that RSA is reflective of homeostatic adaptability and the capacity of warm-blooded animals to self-regulate (Porges, 1995b). It has been further suggested that RSA indexes the ability of the CNS to regulate emotional responding and serves as an indicator of individual differences in emotion regulation functioning (Appelhans & Luecken, 2006; Porges, 1995a; Thayer & Lane, 2000). Indeed, much of the recent interest in RSA within the field of psychophysiology is due to its presumed sensitivity to, and influence on, behavioral and cognitive processes (Grossman, 1983; Grossman, et al., 1990; Porges, 1986; Porges, et al., 1982). These postulations are based on the fact that the vagus nerve projections from the nucleus ambiguous are influenced by cortical, sub-cortical, and adjacent brain stem nuclei (i.e. the limbic system, anterior cincgulate cortex, medial and dorsal prefrontal cortex) that are associated with arousal, attention, motion, emotion, and communication (Porges, 1995b; Thayer and Lane 2000; Richter & Spyer, 1990; Rottenberg, 2007). Moreover, due to its anatomical position, the vagus nerve itself coordinates motor pathways that influence primary emotions (i.e. happiness, sadness, anger, fear, etc)--as it affects shifts in the regulation of facial expressions, vocalizations (Ross, Homan, & Buck, 1994), as well as in the capacity to communicate internal states to others (Porges, 1995a, 1995b; Thayer & Lane, 2000).

Thus, by virtue of its anatomical and physiological correlates, there is a general consensus within the literature that RSA magnitude can be considered an indirect index of, among other things, emotion regulation, and thus, psychopathology.

A considerable body of research is mounting that supports this contention. For example, high levels of RSA have been associated with resilience from stress (Fabes & Einsenberg, 1997), the ability to self-soothe (Fox, 1989), social competence (Eisenberg, et al., 1995), and the capacity to cope (Fabes and Eisenberg, 1997); whereas low levels of RSA have been found to correlate with anxiety (Cohen, et al., 2000; Lyonfields, Borkovex, & Thayer, 1995), internalizing and externalizing psychopathology (Pine et al., 1998), hostility (Sloan, et al., 1994), alexithymia (Neumann, et al., 2004), impulse control disorders (Beauchaine, 2001), defensiveness (Movius and Allen, 2005), sadness (Dywan, et al., 2008), and depression (Chambers and Allen, 2002; Rottenberg, 2007).

HRV/RSA and Depression: Studies

As depression seems to involve the same types of social and behavioral deficits that are thought to be characteristic of RSA compromise (Ellgring, 1989; Rottenberg & Gotlib, 2004; Rottenberg, Gross, & Gotlib, 2005), HRV/RSA is increasingly being examined with respect to its relation to MDD.

Thus far, studies investigating the relationship between depression and RSA have yielded somewhat conflicting results (Bar, et al., 2004). For example, while there have been numerous studies that have found a significant associated between depression and reduced RSA in ADM (Balogh, et al., 1993; Nahshoni, et al., 2004; Rechlin, et al., 1994; Tulen, et al., 1996a,b), as well as non-ADM medicated, medically-well (i.e. non-cardiac) depressed patients (Chambers & Allen, 2002), there have been yet other studies that have

found no such relationship (Bar, et al., 2004; Moser, et al., 1998; Yeragani et al., 1991). However, it has been suggested that these inconsistencies are likely a product of several variables, including the heterogeneity of depression itself and the application of different diagnostic criteria (Bar, et al., 2004; Koschke, et al., 2009), relatively small sample sizes (Chambers, et al., 2002), and medication confounds (Kemp, et al., 2010). .

Much of the recent literature has indeed been consistent with the hypothesis of MDD and concomitant RSA attenuation (Kemp, et al., 2010; Koschke, et al., 2009; Licht, et al., 2008; Pichon, et al., 2010; Shea, et al., 2008). For instance, in a meta-analysis conducted by Rottenberg (2007), depressed patients were found to exhibit significantly attenuated RSA levels. Data from an even larger cross-sectional analytic cohort study supported these findings (Licht, et al., 2008). In fact, Nahshoni, et al., (2004), found depressed patients to be virtually indistinguishable from heart transplant recipients--a group exemplifying cardiac autonomic dysfunction--with regards to measures of HRV.

Fortifying the evidence for an association between MDD and RSA even further is the work done by Su, et al., (2009), which demonstrated that RSA and depression share a common genetic pathway--suggesting a linkage between the underlying neurobiological dysregulation of both phenomena.

HRV Biofeedback: General Applications

As reviewed previously, the research shows that current treatment paradigms for MDD are limited in their efficacy. As such, the field of psychophysiology has increasingly explored the utility of what has been termed HRV/RSA biofeedback for the purposes of treating depression.

Biofeedback is the process by which individuals are able to gain voluntary control over, and alter, the level of a physiological process (Lehrer, et al., 2003; Schwartz, 1995), through the use of real-time displayed output of a physiological function (Lehrer, et al., 2003). Over the past several decades various types of biofeedback (i.e. electromyographic (EMG), electrodermal (EDG), thermal) have been employed in the treatment of a wide variety of physical and psychological disorders, including headaches (Blanchard, et al., 1986; Nestoriuc, et al., 2008), essential hypertension (McGrady, 1994), post traumatic stress disorder (Hickling, et al., 1986), and panic disorder with agoraphobia (Goodwin & Montgomery, 2006). Recently, biofeedback researchers have taken interest in training people to increase the amplitude of their RSA oscillations as a method of improving autonomic homeostasis (Gevirtz, 1999; Herbs, Gevirtz, & Jacobs, 1993).

In healthy adults, RSA usually occurs approximately within the 0.15-.5 Hz frequency band, which corresponds to 9-24 breaths/minute (Berntson et al., 1997; Lehrer, et al., 2000). Wilhelm, et al., (2004) found that, under steady-state conditions, there is an inverse relationship between the magnitude of RSA and respiration rate. RSA was also found to be directly related to tidal volume (Wilhelm, et al., 2004). Therefore, whereas slow, deep breathing will generally augment RSA levels, rapid, shallow breathing tends to attenuate RSA (Wilhelm, et al., 2004). Individuals being trained in HRV/RSA biofeedback have consistently been shown to produce higher magnitude RSA oscillations, even at the outset of training (Vaschillo, 1984; Vaschillo, Lehrer, Rische, & Konstatinov, 2002).

The mechanism chiefly responsible for the amplificatory effect of HRV/RSA biofeedback on RSA oscillations is the baroreflex. The baroreflex is a basic constituent

of a more complex system that modulates blood pressure in the body (Reyes del Paso & Gonzalez, 2004; Vaschillo, et al., 2002). Stretch receptors (or baroreceptors) in the aortic arch and carotid artery (Eckberg & Sleight, 1992), detect changes in blood pressure, and, in turn, modulate vagal activity at the sinoatrial node, producing contingent changes in heart rate (Eckberg & Sleight, 1992; Vaschillo, et al., 2002). (These reflexes also modulate brain structures involved in controlling changes in vascular tone (Vaschillo, et al., 2002); however, for the purposes of the current study, vascular tone can be neglected.) By doing so, the baroreflex system (BRS) protects the body against rapid swings in blood pressure (Vaschillo, et al., 2002).

Thus, the BRS has been characterized as a "two closed loop" feedback system (Hammer & Saul, 2005; Ringwood & Malpas, 2001; Vaschillo, et al., 2002), with oscillation. Oscillation exists in any feedback system in which there is a delay—in this case referring to the fact that, due to factors such as inertia, blood volume and length of vasculature, baroreflex-induced shifts in blood pressure are never *instantaneously* accompanied by shifts in heart rate, and vice versa (Grodins, 1963; Ringwood & Malpas, 2001). The value of the delay in the BRS (i.e. the delay between heart rate oscillations and blood pressure oscillations) has been determined to be 5 sec (Vaschillo, et al., 2006). Oscillatory systems such as these exhibit properties of resonance at a distinct frequency (Vaschillo, et al., 2006)—meaning that high-amplitude oscillations occur when they are rhythmically stimulated at their respective resonant frequencies (Vaschillo, et al., 2006).

As previously stated, RSA is characterized by increases in heart rate with inspiration and decreases in heart rate upon expiration. However, these associated changes in heart rate and respiration phase are usually *not simultaneously* coupled—

except, however, in instances in which individuals breathe at the cardiovascular system (CVS)/BRS resonant frequency (Vaschillo, Vaschillo, & Lehrer, 2004). The value of the resonant frequency for the CVS/BRS has been calculated at ½ (delay)= ½(5secs)=1/10=0.1 Hz (Vaschillo, Vaschillo, & Lehrer, 2006). Thus, when individuals breathe at the CVS/BRS resonant frequency ~0.1 Hz, which is equal to about 6 breaths/min, they generate the highest amplitude possible of RSA oscillations (Vaschillo, et al., 2004).

It has been theorized that the processes involved in HRV/RSA biofeedback stimulate, retrain, and, through neuroplasticity (i.e., the changeability of neural pathways), both acutely and chronically amplify vagal baroreflexes (Lehrer, et al., 2003). In turn, it is thought that central vagal nerve projections to areas of the brain, such as the hypothalamus and the limbic system, are modulated in such a way that brings about greater autonomic balance and regulation (Lacey & Lacey, 1978; Mini, et al., 1995).

Indeed, numerous studies have been conducted that support this notion. For example, HRV/RSA biofeedback has been used successfully in the treatment of disorders such as hypertension and asthma (Chernigovskaya, et al., 1990; Herbs, Gevertz, & Jacobs, 1993; Lehrer, et al., 2000), as well as in the treatment of irritable bowel syndrome (Gevirtz, 1999), fibromyalgia (Hassett, et al., 2007), and COPD (Giardino, et al., 2004)—disorders which are thought to be characterized and/or influenced by autonomic dysfunction (Hassett, et al., 2007; Lehrer, et al., 2000). Moreover, HRV/RSA biofeedback is increasingly being employed in the treatment of various psychological disorders linked to autonomic dysfunction (Reiner, 2008; Zucker, et al., 2009). For example, Zucker, et al., (2009), found the use of HRV/RSA biofeedback to be associated

with significant reduction in PTSD symptoms. Another study involving individuals with diagnoses such as generalized anxiety disorder (GAD), Specific Phobia, Social Phobia, and/or OCD, demonstrated that RSA biofeedback significantly reduced associated symptoms such as anger, anxiety, and certain sleep disturbances (Reiner, 2008).

HRV/RSA Biofeedback and Depression: Extant Research

A number of studies examining the utility of HRV/RSA biofeedback in the treatment of a variety of physiological and psychological disorders besides MDD have provided valuable data as to the potential impact of such an intervention on depression symptomatology (see Appendix for summary of studies). For example, in a pilot study examining the efficacy of a 10-week HRV/RSA biofeedback training protocol in the treatment of fibromyalgia in 12 women—a condition that commonly presents with comorbid depression (Epstein et al., 1999; Martinez, Ferraz, Fontana, & Atra, 1995)--, the investigators found there to be a significant decrease in the subjects' scores on the Beck Depression Inventory II (BDI-II) from pre-treatment, post-treatment, and 3-month follow up sessions (Hassett, et al., 2007). In a randomized control trial, Nolan, et al., (2005) found that, among 46 patients with coronary heart disease (CHD), those whom received five 1.5 hour HRV/RSA biofeedback training sessions exhibited significantly reduced depression symptoms, as measured by the Centre for Epidemiologic Studies in Depression (CES-D) scale. In a case study conducted by Fourie (2006), a 23-year-old male diagnosed with PTSD experienced a significant decrease in his depression symptoms (as measured by the Zung self-rating depression scale) after having received 7 sessions of RSA biofeedback training. Additionally, in a randomized-controlled pilot study evaluating the effects of a HRV/RSA biofeedback device versus progressive

muscle relaxation (PMR) in the treatment of 38 patients with PTSD, Zucker, et al., (2008) found there to be a significantly greater reduction in BDI-II depression scores of the HRV biofeedback group as compared to the PMR group.

Adding to the aforementioned literature, there is a modest but growing body of research inquiring explicitly into the efficacy of HRV/RSA biofeedback for the treatment of MDD. For example, in an open label pilot study previously conducted by this lab which examined the use of a weekly, 10-session HRV/RSA biofeedback protocol for the treatment of 11 individuals meeting diagnostic criteria for MDD, there was found to be a significant decrease in depression symptoms, as measured by both the BDI-II and Hamilton Depression Inventory (HAM-D)—with particular improvement exhibited within the neurovegetative indices (i.e. fatigue, sleep hygiene, concentration) (Karavidas, et al., 2007). In another open label study with an active, healthy control by Siepmann, et al., (2008), fourteen patients diagnosed with MDD of varying severity who underwent a two week, six session HRV/RSA biofeedback protocol, experienced significant decreases in depression symptoms, as measured by the BDI-II.

Despite there being studies demonstrating its potential efficacy, the literature is inconsistent, and there are also studies that for which the same effects of HRV/RSA biofeedback on depression were not found (i.e., Giardino, Chan, & Borson, 2004; McCraty, et al., 2009; Mussgay, et al., 2008; Reineke, 2007; Swanson, et al., 2009).

In addition to inconsistent findings in the literature, the above studies that do support the efficacy of HRV biofeedback in treating depression have a number of methodological limitations—particularly with regards to control group design, and/or lack thereof. For example, several of the aforementioned studies had no control group,

but used either a case study or an uncontrolled open-label study design (Fourie, 2006; Hassett, et al., 2007; Karavidas, et al., 2007). For those studies that were controlled, none of them utilized a placebo biofeedback control as their comparison group. For example, control participants were randomized to active/comparator control protocols (Siepmann, et al., 2008), consisting of treatments such as autogenic relaxation, cognitive-behavioral skills for stress management (Nolan, et al., 2005), and progressive muscle relaxation (Zucker, et al., 2009). In a controlled study by Hallman, et al. (2011), the treatment group received ten sessions of HRV biofeedback training, while the control group only partook in a 'breathing protocol' in the first and last session, with no sham sessions in between. In general, the purpose of the placebo-controlled design in medical and psychological research is to rule out factors that are incidental to the purported active ingredients in the treatment protocol, in order to ascertain the treatment specificity of said active ingredients (Rosenthal & Frank, 1956). In order to adequately differentiate non-specific factors, comparison conditions should be as identical as possible, save for the supposed active components (Gaurdiano & Herbert, 2003; Howard, et al., 1986). The lack of the use of respiratory biofeedback placebo control protocols in the reviewed literature is a key weakness of the extant research—as previous studies have, therefore, not adequately controlled for factors such as demand characteristics, patient expectancy effects, healthcare provider attention, and treatment credibility and rationale (Lohr, et al., 1999). Thus, the current body of HRV biofeedback literature is limited in its internal validity with regards to establishing treatment specificity vis-à-vis inadequate comparison conditions.

Taken together, however, the extant data regarding the effects of HRV/RSA biofeedback interventions on depression symptomatology suggests that the technique may indeed be a viable, non-invasive treatment alternative and/or adjunct for improving MDD symptomatology, and the current evidence certainly warrants further investigation into this relation.

Current Study: Goals and Hypotheses

The current study was a preliminary efficacy, randomized controlled trial to follow-up the open label pilot study previously conducted by this lab, (Karavidas, et al., 2007) which, using a similar biofeedback protocol, showed evidence to suggest the efficacy of HRV/RSA biofeedback for the treatment of depression. The primary goal of the current study was to gather data regarding the utility of HRV/RSA biofeedback as a viable adjunct treatment modality for MDD by testing its cumulative effects on depression indicators (i.e., affective, cognitive, neurovegetative). Although the number of studies that have explored the effects of HRV/RSA biofeedback on depression symptomatology is limited, trends in the data from the extant literature suggests that HRV/RSA biofeedback may be an effective, non-invasive intervention for improving depression symptoms with minimal risk posed to patients. In the current study, participants meeting diagnostic criteria for MDD were randomly assigned to either a 10-session HRV/RSA biofeedback intervention group, or a credible sham respiratory control group.

The secondary goal of the current study was to evaluate the viability of implementing a credible sham respiratory control group. This aspect of the current study is uniquely additive to the existing body of research. As compared to a no-treatment

control group (i.e. a wait list control) or a non-respiratory biofeedback placebo control (i.e. CBT, EEG biofeedback), the credible sham biofeedback control protocol is a more powerful way of demonstrating treatment specificity, as it is designed to control for the various threats to internal validity discussed above. Thus, in addition to our outcome measures, we evaluated the utility, tolerability, and effectiveness of this credible sham respiratory placebo control protocol.

Moreover, as randomized control trials (RCT) are the most methodologically rigorous, and as much of the existing research was done with various case study designs (see Appendix A for summary of studies), that the current study is an RCT is yet another strength.

Lastly, a more exploratory goal was to evaluate the relationship between subjects' negative self-complexity scores and those on the primary outcome measures of depression. In particular, the current study sought to ascertain the degree to which, if at all, negative self-complexity was correlated with the scores on outcome measures of depression for all subjects, and if any group differences existed with respect to this.

To this end, our hypotheses were as follows:

Main Hypotheses

H1: The participants who complete the 10-session HRV/RSA biofeedback intervention (N=6) will experience greater improvement in depression symptoms than those assigned to the sham respiratory biofeedback control condition (N=5).

H2: Improvements in depression exhibited by the biofeedback intervention group will persist at 1-month post-treatment (N=6).

H3: There will be a greater percentage of clinical response to the biofeedback intervention (N=6) as compared to the sham control (N=5), with clinical response operationally defined as a reduction of at least 50% in HAM-D scores from baseline to session 10 or a final score of 10 or fewer on the HAM-D scale.

Exploratory Hypothesis

H4: Negative self-complexity scores will be positively correlated with depression symptoms (N=11).

CHAPTER II

Methods

Participants

Eleven individuals who met DSM-IV criteria for major depression completed participation in the study.

Location

The screening, enrollment, and evaluations of prospective candidates and participating individuals took place at the Psychopharmacology Division, University of Medicine and Dentistry of New Jersey/Robert Wood Johnson Medical, 671 Hoes Lane, Piscataway, NJ 08855-1392. Treatment was conducted at the Psychophysiology Laboratory at UBHC, 671 Hoes Lane, Piscataway, NJ 08855-1392.

Recruitment Procedures

Participants were recruited from the population served by UMDNJ-University Behavioral HealthCare (UBHC) which treats over 20,000 patients a year (approximately 3000 of those having a diagnosis of MDD); from the practices of faculty members in the Psychiatry Department of UMDNJ-RWJ Medical School; from various community and private medical and mental health clinics and practices in Middlesex County, and from the population in the surrounding communities of Piscataway, New Brunswick, and Highland Park- including the UMDNJ and Rutgers University student population. Recruitment methods included flyer and pamphlet advertisement, as well as brief, in-person informationals with interested health care providers such that they may refer appropriate clientele.

Inclusion and Exclusion Criteria

Inclusion criteria for participation in the study was: individuals between 18-75 years of age, who met criteria of Major Depressive Disorder as defined by the Structured Clinical Interview for the DSM-IV (SCID), and who are fluent in English.

Exclusion criteria for participation in the proposed study were as follows: 1) the clinical interviews and rating scales demonstrated that the participant may not be suffering from depression; 2) it had been determined that the participant suffered from any other disorder besides major depression, dysthmymic disorder, or anxiety disorder; 3) the participant was found to be actively grieving; 4) the participant suffered from any medical conditions that may have interfered with his/her full participation, or that posed a health risk, such as irregular heart beat, slow heart beat (under 40 beats/minute), heart palpitations, hypertension, diabetes or kidney disease; 5) it had been determined that the participant was at risk for suicide and/or had made a suicide attempt within the past year; 6) the participant was younger than 18 or older than 75; 7) the study participant was taking medications such as antipsychotics, anticonvulsants, lithium, sedatives/tranquillizers; 8) the participant refused to participate in any of the necessary study procedures (e.g. completing questionnaires, submitting to psychological tests, etc.); 9) there was evidence of alcohol, illicit drug, or prescription drug use/dependence; 10) the participant did not exhibit fluency in English; 11) the participant initiated participation is psychotherapy or the use of depression/anti-anxiety medication more recently than 3 months prior to screening.

Demographic Characteristics of the Study Sample

The current study sample was comprised of eleven participants, whose ages ranged from 20-46 years. Four of the participants were male, and seven were female. Six participants were Caucasian, four were Asian, and one participant was Hispanic. Table 1 below shows a summary of the demographic data of the total sample.

Table 1
Summary of Demographic Variables at Baseline

		Frequency	Percent
Gender			
	Female	7	64%
	Male	4	36%
Age			
	18-25	4	36%
	25-30	0	
	31-40	4	36%
	41-50	3	28%
Ethnicity			
	Caucasian	6	55%
	Hispanic	1	9%
	Asian*	4	36%

*Includes both east and south-east Asian individuals

Protection of Human Participation

Investigators explained the study to the participant in simple terms and Informed Consent was obtained prior to the participant entering the study. The Informed Consent document was read and any questions or concerns raised by the participant were answered and addressed. The participant initialed all appropriate pages and then signed

the consent form. A witnessed, dated, and signed copy was given to the participant for his/her records.

It was the investigator's responsibility to ensure that informed consent, with all the appropriate signatures and dates on the document, had been obtained from each participant prior to the initiation of any of the proposed protocol procedures of the study. Informed consent must have also been obtained prior to any changes made to a participant's medical treatment plan for the purpose of study participation.

All research files pertaining to this study were kept completely confidential, except as required by the law. Files were only accessible to researchers directly involved with scoring and interpreting the research data. However, under certain conditions, the Institutional Review Boards (IRB) of the Robert Wood Johnson Medical School and/or Rutgers University, as well as the American agencies designated by law may be permitted to examine participants' records for the purposes of verifying clinical trial procedures and/or data. Participants will be duly informed if this were to transpire. Complete confidentiality cannot be guaranteed as records may be released to any party required by law. If any results from the study should be published, the results will be written in a manner that protects participants' identity.

In anticipation of any psychiatric emergencies, procedures were in place to identify the presence of such an event and to coordinate with UBHC's resources in order provide adequate care to the participant. As stated above, consent to release information was obtained for each participant. This would allow our research team to more easily coordinate with the participants' treating clinician(s) at UBHC or elsewhere in the event of a psychiatric emergency, such as clinically significant suicidal ideation. An acute

psychiatric service center (APS) is housed in UBHC, and could be utilized in the event of an emergency. Study clinicians, who held master's degrees in clinical psychology, and who were trained and closely supervised by a licensed clinical psychologist within the department, conducted most evaluations. A licensed clinical psychologist within the department conducted all other evaluations. All master's level clinicians had been trained to identify the signs of a psychiatric emergency and the supervisor was immediately contacted in such an event.

Patients were regularly assessed for potential suicidality, as is standard practice in research with depressed patients. At the outset of each session, participants were informally queried regarding the possibility of suicide ideation or plans. Additionally, the Beck Hopelessness Scale (BHS) and the Beck Scale for Suicide Ideation (BBSI) were administered during orientation and at each subsequent session. These measures tracked risk of suicide across sessions. If, during the weekly suicide screening it was determined that a participant was suicidal (suicidal ideation), they were escorted by the clinician to Acute Psychiatric Services (APS), located onsite (UMDNJ-Piscataway campus) which was open 24 hours per day, seven days per week. Participants may have also been escorted to the unit on an involuntary basis. Participants requiring security management could be safely assessed and treated in this secure area. Crisis services maintained active coordination/liaison relationships with other University Behavioral Health Care (UBHC) departments while providing crisis evaluation and treatment for individuals with acute distress or dysfunction that require immediate intensive intervention. Participants who presented with acute conditions may have been referred out for prompt medical stabilization before an evaluation is completed. Participants, not meeting APS criteria for

hospitalization, were linked to appropriate community resources. Follow-ups were provided, by APS, to support patients awaiting outpatient treatment and to reiterate treatment plan or develop alternatives. Active coordination was maintained to ensure exchange of information. APS's policy is to report dispositions to referring professionals whenever possible. Between sessions, participants were also instructed to call APS (732-235-5700) if they felt at risk of harming themselves or others. Participants were informed that they might withdraw from the study at any time (even in the midst of an evaluation or treatment session). If any aspect of the procedure caused significant emotional distress to a participant that was not ameliorated by debriefing or if a participant's depression worsened, the investigators developed an individualized treatment plan with the participant, including possible withdrawal from the study and a referral for additional treatment. Thorough documentation was required from clinicians regarding every aspect of this study, including explicit documentation regarding suicidal ideation, and follow-up procedures.

1. Beck Scale for Suicide Ideation (BSI) (Beck, 1991). This is a 21-item self-administered scale that explores possibility of suicide during the past week. Administration time ranges from 5-10 minutes and age ranges appropriate for its use are 17-older. It consists of five screening items. If the respondent reports any active or passive desire to commit suicide, then an additional 14 items are administered.

2. Beck Hopelessness Scale (BHS) (Beck, 1993). Research consistently supports a positive correlation between BHS scores and measures of suicidal intent, ideation and depression (Katz, et al., 1999). Hopelessness appears to be a stable indicator of suicide intent (Pope and Vasqez, 1998); thus it seems warranted to include this construct as part

of a thorough suicide assessment. This is a 20-item true/false scale that includes domains regarding feelings about the future, loss of motivation and expectations.

Documentation

Strict enforcement of documentation was mandated. All study personnel were required to submit a progress note to the supervising licensed clinical psychologist after each interaction (telephone and in-session). It was this psychologist's responsibility to maintain an e-record of all session and general participant notes. Additionally, a hard copy of each participant interaction was required in the actual record. These notes were identified only be a participants assigned ID code, and the date of contact.

Telephone Screening

Prospective candidates were initially screened via telephone interview from the Psychopharmacology Division, University of Medicine and Dentistry of New Jersey/Robert Wood Johnson Medical, 671 Hoes Lane, Piscataway, NJ 08855-1392. This telephone interview was an informal assessment of depression using DSM-IV diagnostic criteria for Major Depressive Disorder. Additionally, prospective candidates were queried as to possible unstable medical conditions that might interfere with HRV biofeedback (e.g. medical exclusion criteria). Candidates were also questioned regarding current usage of psychotropic medication and involvement in psychological therapy. A formal diagnostic assessment was scheduled for interested candidates not meeting immediate exclusion criteria. Those candidates who, upon inquiry, endorsed answers consistent with our exclusion criteria were provided the contact information for Acute Psychiatric Services (APS) and the UMDNJ-UBHC Access Center. The approximate duration of the initial telephone screening was 15 minutes.

In-Personal Screening and Baseline Assessment

In the first appointment at the Psychophysiology Laboratory, participants were introduced to the setting, equipment and basic procedure of biofeedback. Among other details about the study, it was indicated to participants in the informed consent form that they would be randomized to either an active treatment group or a control group, and that these training environments would be identical and would both involve breathing at specific rates. Once participants read and signed the informed consent, they were screened using the primary outcome measure, the Hamilton Rating Scale for Depression (HAM-D), and the diagnosis was confirmed with the Structured Clinical Interview (SCID) for DSM-IV. The SCID enabled the investigators to screen for alcohol, cocaine, amphetamine or other illicit or prescription drug use. Upon entry participants were informally queried regarding the possibility of suicide, specifically, whether life is worth living, thoughts of suicide, or if they have suicide plans. The Beck Hopelessness Scale (BHS) and the Beck Scale for Suicide Ideation (BBSI) were also given during orientation and at each subsequent session. Participants endorsing indicators of suicide potential were immediately referred to a mental health professional. Participants not meeting diagnostic criteria for Major Depression (as evidenced by SCID assessment), or that met other exclusion criteria, were be dropped from the study at this point and additional measures were not completed. Participants were provided the contact information for Acute Psychiatric (APS) and UMDNJ-Access Center prior to termination. Participants meeting diagnostic criteria for Major Depression were then asked to fill out exploratory measures, including the Beck Depression Inventory (BDI), and the Medical Outcomes Study 36-Item Short-Form (SF-36) health survey, Beck Anxiety Inventory (BAI),

Cognitive Complexity Scale and the Credibility/Expectancy Questionnaire (CEQ) in a quiet, private room.

Participants who met study criteria were then asked to return for an appointment at the Psychophysiology Laboratory at UMDNJ-RWJMS. These participants were instructed to refrain from consuming any caffeine or alcohol for twelve hours prior to this session and all other sessions in which physiologic measures were to be collected. Participants were reminded to make use of the contact information for Acute Psychiatric Services (APS) in the case of a psychiatric emergency. In the first appointment at the Psychophysiology Laboratory, participants were introduced to the setting, equipment and basic procedures of biofeedback. In order to obtain baseline physiological measures, we took a 5-minute recording of heart period and respiration.

Group Assignment

Participants were randomly assigned to either the active treatment group or the sham control group using a restricted randomization procedure controlling for gender, current psychological treatment/medication (Yes/No), and depression status. Participants assigned to the active treatment group received four weekly training sessions in HRV biofeedback[45](the participant was taught how to breathe at his/her resonant frequency and produce maximal increases in amplitude of HRV), while those assigned to the control group receive four weekly sessions of a "sham" HRV control group (breathing at rates specific to spontaneous breathing with no training to maximize HRV) (Bernardi, et al., 2001). All questionnaires and psychophysiological data collected at baseline were repeated at weeks 7 and 10. Table 2 lists the time frame for the measures and procedures.

Table 2
Timeline for Measures and Procedures

PROCEDURES	**Screening**	**Biofeedback sessions** *(weekly)*			**Follow-up (FU) sessions**	
Sessions	***Baseline/Pre-test***	***Session 1***	***Sessions 2, 3***	***Session 4***	***Session 5*** *Week 7*	**Session 6** *Week 10*
Structured Clinical Interview for DSM-IV (SCID)	X					
Questionnaires (BDI-II, HAMD, CAS, SF-36, BSSI, BHS, CEQ, CCPRQ)	X			X	X	X
Biofeedback Training		X	X	X	X	X
Physiological data collection session		X		X	X	X

HRV Biofeedback Condition

The HRV biofeedback intervention consisted of 4 weekly sessions of training, at approximately the same time of day for each subject. Participants were measured on the following physiological parameters: thoracic and abdominal breathing (respiration rates) and tidal CO2 volume. Details regarding the procedure for RSA biofeedback are elaborated in Appendix B. In each session, 20 minutes of biofeedback was delivered using a J&J I-330-C2 physiography. The participant was taught to breathe at his/her unique resonant frequency, as the first step in training the individual to produce maximal increases in RSA amplitude. During the first session, the amplitude of heart rate oscillation were measured while the individual breathes for two-minute intervals, each at

specific frequencies, ranging between 4.5 and 6.5 breaths per minute. A "pacing stimulus"-- a light display that moves up and down on the computer screen at the target respiratory rate-- was provided for the purposes of facilitating this process. Participants were instructed to breathe at the rate of that stimulus. The frequency yielding the highest frequency peak on the moving Fourier analysis data collected and displayed by the J&J I-330-C2 physiography was considered to be the participants' resonant frequency. The participant was then instructed to practice breathing at his/her resonant frequency at home twice a day for 20 minute periods, and/or when feeling particularly "down" or depressed. Participants were provided a pacer program (EZ-Air Pacer) to facilitate at-home practicing. In the third session, a stand-alone device was provided for home practice, the HeartMath Institutes's (Coulder Creek, CA) Freeze Framer. This system analyzed heart rhythms and provides a display sensitive to properties of total heart rate variability that is explained by activity at the frequency showing the greatest spectral amplitude within the low frequency range. This interval yields results that are the same as obtained from biofeedback using a cardiotachometer. An interactive game format uses a reward system to help participants maximize heart rate variability, thereby increasing the amplitude of HRV. A HRV home trainer was used versus instructing participants to breathe at their resonant frequency for the following reasons: 1) All previous literature has supported the use of home HRV biofeedback trainers (Hassett, et al., 2007; Lehrer, et al., 2000; Lehrer, et al., 2000; Vaschillo, et al., 2002). 2) It has a motivational component (McGrady, 1994; McGrady, et al., 1997; McGrady, et al., 2003). 3) Previous studies find that maximum low frequency spectral peaks only occur after several sessions of training. Determination of the exact frequency occurs only after several weeks biofeedback training, where the

biofeedback task forces the person to breathe at the exact resonant frequency (Hassett, et al., 2007; Lehrer, et al., 2000; Lehrer, et al., 2000; Lehrer, et al., 2003; Lehrer, et al., 2003; Vaschillo, et al., 2002). Throughout training, participants were cautioned against breathing too deeply and encouraged to breathe naturally, in order to avoid hyperventilation.

Control Condition

This sham condition enabled us to control for the following variables: therapeutic attention, assignment of regular training, passage of time, signing up for a research directed program of therapy and mild untrained relaxation. The protocol for this condition was adapted from the HRV Biofeedback condition and the training environment was identical to that of the HRV group, except that in this condition the respiration rates did not target increased HRV. This condition functioned as a viable alternative to a wait-list or a straight control group, as it allowed for the frequent assessment of participants for depression exacerbation and suicidality, and because it provided an intervention with the same demand characteristics and format as the HRV biofeedback condition (Pope & Vasqez, 1998). Details regarding the procedure for sham respiratory biofeedback are elaborated in Appendix A. The participants assigned to this condition received 4 sessions of a "sham" HRV biofeedback intervention. During the first session, participants were instructed to follow a pacer at 10, 11, 12, 13, and 14 breaths per minute, for one minute each. It has been demonstrated that these frequencies yield nonsignificant changes in baroreflex sensitivity and are not likely to result in any harmful effects (Bernardi, et al., 2001; Bernardi, et al., 2002; Halamek, et al., 2003; Song & Lehrer, 2003). Again a "pacing stimulus"-- a light display that moves up and down on

the computer screen at the target respiratory rate-- was provided for the purposes of facilitating this process. Participants were instructed to breathe at the rate of that stimulus. The participant was then instructed to practice breathing at his/her "designated frequency" at home twice a day for 20 minute periods, and/or when feeling particularly "down" or depressed. Throughout training, participants were cautioned against breathing too deeply and encouraged to breathe naturally, in order to avoid hyperventilation. The participants were measured on the physiological parameters identical to the HRV treatment group. Participants were provided a pacer program (EZ-Air Pacer) to facilitate at-home practicing. Instead of programming the pacer to one's resonant frequency, participants in the control were instructed to breathe at their "designated frequency"- a rate indicative of spontaneous breathing (Bernardi, et al., 2001). Upon completion of the study, participants in this group were offered the option of participating in the treatment group.

Follow-up session

After the completion of the 4th session, participants were asked to return to the laboratory three weeks later (7th week), and also on the 10th week, for a total of two follow-up sessions. These sessions provided an opportunity for data collection and monitoring of depression symptoms. Additionally, in the weeks preceding the designated follow-up sessions (7th and 10th week), participants were contacted via telephone in order to address any questions regarding home practice. Participants were also queried as to improvements and/or deterioration in mood. The weekly contacts made to participants between follow-up sessions also allowed the investigators to determine whether the intervention was appropriate for the participant.

Biofeedback Data Collection Procedure

During the sessions for weeks 1, 4, 7 and 10, a 50-minute recording of resting heart period was obtained prior to commencing biofeedback, as well as at the end of the sessions. During biofeedback, two 5-minute recordings of heart period were taken, one towards the beginning of the session and another at the end. Questionnaire data was then collected.

Equipment

Biofeedback Instrument: RSA biofeedback was provided through a J&J Engineering (Poulsbo, WA) I-330-C2 physiograph unit, using HRDFT software. This device provides a cardiotachometer and on line Fourier analysis of respiratory sinus arrhythmia. The limits for maximum and minimum heart rate in each oscillation can be set manually, so that the size of the fluctuation can be shaped. For daily practice at home, participants were be lent a HeartMath Freeze Framer (Institute of HeartMath, Creek, CA).

Heart Period: For each 5 minute period, we calculated HRV for the high-frequency (0.15-0.4Hz) and low frequency (0.05-0.5Hz) ranges using a Fourier transformation on successive normal R-R intervals.

Respiration: Respiration was recorded using a Respitrace inductance pneumograph(non-invasive monitoring system, Miami, FL) with sensors on the abdomen, and digitized at the rate of 32 samples/sec. These measures were calibrated by breathing into an 8ml bag at the beginning of the session. One channel assessed thoracic breathing and was attached around the chest approximately 2 cm below the armpits. The second belt for assessment of abdominal breathing was attached at the level of the umbilicus.

Primary Outcome Measures

Hamilton Depression Scale (HAM-D) (Hamilton, 1960). The HAM-D is a 17-item clinician-rated measure that was completed in tandem with the SCID in order to assess depression. This served as the primary outcome measure.

Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4thed.(DSM-IV) SCID**.** Developed by First, Gibbons, Spitzer, and Williams (First, et al., 1996). This is a standardized clinical interviewing tool that covers DSM-IV diagnoses by including the diagnostic criteria with corresponding interview questions. The SCID-I is divided into six self-contained modules: mood episode, psychotic symptoms, psychotic disorders, mood disorders, substance abuse disorders, anxiety, adjustment and other disorders.

Exploratory Outcome Measures

The Beck Depression Inventory (Beck, et al., 1961) was also administered. It is a well-validated 21-item self-report measure that assesses the cognitive, affective, and neurovegatative symptoms of depression (Beck, et al., 1996; Steer & Clark, 1997).

Medical Outcome Study Short Form (SF 36) (Ware & Sherebourne, 1992): The SF-36 comprises 36 questions with two to five response possibilities. Eight different sub-dimensions and a physical and mental summary score can be derived from these; the maximum score of 100 indicates best possible health status with low-disease related disability. It has been shown to be valid, reliable, and sensitive in the general population and in a variety of disorders. Its seven sub-scales are physical functioning, social functioning, role functioning, mental health, energy, pain, and general health perceptions.

Clinical Anxiety Scale (CAS) (Westhuis &Thyer, 1989). This is a 25-item self-report questionnaire rated on a scale from 1 to 5. Each item is descriptive of subjective, somatic, or panic-related symptoms of anxiety. The CAS has been found to adequately differentiate between anxious and non-anxious groups in a clinical population.

Beck Scale for Suicide Ideation (BSSI) (Beck, 1991). This is a 21-item self-administered scale that explores possibility of suicide. Administration time ranges from 5-10 minutes and age ranges appropriate for its use are 17-older.

Beck Hopelessness Scale (BHS) (Beck, 1993). This is a 20 item true/false scale that includes domains regarding feelings about the future, loss of motivation and expectations. Research consistently supports a positive correlation between BHS scores and measures of suicidal intent, ideation and depression (Katz, et al., 1999). Hopelessness appears to be a stable indicator of suicide intent (Pope & Vasqez, 1998); thus it seems warranted to include this construct as part of a thorough suicide assessment.

Credibility/Expectancy Questionnaire (CEQ) (Devilly & Borkovec, 2000). This is a six-item questionnaire that defines belief in treatment as a multidimensional construct. Placebo effects of treatment were assessed by examining subjects' beliefs in treatment. The CEQ was designed as a brief and easy-to-use instrument to measure subject attitude toward rationale (i.e. credibility) and potential benefits (i.e. expectancy) of treatments. Four items, rated on a 9-point Likert scale, that asks subjects how logical, useful and helpful treatment might be while two of the questionnaire items ask subjects to rate the percentage of improvement in their symptoms that is likely to occur as a result of the treatment. The CEQ has exhibited strong internal consistency, test-retest reliability,

and construct validity. The total scale (both factors) yielded a standardized alpha of r=0.85.

The Cognitive Complexity and the Placebo Response Questionnaire (CCPRQ) (Gara, et al., 2002). A clustering program (HICLAS) analyzed, separately for each subject, the pattern of trait ratings across the 6 targets corresponding to self complexity, specifically. A statistic, based on the number of underlying clusters, provides a measure of each subject's self complexity. Low complexity patients are hypothesized to be more likely to evidence a placebo response.

Statistical Analysis

The focus of data analyses was on the primary dependent variables: the Hamilton Depression Scale (HAM-D) and the Beck Depression Inventory (BDI-II). Additionally, we assessed secondary measures: SF-36 and CAS (We computed a repeated measures mixed model analysis on pretest/baseline, mid-treatment, post-treatment ($1^{st,}$ 4^{th}, 7 and 10th week follow-up testing sessions). If the Treatment x Session interaction were significant, we did individual comparisons between values at the first session and at each subsequent session for each group, and between groups at each session. The Huynh-Feldt and/or the Greenhouse-Geisser epsilon statistics will be used, as appropriate, to control for sphericity effects. We also computed a Pearson's r and Chi-square analyses to evaluate the relationship between negative self-complexity, depression, and treatment group. Physiological data were not included in the data analyses of the current study.

Potential Risks

During the early stages of HRV biofeedback training, some patients may experience hyperventilation, the symptoms of which can include dizziness, rapid heart

rate, smothering sensations, and feelings of unreality. These symptoms are usually quite transient, as they tend to stop as soon as the participant discontinues doing the biofeedback technique. In order to prevent this, participants are instructed as to how to do the technique without hyperventilating. There are several medical conditions that can potentially be affected by hyperventilation and would have been noted upon initial interview, including: insulin-dependent diabetes, low blood pressure, any condition causing metabolic acidosis such as kidney disease, heart disease and severe hypoglycemia (Fried, 1993). Participants were reminded that if the abdominal breathing exercise causes any pain or discomfort, it should be discontinued immediately.

It was possible that participants' depression symptoms may have worsened if HRV biofeedback was not effective for them. In order to assess this in a timely manner, participants were assessed for depression and suicidality on weeks 1, 4, 7 and 10, and protective measures were taken when necessary, referring the patients to the appropriate level of care. Participants took a mood scale before each session, allowing for assessment of problems. Participants were also given instructions usually provided depressed patients being treated at UBHC, in terms of encouraging them to call or attend APS if they felt at risk of harming themselves or others.

CHAPTER III

Results

Sample Characteristics

One hundred and three individuals completed the initial telephone pre-screening. Of those, thirty-eight met criteria for and completed the in-person diagnostic screening. Of those, twenty-seven met inclusion criteria for the study. Of those, sixteen individuals dropped out at various point during their enrollment in the study, including pre-baseline discontinuation. Eleven participants in total completed the study in its entirety.

Group Equivalence at Baseline

Group equivalence was assessed based on demographic and outcome measures for each group at baseline. ANOVA was used to analyze continuous variables, while chi-square analyses were conducted to analyze categorical variables. The two groups did not differ significantly in age, gender, or ethnicity. One-way ANOVAs did not reveal any significant pre-treatment differences between the biofeedback and control group on the psychological measures. See Tables 3 and 3.A below.

Table 3
Group Equivalence at Baseline for Outcome Measures

Variable	Group	*N*	*M*	*SD*	*F*	*p*
BDI Total	Biofeedback	6	31.33	10.11	.002	.963
	Control	5	31.00	12.86		
	Total	11	31.18	10.83		
BDIcog	Biofeedback	5	13.80	3.19	.025	.879
	Control	5	13.40	4.7		
	Total	10	13.60	3.81		
BDIneuro	Biofeedback	5	7.40	2.51	.011	.920
	Control	5	7.60	3.51		
	Total	10	7.50	2.88		

Table 3 – Continued

HAMD	Biofeedback	6	18.17	4.79	.163	.696

Table 3- Continued

	Control	5	19.60	6.99		
	Total	11	18.82	5.62		
CEQ	Biofeedback	6	5.98	1.90	.002	.962
	Control	5	6.04	1.91		
	Total	11	6.01	1.81		
HopeTotal	Biofeedback	5	14.40	2.70	.100	.760
	Control	5	13.80	3.27		
	Total	10	14.10	2.85		
SF-physical functioning	Biofeedback	6	64.17	28.18	3.06	.114
	Control	5	88.00	12.04		
	Total	11	75.00	24.70		
SF-role limit. Physical	Biofeedback	6	37.50	49.37	.007	.935
	Control	5	35.00	48.73		
	Total	11	36.36	46.59		
SF-role limit. Emotion	Biofeedback	6	.00	.00	1.23	.297
	Control	5	6.67	14.89		
	Total	11	3.03	10.04		
SF-emotional funct.	Biofeedback	6	10.00	11.40	11.16	.009
	Control	5	31.00	8.94		
	Total	11	19.55	14.74		

Table 3 – Continued

Variable	Group	*N*	*M*	*SD*	*F*	*p*
SF-emotional	Biofeedback	6	33.33	9.00	1.11	.319
	Control	5	43.20	20.86		
	Total	11	37.82	15.53		
SF-social	Biofeedback	6	37.50	11.18	.413	.537
	Control	5	47.10	24.84		
	Total	11	41.86	23.94		
SF-pain	Biofeedback	6	41.25	22.90	5.93	.037
	Control	5	71.50	16.83		
	Total	11	55.00	25.00		
SF-general health	Biofeedback	6	26.67	21.13	3.40	.098
	Control	5	49.00	18.51		
	Total	11	36.82	22.28		

Table 3 – Continued

CAS	Biofeedback	5	65.60	18.41	.297	.601
	Control	5	73.20	25.17		
	Total	10	69.40	21.17		
Negative Self-Complex.	Biofeedback	6	2.69	.302	.343	.572
	Control	5	2.56	.462		
	Total	11	2.63	.369		
Positive Self-Complex.	Biofeedback	6	2.58	.586	.011	.917
	Control	5	2.62	.465		
	Total	11	2.60	.509		
HopeFeelingsFuture	Biofeedback	5	3.40	1.34	.267	.620
	Control	5	3.80	1.10		
	Total	10	3.60	1.17		
HopeLossMotivation	Biofeedback	5	5.20	1.64	.360	.565
	Control	5	4.60	1.52		
	Total	10	4.90	1.52		
HopeFutureExpect	Biofeedback	5	4.20	.837	.167	.694
	Control	5	4.00	.707		
	Total	10	4.10	.738		
HopeRiskFatalSuicide	Biofeedback	5	1.0	.00	.	.
	Control	5	1.0	.00		
	Total	10	1.0	.00		

Table 3.A

Group Equivalence at Baseline for Demographic Variables

Variable				X^2	***p***
Gender	Female	Male		2.21	.137
Biofeedback	5	1			
Control	2	3			
Total	7	4			
Ethnicity	Caucasian	Asian	Hispanic	.917	.632
Biofeedback	3	2	1		
Control	3	2	0		
Total	6	4	1		
Age					
Biofeedback					
Control					
Total					

Baseline Analysis

Bivariate Pearson correlations were run to investigate the relationships between demographic information and baseline outcome measures for the whole sample and by group. Age was negatively correlated with SF-36 pain scores, $r(9)=-.70$, $p<.05$. (It is important to note here that on the SF-36, lowers scores are indicative of lower functioning; thus age was positively correlated with *higher* pain *symptoms*.) No other significant correlations were found between demographic variables and baseline outcome measure scores.

Table 4
Means and Standard Deviations of Outcome Measures

Measure	**Group**	**N**	***M (SD)*** Baseline	***M (SD)*** Session 4	***M (SD)*** Session 7 (fu1)	***M (SD)*** Session 10 (fu2)
BDI Total	Biofeedback	6	31.33 (10.11)	16.67 (3.50)	19.50 (4.89)	19.67 (8.55)
	Control	5	31.00 (12.86)	22.00 (16.15)	12.60 (4.72)	10.20 (5.72)
	Total	11	31.18 (10.83)	19.09 (10.88)	16.36 (5.81)	15.36 (8.61)
BDIcog	Biofeedback	5	13.80 (3.19)	8.60 (1.82)	8.80 (4.87)	9.60 (4.62)
	Control	5	13.40 (4.72)	8.80 (7.63)	5.20 (2.95)	5.20 (2.95)
	Total	10	13.6 (3.81)	8.70 (5.23)	7.00 (4.24)	7.40 (4.53)
BDIneuro	Biofeedback	5	7.40 (2.51)	4.20 (1.31)	5.00 (1.41)	4.60 (2.07)
	Control	5	7.60 (3.51)	6.0 (3.39)	3.60 (.89)	2.20 (1.30)
	Total	10	7.5 (2.88)	5.10 (2.60)	4.30 (1.34)	3.40 (2.07)
HAMD	Biofeedback	6	18.17 (4.79)	10.50 (4.14)	10.33 (3.67)	8.00 (3.58)
	Control	5	19.60 (6.99)	11.80 (7.60)	6.80 (3.70)	9.00 (4.90)
	Total	11	18.82 (5.62)	11.09 (5.66)	8.73 (3.95)	8.45 (4.03)
HopeTotal	Biofeedback	5	14.40 (2.70)	9.40 (2.70)	7.20 (5.12)	7.20 (4.55)
	Control	5	13.80 (3.27)	8.20 (5.63)	5.40 (1.82)	5.80 (3.90)
	Total	10	14.10 (2.85)	8.80 (4.21)	6.30 (3.74)	6.50 (4.06)
HopeLoss Motivation	Biofeedback	5	5.20 (1.64)	2.0 (1.41)	1.0 (1.41)	1.20 (1.30)
	Control	5	4.60 (1.52)	1.60 (1.34)	1.0 (.71)	1.40 (2.07)
	Total	10	4.90 (1.52)	1.80 (1.32)	1.0 (1.05)	1.30 (1.64)
HopeFeelingsFuture	Biofeedback	5	3.40 (1.34)	1.80 (1.48)	1.60 (1.82)	1.00 (1.22)
	Control	5	3.80 (1.10)	2.40 (1.82)	1.20 (1.10)	1.20 (.45)

Table 4 Continued

	Total	10	3.60 (1.17)	2.10 (1.60)	1.40 (1.43)	1.10 (.88)

Measure	**Group**	**N**	***M (SD)*** Baseline	***M (SD)*** Session 4	***M (SD)*** Session 7 (fu1)	***M (SD)*** Session 10 (fu2)
HopeFutureExpect	Biofeedback	5	4.20 (.84)	4.0 (1.22)	3.20 (1.79)	3.60 (2.07)
	Control	5	4.00 (.71)	3.00 (1.87)	2.60 (.89)	2.20 (1.30)
	Total	10	4.10 (.74)	3.50 (1.58)	2.90 (1.37)	2.90 (1.79)
HopeRiskFatalSuicide	Biofeedback	5	1.0 (.00)	.60 (.55)	.40 (.55)	.40 (.55)
	Control	5	1.0 (.00)	.60 (.55)	.00 (.00)	.20 (.45)
	Total	10	1.0 (.00)	.60 (.52)	.20 (.42)	.30 (.48)
CAS	Biofeedback	5	65.60 (18.41)	53.60 (9.07)	48.60 (7.44)	49.20 (7.01)
	Control	5	73.20 (25.17)	62.20 (20.63)	50.40 14.28)	49.40 (14.26)
	Total	10	69.40 (21.17)	57.90 (15.69)	49.50 (10.77)	49.30 (10.59)
SF-physical functioning	Biofeedback	6	64.17 (28.18)	60.00 (18.71)	70.83 (15.63)	66.67 (8.16)
	Control	5	88.00 (12.04)	81.00 (26.08)	88.00 (15.25)	88.00 (19.56)
	Total	11	75.00 (24.70)	69.55 (23.82)	78.64 (17.19)	76.36 (17.62)
SF-role limit. physical	Biofeedback	6	37.50 (49.37)	41.67 (34.16)	40.27 (32.66)	16.67 (30.28)
	Control	5	35.00 (48.73)	50.00 (50.00)	70.00 (44.72)	70.00 (44.72)
	Total	11	36.36 (46.59)	45.45 (40.03)	53.78 (39.68)	40.91 (45.10)

Table 4 Continued

SF-role limit. emotion	Biofeedback	6	.00 (.00)	16.65 (27.86)	16.65 (27.86)	16.67 (40.82)
	Control	5	6.66 (14.89)	26.64 (36.48)	53.20 (50.51)	39.98 (36.51)
	Total	11	3.03 (10.04)	21.19 (30.78)	33.26 (42.11)	27.26 (38.92)
SF-emotional funct.	Biofeedback	6	10.00 (11.40)	17.50 (13.69)	21.67 (10.80)	20.00 (14.83)
	Control	5	31.00 (13.69)	42.00 (21.68)	50.00 (16.96)	48.00 (18.23)
	Total	11	19.55 (14.74)	28.63 (21.11)	34.55 (19.81)	32.73 (21.37)
Measure	**Group**	**N**	***M (SD)*** Baseline	***M (SD)*** Session 4	***M (SD)*** Session 7 (fu1)	***M (SD)*** Session 10 (fu2)
SF-emotional	Biofeedback	6	33.33 (9.00)	44.00 (13.15)	51.33 (12.75)	47.67 (21.26)
	Control	5	43.20 (20.86)	49.6 (22.20)	64.00 (14.70)	62.40 (14.31)
	Total	11	37.82 (15.53)	46.55 (17.09)	57.09 (14.54)	54.36 (19.16)
SF-social	Biofeedback	6	37.50 (11.18)	50.00 (13.69)	60.42 (12.29)	54.17 (18.82)
	Control	5	47.10 (34.84)	62.50 (36.44)	71.90(21.79)	75.00 (17.68)
	Total	11	41.86 (23.94)	55.68 (25.84)	65.64 (17.36)	63.64 (20.50)
SF-pain	Biofeedback	6	41.25 (22.90)	50.42 (27.99)	57.92 (18.06)	54.17 (22.95)
	Control	5	71.50 (16.83)	62.50 (34.64)	76.50 (23.82)	72.00 (31.99)
	Total	11	55.00 (25.00)	55.91 (30.19)	66.36 (22.00)	62.27 (27.56)
SF-general health	Biofeedback	6	26.67 (21.13)	33.33 (10.33)	33.33 (18.62)	28.33 (12.91)
	Control	5	49.00 (18.51)	58.00 (31.74)	55.00 (27.16)	57.00 (29.07)
	Total	11	36.82 (22.28)	44.55 (24.95)	43.18 (24.42)	41.36 (25.41)

Table 4 Continued

CEQ	Biofeedback	6	5.98 (1.90)	5.88 (1.81)	6.32 (1.64)	6.17 (1.79)
	Control	5	6.04 (1.91)	5.64 (1.69)	6.20 (2.02)	5.36 (1.73)
	Total	11	6.00 (1.81)	5.77 (1.67)	6.26 (1.72)	5.80 (1.73)
Negative Self Complex.	Biofeedback	6	2.69 (.30)	2.61 (.25)	2.70 (.43)	2.81 (.57)
	Control	5	2.56 (.46)	2.68 (.51)	2.55 (.64)	2.40 (.57)
	Total	11	2.63 (.37)	2.64 (.37)	2.63 (.51)	2.63 (.58)
Positive Self Complex.	Biofeedback	6	2.58 (.59)	2.71 (.68)	2.50 (.41)	2.77 (.66)
	Control	5	2.62 (.47)	2.57 (.77)	2.66 (.63)	2.75 (.74)
	Total	11	2.60 (.51)	2.65 (.69)	2.57 (.50)	2.76 (.665

Main Analysis of Outcome Measures

Statistical analyses were performed in SPSS version 18, SAS version 9.2, and Microsoft Excel version 14.1.4. In order to generate self complexity scores from participants' CCPRQ responses, the proc factor procedure was employed to conduct a principal components analysis with no rotation—yielding complexity measures represented by the eigenvalue of the first factor. We utilized an analysis of variance with a linear repeated measures mixed model design for all outcome measures. A Pearson's r was computed to assess the relationship between negative self complexity and depression severity. See Table 5 below for a summary of main effects data.

Table 5
2x4 Repeated Measures ANOVA for Outcome Measures

Measure	*df*	*F*	*H*	*P*
BDI Total [a]	3	2.28	.20	.10
HAMD [a]	3	1.29	.13	.23
BDIcog [a]	3	1.42	.15	.26
BDIneuro [a]	3	1.91	.19	.16
HopeTotal [a]	3	0.07	.01	.98
HopeLossMotivation [a]	3	0.23	.03	.88
HopeFeelingsFuture [a]	3	0.51	.06	.68
HopeFutureExpect [b]	3	0.45	.05	.72
HopeRiskFatalSuicide [a]	3	0.85	.10	.48
Clinical Anxiety Scale [a]	1.478	0.63	.07	.61
SF-physical functioning [b]	3	0.15	.02	.93
SF-role limit. Physical [b]	3	1.57	.15	.22
SF-role limit. Emotional [b]	3	0.56	.06	.64
SF-energy/fatigue [a]	3	0.24	.03	.87
SF-emotional functioning [a]	3	0.34	.04	.80
SF-social functioning [a]	3	0.23	.03	.87
SF-pain [b]	3	0.91	.10	.45
SF-general health [b]	3	0.29	.03	.83
Credibility Expectancy Scale [b]	1.6	1.33	.13	.29
Negative Self Complexity [b]	1.603	1.67	.16	.20
Positive Self Complexity [b]	1.762	0.39	.04	.76

a=Main effects for time, significant; b= Main effects for time, not significant

Level of Depression. Overall, there was a decrease in depression severity across treatment sessions for both groups. Main effects for time for total BDI, cognitive, neurovegitative, and HAM-D scores were all statistically significant (HAM-D: $F(3, 27)=23.21$, p=.00; BDITotal: $F(3,27)=11.34$, p=.00; BDIcognitive: $F(3, 24)=10.00$, p=.00; BDIneuroveg.: $F(3, 24)=6.95$, p=0.002). However, main effects for treatment group were not statistically significant for any of the depression measures (HAM-D: $F(3, 27)=1.29$, p=.27; BDITotal: $F(3, 27)=2.28$, p=0.10; BDIcognitive: $F(3, 24)=1.42$, p=0.26; BDIneuroveg.: $F(3, 24)=1.91$, P=0.16). Post hoc paired t test analyses for main effects for time were performed. Reduction in BDITotal scores were statistically significant between baseline and week 4 (t(10)=4.02, p=0.002), baseline and follow-up 1 (week 7) (t(10)=4.15, p=0.002), and baseline and follow-up 2 (week 10) (t(10)=4.45, p=0.001). Reduction in BDIcognitive scores were statistically significant between baseline and week 4 (t(9)=4.50, p=0.001), baseline and follow-up 1 (week 7) (t(9)=4.67, p=0.001), and baseline and follow-up 2 (week 10) (t(9)=4.39, p=0.002). Reductions in BDIneuroveg. scores were statistically significant between baseline and follow-up 1 (t(9)=3.54, p=0.006), and week 4 and follow-up 2 (week 7) (t(9)=4.13, p=0.003). Reduction in HAMD scores were statistically significant between baseline and week 4 (t(10)=4.14, p=0.002), baseline and follow-up 1 (week 7) (t(10)=5.80, p=0.00), baseline and follow-up 2 (week 10) (t(10)=8.23, p=0.00), and week 4 and follow-up 2 (week 10) (t(10)=2.40, p=.037). Analyses were also performed using gender, therapist, age, and ethnicity as covariates—none of which affected the outcome.

The average percentage of clinical response to the sham control protocol from baseline to follow-up 2 was 59.80% (13.19). The average percentage of clinical respons2e to the biofeedback intervention from baseline to follow-up 2 was 40% (28.79).

Levels of Hopelessness and Suicidality. Overall, there was a decrease in severity of hopelessness across treatment sessions for both groups. Main effects for time for total hopelessness, loss of motivation, feelings about the future, and risk of fatal suicide scores were all statistically significant (total hopelessness: $F(3, 24)=13.80$, p=.00; loss of motivation: $F(3, 24)=22.40$, p=.00; feelings about the future: $F(3, 24)=13.70$, p=.00; risk of fatal suicide: $F(3, 24)=11.92$, p=.000). However, main effects for treatment group were not statistically significant for any of the hopelessness measures measures (total hopelessness: $F(3, 24)=0.07$, p=.98; loss of motivation: $F(3, 24)=0.23$, p=0.88; feelings about the future: $F(3, 24)=0.51$, p=0.68; risk of fatal suicide: $F(3, 24)=0.85$, P=0.48). Also, main effects both for time and for treatment group were non-significant for improvements in future expectations. Post hoc paired t test analyses for main effects for time were performed. Reduction in total hopelessness scores were statistically significant between baseline and week 4 (t(9)=4.34, p=0.002), baseline and follow-up 1 (week 7) (t(9)=5.79, p=.00), and baseline and follow-up 2 (week 10) (t(9)=4.86, p=0.001). Improvements in feelings about the future scores were statistically significant between baseline and week 4 (t(9)=3.74, p=0.005), baseline and follow-up 1 (week 7) (t(9)=4.98, p=0.001), and baseline and follow-up 2 (week 10) (t(9)=6.71, p=.00). Reduction in loss of motivation scores were statistically significant between baseline and week 4 (t(9)=6.77, p=.00), baseline and follow-up 1 (week 7) (t(9)=6.88, p=.000), baseline and follow-up 2 (week 10) (t(9)=4.81, p=.001, and week 4 and follow-up one (t(9)=2.45,

p=.037. Reduction in risk of fatal suicide scores were statistically significant between baseline and week 4 (t(9)=2.50, p=0.04), baseline and follow-up 1 (week 7) (t(9)=6.0, p=.000), baseline and follow-up 2 (week 10) (t(9)=4.58, p=0.001), and week 4 and follow-up 2 (week 10) (t(9)=2.45, p=.037).

Exploratory Analyses

Levels of Anxiety. Overall, there was a decrease in severity of anxiety across treatment sessions for both groups. Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated, $\chi^2(5)=12.41$, p=.031, and, therefore, a Greenhouse-Geisser correction was used. Main effects for time for CAS was statistically significant, $F(1.478, 11.27)=23.21$, p=.00). However, main effects for treatment group were not statistically significant for anxiety as measured by CAS, $F(1.478, 11.27)=0.63$, p=.61. Post hoc paired t test analyses for main effects for time were performed. Reduction in CAS scores were statistically significant between baseline and week 4 (t(10)=4.18, p=0.002), baseline and follow-up 1 (week 7) (t(10)=4.05, p=0.003), baseline and follow-up 2 (week 10) (t(10)=4.23, p=0.002), week 4 and follow-up 1 (t(10)=2.36, p=0.04, and week 4 and follow-up 2 (t(10)=2.79, p=.02).

Functional Health and Wellbeing. Main effects for time for improvements in energy level, emotional well-being, and social functioning as measured by the SF-36 were statistically significant (energy/fatigue: $F(3, 37)=3.77$, p=0.02; emotional well-being: $F(3, 27)=6.69$, p=0.002; social functioning: $F(3, 27)=4.47$, p=0.01). However, main effects for time for all other SF-36 measures (i.e., physical functioning, role limitations due to physical health, role limitations due to emotional problems, pain and general health) were not statistically significant. Moreover, main effects for treatment

group were not statistically significant for any of the SF-36 measures. Post hoc paired t test analyses for main effects for time were performed. Improvements in emotional well-being and social functioning scores were statistically significant between baseline and all other all other data points. Improvements in energy/fatigue scores were statistically significant between baseline and follow-up 1, t(10)=2.68, p=0.02.

Negative Self Complexity. Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated, $\chi^2(5)=14.51$, p=.01, and, therefore, a Greenhouse-Geisser correction was used. Both the main effects for time and for treatment group were not significant for differences in negative self complexity scores (time:$F(1.603)=14.43$, p=0.94; treatment group:$F(1.603)=0.39$, p=0.76).

Relationship Between Negative Self Complexity and Levels of Depression. A Pearson r correlation coefficient was computed to assess the relationship between negative self complexity and depression. There was no correlation between baseline negative self complexity measures on the CCPRQ and baseline depression scores measured by the HAM-D, r = 0.34, n = 11, p = 0.33. There was also no correlation between baseline negative self complexity measures on the CCPRQ and baseline depression scores measured by the BDI (total score), r = 0.34, n = 11, p = 0.31.

Credibility/Expectancy Levels. Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated, $\chi^2(5)=12.15$, p=.03, and, therefore, a Greenhouse-Geisser correction was used. Both the main effects for time and for treatment group were not significant for differences in credibility/expectancy scores (time:$F(1.6)=14.40$, p=0.16; treatment group:$F(1.6)=1.33$, p=0.29.

CHAPTER IV

Discussion

Biofeedback and Depression

The current study was a follow-up study to the open label pilot study conducted by this lab (Karavidas, et al., 2007) which, using a similar biofeedback protocol, showed evidence to suggest the efficacy of HRV/RSA biofeedback for the treatment of depression. As a follow-up, we wanted to compare the effects of a HRV/RSA biofeedback intervention with that of a credible sham respiratory control protocol. Our first hypothesis was that the participants who completed the 10-session HRV/RSA biofeedback intervention would experience greater improvement in depression symptoms than those assigned to the credible sham respiratory control condition. This hypothesis was based on the results of a number of previous studies suggesting that HRV/RSA biofeedback may be effective at significantly reducing symptoms of depression (Hassett, et al., 2007; Karavidas, et al., 2007; Nolan, et al., 2005; Siepmann, et al., 2008; Zucker, et al., 2008). In the current study, we found no significant difference in the degree of improvement in depression symptoms between participants in the credible sham respiratory control condition and the HRV/RSA biofeedback intervention. Participants in both groups experienced significant improvement in depression symptoms over time. Overall, for BDI Total and HAM-D scores, the significant decreases in depression symptoms were found mainly between baseline measures and all other time points. These improvements over time may be attributable to regression towards the mean. Observed improvements in depression severity over the 10 weeks (2.5 months) in both

groups may also reflect the natural course of the disease—as depressive episodes have been found to remit as early as 3 months after the index date in individuals for whom depression symptoms were left untreated (Maxmen & Ward, 1995). Another hypothesis to account for the observed improvements in both groups over time is that the two protocols may share elements apart from the purported active/inert components that are unintentionally therapeutic. For example, participants' increased attention to their breathing over the course of the study might have served as a form of distraction from depressive thoughts and feelings.

Our findings reflect those of other studies found in the literature for which the effects of HRV/RSA biofeedback on depression were not found (i.e., Giardino, Chan, & Borson, 2004; McCraty, et al., 2009; Mussgay, et al., 2008; Reineke, 2007; Swanson, et al., 2009). One hypothesis for the lack of significant group differences in depression scores found in the current study is possible variation in participants' treatment compliance—especially with regards to in-session practice efforts and at-home breathing practice. Although study clinicians gave instructions, inquired about, problem solved, and reinforced participants' practice efforts in each session, no objective data was collected about participants' in-session efforts or actual at-home compliance. It is plausible that differences in participants' treatment compliance—both between and within groups—existed, and that this unaccounted for variance could be obscuring the treatment effect. Another hypothesis for the lack of significant group differences found in the depression measures is that the very small sample size of the study was not adequate to detect a significant difference between groups. Although the study sought out to recruit a final N of at least 20 participants, challenges with recruitment (i.e.,

prospective participants' difficulties related to: traveling to the study site; lack of consistent availability for the 10-week time commitment of the study) and retention (i.e., attrition due to study fatigue—a common drawback of the repeated-measures design; scheduling difficulties) precluded this. That our results did not corroborate the findings of previous studies that support the efficacy of HRV biofeedback in the treatment of depression might also be attributable to our study being the first in this line of research that employed a credible sham respiratory control group. As our control protocol appears to have been sufficiently structurally indistinguishable from the intervention protocol, it is possible that our study was able to control for common factors that were not previously controlled for in the extant literature—thus ruling out incidental factors that may, at least in part, account for the significant findings of those studies. The viability of our control protocol will be discussed further in a subsequent section.

Our second hypothesis was that improvements in depression exhibited by the biofeedback intervention group would persist at 1-month post-treatment. In the current study, although the improvements in depression of participants in the biofeedback intervention group did persist at 1-month post-treatment, this improvement was also seen in the control group, with no significant difference between the two groups in this respect. This improvement may be likewise attributable to the aforementioned factors (i.e., regression to the mean; natural course of the disease).

Our third hypothesis was that there would be a greater percentage of clinical response to the biofeedback intervention as compared to the sham control, with clinical response operationally defined as a reduction of at least 50% in HAM-D scores from baseline to session 10 or a final score of 10 or fewer on the HAM-D scale. In the current

study, this was not found to be the case, as the biofeedback intervention response was 19.80% lower than that of the sham control. That a greater clinical response among participants in the biofeedback group on HAM-D scores was not found in our study may, as well, be likewise attributable to the factors discussed above (i.e., possible variability in participants' treatment compliance; small sample size; utilization of placebo control group).

Biofeedback and Anxiety & Functional Health and Wellbeing

For our exploratory measures CAS and SF-36, we found no significant difference in the degree of improvement in symptoms of anxiety, and health and wellbeing (i.e., physical and emotional functioning, physical and emotional role limitations, energy/fatigue, social functioning, pain, and general health) between participants in the sham respiratory biofeedback control condition and the HRV/RSA biofeedback intervention. Participants in both groups experienced significant improvement in anxiety, social and emotional functioning, and energy/fatigue symptoms over time. This may be attributable to regression towards the mean. As depression has been found to be associated with both anxiety and deterioration of various indicators of physical health (APA, 2000), the improvement seen in these variables may also be related to observed improvements in depression symptoms over time.

Negative Self-Complexity and Depression

Our fourth and final hypothesis was that negative self-complexity scores would be positively correlated with depression severity. This hypothesis was based on previous research findings suggesting that higher measures of negative self-complexity are associated with depressive symptoms, and are predictive of their persistence post-

treatment (Gara et al., 1993; Woolfolk et al., 1995; Woolfolk, et al., 1999; Woolfolk, et al., 2004). As such, it has been proposed that negative self-complexity may potentially hinder optimal recovery from depression (Woolfolk, et al., 1999)--therefore, moderating major depression treatment outcomes. In the current study, we found no significant correlation between depression scores and negative self-complexity scores, although the positive directionality of the correlation was that which was predicted. One hypothesis as to why our results did not corroborate previous findings is that our sample size might have been too small to detect a significant relation in our analyses. Another hypothesis is that there are perhaps important demographic and clinical population differences between the participant sample of the current study and those used in the studies supporting an association between negative self-complexity and depression severity. Yet another consideration is that, given the etiological heterogeneity that exists among depressed individuals (Winokur, 1997), negative self-complexity is just one of a myriad potential biopsychosocial factors that can contribute to and moderate depression severity and persistence—in the general population and in our sample.

Credibility, Expectancy & the Feasibility of the Credible Sham Control Condition

As previously mentioned, one of the most notable methodological limitations of the extant studies supporting the efficacy of HRV biofeedback in treating depression is the absence of control and placebo control group designs (Fourie, 2006; Hallman, et al., 2011; Hassett, et al., 2007; Karavidas, et al., 2007; Nolan, et al., 2005; Siepmann, et al., 2008; Zucker, et al., 2009). The placebo-controlled design is deemed ideal, as it rules out incidental, common factors—allowing treatment specificity of the purported active ingredients to be optimally ascertained (Rosenthal & Frank, 1956). In order for this

differentiation to be adequately achieved, with the exception of the active component, the placebo control should be structurally indistinguishable from the treatment (Gaurdiano & Herbert, 2003; Howard, et al., 1986). Structural equivalence is characterized by being identical with regards to treatment modality, number of sessions, and session length, for example (Baskin, et al., 2003). The current study is unique in that a credible sham respiratory control protocol was developed and employed as the comparison group. This protocol was structurally indistinguishable from the active biofeedback protocol, in that: 1) both utilized the respiratory biofeedback format; 2) both used the same number of training sessions; 3) both utilized the same session length. The only differentiating feature between the groups was the frequency at which participants breathed: while the participants in the treatment group were trained to increased their heart rate oscillations by practicing breathing at their determined resonant frequency, the participants in the control group breathed at an assigned "designated frequency" shown to yield non-significant changes in baroreflex sensitivity. (see Appendix for a detailed description of both protocols.)

The current study sought to determine the viability of the credible sham respiratory control protocol. One strategy commonly employed to evaluate the adequacy of placebo controls is to derive this empirically from ratings of credibility and expectation (e.g., Barker, Funk, & Houston, 1988; Bowers & Clum, 1988; Stevens, Hynan, & Allen, 2000). Treatment credibility refers to how logical, believable, and convincing a treatment is perceived to be (Devilly & Borkovec, 2000), while expectancy refers to expectations regarding anticipated outcome (Rutherford, et al, 2010). The Credibility and Expectancy Questionnaire (CEQ) was thus administered to participants in

the current study as a means of ascertaining the adequacy of the credible sham respiratory control protocol. Our analyses found no significant differences between groups on CEQ scores at baseline (administered right after participants' initial orientation to the study rationale and format), or at any subsequent time point. These results may imply that the control and intervention protocols were essentially equivalent with respect to participants' perceptions of how logical, believable, and effective the respective protocols were. That there were no reported complaints of discomfort or adverse side effects among individuals assigned to either protocol is an important consideration as well with regards its tolerability. Thus, with both protocols being structurally indistinguishable, both yielding statistically identical CEQ ratings, and both having been well tolerated by participants, the credible sham respiratory control protocol utilized in the current study has been found to be an effective and feasible placebo control for utilization in HRV/RSA biofeedback research.

Limitations of Current Study

The most obvious, and most significant, methodological limitation of the current study is the very small sample size. As discussed in the preceding sections, although no significant group differences were found on any of the primary or exploratory outcome measures, because of its very small sample size the study likely did not have enough power to detect these significant differences, if they did, in fact, exist—possibly contributing to a Type II error. As the utilization of a waitlist comparison group in research involving depressed persons would be ethically untenable, the present study could not control for the natural course of the disease. As a result, the extent to which improvements over time in either group can be attributed to the elements of the respective

protocols remains unclear. As discussed earlier, not standardizing participants' home practice efforts restricted the study's ability to control for the variation in the analyses. That the current study did not include an analysis of physiological data is another limitation. Thus, although previous research supports the efficacy of using HRV biofeedback to stimulate baroreflex gain, thereby stimulating the vagus nerve in such a way that promotes autonomic balance, we could not corroborate these autonomic changes among our treatment participants, nor could we control for any variations in autonomic effects in our analyses.

The current study consisted of mostly Caucasian and Asian/Southeast Asian participants of medium socio-economic status with an average age of 31 years. Most of the participants had obtained at least some college-level education, and several were pursuing graduate degrees. As such, the results of the study may be limited to the sample characteristics of our population and may not generalize to individuals of other demographics—particularly those from other socio-economic, education, and ethnic backgrounds. That 45% of the participants in the current study were either severely or very severely depressed, and only 9% were mildly depressed (as measured by HAMD) may also partially restrict its generalizability with respect to depression severity. Also, due to limited/incomplete access to the participants' demographic information at the time of analysis, the current study did not report nor control for variability in participants' comorbid psychiatric diagnoses, past experience with biofeedback or similar modalities involving awareness of the breath (i.e., yoga, meditation), education level, marital status and employment status.

The consumption of caffeine, nicotine, alcohol, as well as the engagement in vigorous exercise, were not controlled for in a standardized manner in the current study. Finally, study clinicians who entered and edited the data were not blind to participant condition. Therefore, it is possible that some degree of bias was introduced during the management of the data, which could have affected the outcome of the group comparisons.

Recommendations for Future Directions

There are several key areas of future research suggested by the results, and limitations, of the present study. Particularly because the literature both investigating the relationship between depression and RSA, and examining the efficacy of HRV/RSA biofeedback for depression are, at this point, somewhat equivocal, it is critical for future studies to measure and analyze HRV physiological data in order to truly advance the pursuit of using HRV biofeedback for clinical applications. In a similar vein, in order to truly establish and confirm the purported therapeutic properties of HRV biofeedback in the context of clinical outcome research, and also bolster the internal validity of such investigations, it would seem beneficial for future research to utilize placebo control protocols such as the credible sham respiratory protocol developed and used in the current study. Another relatively novel characteristic of the current study that should be utilized in the methodology of future HRV biofeedback research is randomization. Subsequent investigations in this area should replicate the current study, with the addition of a larger sample size, standardized at-home practice, and analysis of physiological data. Future studies should also evaluate population differences of completers and non-completers.

Summary/Conclusions

In conclusion, the current preliminary efficacy study was the first known study to utilize a credible sham respiratory control protocol as the comparison for HRV/RSA biofeedback in the treatment of depression. The overall findings indicated that, irrespective of group assignment, participants experienced significant improvements in the symptoms of depression, anxiety, and general health over the 10-week study course. Factors such as regression to the mean, natural disease course, and extraneous therapeutic elements may account for this. No significant differences on depression scores, or any other outcome measures, were found between groups. However, the study had limited power to detect significant differences, due to its very small sample size; thus definitive conclusions regarding the efficacy of HRV biofeedback in the treatment of depression cannot be drawn from the results of the present study. Limited power notwithstanding, other hypothesized factors that may account for this include use of placebo control (not used in previous research supporting HRV biofeedback efficacy for depression) and variable treatment compliance. An important finding of the present study was that the credible sham respiratory protocol developed by this laboratory was an effective, viable, and tolerable placebo control comparison. The efficacy of HRV biofeedback as an alternative or adjust treatment modality for depression may be established in future studies, with the implementation of improved experimental design.

References

Abbass, A.A., Hancock, J.T., Henderson, J., & Kisely, S. (2006). Short-term psychodynamic psychotherapies for common mental disorders. Cochrane Database of Systematic Reviews, 4. CD004687, 1-47.

Abramson, L.Y., Alloy, L.B., & Metalsky, G.I. (1995). Hopelessness depression. In G.M. Buchanan & M.E.P. Seligman (Eds.), *Explanatory style* (pp. 113-134). Hillsdale, New Jersey: Erlbaum.

Abramson, L.Y., Seligman, M.E.P., & Teasdale, J. (1978). Learned helplessness in humans: Critique and reformulation. *Journal of Abnormal Psychology*, 87, 49-74.

American Psychiatric Association. (1993): Practice Guidline for Major Depressive Disorder in Adults. *American Journal of Psychiatry*, 150.

American Psychiatric Association. (1995). Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Primary Care version. Washington DC.

American Psychiatric Association. (2000). Practice guidelines for the treatment of patients with major depressive disorder. 2nd ed. Washington, DC. American Psychiatric Association.

American Psychiatric Association. The Diagnostic and Statistical Manual for Mental Disorders, IV-TR. American Psychiatric Association, 2000.

Applehans, B.M., & Luecken, L.J. (2006). Heart rate variability as an index of regulated emotional responding. *Review of General Psychology*, 10, 229-240.

Balogh, S., Fitzpatrick, D.F., Hendricks, S.E., & Paige, S.R. (1993). Increases in heart rate variability with successful treatment in patients with major depressive disorder. *Psychopahrmacol. Bull*., 29, 201-206.

Bar, K., Greiner, W., Jochum, T, Friedrich, M., Wagner, G., & Sauer, H. (2004). The influence of major depression and its treatment on heart rate variability and papillary light reflex parameters. *Journal of Affective Disorders*, 82, 245-252.

Barker, S.L., Funk, S.C., & Houston, B.K. (1988). Psychological treatment versus nonspecific factors: a meta-analysis of conditions that engender comparable expectations for improvement. *Clinical Psychology Review*, 8, 579-594.

Barlow, D. (2007). *Clinical Handbook of Psychological Disorders, Fourth Edition: A Step-by-Step Treatment Manual*. The Guilford Press.

Barnes, R.F., Veith, R.C., Borson, S., Verhey J., Raskind, M.A., & Halter, J.B. (1983). High levels of plasma catecholamines in dexamethasone-resistant depressed patients. *American Journal of Psychiatry*, 140, 1623-5.

Bass, C., & Gardner, W. (1985). Emotional influences upon breathing and breathlessness. *Journal of Psychosomatic Research*, 29, 592-609.

Baskin, T.W., Tierney, S.C., Minami, T., & Wampold, B.E. (2003). Establishing specificity in psychotherapy: a meta-analysis of structural equivalence of placebo controls. Journal of Consulting and Clinical Psychology, 71(6), 973-979.

Beauchaine, T. (2001). Vagal tone, development, and Gray's motivational theory: Toward an integrated model of autonomic nervous system functioning in psychopathology. *Development and Psychopathology*, 13, 183-214.

Beauchaine, T., Gatzke-Kopp, L., & Mead, H. (2007). Polyvagal theory and developmental psychopathology: emotion dysregulation and conduct problems from preschool to adolescence. *Biological Psychology*, 74(2), 174-184.

Beck, A.T. (1967). *Depression: Clinical, experimental and theoretical aspects*. New York: Harper & Row.

Beck, A.T. (1991). *Beck Scale for Suicide Ideation*. San Antonio, TX: Psychological Corporation.

Beck, A.T. (1993). *Beck Anxiety Inventory (BAI)*. San Antonio, TX: Psychological Corporation.

Beck, A.T. (1993). *Beck Hopelessness Scale*. San Antonio, TX: Psychological Corporation.

Beck, A.T., Rush, A.J., Shaw, B.F., & Emery, G. (1979). *Cognitive therapy of depression*. New York: Guilford.

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). *Manual for Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, 4, 561-571.

Berlim, M.T., Fleck, M.P., & Turecki, G. (2008). Current trends in the assessment and somatic treatment of resistant/refractory major depression: an overview. Annals of Medicine, 40(2), 149-159.

Berger, B.C., & Gevirtz, R. (2001). The treatment of panic disorder: a comparison between breathing retraining and cognitive behavioral therapy. Citation paper

presented at the 32nd annual meeting of the Associated for Applied Psychophysiology and Biofeedback. *Applied Psychophysiology and Biofeedback*, 23(3).

Bernardi, L., Rossi, M., Leuzzi, S., Mevio, E., Fornasari, G., Calciati, A., et al. (1997). Reduction of 0.1 Hz microcirculatory fluctuations as evidence of sympathetic dysfunction in insulin-dependent diabetes. *Cardiovascular Research*, 34, 185-191.

Bernardi, L., Porta, C., Gabutti, A., Spicuzza, L., & Sleight, P. (2001). Modulatory effects of respiration. *Autonomic Neuroscience*, 90(1-2), 47-56.

Bernardi, L., Porta, C., Spicuzza, L., et al. (2002). Slow breathing increases arterial baroreflex sensitivity in patients with chronic heart failure. *Circulation January*, 105(2), 143-145.

Berntson, G.G., Bigger, T. Jr., Eckberg, D.L., Grossman, P., Kaufmann, P.G., et al. (1997). Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology*, 34, 623-648.

Berntson, G.G., Cacioppo, J.T., & Quigley, K.S. (1993). Respiratory sinus arrhythmia: autonomic origins, physiological mechanisms, and psychophysiological implications. *Psychophysiology*, 30, 183-196.

Berto, P., D'Ilario, D., Ruffo, P., Di Virgilio, R., & Rizzo, F. (2000). Depression: Cost-of-Illness Studies in the International Literature, a Review. *Journal of Mental Health Policy and Economics*, 3, 3-10.

Blanchard, E.B., Andrasik, F., Appelbaum, K.A., Evans, D.D., Myers, P., & Barron, K.D. (1986). Three studies of the psychologic changes in chronic headache patients associated with biofeedback and relaxation therapies. *Psychosomatic Medicine*, 48,1/2, 73-83.

Blechert, J., Michael, T., Grossman, P., Lajtamn, M., & Wilhelm, F. H. (2007). Autonomic and respiratory characteristics of posttraumatic stress disorder and panic disorder. *Psychosomatic Medicine*, 69, 935-943.

Bowers, T.G., & Clum, G.A. (1988). Relative contributions of specific and nonspecific treatment effects: meta-analysis of placebo-controlled behavior therapy research. *Psychological Bulletin*, 103, 315-323.

Brown, G.W., Bifulco, A., & Andrews, B. (1990). Self-esteem and depression. *Soc. Psychiatry Psychiat. Epidemiol*., 25, 244-249.

Burkholder, T., Chambers, M., Hotmire., K., Wurster, R.D., Moody, S., & Randall, W.C. (1992). Gross and microscopic anatomy of the vagal innervation of the rat heart. Anatomical Record, 232, 444-452.

Busch, F.N. (2005). Psychodynamic Treatment of Depression. Directions in Psychiatry, 25(3), 23-34.

Cain, R.A. (2007). Navigating the sequenced treatment alternatives to relieve depression (STAR*D) study: practical outcomes and implications for depression treatment in primary care. *Primary Care*, 34(3), 505-519.

Carney, R. M., Rich, M.W., teVelde, A., Saini, J., Clark, K., & Freedland, K.E. (1988). The relationship between heart rate variability and depression in patients with cornary artery disease. *Journal of Psychosomatic Research*, 32, 159-64.

Carney, R.M., Blumenthal, J.A., Freedland, K.E., et al. (2005a). Change in heart rate and heart rate variability during treatment for depression in patients with coronary heart disease. Psychosomatic Medicine, 62, 639-647.

Carney, R.M., Blumenthal, J.A., Freedland, K.E., Stein, P.K., Howells, W.B., et al. (2005b). Low heart rate variability and the effect of depression on post-myocardial infarction mortality. *Archives of Internal Medicine*, 165, 1486-91.

Carney, R.M., Blumenthal, J.A., Stein, P.K., Watkins, L., Catellier, D., Berkman, L.F., et al. (2001). Depression, heart rate variability, and acute myocardial infarcation. *Circulation*, 104, 2024-8.

Carney, R.M., Freedland, K.E., & Rich, M.W. (1995). Depression as a risk factor for cardiac events in established coronary heart disease: a review of possible mechanisms. *Annals of Behavioral Medicine*, 17, 142-9.

Carney, R.M., Saunders, R.D., Freedland, K.E., Stein P., Rich, M.W., & Jaffe, A.S. (1995). Association of depression with reduced heart rate variability in coronary artery disease. *American Journal of Cardiology*, 76, 562-564.

Chambers, A.S., & Allen, J.J.B. (2002). Vagal tone as an indicator of treatment response to major depression. *Psychophysiology*, 39, 861-864.

Chambless, D.L., & Ollendick, T.H. (2001). Empirically supported psychological interventions: Controversies and evidence. *Annual Review of Psychology*, 52, 685-716.

Chernigovskaya, N.V., Vaschillo, E.G., Petrash, V.V., & Rusanovskii, V.V. (1990). Voluntary control of the heart rate as a method of correcting the functional state of neurosis. *Human Physiology*, 16, 58-64.

Cohen, H., Benjamin, J., Geva, A.B., Matar, M.A., Kaplan, Z., & Kotler, M. (2000). Autonomic dysregulation in panic disorder and in posttraumatic stress disorder: Application of power spectrum analyses of heart rate variability at rest in response to recollection of trauma or panic attacks. *Psychiatry Research*, 96, 1-13.

Cohen, H., Matar, M., Kaplan, Z., & Kotler, M. (1999). Power spectral analysis of heart rate variability in psychiatry. *Psychotherapy and Psychomatics*, 2, 59-66.

Cornes, C.L., & Frank, E. (1994). Interpersonal Psychotherapy for Depression. *The Clinical Psychologist*, 47(3), 9-10.

Cox, T. (1978). *Stress*. Baltimore, MD. University Press.

Cozolino, L. (2006). *The Neuroscience of Human Relationships: Attachment and the Developing Social Brain*. New York, NY: W.W. Norton & Co.

Cuijpers, P., van Straten, A., & Warmerdam, L. (2007). Behavioral activation treatments of depression: A meta-analysis. *Clin Psychol Rev*, 27, 318-326.

Cuijpers, P., van Straten, A., Andersson, G., & van Oppen, P. (2008). Psychotherapy for Depression in Adults: A meta-analysis of comparative outcome studies. *Journal of Counseling and Clinical Psychology*, 76(6), 909-922.

Cuijpers, P., van Straten, A., Schuurmans, J., van Oppen, P., Hollon, S.D., & Andersson, G. (2010). Psychotherapy for chronic major depression and dysthymia: a meta-analysis. *Clinical Psychology Review*, 30, 51-62.

Daly, M. de B. (1985). Interactions between respiration and circulation. In N.S. Cherniack & J.G. Widdicombe (Eds.), *Handbook of physiology: The respiratory system II* (PP. 529-594). Bethesda, MD: American Physiological Society.

Dantzer, R., Wollman, E., Vitkovic, L, Yirmiya, R. (1999). Cytokines and depression: fortuitous or causative association: *Molecular Psychiatry*, 4, 328-32.

Davidson, R.J., Jackson, D.C., & Kalin, N.H. (2000). Emotion, plasticity, context, and regulation: perspectives from affective neuroscience. *Psychological Bulletin*, 126, 890-909.

Davies, C.T., & Neilson, J.M.M. (1967a). Disturbance of hart rhythm during recovery from exercise. *Journal of Applied Physiology*, 22, 943-946.

Davies, C.T. & Neilson, J.M.M. (1967b). Sinus arrhythmia in man at rest. *Journal of Applied Physiology*, 22, 947-955.

Dawson, M.E., Schell, A.M., & Catania, J.J. (1977). Autonomic correlates of depression and clinical improvement following electroconvulsive shock therapy. *Psychophysiology*, 14, 569.

Dawson, M.E., Schell, A.M., Braaten, J.R., & Catania, J.J. (1985). Diagnostic utility of autonomic measures of major depressive disorders. *Psychiatry Research*, 15, 261-270.

De Guevara, M.S., Schauffele, S.I., Nicola-Siri, L.C., Fahrer, R.D., Ortiz-Fragola, E., et al. (2004). Worsening of depressive symptoms 6 months after an acute coronary event in older adults is associated with impairment of cardiac autonomic function. *Journal of Affective Disorders*, 80, 257-262.

De Maat, S., Dekker, J., Schoevers, R., van Aalst, G., Wijk, G., et al. (2008). Short psychodynamic supportive psychotherapy, antidepressants, and their combination in the treatment of major depression: A mega-analysis based on three randomized clinical trials. *Depression and Anxiety*, 25, 565-574.

Depression in Primary Care: Vol 2, Treatment of Major Depression [Clinical Practice Guideline No. 5; AHCPR Publication No. 93-0551]. Depression Guideline Panel. Rockville, MD: US Dept of Health and Human Services; 1993.

DeRubeis, R.J., Hollon, S.D., Amsterdam, J.D., et al. (2005). Cognitive therapy vs medications in the treatment of moderate to severe depression. *Arch Gen Psychiatry*, 62, 409-416.

Devilly G.J., & Borkovec, T.D. (2000). Psychometric properties of the Credibility/Expectancy Questionnaire. *Journal of Clinical and Experimental Hypnosis*, 50, 17-32.

Dietrich, A., Riese, H., Sondeijker, F., Greaves-Lorder, K., van Roon, A.M., et al. (2007). Externalizing and internalizing problems in relation to autonomic function: A population-based study in preadolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46(3), 378-386.

Donohue, J.M., & Pincus, H.A. (2007). Reducing the Societal Burden of Depression: A Review of Economic Costs, Quality of Care and Effects of Treatment. *Pharmacoeconomics*, 25(1), 7-24.

Driessen, E., Cuijpers, P., de Maat, S.C.M., Abbass, A.A., de Jonghe, F., & Dekker, J.J.M. (2010). The efficacy of short-term psychodynamic psychotherapy for depression: a meta-analysis. Clinical Psychology Review, 30(1), 25-36.

Dywan, J., Mathewson, K.J., Choma, B.L., Rosenfeld, B., & Segalowitz, S.J. (2008). Autonomic and electrophysiological correlates of emotional intensity in older and younger adults. *Psychophysiology*, 45, 389-397.

Eckberg, D.L. (1982). Human sinus node responses to repetitive, ramped carotid baroreceptor stimuli. *American Journal of Physiology*, 242, 638-644.

Eckberg, D.L., & Sleight, P. Human baroreflexes in health and disease. Oxford: Clarendon Press; 1992.

Eisenberg, N., Fabes, R., Murphy, B., Maszk, P., Smith, M., & Karbon, M. (1995). The role of emotionality and regulation in children's social functioning: A longitudinal study. *Child Development*, 66, 1360-1384.

Elhwuegi, A.S. (2004). Central monoamines and their role in major depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*,28, 435-451.

Ellgring, H. (1989). *Nonverbal communication in depression*. New York: Cambridge University Press.

Epstein, S.A., Kay, G., Clauw, D., Heaton, R., Klein, D., Krupp, L., et al. (1999). Psychiatric disorders in patients with fibromyalgia. A multicenter investigation. *Psychometrics*, 40, 57-63.

Fabes, R.A., & Einsenberg, N. (1997). Regulatory control and adults' stress-related responses to daily life events. *J. Pers. Soc. Psychol*., 73, 1107-1117.

Fava, G.A. (1999). Subclinical symptoms in mood disorders: pathophysiological and therapeutic implications. *Psychol. Med*., 29, 47-61.

Fava, G.A., Kellner, R., Lisansky, J., Park, S., Perini, G.I., & Zielezny, M. (1986). Rating depression in normals and depressives. *Journal of Affective Disorders*, 11, 29-33.

Fava, M. (2003). Diagnosis and definition of treatment-resistant depression. Society of Biological Psychiatry, 53, 650-659.

Fava, M., Fabbri, S., & Sonino, N. (2002). Residual symptoms in depression: an emerging therapeutic target. *Progress in Neuro-Psychoopharmacology & Biological Psychiatry*, 26, 1019-1027.

Fawcett, J., Scheftber, W., Clark, D., Hedeker, D., Gibbons, R., & Coryell, W. (1987). Clinical predictors of suicide in patients with major affective disorders: A controlled prospective study. *American Journal of Psychiatry*, 144(1), 35-40.

Feldman, J.L., & Ellenberger, H.H. (1988). Central coordination of respiratory and cardiovascular control in mammals. *Annual Review of Physiology*, 50, 593-606.

Fennell, M.J.V. (2004). Depression, low self-esteem and mindlfulness. *Behaviour Research and Therapy*, 42, 1053-1067.

First, M.B., Gibbons, M., Spitzer, R.L., & Williams, J.B.W. (1996). *User's guide for the Structured Clinical Interview for DSM-IV Axis I Disroders-Research Version (SCID-I, Version 2.0)*. New York: Biometric Research Department.

Fourie, P. (2006). Effects of RSA feedback on posttraumatic stress disorder symptomatology. *Australian Journal of Guidance & Counseling*, 16(2), 249-255.

Fournier, J.C., DeRubeis, R.J., Hollon, S.D., et al. (2010). Antidepressant drug effects and depression severity: a patient-level meta-analysis. *Journal of the American Medical Assocation*, 303(1), 47-53.

Fox, N.A. (1989). Psychophysiological correlates of emotional reactivity during the 1st year of life. *Developmental Psychology*, 25, 364-372.

Frasure-Smith, N., Lesperance, F., & Talajie, M. (1993). Depression following myocardial infarction: impact on 6 month survival. *Journal of American Medical Association*, 270, 1819-25.

Fried, R. (1993). The role of respiration in stress and stress control: Towards a theory of stress as a hypoxic phenomenon. In Lehrer, P.M. & Woolfolk, R.L., (Eds.) *Principles and Practice of Stress Management* (2nd Ed). New York: Guilford Press.

Freud, S. (1957). Mourning and Melancholia (1917[1915]), in Complete Psychological Works, standard ed, vol 14. London, Hogarth Press, 1957.

Gara, M, Woolfolk, R., & Allen, L. (2002). Social cognitive complexity and depression: Social cognitive complexity moderates the correlation of depression self-ratings to global self-evaluation. *Journal of Nervous and Mental Disease*, 190, 670-676.

Gara, M.A., Woolfolk, R.L., Cohen, B.D., Goldston, R.B., Allen, L.A., & Novalany, J. (1993). Perception of self and other in major depression. *Journal of Abnormal Psychology*, 102(1), 93-100.

Gevirtz, R. (1999). Resonance frequency training to restore autonomic homeostasis for treatment of psychophysiological disorders. *Biofeedback*, 4, 7-9.

Gaudiano, B.A., & Herbert, J.D. (2003). Antidepressant-placebo debate in the media. *The Scientific Review of Mental Health Practice*, 2(1).

Giardino, N.D., Chan, L., & Borson, S. (2004). Combined heart rate variability and pulse oximetry biofeedback for chronic obstructive pulmonary disease:

preliminary findings. *Applied Psychophysiology and Biofeedback*, 29(2), 121-133.

Giardino, N., Lehrer, P.M., & Feldman, J. (2000). The role of oscillations in self-regulation: Their contribution to homeostatis. In D. Kenney & F.J. McgUIGAN (Eds.), Stress and health: Research and clinical applications (pp. 27-52). Amsterdam: Harwood.

Glassman, A.H., & Shapiro, P.A. (1998). Depression and the course of coronary artery disease. *American Journal of Psychiatry*, 155, 4-11.

Goodwin, E.A., & Montgomery, D.D. (2006). A cognitive-behavioral, biofeedback-assisted relaxation treatment for panic disorder with agoraphobia. *Clinical Case Studies*, 5(2), 112-125.

Grippo, A.J., & Johnson, A.K. (2002). Biological mechanisms in the relationship between depression and heart disease. *Neuroscience and Biobehavioral Reviews*, 26, 941-962.

Grodins, F.S. (1963). Control theory and biological systems. New York: Columbia University Press.

Gross, J.J. (1998). The emerging field of emotion regulation: an integrative review. *Review of General Psychology*, 2, 271-299.

Grossman, P. (1983). Respiration, stress and cardiovascular function. *Psychophysiology*, 20, 284-300.

Grossman, P., Stemmler, G., & Meinhardt, E. (1990). Paced respiratory sinus arrhythmia as an index of cardiac parasympathetic tone during varying behavioral tasks. *Psychophysiology*, 27, 404-416.

Grossman, P. (1992). Respiratory and cardiac rhythms as windows to central and autonomic biobehavioral regulation: Selection of window frames, keeping the panes clean and viewing the neural topography. *Biological Psychology*, 34, 131-161.

Grossman, P., & Sveback, S. (1987). Respiratory sinus arrhythmia as an index of parasympathetic control during active coping. *Psychophysiology*, 24, 228-235.

Grossman, P., & Taylor, E.W. (2007). Toward understanding respiratory sinus arrhythmia: relations to cardiac vagal tone, evolution and biobehavioral functions. *Biological Psychology*, 74, 263-285.

Guinjoan, S.M., Bernabo, J.L., & Cardinali, D.P. (1995). Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression. *Journal of Neurol Neurosurg Psychiatry*, 59(3), 299-302.

Halamek, J.P., Kara, T.M.D., Jurak, P.P., et al. (2003). Variability of phase shift between blood pressure and heart rate fluctuations: A marker of short-term circulation control. *Circulation July*, 108(3), 292-297.

Hallman, D.M., Olsson, E.M.G., von Scheele, B., Melin, L., Lyskov, E. (2011). Effects of heart rate variability biofeedback in subjects with stress-related chronic neck pain: a pilot study. *Applied Psychophysiology and Biofeedback*, 36, 71-80.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurological Neurosurgery in Psychiatry*, 23, 56-62.

Hammer, P.E., & Saul, J.P. (2005). Resonance in a mathematical model of baroreflex control: arterial blood pressure waves accompanying postural stress. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*, 288(6), R1637-1648.

Hassett, A.L., Radvanski, D.C., Vaschillo, E.G., Vaschillo, B., Sigal, L.H., Katsamanis Karavidas, M., Buyske, S., & Lehrer, P.M. (2007). A pilot study of the efficacy of heart rate variability (HRV) biofeedback in patients with fibromyalgia. *Applied Psychophysiology and Biofeedback*, 32, 1-10.

Henriques, G., Keffer, S., Abrahamson, C., & Horst, S.J. (2011). Exploring the effectiveness of a computer-based heart rate variability biofeedback program in reducing anxiety in college students. *Applied Psychophysiology and Biofeedback*, 36, 101-112.

Herbs, D., Gevirtz, R.N., and Jacobs, D. (1993). The effect of heart rate pattern biofeedback for the treatment of essential hypertension. First prize research paper at the 19th Biofeedback Society of California (November) meeting and Citation Poster at the 25th annual meeting of the Association for Applied Psychophysiology and Biofeedback, Atlanta, GA.

Hickling, E.J., Sison, G.F.P., Jr., & Vanderploeg, R.D. (1986). Treatment of posttraumatic stress disorder with relaxation and biofeedback training. Biofeedback and Self-Regulation, 11(2), 125-134.

Hirsch, J.A., & Bishop, B. (1981). Respiratory sinus arrhythmia in humans: how breathing patterns modulate heart rate. *American Journal of Physiology*, 241, H620-H629.

Hoffmann, S.G., Moscovitch, D.A., Litz, B.T., Kim, H., Davis, L.L., & Pizzagalli, D.A. (2005). The worried mind: Autonomic and prefrontal activation during worrying. *Emotion*, 5(4), 464-475.

Hollon, S.D., Thase, M.E., & Markowitz, J.C. (2002). Treatment and prevention of depression. *Psychol Sci Public Interest*, 3(2), 39-77.

Hollon, S.D., Thase, M.E., Markowitz, J.C. (2002). Treatment and prevention of depression. *Psychol Sci Public Interest*, 3, 39-77.

Horsten M., Ericson, M, Perski, A., Wamala, S.P., Schenck-Gustafsson, K., & Orth-Gomer, K. (1999). Psychosocial factors and heart rate variability in healthy women. Psychosomatic Medicine, 61, 49-57.

Howard, K.L., Kopta, S.M., Krause, M.S., & Orlinsky, D.E. (1986). The dose-effect relationship of psychotherapy. *American Psychologist*, 41, 159-164.

Imel, Z.E., Malterer, M.B., McKay, K.M., & Wampold, B.E. (2008). A meta-analysis of psychotherapy and medication in unipolar depression and dysthymia. *Journal of Affective Disorders*, 110, 197-206.

Karasu, T.B. (1990). Toward a clinical model of psychotherapy for depression, I: Systematic comparison of three psychotherapies. *The American Journal of Psychiatry*, 147, 133-147.

Karavidas, M., Lehrer, P.M., Vaschillo, E., Vaschillo, B., Marin, H., Malinovsky, I., Radvanski, D., Hasset, A. (2007). Preliminary results of an open label study of heart rate variability biofeedback for the treatment of major depression. *Applied Psychophysiology and Biofeedback*, 32, 19-30.

Katona, C., Peveler, R., Dowrick, C., Wessely, S., Feinmann, C., Gask, L., et al. (2005). Pain symptoms in depression. Definition and clinical significance. *Clinical Medicine*, 5, 390-395.

Katz, R., Katz, J., & Shaw, B.F. (1999). Beck Depression Inventory and Hopelessness Scale. *Maruish, Mark, E*.

Kemp, A.H. Quintana, D.S., Gray, M.A., Felmingham, K.L., Brown, K., & Gatt, J.M. (2010). Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biological Psychiatry*, 67, 1067-1074.

Kendell, P.C. (1992). Healthy thinking. *Behavior Therapy*, 23, 1-11.

Kessler, R.C., Bergland, P., Demler, O., Jin, R., Merikangas, K.R. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey replication. *Arch Gen Psychiatry*, 62, 593-

Kiecolt-Glaser, J.K., and Glaser, R. (2002). Depression and Immune Function: Central Pathways to Morbidity and Mortality. *Journal of Psychosomatic Research*, 53, 873-876.

Kihlstrom, J.F., & Cantor, N. (1984). Mental representations of the self. In L. Berkowitz (Ed.), *Advances in experimental social psychology* (Vol. 15, pp. 1-47). New York: Academic Press.

Kim, C.K., McGorray, S.P., Bartholomew, B.A., Marsh, M., Dicken, T., et al. (2005). Depression symptoms and heart rate variability in postemenopausal women. *Archives of Internal Medicine*, 165, 1239-1244.

Kleinman, M. (1977). Depression, somatization and the "new cross-cultural psychiatry. *Social Science Medicine*, 11, 3-10.

Klerman G.L., Weissman, M.M., Rounsaville, B.J., et al. (1984). *Interpersonal Psychotherapy of Depression*. New York: Basic Books.

Kobele, R., Koschke, M., Schulz, S., Wagner, G., Yeragani, S., et al. (2010). The influence of negative mood on heart rate complexity measures and baroreflex sensitivity in healthy subjects. *Indian Journal of Psychiatry*, 52(1), 42-47.

Kollai, M., & Mezsei, G. (1990). Respiratory sinus arrhythmia is a limited measure of of cardiac sympathetic control in man. *Journal of Physiology*, 424, 329-342.

Koschke, M., Boettger, M.K., Schulz, S., Berger, S., Terhaar, J., Voss, A., Yeragani, V., & Bar, K. (2009). Autonomy of Autonomic Dysfunction in Major Depression. *Psychosomatic Medicine*, 71, 852-860.

Krantz, D.S., & McCeney, M. (2001). Do psychological and social factors have an impact on organic disease? A critical assessment of rsearch on coronary heart disease. *Annual Review of Psychology*, 53, 341-69.

Krantz, D.S., & McCeney, M. (2001). Do psychological and social factors have an impact on organic disease? A critical assessment of research on coronary heart disease. *Annual Review of Psychology*, 53, 341-69.

Lacey, J., & Lacey, B. (1978). Two-way communication between the heart and the brain: Significance of time within the cardiac cycle. *American Psychologist*, 99-113.

Ladwig, K.H., Kieser, M., Konig, M., Breithardt, G., & Borggrefe, M. (1991). Affective disorders and survival after acute myocardial infaction: results from the post-infarction late potential study. *European Heart Journal*, 12, 959-64.

Lagos, L., Vaschillo, E., Vaschillo, B., Lehrer, P., Bates, M., Pandina, R. (2008). Heart rate variability biofeedback as a strategy for dealing with competitive anxiety: a case study. *Biofeedback*, 36(3), 109-115.

Lahmeyer, H.W., & Bellur, S.N. (1987). Cardiac regulation and depression. *Journal of Psychiatric Research*, 21, 1-6.

Lam, R.W., Wan, D.D.C., Cohen, N.L., & Kennedy, S.H. (2002). Combining antidepressants for treatment-resistant depression: a review. *Journal of Clinical Psychiatry*, 63, 685-693.

Lehofer, M., Moser, M., Hoehn-Saric, R., McLeod, D., Liebmann, P., et al. (1997). Major depression and cardiac autonomic control. *Biological Psychiatry*, 42(10), 914-919.

Lehrer, P.M., Smetankin, A., & Potapova, T. (2000). Respiratory sinus arrhythmia feedback therapy for asthma: A report of 20 unmedicated pediatric cases using Smetankin method. *Applied Psychophysiology and Biofeedback*, 25, 193-200.

Lehrer, P., Vaschillo, E., & Vaschillo, B. (2000). Resonant frequency biofeedback training to increase cardiac variability: rationale and manual for training. *Applied Psychophysiology and Biofeedback*, 25(3), 177-191.

Lehrer, P. M., Vaschillo, E., Vaschillo, B., Lu, S., Eckberg, D.L., Edelberg, R., et al. (2003). Heart rate variability biofeedback increases baroreflex gain and peak expiratory flow. *Psychosomatic Medicine*, 65, 796-805.

Leichsenring, F. (2001). Comparative effects of shrot-term psychdynamic psychotherapy and cognitive-behavioral therapy in depression: a meta-analytic approach. *Clinical Psychology Review*, 21, 401-419.

Leventhal, H., Patrick-Miller, L, Leventhal E.A., Burns, E.A. (1998). Does stress-emotion cause illness in elderly people? In: Schaie K.W., Lawton M.P., editors. Annual review of gerontology and geriatrics, vol. 17: focus on emotion and adult development. New York, NY: Springer Publishing; vol. 17. Pp. 138-84.

Levy, M.N., & Warner, M.R. (1994). Parasympathetic effects on cardiac function. In J.A. Amour & J.L. Ardell (Eds). *Neurocardiology* (pp. 53-76). New York: Oxford University Press.

Licht, C.M.M., de Geus, E.J.C., Zitman, F.G., Hoogendijk, W.J.G., van Dyck, R., & Penninx, B.W.J.H. (2008). Association between major depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). *Arch. Gen. Psychiatry*, 65(12), 1358-1367.

Little, A. (2009). Treatment-resistant depression. American Family Physician. 80(2), 167-172.

Lohr, J.M., Lilienfeld, S.O., Tolin, D.R., Herbert, J.D. (1999). Eye movement desensitization and reprocessing: An analysis of specific versus nonspecific treatment factors. *Journal of Anxiety Disorder*, 13, 185-207.

Luppa, M., Heinrich, S., Angermeyer, M.C., Konig, H., & Riedel-Heller, S.G. (2007). Cost-of-illness studies of depression: A systematic review. *Journal of Affective Disorders*, 98, 29-43.

Lyonfields, J.D., Borkovec, T.D., & Thayer, J.F. (1995). Vagal tone in generalized anxiety disorder and the effects of aversive imagery and worrisome thinking. *Behavior Therapy*, 26, 457-466.

Maina, G., Rosso, G., & Bogetto, F. (2009). Breif dynamic therapy combined with pharmacotherapy in the treatment of major depressive disorder: Long-term results. *Journal of Affective Disorders*, 114, 200-207.

Manber, R., Allen, J.J.B., & Morris, M.M. (2002). Alternative treatments for depression: Empirical support and relevance to women. *Journal of Clinical Psychiatry*, 63(7), 628-640.

Mandel, D.M. (2003). Psychophysiological reslience: A theoretical constuct based on threat perception and early programming of restorative and arousal based adaptive mechanisms. *Journal of Prenatal and Perinatal Psychology and Health*, 17(3), 235-250.

Martinez, J.E., Ferraz, M.B., Fontana, A.M., & Atra, E. (1995). Psychological aspects of Brazilian women with fibromyalgia. *Journal of Psychosomatic Research*, 39(2), 167-174.

Maxmen, J., & Ward, N. (1995). Essential Psychopathology and Its Treatment. Norton & Company.

McCraty, R., Atkinson, M., Lipsenthal, L., & Arguelles, L. (2009). New hope for correctional officers: an innovative program for reducing stress and health risks. *Applied Psychophysiology and Biofeedback*, 34, 251-272.

McGrady, A. (1994). Effects of group relaxation training and thermal biofeedback on blood pressure and related physiological and psychological variables in essential hypertension. *Biofeedback and Self-Regulation*, 19(1), 51-66.

McGrady, A. V., Bush, E.G., & Grubb, B.P. (1997). Outcome of biofeedback-assisted relaxation for neurcardiogenic syncope and headache: A preliminary study of resonance in the cardiovascular system. *Applied Psychophysiology & Biofeedback*, 27(1), 1-27.

McGrady, A.V., Kern-Buell, C., Bush, E., Devonshire, R., Claggett, A.L., & Grubb, B.P. (2003). Biofeedback-assisted relaxation therapy in neurocardiogenic syncope: A pilot study. *Applied Psychophysiology & Biofeedback*, 28(3), 183-192.

McEwen, B. (1998). Protective and damaging effects of stress mediators. *New England Journal of Medicine*, 338(3), 171-179.

Middleton, H.C. & Ashby, M. (1995). Clinical recovery from panic disorder is associated with evidence of changes in cardiovascular regulation. *Acta Psychiatrica Scandinavica*, 91, 108-113.

Miller, A.H. (1998). Neuroendocrine and immune system interactions in stress and depression. *Psychiatr Clin North Am*, 21, 443-63.

Mini, A., Rau, H., Montoya, P., Palomba, D., & Birbaumer, N. (1995). Baroreceptor cortical effects, emotions and pain. International Journal of Psychophysiology, 19, 67-77.

Moser, M., Lehofer, M., Hoehn-Saric, R., McLeod, D.R., Hildebrandt, G., et al. (1998). Increased heart rate in depressed subjects in spite of unchanges autonomic balance? *Journal of Affective Disorders*, 48(2-3), 115-124.

Movius, H.L., & Allen, J.J. (2005). Cardiac vagal tone, defensiveness, and motivational style. *Biological Psychology*, 68,147-162.

Mulder, G. (1985). Attention, effort and sinus arrhythmia: How far are we? In J. F. Orlebeke, G., Mulder, & L.J.P. van Dorman (Eds.), *Psychophysiology of cardiovascular control* (pp. 407-424). New York: Plenum Press.

Mulder, L.J.M. (1992). Measurement and analysis methods of heart rate and respiration for use in applied environments. Biological Psychology, 34, 205-236.

Murray C., & Lopez, A.D. (1996). The Global Burden of Disease: A Comprehensive Assessment of Mortality and Morbidity from Diseases, Injury and Risk Factors in 1990 and Projected to 2020. Harvard University Press.

Mussgay, L., Reineke, A., Mohnke, E., Gevirtz, R., & Ruddel, H. (2008). Does heart rate variability help to reduce depression? Poster at the 12th annual (February) meeting of the Biofeedback Foundation of Europe, Salzburg, Austria.

Nashoni, E., Aizenberg, D., Zalsman, G., Imbar, S., & Weizman, A. (2004). Heart rate variability in patients with major depression. *Psychosomatics*, 45(2), 129-134.

Nemeroff, C.B. (2007). The burden of severe depression: A review of diagnostic challenges and treatment alternatives. *Journal of Psychiatric Research*, 41, 189-206.

Nestoriuc,Y., Rief, W., & Martin, A. (2008). Meta-analysis of biofeedback for tension-type headache: Efficacy, specificity, and treatment moderators. *Journal of Consulting and Clinical Psychology*, 76(3), 379-396.

Neumann, S.A., Sollers, J.J., Thayer, J.F., & Waldstein, S.R. (2004). Alexithymia predicts attenuated autonomic reactivity, but prolonged recovery to anger recall in young women. *International Journal of Psychophysiology*, 53, 183-195.

Nolan, R.P., Kamath, M.V., Floras, J.S., Stanley, J., Pang, C., Picton, P., & Young, Q.R. (2005). Heart rate variability biofeedback as a behavioral neurocardiac intervention to enhance vagal heart rate control. *American Heart Journal*, 149, 1137.e1-1137.e7.

Oatley, K., Jenkins, J.M. (1992). Human emotions: Function and dysfunction. *Annual Review of Psychology*, 43, 55-85.

Ogrodniczuk, J.S., Piper, W.E., & Joyce, A.S. (2004). Residual symptoms in depressed patients who successfully respond to short-term psychotherapy. *Journal of Affective Disorders*, 82, 469-473.

Pellizzer, A.M., Kamen, P.W.., Jackman, G., Brazzale, D., & Krum, H. (1996). Non-I nvasive assessment of baroreflex sensitivity and relation to measures of heart rate variability in man. *Clinical and Experimental Pharmacology and Physiology*, 23, 621-623.

Penaz, J. (1978). Mayer waves: history and methodology. *Automedica*, 2. 135-141.

Penninx, B.W., Beekman, A.T.F., Honig, A., et al. (2001). Depression and cardiac mortality: results from community based longitudinal study. Archives of General Psychiatiry, 58, 221-227.

Pichon, A., Nuissier, F., & Chapelot, D. (2010). Heart rate variability and depressed mood in physical education students: a longitudinal study. *Autonomic Neuroscience: Basic and Clinical*, 156, 117-123.

Pine, D. S., Wasserman, G.A., Miller, L., Coplan, J.D., Bagiella, E., Kovelenku, P., et al. (1998). Heart period variability and psychopathology in urban boys at risk for delinquency. *Psychophysiology*, 35, 521-529.

Pineyro, G., Blier, P., 1999. Autoregulation of serotonin neurons: role in antidepressant drug action. *Pharmacol. Rev.*, 51, 533-591.

Pope, K.S., & Vasqez, M.J.T. (1998). Assessment of suicidal risk. In: Koocher, G.P., Norcross, J.C., & Hills, S.S.I., eds. *Psychologists' Desk Reference*. New York: Oxford University Press.

Porges, S.W., McCabe, P.M., & Yongue, B. G. (1982). Respiratory heart rate interaction: Psychophysiological implications for pathophysiology and behavior. In J.T. Cacioppo & R.E. Petty (Eds.), *Perspectives in cardiovascular psychophysiology* (pp. 223-264). New York: Guilford Press.

Porges, S. W. (1986). Respiratory sinus arrhythmia: physiological basis, quantitative methods, and clinical implications. In P. Grossman, K. Janssen, & D. Vail (Eds.), *Cardiorespiratory and Cardiosomatic Psychophysiology* (pp.101-115). New York: Plenum.

Porges, S. (1995a). Cardiac vagal tone: a physiological index of stress. *Neurosciences and Biobehavioral Reviews*, 19, 225-233.

Porges, S. (1995b). Orienting in a defensive world: Mammalian modifications of our evolutionary heritage. A polyvagal theory. *Psychophysiology*, 32, 301-318.

Porges, S. (2001). The polyvagal theory: phylogenetic substrates of a social nervous system. *International Journal of Psychophysiology*, 42, 123-146.

Porges, S. (2003a). Social engagement and attachment: a phylogenetic perspective. *Annals of the New York Academy of Sciences*,1008, 31-47.

Porges, S. (2003b). The polyvagal theory: phylogenetic contributions to social behavior. *Physiology & Behavior*, 79(3), 503-513.

Porges, S., (2007). The polyvagal perspective. *Biological Psychology*, 74, 116-143.

Ramana, R., Paykel, E.S., Cooper, Z., Hayhurst, H., Saxty, M., Surttes, P.G. (1995). Remission and relapse in major depression. *Psychol. Med*. 25, 1161-1170.

Randall, W.C. (1994). Efferent sympathetic innervation of the heart. In J.A. Armour & J.L. Ardell (Eds). *Neurocardiology* (pp. 77-94). New York: Oxford University Press.

Rechlin, T, Weis, M., Spitzer, A., & Kaschka, W.P. (1994). Are affective disorders associated with alterations of heart rate variability? *Journal of Affective Disorders*, 32(4), 271-275.

Regler, D., Kaelber, C., Rae, D., Farmer, M., et al. (1998). Limitations of Diagnostic Criteria and Assessment Instruments for Mental Disorders: Implications for Research and Policy. *Arch Gen Psychiatry*, 55, 109-115.

Reineke, A. (2007). *The effects of heart rate variability biofeedback in reducing blood pressure for the treatment of essential hypertension*. Unpublished Doctoral dissertation. San Diego, CA: Alliant University International, San Diego.

Reiner, R. (2008). Integrating a portable biofeedback device into clinical practice for patients with anxiety disorders: results of a pilot study. *Applied Psychophysiology and Biofeedback*, 33, 55-61.

Reyes del Paso, G.A., & Gonzalez, M.I. (2004). Modification of baroreceptor cardiac reflex function by biofeedback. *Applied Psychophysiology and Biofeedback*, 29(3), 197-211.

Richards, J.E., & Casey, B.J. (1991). Heart rate variability during attention phases in young infants. Psychophysiology, 28, 43-53.

Richter, D.W., & Spyer, K.M. (1990). Cardiorespiratory control. In A.D. Loewy & K.M. Spyer (Eds.), Central regulation of autonomic function (pp.189-207). New York: Oxford University Press.

Ringood, J.V., & Malpas, S.C. (2001). Slow oscillations in blood pressure via a nonlinear feedback model. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*, 261(4 Pt 2), H1231-1245.

Robey, K.L., Cohen, B.D., & Gara, M.A. (1989). Self-structure in schizophrenia. *Journal of Abnormal Psychology*, 98(4), 436-442.

Rosenthal, D., & Frank, J.D. (1956). Psychotherapy and the placebo effect. *Psychological Bulletin*, 53, 294-302.

Ross, E.D., Homan, R.W., & Buck, R. (1994). Differential hemispheric lateralization of primary and social emotions. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, 7, 1-19.

Rottenberg, J. (2007). Cardiac vagal control in depression: a critical analysis. *Biological Psychology*, 74, 200-211.

Rottenberg, J., & Gotlib, I.H. (2004). Socioemotional functioning in depression. In M. Power (Ed.), *Mood Disorders: A handbook of science and practice* (pp. 61-77). New York: Wiley.

Rottenberg, J., Gross, J.J., & Gotlib, I.H. (2005). Emotion context insensitivity in major depressive disorder. *Journal of Abnormal Psychology*, 114, 627-639.

Rush, A.J., Fava, M., Wisniewski, S.R., Lavori, P.W., Trivedi, M.H., Sackeim, H.A., … Niederehe, G. (2004). Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Controlled Clinical Trials*, 25, 119-142.

Rutherford, B.R., Wager, T.D., & Roose, S.P. (2010). Expectancy and the treatment of depression: a review of experimental methodology and effects on patient outcome. *Current Psychiatry Reviews*, 6, 1-10.

Salovey, P., & Rodin, J. (1985). Cognitions about the self. In L. Wheeler (Ed.), *Review of personality and social psychology* (Vol. 6, pp. 143-167). Beverly Hills, CA: Sage.

Saul, J.P., Berger, R.D.., Albrecht, P., Stein, S.P., Chen, M.H., & Cohen, R.J. (1991). Transfer function analysis of the circulation: unique insights into cardiovascular regulation. *American Journal of Physiology*, 261. H1231-H1245.

Saul, J.P., Rea, R.F., Eckberg, D.L., Berger, R.D., & Cohen, R.J. (1990). Heart rate and muscle sympathetic nerve variability during reflex changes of autonomic activity. *American Journal of Physiology*, 258, H713-H721.

Saul, J.P., Parati, G., Cohen, R.J., & Lam, K.H. (1992). Identification of dynamic baroreflex responses using random interval neck stimulation. *Circulation*, 86, I-481.

Schildkraut, J.J., 1965. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *American Journal of Psychiatry*, 122, 509-522.

Schwartz, M.S. (1995). *Biofeedback: A practitioner's Guide*. New York: Guilford Press; 1995.

Segal, Z.V. (1988). Appraisal of the self-schema construct in cognitive models of depression. *Psychological Bulletin*, 103, 147-162.

Shea, A.K., Kamath, M.V., Fleming, A., Streiner, D.L., Redmond, K., & Steiner, M. (2008). The effect of depression on heart rate variability during pregnancy. *Clin. Auton. Res*., 18, 203-212.

Sheridan, C., & Radmacher, S. (1992). *Health psychology challenging the biomedical model*. New York; Chichester, West Sussex, UK; Brisbane, Australia; Toronto, Ontario, Canada; Singapore: Jon Wiley & Sons.

Siepmann, M., Aykac, V., Uterdorfer, J., Petrowski, K., & Mueck-Weymann, M. (2008). A pilot study on the effects of heart rate variability biofeedback in patients with depression and in healthy subjects. *Applied Psychophysiology and Biofeedback*, 33, 195-201.

Siever L., & Davis K. (1985). Overview: toward a dysregulation hypothesis of depression. *American Journal of Psychiatry*, 142, 1017-31.

Sloan, R.P., Shapiro, P.A., Bigger, J.T., Bagiella, M., Steinman, R.C., & Gorman, J.M. (1994). Cardiac autonomic control and hostility in healthy subjects. *American Journal of Cardiology*, 74, 298-300.

Song, H.S., & Lehrer, P.M. (2003). The effects of specific respiratory rates on heart rate and heart rate variability. *Applied Psychophysiology & Biofeedback*, 28(1), 13-23.

Spyer, K.M. (1990). The central nervous organization of reflex circulatory control. In A.D. Loewy & K.M. Spyer (Eds.), Central regulation of automomic function (pp. 1168-1188). New York: Oxford University Press.

Steer, R.A., & Clark, D.A. (1997). Psychometric characteristics of the Beck Depression Inventory-II with college students. *Measures Evaluating Counseling Deviations*, 30, 128-136.

Stein, P.K., Carney, R.M., Freedland, K.E., Skala J.A., Jaffe, A.S., et al. (2000). Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. *Journal of Psychosomatic Research*, 48, 493-500.

Stevens, S.E., Hynan, M.T., & Allen, M. (2000). A meta-analysis of common factor and specific treatment effects across domains of the phase model of psychotherapy. *Clinical Psychology: Science and Practice*, 7, 273-290.

Strine, G.N. (2002). Self-reports of pain reduction through paced respiration and heart rate variability biofeedback with nursing home residents. Doctoral thesis. Widener University, MA.

Su, S., Lampert, R., Lee, Forrester, Bremner, J.D., Snieder, H., Jones, L., Murrah, N.V., Goldberg, J., & Vaccarino, V. (2009). Common genes contribute to depressive symptoms and heart rate variability: the twins heart study. *Twin Research and Human Genetics*, 13(1), 1-9.

Swanson, K.S., Gevirtz, R.N., Brown, M., Spira, J., Guarneri, E., & Stoletniy, L. (2009). The effect of biofeedback on function in patients with heart failure. *Applied Psychophysiology and Biofeedback*, 34, 71-91.

Task Force of the European Society of Cardiology and the North American Society of Racing and Electrophysiolog. (1996). Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Circulation*, 93, 1043-1065.

Thayer, J., & Lane, R. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders*, 61, 201-216.

Treatment of Depression: Newer Pharmacotherapies [AHCPR publication No. 99-E014]. Mulrow C.D., Williams J.W. Jr., Trivedi, M., et al. Rockville, MD: US Dept of Health and Human Services; 1999.

Tulen, J.H., Bruijn, J.A., de Man, K.J., Pepplinkhuizen, L., van den Meiracker, A.H., Man in 't Veld, A.J.. (1996a). Cardiovascular variability in major depressive disorder and effects of imipramine or mirtazapine (Org 3770). J. Clin. Psychopharmacol. 16, 135-145.

Tulen, J.H., Bruijn, J.A., de Man, K.J., Pepplinkhuizen, L., van den Meiracker, A.H., Man in 't Veld, A.J.. (1996b). Anxiety and autonomic regulation in major depressive disorder: an exploratory study. *Journal of Affective Disorders*, 40, 61-71.

Uhlmann, C., & Froscher, W. (2001). Biofeedback treatment in patients with refractory epilepsy: changes in depression and control orientation. *Seizure*, 10, 34-38.

Vaccarino, A.L., Sills, T.L., Evans, K.R., & Kalali, A.H. (2008). Prevalence and association of somatic symptoms in patients with major depressive disorder. *Journal of Affective Disorders*, 110, 270-276.

Van der Kooy, K.G., van Hout H.P., van Marwijk, H.W., de Haan, M., Stehouwer C.D., & Beekman, A.T. (2006). Differences in heart rate variability between depressed and non-depressed elderly. *International Journal of Geriatric Psychiatry*, 21, 147-150.

Van Zyl, L.T., Haegawa, T., & Nagata, K. (2008). Effects of antidepressant treatment on heart rate variability in major depression: A quantitative review. *Biopsychosocial Medicine*, 2, 12.

Vaschillo, E.G. (1984). *Dynamics of slow-wave cardiac rhythm structure as an index of functional state of an operant*. Unpublished Doctoral dissertation. Saint Petersburg, Russia: Institute of Experimental Medicine.

Vaschillo, E., Lehrer, P., Riche, N., & Konstantinov, M. (2002). Heart rate variability biofeedback as a method for assessing baroreflex function: a preliminary study of resonance in the cardiovascular system. *Applied Psychophysiology and Biofeedback*, 27(1), 1-27.

Vaschillo, E., Vaschillo, B., & Lehrer, P. (2004). Heartbeat synchronizes with respiratory rhythm only under specific circumstances. *Chest*, 126(4), 1385-1406.

Vaschillo, E.G., Vaschillo, B.V., & Lehrer, P.M. (2006). Characteristics of resonance in heart rate variability stimulated by biofeedback. *Applied Psychophysiology and Biofeedback*, 31(2), 129-140.

Veith, R.C., Lewis, N., Linares, O.A., Barnes, R.F., Raskind, M.A., et al. (1994). Sympathetic nervous system activity in major depression: basal and desipramine-induced alternations in plasma norepinephrine kinetics. *Archives of General Psychiatry*, 51(5), 411-422.

Vieta, E., Sanchez-Moreno, J., Lahuerta, J., Zaragoza, S., Group, E.D.H.I.P.O., (2008). Subsyndromal depressive symptoms in patients with bipolar and unipolar disorder during clinical remission. *Journal of Affective Disorders*, 107, 169-174.

Ware, J.E., & Sherbourne, C.D. (1992). The MOS 36-item short-form health survey (SF-36). *Medical Care*, 30, 473-483.

Weber, R.J.M., van der Molen, M.W., & Molenaar, P.C.M. (1994). Heart rate and sustained attention during childhood: Age-changes in anticipatory heart rate, primary bardycardia, and respiratory sinus arrhythmia. *Psychophysiology,* 31, 164-174.

Weissman M.M., Markowitz M.C., Klerman., G.L. (2007). *Clinician's Quick Guide to Interpersonal Psychotherapy*. New York: Oxford University Press.

Westthuis, D., and Thyer, B.A. (1989). The development and validation of the clinical anxiety scale: A rapid assessment instrument for empirical practice. *Educational and Psychological Measurement*, 49, 153-163.

Wilhelm, F.H., Grossman, P., Coyle, M.A., 2004. Improving estimation of cardiac vagal tone during spontaneous breathing using a paced breathing calibration. *Biomedical Science Instruments*, 40, 317-324.

Winokur, G. (1997). All roads lead to depression: clinically homogenous, etiologically heterogeneous. *Journal of Affective Disorders*, 45, 97-108.

Woolfolk, R.L., Gara, M.A., Allen, L.A., & Polino, M. (1995). Self-complexity, self-evaluation, and depression: An examination of form and content within the self-schema. *Journal of Personality and Social Psychology*, 68(6), 1108-1120.

Woolfolk, R.L., Gara, M.A., Ambrose, T.K., Williams, J.E., Allen, L.A., Irvin, S.L., & Beaver, J.D. (1999). Self-complexity and the persistence of depression. *Journal of Nervous and Mental Disease*, 187(7), 393-399.

Woolfolk, R.L., Gara, M.A., Allen, L.A., & Beaver, J.D. (2004). Self-complexity: An assessment of construct validity. *Journal of Social and Clinical Psychology*, 23(4), 463-474.

Wyatt R.J., Portnoy, B., Kupfer, D.J., Snyder, F., Engelman, K. (1971). Resting plasma catecholamine concentrations in patients with depression and anxiety. *Arch Gen Psychiatry*, 24, 65-70.

Yeragani, V.K., Pohl, R., Balon, R., Ramesh, C., Glitz., D., Jung, I., & Sherwood, P. (1991). Heart rate variability in patients with major depression. *Psychiatry Research*, 37, 35-46.

Zucker, T.L., Sammuelson, K.W., Muench, F., Greenberg, M.A., & Gevirtz, R.N. (2009). The effects of respiratory sinus arrhythmia biofeedback on heart rate variability and posttraumatic stress disorder symptoms: a pilot study. *Applied Psychophysiology and Biofeedback*, 34, 135-143.

APPENDIX A

Summary of Studies Evaluating the Efficacy of heart rate variability biofeedback (HRV) methods for depression

Author(s) (year)	Type of Study (RCT, multiple case, FU trial)	Method of Treatment	Sample size; Respiration Rate Achieved	Treatment conditions; Training format; Training site	Target of Treatment Primary outcome measure	Variable outcomes (ie. statistical significance, clinical significance, percent change)
Mussgay et al. (2008)	RCT	HRV BF Vs. quasi false EEG biofeedback Vs. standard cognitive therapy	54	HRV and EEG group received ten (10) training sessions (45 min). Placebo was a standard cognitive therapy protocol	Target population: Depression	Study demonstrated improvement in depression for HRV group but no differential difference between groups. HRV was able to elicit in-session autonomic changes as evidenced by increased HRV and baroreflex sensitivity
Siepman et al. (2008)	CCT	HRV BF	14 patients with depression 12 healthy volunteers	Six sessions over a two week period	Target population: Depression	At follow up BDI was found significantly decreased (BDI 6; 2-20; median 25%-75% quartile) as compared to baseline conditions (BDI 22; 15-29) in patients with depression. In addition, depressed patients had reduced anxiety, decreased heart rate and increased HRV after conduction of biofeedback ($p<0.05$). By contrast, no changes were noted in healthy subjects receiving biofeedback or in normal controls.

Author(s) (year)	Type of Study (RCT, multiple case, FU trial)	Method of Treatment	Sample size; Respiration Rate Achieved	Treatment conditions; Training format; Training site	Target of Treatment Primary outcome measure	Variable outcomes (ie. statistical significance, clinical significance, percent change)
Zucker et al. (2008)	RCT	RSA (HRV) BF versus PMR as adjunctive treatments Participants were assigned to use either an RSA biofeedback device, a Stress Eraser, or a 20-minute PMR recording. 4 week intervention	n=38 19 in each group 21 males 17 females 55% African-American 31.6% Caucasian 5.3% Asian 2.6% Hispanic	Setting: A residential treatment facility for treatment of substance disorders.	Target population: Individuals with PTSD symptoms Primary Outcome measures: PTSD symptoms: 1.PTS-T 2.PTSD Civilian Checklist version Secondary measures: 1.Beck Depression Inventory II 2.nsomnia Severity Index	Significant group x time interaction effect for depression on the BDI, $F(1,34)=9.39, p<.01$ between baseline and week 4. Both groups met criteria for moderate depression at baseline. The RSA group demonstrated clinically significant changes in depression (53.4%) as compared to a 25% depression reduction in the PMR group. There were no significant group x time interactions on neither of the PTSD scales. The baseline recordings at each of the two timepoints for the physiological marker SDNN showed significant effect for group x time, $F(1,33)=5.81, p<.02$.
Reiner et al.(2008)	Multiple case study; all subjects received tx	Outpatient CBT treatment + HRV biofeedback (Stress Eraser)	N=24, 50% female, 50% male Physiological markers were not reported	Participants were introduced to the stress eraser (15 minutes) and given instructions on using the stress eraser, and instructed to use it at home for 20 minutes per day for three weeks. Follow-up questions were 3-5 minutes. Training sites: Two outpatient CBT clinics	Target population: Individuals with disorders associated with sympathetic overarousal: GAD, Specific phobia, Social phobia, OCD, IBS, **Insomnia and comorbid depression.** Primary Outcome measures: markers of Autonomic Arousal: Anxiety, Sleep, and Anger 1. State-Trait Anxiety Inventory (STAI-Y) 2. Pittsburgh Sleep Quality Index(PSQI) **3.** State-Trait Anger Expression Inventory	Significant improvements in anxiety and anger scores between baseline and end of study (3-4 weeks assessment point): State anxiety $t(18)= 2.73$, $p=.009$, Trait anxiety $t(17)=4.37$, $p=.000$ and Trait Anger temperament $t(18)=3.01$, $p=.009$. Significant improvement on overall sleep quality $t(18) = 2.67$ ($p<.05$); sleep latency $t(18) = 2.16$ ($p<.05$), and sleep disturbances $t(19) = 2.65$ ($p<.05$).

Author(s) (year)	Type of Study (RCT, multiple case, FU trial)	Method of Treatment	Sample size; Respiration Rate Achieved	Treatment conditions; Training format; Training site	Target of Treatment Primary outcome measure	Variable outcomes (ie. statistical significance, clinical significance, percent change)
Reineke (2007)	Dissertation RCT	HRV vs. EEG placebo BF	N=37	Each group received 10 sessions and instructions for daily home practice twice a day for 20 minutes	Target population: Hypertension Secondary outcome measure: depression scale, German version of the Centre for Epidemiologic Studies in Depression(CES-D) Scale	HRV and psychological measures were not significantly different between the two groups. There was, however, a main effect of time for both groups indicating increased HRV (p<.05), and depression symptoms (p<.01). These changes were not maintained at three month follow-up.
Karavidas et al. (2007)	Multiple Case study All subjects received TX condition	HRV Biofeedback	n=11 Age ranges 25-58 Four males Seven females	10 weekly sessions of HRV Biofeedback Home practice 20 minutes 2X/ day, and when feeling down/ depressed	Target population: Major Depression Primary Outcome Measure: Hamilton Depression Scale Secondary measures: 1. Beck Depression Inventory-II	Decrease in level of depression according to HAM-D and BDI-II (neurovegetative component and cognitive component) from session 1 to sessions 4, 7, and 10 (p<.001), with observable decreases by session 4 with concurrent increases in SDNN, standard deviation of normal cardiac interbeat intervals) an electrocardiographic estimate of overall measure of adaptability. SDNN decreased to baseline levels at the end of treatment and at follow-up, but clinically and statistically significant improvement in depression persisted. Six participants had clinically significant improvements (≥50%) on the HAM-D by session 10, and three had a partial response (›25% but <50%) by session 10. The effect size was d = 3.6 for the HAM-D change between sessions 1 and 10.

Author(s) (year)	Type of Study (RCT, multiple case, FU trial)	Method of Treatment	Sample size; Respiration Rate Achieved	Treatment conditions; Training format; Training site	Target of Treatment Primary outcome measure	Variable outcomes (ie. statistical significance, clinical significance, percent change)
Hassett et al. (2007)	Multiple case study All subjects received TX condition	HRV Biofeedback	n= 12 All female Age range 18-60	10 weekly sessions of HRV Biofeedback Home practice 20 minutes 2X/ day	1.Fibromyalgia 2. Fibromyalgia impact questionnaire (FIQ) 2. Secondary:BDI-II, McGill Pain Questionnaire and Pittsburgh Sleep Quality Index	Significant decreases on total BDI-II scores between sessions 1 and 10 (unadjusted p=.0089, adjusted p=.0444) and at 3 months (unadjusted p=.0055, adjusted p=.0362). HRV increased from Session 1 to Session 10 (*p*=.0022) but no significant changes were noted across sessions for blood pressure and baroreflex gain. HRV effects were immediate, but blood pressure, baroreflex, and therapeutic effects were delayed.
Nolan et al. (2005)	RCT	HRV Biofeedback Vs Active control condition	n=46	1. Five 1.5 hr. sessions of HRV Biofeedback 2. Control condition (Five 1.5 hr. 98essions of CBT skills and autogenic relaxation)	Target population: Patients with coronary heart disease. 1. Vagal HR regulation: Absolute and normalized high-freq. spectral components of HRV (.15 - .5 Hz) 2. Centre for Epidemiologic Studies in Depression(CES-D) Scale 3. Perceived Stress Scale (PSS)	Subjects receiving HRV Biofeedback showed reduced symptoms of depression (*p*=.004) and psychological stress (*p*=.001), and this improvement was associated with the high-frequency index of vagal HR. The active control condition also showed reduced depression and psychological stress, but this outcome was not associated with vagal cardiac control. There were no significant group differences.

Author(s) (year)	Type of Study (RCT, multiple case, FU trial)	Method of Treatment	Sample size; Respiration Rate Achieved	Treatment conditions; Training format; Training site	Target of Treatment Primary outcome measure	Variable outcomes (ie. statistical significance, clinical significance, percent change)
Giardino, Chan, & Borson (2004)	Multiple case study All subjects received TX condition	HRV Biofeedback and walking practice with oximetry feedback	n=20 10 female 10 male Ages 48-79	1.Five weekly sessions of HRV Biofeedback and 2.Four weekly sessions of walking practice with oximetry feedback Daily home practice	Target population: Patients with chronic obstructive pulmonary disease. 1. St. George's Respiratory Questionnaire (SGRQ) Secondary outcome measures: 2. Hospital Anxiety and Depression Scale (HADS) 3. Pulmonary Functional Status and Dyspnea (PFSDQ-M) **4.** COPD Self Efficacy Scale	No improvements in depression or anxiety scores.
Strine (2002)	Dissertation RCT	HRV BF Vs. Wait-list control group	N=22 Age ranges:48-89 14 males 8 females	Biweekly (20 minutes each time) for approximately 2 months	Target population: Nursing home residents 1. BDI-II 2. BAI 3.McGill Pain Questionnaire 3.Nurses behavioral reports (according to Behavioral Commentary Form)	Although significant group effects emerged for all pain indices (number of pain symptoms, intensity of pain, affective component of pain) there were no significant group x time interactions for either the depression or anxiety measures.
Berger & Gevirtz (2001)	RCT	Six weeks of Breathing retraining based in DeGuire et al. (1992) protocol Vs 10 weeks of CBT	n= 21 14 females 7 males Ages 18-60	Six weekly sessions (30-60 minutes). The cognitive therapy protocol used was a revised version of the Therapist's Guide for the Mastery of Your Anxiety and Panic II and Agoraphobia Supplement (MAP II Program) by Craske, Meadows, and Barlow (1994).	Target population: Panic Disorder 1.Panic attacks (Panic Disorder Severity Scale) 2.Beck Depression Inventory	Both treatments resulted in significantly decreasing the frequency and severity of panic attacks (as measured by the PDSS) and depression. There were no significant between-group differences. The CBT group did, however, have lower BDI scores than the breathing retraining group at four weeks post-treatment indicating that CBT may be more effective at decreasing depressive symptoms.

Author(s) (year)	Type of Study (RCT, multiple case, FU trial)	Method of Treatment	Sample size; Respiration Rate Achieved	Treatment conditions; Training format; Training site	Target of Treatment Primary outcome measure	Variable outcomes (ie. statistical significance, clinical significance, percent change)
Lagos et al (2008)	Single Case Study	10 week HRV BFB (as outlined by Lehrer, Vaschillo and Vaschillo, 2000)	N=1 (male; 14 y.o.)	Once a week HRV BRB training at University Lab. Easch session lasted 45-60 minutes and included abdominal breathing and pursed lips techniques.	Target Population: competitive athletes with performance Anxiety symptoms 1. Profile of Mood States (POMS) 2. Competetive State Anxiety Inventory (CSAI-2)	After 10 weeks of training athlete (golfer) reported complete absence of depression symptoms, as measured by POMS. However, at week 1 depression rating was already relatively low (scored 1/16 on POMS). Clinically significant reductions in anxiety symptoms.
Fourie (2006)	Single Case Study	7 sessions of Respiratory Sinus Feedback	N=1 (male; 23 y.o.)	University PTSD/Anxiety Disorders Clinic. Heart Rate and RSA data collected by BIOVIEW series IV. 7 weekly sessions of RSA BFB, with visualization, progressive muscle relaxation, and desensitization exercises incorporated.	Target Population: individuals with PTSD symptoms 1. Zung Self-Rating Depression Scale 2. Clinical Administered PTSD scale (CAPS) 3. Zung Self-Rating Anxiety Scale	Clinically significant decrease in depression symptoms, with Pre-treatment depression score=.76 (moderate to severe depression), and post-treatment score=.60 (no depressed),along with clinically significant decreases in PTSD symptoms.
McCraty et al (2009)	RCT	Emotion Self Regulation techniques & HRV BFB group Vs. Wait List Control group	N=75; treatment group: mean age=39; 69% male Control group: mean age=40; 70% male	"Power to Change Performance" stress reduction program (by HeartMath) with Freeze Framer HRV Coherence BFB training. 5 training modules delivered over 2 consecutive days.	Target Population: symptoms of Stress in Correction Officers 1. Personal Wellness Profile (PWP) 2. Jenkins Activity Survey 3. Brief Symptoms Inventory (BSI) 4. Personal and Organizational Assessment	No significant difference between groups scores on BSI (including its depression sub-scale).

Author(s) (year)	Type of Study (RCT, multiple case, FU trial)	Method of Treatment	Sample size; Respiration Rate Achieved	Treatment conditions; Training format; Training site	Target of Treatment Primary outcome measure	Variable outcomes (ie. statistical significance, clinical significance, percent change)
Swanson et al (2009)	RCT	HRV BFB and breathing retraining Vs. quasi-false alpha-theta biofeedback	N=29	University Heart Failure Clinic. 6 weekly session of HRV BFB training for 45 mins and home training with Freeze Framer (by HeartMath).	Target Population: individuals with Heart Failure 1. Center for Epidemiological Studies-Depression Scale (CES-D) 2. Positive and Negative Affect Scale 3. Stress Management and Exercise Practices Questionnaire 4. Daily Stress Management and Exercise Record	No significant interaction or main effects were found on CES-D
Uhlmann & Froscher (2001)		Respiration feedback vs. slow cortical potentials feedback	N=20	Biofeedback treatment with each method consisted of the study of 35 feedback sessions within 3 months. In respiration feedback each training session lasts 10 minutes. Patients are asked to produce a specific respiratory pattern with an ETCO2 higher than 5%, and a respiration rate lower than 15 breaths per minute.	Target population: epilepsy	Mean depression rates before biofeedback in 20 patients were 10.50 (SD 7.9). The depression scores dropped significantly to a BDI score of 7.65 (SD 7.0) 6 months after biofeedback treatment (*T* D 2:41, df D 19, *P* < 0:026). Between group differences were not reported. Respiration feedback might be superior to feedback of slow cortical potentials in initiating internal control. It has to be stressed, however, that *T* - scores of internal control measures before treatment were significantly lower in the

						respiration group in comparison with the feedback group of slow cortical potentials. Patients with low internal control orientation might profit the most from biofeedback treatment in terms of depression and locus of control.
Author(s) (year)	**Type of Study** (RCT, multiple case, FU trial)	**Method of Treatment**	**Sample size; Respiration Rate Achieved**	**Treatment conditions; Training format; Training site**	**Target of Treatment Primary outcome measure**	**Variable outcomes** (ie. statistical significance, clinical significance, percent change)
Hallman et al. (2011)	RCT	HRV BF Vs. control (non-resonant frequency training) (?)	N=24, 12 in treatment group (10 female; mean age=40), and 11 in control group (10 female; mean age=43). Swedish population sample.	HRV group received ten (10) training sessions (28 min), and instructed to practice with pacer at home for 15 mins/day, 5 days/wk. Control received session 1 and session 10 "breathing protocol" with no instruction in between.	Target population: Chronic neck pain 1. Short Form 36 Item Health Survey (SF-36) 2. Borg CR10 Scale 3. Stress Medicine Symptom Scale (SMSS) 4. Neck Disability Index (NDI) 5. Hospital Anxiety and Depression Scale (HAD)	Although ratings of perceived depression (as measured by the Hospital Anxiety and Depression Scale) were reduced after 10 weeks, no effect of treatment (group x time) was seen (p=.78).

Author(s) (year)	Type of Study (RCT, multiple case, FU trial)	Method of Treatment	Sample size; Respiration Rate Achieved	Treatment conditions; Training format; Training site	Target of Treatment Primary outcome measure	Variable outcomes (ie. statistical significance, clinical significance, percent change)
Henriques et al. (2011)	Multiple case study All subjects received TX condition	HRV BF	N=9, 7 women, 2 men. University students.	Subjects engaged in independent biofeedback practice 20 mins/day, 5 days/wk for 4 weeks. Lab at mid-Atlantic university.	Target population: Anxiety Primary Outcome Measure: Mood and Anxiety Symptom Questionnaire.	At follow up depression scores (as measured by the General Stress, Depressed subscale) were found significantly decreased, mean difference=16.6, SD=11.4, t(1,8)=4.3, p=.002. Anxiety scores were also found to be significantly decreased.
Henriques et al. (2011)	? (Immediate vs. Delayed TX design)	HRV BF	n=30 (?), 16 in immediate group and 14 in delayed group. Gender ? University students.	Subjects engaged in independent biofeedback practice 20 mins/day, 5 days/wk for 4 weeks. Lab at mid-Atlantic university.	Target population: Anxiety Primary Outcome Measure: Mood and Anxiety Symptom Questionnaire.	In both the immediate and the delayed treatment groups, no significant changes were found over time for depression scores (as measured by the General Stress, Depressed subscale), p=.779 and p.180, respectively.

BF = biofeedback; CCT = controlled clinical trial; EMG = electromyography; FU = follow-up; RCT = randomized controlled trial; PMR=Progressive Muscle Relaxation; PTST-T= Posttraumatic Stress-Total; n.s.=non-significant

APPENDIX B

HRV Biofeedback Protocol

This is a four-session protocol (with two follow-ups) for HRV Biofeedback study. The following procedure is described by Lehrer, Vaschillo and Vaschillo, 2000[1].

SESSION 1: INTRODUCTION TO THE METHOD AND OBTAINING INITIAL ESTIMATE OF RESONANCE FREQUENCY
Follow the preset schedule using J&J c2+ "HRV Resonance Frequency Determination"

Therapist's Script for Introduction: "Your hear rate goes up and down with your breathing. When you breathe in, your heart rate tends to go up. When you breathe out, your heart rate tends to go down. These changes in heart rate are called "respiratory sinus arrhythmia," or RSA. RSA triggers powerful reflexes in the body that help it to control the whole autonomic nervous system (including your heart rate, blood pressure, and breathing). We will train you to increase the size of these heart rate changes. Increasingly the size of the heart rate changes will exercise these important reflexes, and help them to control your body more efficiently. As part of this treatment we will measure your RSA and give you information about the swings in heart rate that accompany breathing. That will be the RSA biofeedback. You will use this information to teach yourself to increase your RSA. If you practice the technique regularly at home, your will strengthen the reflexes that regulate the autonomic nervous system. This should help improve your health and ability to manage everyday stress. There is evidence that training these reflexes will help you to cope with various somatic and emotional problems (high blood pressure, anxiety attacks, hyperventilation, asthma, some digestive problems). Do you have any questions?"

Therapist's Script for Baseline: "For the next 2.5 minutes, I'd like that you find a spot on the wall or on the floor and focus on it. If your mind starts to wander, bring it back to the spot. Try to focus on a neutral thought. An example of a neutral thought is going to the library, where you notice the books on the shelves or the various newspapers. Afterwards, I will instruct you to follow the pacer (see instructions below) for 2.5 minutes. After each period, I will ask you to rate it by giving me a number from 1-10. 10 is very uncomfortable and 0 is no problem at all/comfortable. Please refrain from talking at that time, simple provide the number. Stay as still as you can and refrain from talking throughout this exercise."

Therapist's Script for breathing at 6.0 BPM: "Breathe at the rate of this pacer, moving up and down. Breathe in as the pacer goes up, along with the pacer and out as it goes down. Try it. (Give feedback about whether the trainee is accurately following instructions). Some people find it easier to follow the pacer by inhaling through the nose and exhaling through pursed lips. Now continue to breathe at this rate. Do not breathe too deeply or you will hyperventilate. If this happens you may experience some lightheadedness or dizziness. If lightheadedness or dizziness occurs, breathe more shallowly. Now try to breathe out longer than you breathe in. Follow along with the pacer to point in the upper part of the pacer where it is the most comfortable for you to start the exhalation. From

this point near the top follow all the way down to the bottom along with the pacer. In all breathing instruction exercises we will teach you here, the most important thing is to breathe in a relaxed way. Breathe easily and comfortably. Do not try too hard. (Give participant about a minute or so until they are able to breathe at the rate of 6.0 breaths/min. Then start recording.) Now, breathe naturally, at your normal pace. Please do not move, stay as still as possible."

Therapist's Script: "After the first 5-minute period we will find your own "resonant frequency"—the speed of breathing at which your RSA is the highest. In this procedure we will ask you to breathe at various slow rates for periods of about two minutes each. You should not find this task difficult. I would like you to keep a mental record of which rates fell most comfortable/uncomfortable and let me know at the very end. Breathe easily and comfortably. Do not try too hard. Do you have any questions?"

TASK A (Total 5 minutes): 2.5 minute baseline (press FN +F9 so monitor is OFF for subject). Now please follow the pacer. 2.5 minutes-recording at 6.0 SS follow pacer (press FN+F9 so monitor is ON for subject

TASK B (Total 5 minutes): RESONANCE FREQUENCY DETERMINATION. 1-minute recordings at 4.5, 5.0, 5.5, 6.0, 6.5. At each minute mark, change the pacer to the next rate and provide the following instructions "Now, try this one."
After this procedure, inform the trainee of his(her) resonance frequency (i.e., the frequency at which maximum amplitude of RSA is achieved & heart rate and breathing are in the same phase.

TASK C:2.5 minutes for the 2 resonance frequencies

Therapist's Instructions: Have SS breathe at the two determined resonance frequencies.

TASK D: 5 minutes at SS RESONANCE FREQUENCY

Therapist's Instructions: have ss breathe normally and remind the ss not to move because movement will interfere with recording.

HOME PRACTICE: The trainee is told to practice breathing easily and comfortably at his/her resonance frequency, with longer exhalation than inhalation for two 20-minute periods. The trainee is told how long (in seconds) each breath should be (60 divided by the resonance frequency in breaths per minute). For example, if SS resonance frequency is 5, the inhalation could be for 4 or 5 sec. and exhalation could be for 7 or 8 sec. What is important is that together the whole breath will be for 12 seconds total. The trainees should use the second-hand of a watch to time the breathing cycle. Give participant the EZ-Air Pacer. Shoe them how to breathe using both the pacer program and the second-hand of their watch. Note for the therapist: The greater the resonance frequency the fewer breaths per minute (i.e., 6 breaths/minute=10 vs. 5 breaths/minute=12). So if a person's resonance frequency is 5, they need to breath 5 in, 7 out for a total of 12 breaths/minute. At this rate, this is the ideal rate where maximum HRV is achieved.

SESSION 2: (TRAINING SESSION) BEGINNING OF RSA BIOFEEDBACK
Session Objective: To introduce abdominal and pursed lips breathing
45 minutes- 1hour

The therapist first reviews the trainee's understanding and practice of breathing at resonance frequency with longer exhalation than inhalation. The trainee is reminded not to breathe too deeply, to avoid hyperventilation symptoms (lightheadedness or dizziness). The trainee is reminded to breathe easily and comfortably, and not "try too hard. Check-in and brief suicide assessment: During the 10-15 minute hookup, the therapist will query how the subject has been in the past week, assess any changes in mood or activity level, and conduct a brief suicide assessment. "Have you had thoughts of hurting yourself? What have you been doing this week socially? Any changes at work?" Each session, subject will be reminded of the number for Acute Psychiatric Services.

TASK A: 5 minute set at Resonant Frequency
Therapist's Instructions: Breathe at your own resonance frequency, following the pacer, with longer exhalation. Make sure to pause at the top and at the bottom. See that plateau? A pause is an opportunity to hold the breath, swallow, and collect yourself. (Demonstrate for the patient).

TASK B: 5 minutes at participant's resonance frequency (with pursed lips and abdominal breathing). (Press pause button; give Task B instructions; press green button).

Therapist's Instructions (Before the 5-minute practice): Teach participant how to inhale through the nose and exhale through pursed lips and follow pacer. Model for participant how to do this. Allow the participant to practice this. Then teach participant how to breathe abdominally while following pacer. Model for participant how to do this. Allow about a minute for the participant to practice abdominal breathing. Then instruct participant to use both pursed lips and abdominal breathing while following the pacer. Model both types of breathing together for participant. Allow about a minute for participant to practice both pursed lips and abdominal breathing, (i.e., "Abdominal breathing is a very important way of breathing. When we are stressed, worried, or depressed, we tend to not breathe abdominally. We tend to breathe thoracically. However, we were born breathing abdominally, so it is a natural way of breathing properly. Have you ever seen a baby or a pet breathing as they are sleeping? What body part moves up and down?")

(Note: The trainee tries each of these instructions a few times while the therapist continues to model. The therapist gives feedback to the trainee and praises the trainee for doing the method properly. If the trainee finds abdominal breathing too difficult, however, the method is abandoned for this session, and the trainee is told to continue breathing slowly. The trainee is instructed to practice at home. See instructions under "Homework."

TASK C- 5 minutes of participant following heart rate (Stay in the room with the subject for the first few minutes, and instruct them in following their heart rate). Make sure that they understand that the thoracic respiration line should follow HR exactly. For the first minute, have them follow the pacer (the "yellow brick road"); once stable, have them follow their heart rate (the "highway exit").

Therapist's Script: "Now breathe at your resonance frequency for about one minute following the pacing stimulus. Then shift to following your heart rate. Look at this line (Point to the cardiotachometer tracing). When your heart rate goes up, this line will go up. When it goes down, the line goes down. Breathe in phase with your heart. When your heart rate goes up, breathe in. When your heart rate goes down, breathe out. But first, just continue breathing at your resonance frequency. Combine abdominal and pursed lips breathing." After one minute (depending on how well the trainee is doing the task), prompt the trainee when to shift to following his/her heart rate. (In rare cases, if the participant has a hard time following HR or if their HR is unstable, have them return to the pacer). "Follow the pacer until I instruct you to follow the red line (your heart rate). If you are having trouble following the red line, you can always return briefly to the pacer. Try to create "X" number of waves in this hear window.

TASK D: same as Task C but goal is now to increase heart rate variability.

Therapist's Script: "Breathe in phase with your heart rate. When your heart rate goes up, inhale. When your heart rate goes down, exhale. Make your heart rate go up as far as possible and down as far as possible. When your heart rate starts to go up, begin inhaling. When it goes down, begin exhaling. Breathe so that the changes in heart rate with each breath are as being as possible. Breathe easily, without tension. Breathe naturally. Do not try too hard. Breathing should just flow almost automatically. Don't think too much about how to do it. Maybe it won't work right away. It will improve with time."

HOME PRACTICE: The trainee is reminded to continue practicing slow, relaxed, abdominal, pursed-lips, prolong exhalation breathing for two 20-minute sessions each day. Also, the trainee is told to breathe at his/her own resonance frequency in each of these sessions. Have the participant practice abdominal breathing either lying down (at first) or standing in front of a mirror for 5 minutes each day, separately from the 40 minute procedure for one week.

Adherence to Homework: Therapist will enquire as to patient's adherence to homework, i.e., "Have you practiced this week? Tell me what that was like." Therapist will encourage patient to adhere to the practice, and will problem solve barriers to practice with the patient. If a patient is not practicing because they are dissatisfied with the treatment, the therapist will explore their adherence practices.

SESSION 3: (TRAINING SESSION) REVIEW OF PURSED LIPS ABDOMINAL BREATHING WITH LONGER EXHALATION, AND INTRODUCTION TO HOME TRAINING BIOFEEDBACK UNIT.
Session objective: Following heart rate.

These home trainer instructions are specifically designed to use with the HeartMath FreezeFramers other practice material (i.e., StressEraser, Ez-Air pacer, audio pacer). These should be modified according to the display and operating characteristics of the particular instrument used.

The therapist demonstrates, gives feedback, and praises the trainee for good attempts. Biofeedback is given using the HeartMath FreezeFramer on the computer, with the following biofeedback instruments. Twenty minutes of biofeedback is given using the home training unit along with the computerized biofeedback signal. The trainee is told that (s)he will be lent a home training biofeedback machine. Instructions on how to use this machine at home are now given. Therapist will remain in the same room as the subject for this session.

TASK A: 5 minutes at resonance frequency

Therapist's Script: "Follow the pacer at resonance frequency using a combination of pursed lips, abdominal breathing, and longer exhalation."

TASK B: 1 minute with pacer, then 4 minutes following heart rate.

Therapist's Instructions: Instruct participant to follow pacer at resonance frequency, then switch to following their heart rate.

TASK C: 5 minutes- Remain in the room with the subject. Instruct them to imagine a scenario that may be stressful (i.e., finding parking for their car, dealing with bad weather). Do not encourage subject to conjure up extremely noxious or personal stressors. Select a universal stressor. Ask subject to imagine the scenario (to evoke a more descriptive scene, ask them to imagine what they saw, smelled, heard or felt while in that scenario). Continue to prompt them to imagine this scenario until you see the VLF (blue bar) increase significantly. Point out this change to the participant. Remind them that the goal of the study is to decrease VLF and increase LF. Then ask them to follow the pacer with their RF.

Rest.

TASK D: 1 minute with pacer, then 4 minutes following heart rate.

Therapist's Instructions: Instruct participant to follow pacer at resonance frequency, then switch to following their heart rate. Show the participant how to utilize the program. Instruct them to use the "game" modules only after gaining proficiency with the pacer.

Provide instruction on how to use Ez-Air Pacer with the Freeze Framer. Explain that the objective is to increase the "green bar."

HOMEWORK: The trainee is instructed to practice at his/her resonance frequency using the practice device (i.e., FreezeFramer, Ez-Air, StressEraser, audio pacer) twice a day for 20 minutes. The trainee is also instructed to use pursed lips, abdominal breathing while breathing at their resonance frequency.

SESSION 4: ACQUIRING FURTHER EXPERIENCE WITH THE TECHNIQUE (TESTING SESSION)

Feedback Instructions: The trainee is instructed to maximize RSA using the cardiotachometer as biofeedback. This is done by breathing in phase with HR changes. The trainee is reminded not to breathe too deeply, particularly if experiencing dizziness or lightheadedness. If breathing is not in synchrony with RSA, the therapist instructs the patient to adjust respiration rate to see if that causes an increase in the amplitude of RSA. This will determine the trainee's new resonance frequency, and the trainee should be informed of this new frequency.

After approximately one minute (depending on how well the trainee is doing the task) the therapist prompts the trainee to shift to following his/her heart rate, and turns the pacing signal off.

Therapist's Script: "First breathe at your resonance frequency for a few minutes. Follow the pacer, then shift to following your heart rate. Look at this red line (point to cardiotachometer tracing). When your heart rate goes up, this line goes up. When it goes down, the line goes down. Breathe in phase with your heart rate. When your heart rate goes up, breathe in. When your heart rate goes down, breathe out. Make your heart rate go up as far as possible and down as far as possible. Breathe easily, without tension. Breathe naturally. Don't try too hard. It should just flow almost automatically. Don't think too much about how to do it. Maybe it won't work right away. It will improve over time."

HOME PRACTICE: Same as in Session 3. If participant indicates that the HeartMath device makes him/her nervous at home, then instruct them to continue using the pacer (Ez-Air) to follow for breathing at his/her own resonance frequency. Participant should continue using pursed lips and abdominal breathing.

APPENDIX C

Sham Biofeedback Control Protocol

This is a four-Session Sham Protocol (with two follow-ups) for HRV Biofeedback Study. The following procedure is adopted from Lehrer, Vaschillo and Vaschillo[1].

SESSION 1: INTRODUCTION TO THE METHOD AND OBTAINING INITIAL ESTIMATE OF "DESIGNATED FREQUENCY."

Therapist's Script: "Your heart rate goes up and down with your breathing. When you breathe in, your heart rate tends to go up. When you breathe out, your heart rate tends to go down. These changes in heart rate are called respiratory sinus arrhythmia. RSA triggers very powerful reflexes in the body that help it control the whole autonomic nervous system (including your heart rate, blood pressure, and breathing). Our goal is to help decrease sympathetic arousal in your system (the branch of the ANS related to the fight or flight response) and increase parasympathetic arousal (the branch of the ANS related to recover). Oftentimes, when one is depressed, baseline sympathetic arousal is high. The goal of our study is to decrease baseline arousal. This should help improve your health and ability to manage everyday stress. Breathing at your "designated" rate may help you to cope with various somatic and emotional problems. Do you have any questions?"

TASK A: 5 minutes baseline (with monitor off)

Therapist Script: For this task, please breathe naturally, at your own pace. Please do not move, stay as still as possible.

TASK B: 5 minutes (with monitor on)

Therapist's Script: "Breathe at the rate of this pacer, moving up and down. Breathe in as the pacer goes up, breathe out as it goes down. Try it. (Give feedback about whether the trainee is accurately following instructions). Now continue to breathe at this rate. Do not breathe too deeply or you will hyperventilate. If this happens you may experience some lightheadedness or dizziness. If lightheadedness or dizziness occurs, breathe more shallowly. Now try to breathe out longer than you breathe in. Follow along with the pacer to the point in the upper part of the pacer where it is the most comfortable for you to start the exhalation. From this point near the top follow all the way down to the bottom along with the pacer. In all breathing instruction exercises we will teach you here, the most important thing is to breathe in a relaxed way. Breathe easily and comfortably. Do not try too hard. Give participant about a minute or so until they are able to breathe at the rate assigned, then start recording."

Designated Frequency Determinations:

Task B: 1 minute recordings at 11,12, 13, 14, 15 bpm.

Therapist's Script: "We will now find your own designated frequency. In this procedure we will ask you to breathe at various slow rates for periods of about one minute each. You should not find this task difficult. Breathe easily and comfortably. Do not try too hard. Do you have any questions?"

Set a pacing stimulus for each frequency. Ask the trainee to breathe at each frequency for one minute (to allow computation of frequency spectra from at least ten breaths at each frequency). Don not begin this count until the trainee is breathing at the prescribed rate.

After this procedure, inform the trainee of his/her designated frequency (i.e., the frequency at which lowest amplitude of RSA is achieved and where there is a pattern of increased HF (parasympathetic arousal), and slight decrease in VLF (sympathetic arousal) so that they subject is convinced of the "study goal."

TASK C: 5 minutes at designated frequencies

Therapist's Instructions: Have participant breathe at own designated frequency

TASK D: 5 minutes baseline recording (monitor off).

Therapist's Instructions: Have participant breathe normally and remind the participant not to move because any movement will interfere with recording.

HOME PRACTICE: The trainee is told to practice breathing easily and comfortably at his/her designated frequency, with longer exhalation than inhalation for two 20 minute periods. The trainee is told how long (in seconds) each breath should be (60 divided by the designated frequency in breaths per minute). For example, if the participant's designated frequency is 15, the inhalation could be for 1 or 2 seconds, and exhalation could be for 1 or 2 seconds. What is important is that together the whole breath will be for 4 seconds total. The trainee should use the second-hand of a watch to time the breathing cycle. They should also be given an Ez-Air pacer in the first session. The trainee is told that (s)he will be given a pacing program. EZ-Air is an elaboration on Thought Technology's CardioProm^{TM} Breathing Bar Pacer, which is used to help clients establish a consistent breathing pattern. Instead of programming the pacer to one's resonance frequency, participants in the control will be instructed to breathe at a rate indicative of spontaneous breathing. The trainee is also reminded to breathe at the designated frequency when feeling down or depression, in addition to 20-mniute daily practice. The trainee should also be told that frequent practice will allow the body to get used to this rate of breathing and that ultimately they will breathe more naturally, unconsciously without purposeful motivation, throughout the day at this rate. Explain that this automatic pattern is the ideal.

SESSION 2: (TRAINING SESSION) BEGINNING OF SHAM BIOFEEDBACK

The therapist first reviews the trainee's understanding and practice of breathing at their designated frequency. The trainee is reminded not to breathe too deeply, to avoid hyperventilation symptoms (lightheadedness or dizziness). The trainee is reminded to breathe easily and comfortably, and to not try too hard.

TASK A: 5 Minute set at designated frequency

Therapist's Script: Breathe at your own designated frequency, following the pacer.

TASK B: 5 minutes at participant's designated frequency

Therapist's Script: Teach participant how to inhale through the nose and exhale through pursed lips and follow pacer. Model for participant how to do this. Allow about a minute for the participant to practice. Then teach the participant how to breathe abdominally while following the pacer. Model for participant how to do this. Allow about a minute for the participant to practice abdominal breathing. Then instruct participant to use both pursed lips and abdominal breathing while following the pacer. Model both types of breathing together for participant. Allow about a minute for participant to practice both pursed lips and abdominal breathing.
(Note: The trainee tries each of these instructions a few times while the therapist continues to model. The therapist gives feedback to the trainee and praises the trainee for doing the method properly. If the trainee finds abdominal breathing too difficult, however, the method is abandoned for this session, and the trainee is told to continue to breathe slowly. The trainee is instructed to practice at home. See instructions under "Home Practice.")

TASK C- 5 minutes of participant's designated frequency

Therapist's Script: "Now breathe at your designated frequency for the next five minutes following the pacing stimulus. Use these five minutes for additional practice. Combine abdominal and pursed lips breathing. Remember to breathe out longer than you breathe in. Continue to do pursed lips breathing when you exhale. Breathe abdominally. Combine all three styles of breathing, like this. Follow the pacer."

TASK D- Same as Task C.

HOME PRACTICE: The trainee is reminded to continue practicing slow, relaxed, abdominal, pursed-lips, prolonged exhalation breathing for two 20-minute sessions each day. Trainee is also reminded to breathe at designated frequency when feeling down or depressed. Also, the trainee is told to breathe at his/her own designated frequency in each of these sessions. Have the participant practice abdominal breathing either lying down (at first) or standing in front of a mirror for 5 minutes each day, separately from the 40-minute procedure for one week.

SESSION 3: (TRAINING SESSION) REVIEW OF PURSED LIPS ABDOMINAL BREATHING WITH LONGER EXHALATION, AND INTRODUCTION TO RECOGNIZING BIOFEEDBACK INFORMATION.

The therapist demonstrates, gives, feedback, and praises the trainee for good attempts. Remind the trainee that the most important thing is to continue to breath slowly and regularly with the rate of their designated frequency and establish a comfortable breathing pace. This will allow the trainees gradually to begin breathing in synchrony with the monitor. Again, tell the trainee that if he/she feels lightheaded, it may be due to hyperventilation and s(he) breathe less deeply. This session will allow you to elaborate on "parasympathetic activity." By showing the subject the results of both relaxation and stress they will be encouraged to practice their breathing knowing the underlying physiological shifts (as they were demonstrated in this session). This may motivate them to continue their practice since they now will understand more fully the consequential reactions their body manifests as a result of breathing and thoughts.

TASK A- 5 minutes at designated frequency

Therapist's Instructions: Instruct participant to follow pacer at designated frequency.

TASK B- Remain in the room with the participant. Instruct them to imagine a scenario that may be stressful (i.e. finding parking for their car, dealing with bad weather). Do not encourage participant to conjure up extremely noxious or personal stressors. Select a universal stressor. Ask participant to imagine the scenario (to evoke a more descriptive scene ask them to imagine what the saw, smelled, heard or felt while in that scenario). Continue to prompt them to imagine this scenario until you see the VLF (blue bar) increase significantly. Point this change to the participant. Remind them that the goal of the study is to increase HF and decrease VLF.

Rest.

TASK C- 5 minutes at designated frequency

Therapist's Instructions: Instruct participant to follow pacer at designated frequency.

TASK D- 5 minutes at designated frequency

Therapist's Instructions: Instruct participant to follow pacer at designated frequency.

HOMEWORK: The trainee is instructed to practice at his/her "designated" frequency using the EZ-Air Pacer every day for 20 minutes and when feeling "down" or depressed. The trainee is also instructed to use pursed lips, abdominal breathing while breathing at their designated frequency.

SESSION 4: ACQUIRING FURTHER EXPERIENCE WITH THE TECHNIQUE

Biofeedback Instructions: The trainee is reminded not to breathe too deeply, particularly if experiencing dizziness or lightheadedness.

Therapist's Script: "First breathe at your designated frequency for a few minutes. Follow the breath easily, without tension. Breathe naturally. Don't try too hard. It should just flow almost automatically. Don't think too much about how to do it. Maybe it won't work right away. It will improve with time."
The therapist reviews pursed lips abdominal breathing, exhaling longer than inhaling.

HOME PRACTICE: The trainee is instructed to practice at his/her designated frequency using the EZ-Air Pacer every day for 20 minutes and when feeling down or depressed. The trainee is also instructed to use pursed lips, abdominal breathing while breathing at their designated frequency (same as session 3).

REFERENCES

1. Lehrer, P.M., Vaschillo, E., and Vaschillo, B. 2000. Resonance frequency biofeedback training to increase cardiac variability: rationale and manual for training. *Applied Psychophysiology and Biofeedback*, 25(3), 177-191.