2015-12-01

Impact of Heart-Rate Variability Biofeedback on Major Depression Disorder in Resting-State fMRI

Hiu Wai Caldwell
Brigham Young University - Provo

Impact of Heart-Rate Variability Biofeedback on Major Depression Disorder in Resting-State fMRI

Hiu Wai Caldwell

A dissertation submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Patrick Steffen, Chair
Erin Bigler
Brock Kirwan
Dawson Hedges
Julianne Holt-Lunstad

Department of Psychology

Brigham Young University

December 2015

ABSTRACT

Impact of Heart-Rate Variability Biofeedback on Major Depression Disorder in Resting-State fMRI

Hiu Wai Caldwell
Department of Psychology, BYU
Doctor of Philosophy

Major depressive disorder (MDD) is one of the most common psychiatric illnesses and causes significant disturbances in daily functioning. Research on heart-rate variability (HRV) biofeedback training suggests that HRV is an efficacious adjunct to psychotherapy in reducing depressive symptoms. The purpose of this study was to examine neurological changes in depressed individuals who were randomized to either a psychotherapy plus HRV biofeedback training or to a treatment as usual group. A control group with no history of depression was also studied. We collected psychological, physiological, and imaging data from 30 participants (10 in an experimental group, 10 in a treatment as usual group, and the other 10 in a healthy control group) at baseline and follow-up. Regions of interest (ROIs) included anterior cingulate cortex, hippocampus, and amygdala. Participants from the experimental group went through 5 weekly HRV trainings in conjunction with traditional psychotherapy approaches. The treatment as usual group only received psychotherapy. The healthy controls did not receive any HRV training or therapy services. Overall, we found significant improvements in the experimental group's depression score, overall distress level, and HRV measurements relative to the TAU and control groups. However, we did not find significant HRV and resting-state connectivity group differences among experimental group relative to healthy controls. Together, results suggest that HRV training helps to reduce depressed participants' overall distress level and depressive symptoms. However, findings do not show any changes in participants' imaging data. These findings serve as pilot data on literature related to HRV biofeedback training in a depressed population.

Keywords: heart-rate variability, depression, resting-state fMRI

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my faculty mentor Dr. Patrick Steffen who continually fostered my growth as a researcher and clinician. This project could not have been completed without his guidance. I would also like to recognize Dr. Brock Kirwan who showed tremendous patience in teaching me imaging concepts and techniques. Similarly, Dr. Erin Bigler encouraged me since I was a first-year graduate student to formulate and start doing my dissertation projection. Many thanks to the following individuals: Dr. Michelle Nash for her collaboration in scanning participants and scans processing; Dr. Barbara Morrell and Dr. Maureen Rice for letting me use their lab space to make this project possible; Mr. Tracy Abildskov for answering so many of my random questions when I was struggling with this project; Mrs. Sheri Knight for making scheduling participants easier; and all of my participants for letting me scan their brains and collect data. Many thanks also go to the BYU Graduate Research Fellowship Award and The Mentoring Environment Grant for funding a big portion of this project. Finally, I wish to thank my husband, Dallen Caldwell, for recognizing my talents and showing me unlimited support and encouragement throughout graduate school.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Impact of Heart-Rate Variability Biofeedback on Major Depression Disorder in Resting-State fMRI

Major depressive disorder (MDD) is one of the most common psychiatric illnesses (Waraich, Goldner, Somers, & Hsu, 2004). A systematic review reported that MDD has a 12-month prevalence of 3.7% in which women are twice as vulnerable compared to men (Ferrari et al., 2013). Individuals with MDD experience significant emotional distress, such as anhedonia, feelings of worthlessness, and inappropriate guilt, which cause dysfunction in daily functioning. Moreover, empirical evidence suggests that there is approximately 16% - 40% lifetime suicide attempt in MDD (Oquendo, Currier, & Mann, 2006). In general, researchers examine MDD from different perspectives, such as genetic (Elder & Mosack, 2011), biochemical (Gao & Bao, 2011), cognitive (Ciesla, Felton, & Roberts, 2011), sociocultural (Holzel, Harter, Reese, & Kriston, 2011), and neuroanatomical models (Campbell, Marriott, Nahmias, & MacQueen, 2004). Neuroanatomical models of depression have not yet been fully investigated.

With advancing technology, researchers are able to investigate the association between depression and its neurobiological abnormalities as well as develop new interventions. Research findings indicate that individuals suffering from depression have structural and functional abnormalities in the anterior cingulate cortex (ACC), hippocampus, and amygdala (Drevets, Bogers, & Raichle, 2002; Firbank et al., 2005; Gunning et al., 2009; Milne, MacQueen, & Hall, 2012). Pharmacological and psychotherapeutic interventions are typically used to treat depression (Cuijpers, Huibers, Ebert, Koole, & Andersson, 2013; Cuijpers, van Straten, van Oppen, & Andersson, 2008). Newer treatment approaches are also being developed that are used

as adjuncts to standard treatment. One of the adjunct therapy options is heart-rate variability (HRV) biofeedback training (Tonhajzerova et al., 2009).

HRV refers to the unceasing transition between sympathetic and parasympathetic activities resulting in variations in heartbeat. Previous research suggests that individuals' HRV reaches its highest amplitude through breathing at a resonance frequency (Hassett et al., 2007). Maximized HRV has been associated with positive health outcome (Cohen & Benjamin, 2006; Karavidas et al., 2007; Nolan et al., 2005). Reduced HRV has been associated with increased depression symptoms (Glaser & Glaser, 2002). Recent evidence indicates that HRV biofeedback training improves depressed patients' HRV which links with better emotion control (Apelbaum, 2001; Appelhans & Luecken, 2006; Grippo & Johnson, 2002; Karavidas et al., 2007). Depressed individuals report lower levels of depression symptoms after employing HRV biofeedback technique (Siepmann, Aykac, Unterdorfer, Petrowski, & Mueck-Weymann, 2008; Uhlmann & Froscher, 2001). Details relationship between HRV and depression was discussed below. Overall, this research project sought to examine the effects of HRV training on depressive symptoms and connectivity between the ACC, hippocampus, and amygdala.

Depression and Brain Functioning

Numerous studies have been devoted to investigating the relationship between depression, brain anatomy, and brain functioning. Converging findings in depressed individuals indicate disrupted frontal lobe function and limbic system activity (Anand et al., 2005; Ketter et al., 2001). To be specific, brain-imaging techniques have shown hypermetabolism in medial prefrontal cortex (Mayberg, 2003) and decreased functional connectivity between prefrontal cortex and anterior cingulate cortex (Aizenstein et al., 2009) among people with major depressive disorder. Furthermore, similar studies reported volume reduction and abnormal elevations of resting

cerebral blood flow in limbic structures, such as hippocampus and amygdala (Drevets, 2001; Liotti & Mayberg, 2001; Mervaala et al., 2000) In sum, anomalous activities in the ACC regions and subcortical system, such as amygdala and hippocampus have been associated with irregular emotion processing and regulation (Bremner, Vythilingam, Vermetten, Vaccarino, & Charney, 2004; Fitzgerald, Laird, Maller, & Daskalakis, 2008; Heinz et al., 2007; Kupfer, Frank, & Phillips, 2012).

In addition to the findings stated above, researchers also report aberrant resting-state functional connectivity among individuals with major depressive disorder from ACC regions to subcortical structures (Anand et al., 2005; Greicius et al., 2007). Resting-state functional connectivity measures correlations in the blood-oxygen-level-dependent (BOLD) signal between brain regions in a given time series. This methodology has been well established to investigate the integration, changes in brain networks, and their connectivity when no task is performed (Raichle & Mintun, 2006). For example, a recent study on resting-state fMRI found decreasing connectivity between ACC and amygdala in depressed patients compared to a healthy control group (Anand, Li, Wang, Lowe, & Dzemidzic, 2009). The decreased corticolimbic connectivity suggests a trait abnormality in depressive disorder. Furthermore, another study revealed that nonrefractory major depressive patients have reduced connectivity in ACC, hippocampus, amygdala, and prefrontal cortex (Lui et al., 2011). This result indicates a distinct functional deficit in MDD patients' brain networks. Overall, findings from Anand et al. (2009) and Lui et al. (2011) suggest that decreased corticolimbic connectivity is associated with reduced mood regulation ability.

Depression Treatment

Depression is characterized by feelings of sadness and a lack of desire to pursue usual activities. Depressed individuals are relatively less active, hold negative views of themselves, and in high risk of attempting suicide (Bolton, Belik, Enns, Cox, & Sareen, 2008). Due to the adverse effects of depression, a large body of research has been conducted in an attempt to reach effective treatment outcomes for MDD. In light of existing evidence, most treatment outcome studies have focused on antidepressant medications and psychotherapies (Cipriani et al., 2009; Cuijpers, Dekker, Hollon, & Andersson, 2009; Cuijpers et al., 2008; Jakobsen et al., 2012; Zimovetz, Wolowacz, Classi, & Birt, 2012).

Despite the high usage of antidepressants, findings from several studies suggest that only a third to a half of patients find antidepressants to be effective (Pigott, Leventhal, Alter, & Boren, 2010; Rush et al., 2006). After an inadequate response to antidepressant treatment is found, the most common pharmacological strategies are switching antidepressant medication and combining antidepressants with psychotherapy (Garcia-Toro, Medina, Galan, Gonzalez, & Maurino, 2012; Papakostas, 2009). Effective treatment approaches toward depression include cognitive therapy (Jakobsen, Hansen, Storebo, Simonsen, & Gluud, 2011; Wampold, Minami, Baskin, & Tierney, 2002) and cognitive behavior therapy (CBT; Butler, Chapman, Forman, & Beck, 2006; Haby, Tonge, Littlefield, Carter, & Vos, 2004). Cognitive therapy focuses on recognizing and changing maladaptive cognitive process (Beck, Rush, Shaw, & Emery, 1979). CBT includes a number of behavioral techniques that encourage depressed individuals try modify behaviors in addition to the cognitive component. Beside the above two therapies, interpersonal therapy (Cuijpers et al., 2011; van Hees, Rotter, Ellermann, & Evers, 2013) is also found to be helpful in treating depression. Interpersonal therapy emphasizes on exploring

individual's relationship with others and developing social skills for new roles' transition (Weissman & Markowitz, 2002). The combination of psychopharmacology and psychological treatments is effective compared to treatment with pharmacotherapy alone (Friedman et al., 2004; Pampallona, Bollini, Tibaldi, Kupelnick, & Munizza, 2004) or psychotherapy alone (De Maat, Dekker, Schoevers, & de Jonghe, 2007).

In addition to pharmacology and psychotherapy, a sizeable number of adjunct therapy options have been studied in an attempt to help elucidate treatment effectiveness involved in MDD. Those adjunct options consist of, for example, the use of nutrients (Amr, El-Mogy, Shams, Vieira, & Lakhan, 2013; Gertsik, Poland, Bresee, & Rapaport, 2012) and real-time psychophysiological self-regulation, such as neurofeedback (Linden et al., 2012) and HRV biofeedback training (Tonhajzerova et al., 2009).

HRV Biofeedback

HRV is a function of vagal nerve, the nerve that is associated with parasympathetic functioning, control of heart rate (HR). Sympathetic activity such as inhalation inhibits vagal nerve stimulation and results in increasing heart rate (Beevers, Ellis, & Reid, 2011). Parasympathetic activity such as exhalation excites vagal nerve function and results in decreasing heart rate (Lehrer et al., 2013). In a healthy individual, there are large differences in heart rate as people breathe in and breathe out. Many people assume that if someone has a heart rate of 70 beats per minute, that the heart beats constantly at that rate throughout each minute. This is not the case, however. Rather, heart rate is constantly fluctuating as a function of breathing (Lehrer et al., 2013; Shaffer & Venner, 2013) and the unceasing transition between sympathetic and parasympathetic activities results in HRV. In other words, HRV refers to the variations in amplitude between consecutive heartbeats oscillations (Shaffer & Venner, 2013).

When individuals' heart rate and breathing are completely in sync, they are breathing at their optimal breathing rate which results in higher amplitude of HR oscillations and leads to higher HRV (Hassett et al., 2007; Vaschillo, Lehrer, Rishe, & Konstantinov, 2002). In fact, the larger the fluctuation in heart rate, the healthier is the heart (Del Pozo, Gevirtz, Scher, & Guarneri, 2004). Empirical evidences suggest that increasing HRV has been associated with positive health outcomes and well-being (Cohen & Benjamin, 2006; Del Pozo et al., 2004; Karavidas et al., 2007; Nolan et al., 2005; Swanson et al., 2009). Various methods have been employed in increasing individuals' HRV. One of the techniques is optimal breathing HRV biofeedback (Prinsloo, Derman, Lambert, & Rauch, 2013; Siepmann, Aykac, Unterdorfer, Petrowski, & Mueck-Weymann, 2008). This breathing technique teaches individuals to breathe completely in phase with their heartbeat so that the amplitude of heart rate oscillations can be maximized.

To date, findings in HRV biofeedback training demonstrate that such techniques lead to positive outcomes in a variety of health problems. For examples, after receiving HRV biofeedback training, participants show significant improvement in cardiac morbidity (Del Pozo et al., 2004), pulmonary function (Lehrer et al., 2003), and exercise tolerance (Swanson et al., 2009). Indeed, upon receiving HRV biofeedback training, not only patients with cardiovascular and respiratory problems benefit from it (Giardino, Chan, & Borson, 2004; Nolan et al., 2005; Palomba et al., 2011), but also individuals suffering from chronic pain (Hallman, Olsson, von Scheele, Melin, & Lyskov, 2011), headache (Blume, Brockman, & Breuner, 2012; Nestoriuc, Martin, Rief, & Andrasik, 2008), anxiety (Cohen & Benjamin, 2006; Ratanasiripong, Sverduk, Prince, & Hayashino, 2012) and depressive disorders (Karavidas et al., 2007).

HRV Biofeedback and Depression

Empirical findings suggest that HRV and emotion regulation play an important role in depression (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Brockmeyer et al., 2012; Garnefski & Kraaij, 2006; Siepmann et al., 2008). Higher HRV values correlate with better emotion regulation and expression (Appelhans & Luecken, 2006; Segerstrom & Nes, 2007). The mechanism between HRV and emotion regulation lies in flexibility of the autonomic nervous system (ANS; Quintana, Guastella, Outhred, Hickie, & Kemp, 2012). In general, emotion regulation is related to physiological arousal. The sympathetic nervous system (SNS) is more active during high arousal states whereas the parasympathetic nervous system (PNS) is more active during rest and relaxation. The transition between SNS and PNS can be seen in HRV, which reflects the alteration of emotional and physiological changes.

Depressed individuals have impaired HRV relative to healthy control subjects (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012; Patron et al., 2012). In fact, reduced HRV is correlated with increased depressive symptoms (Carney & Freedland, 2008; Champaneri, Wand, Malhotra, Casagrande, & Golden, 2010; Kemp et al., 2012). After receiving biofeedback training, individuals with depression demonstrated higher levels of HRV and reported decreased level of depression symptoms (Karavidas et al., 2007; Siepmann et al., 2008; Uhlmann & Froscher, 2001). Thus, research findings suggest that HRV appears to be an effective adjunct treatment for depression.

The Present Study

Previous studies have only explored the impact of HRV biofeedback training on depressed patients (Apelbaum, 2001; Segerstrom & Nes, 2007), and their brain activity separately (Ketter et al., 2001; Liotti & Mayberg, 2001). While incorporating HRV biofeedback

into treatment for depression yields favorable outcomes (Beckham, Greene, & Meltzer-Brody, 2013; Patron et al., 2013), relevant changes in brain areas have not yet been examined in detail. Therefore, this study aimed to examine the impact of HRV biofeedback training on depression symptoms severity, and resting-state connectivity in individuals with major depression. Specially, the connectivity between the ACC, hippocampus, and amygdala were examined.

Resting-state fMRI was chosen in this study for three main reasons. First and foremost, resting-state fMRI allowed us to examine brain integration and connectivity. Additionally, resting-state fMRI required minimal compliance from the participants – they laid still on the scanner bed with no tasks assigning to them. Errors from movement were reduced in the process of data collection. Also, according to Fox and Raichle (2007) resting-state fMRI allowed more direct comparison between groups.

The regions of interest (ROIs) in this study were the ACC, hippocampus, and amygdala. These three areas have received particular focus in depression research in a series of related studies (Anand et al., 2005; Drevets, 2001; Ketter et al., 2001). A convergence of research findings indicate that dysfunction within these ROIs contributes to maladaptive emotion regulation (Anand et al., 2009; Anand et al., 2005; Cullen et al., 2009). Therefore, this study adopted this research strategy and looked at connectivity between these three ROIs.

Hypotheses. Since both participants from the experimental group (Exp) and the treatment as usual group (TAU) had MDD, it was hypothesized that before HRV training, there would be no significant differences between these two groups in their HRV, severity of depression symptoms, overall distress level, and resting-state connectivity across ROIs. It was also hypothesized that there would be significant differences between the depressed participants (Exp

and TAU groups) and healthy control group (C_h) in their HRV, severity of depression symptoms, overall distress level, and resting-state connectivity across ROIs before HRV training.

After participants from the Exp group received HRV biofeedback training, it was hypothesized that they would show significantly increased HRV and decreased depression symptoms and overall distress level in comparison to their baseline measurement and with the TAU group. In contrast, it was expected that there would be no differences between the Exp and C_h groups in their HRV, depression symptoms, and overall distress level. In addition, it was also hypothesized that after finishing HRV biofeedback training, the Exp group would show significantly higher resting-state fMRI connectivity between the ROIs in comparison with their baseline measurement and the TAU group. Studies on combining fMRI demonstrated that depressed individuals show less connectivity between the cingulate cortex and subcortical structures (Anand et al., 2009; Lui et al., 2011; Napadow et al., 2008). Since HRV biofeedback has been shown to be correlated with improving emotion regulation (Appelhans & Luecken, 2006), our study, therefore, hypothesized that there would be a significant change in the Exp group's resting-state fMRI connectivity between the ROIs before and after the HRV training.

Furthermore, it was hypothesized that after receiving HRV biofeedback training, there would be no significant differences between the Exp and C_h in the follow-up ROIs' resting-state fMRI connectivity. Empirical evidence suggests that depressed individuals have lower connectivity between anterior cingulate cortex and subcortical structures than healthy population (Anand et al., 2005). Therefore, we anticipated there would be a significant difference between the Exp and C_h group in their baseline connectivity measurement. Once again, since HRV techniques have been associated with increasing mood regulation (Appelhans & Luecken, 2006), the presented study, therefore, hypothesized that there would be a significant change in the Exp's

follow-up connectivity measure in which the gap between Exp and C_h group would shift to a non-significant level.

Based on the hypotheses above, dependent variables in this study were the total score of the severity of depression symptoms from the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) and the total score of participants' overall distress level from the Outcome Questionnaire (OQ45; Lambert, Lunnen, Umphress, Hansen, & Burlingame, 1994). Aside from the above two measures, this study also used HRV physiological variables and connectivity between the ROIs as dependent variables. Abnormal activities in ACC, hippocampus, and amygdala have been found across studies of depression (Anand et al., 2009; Anand et al., 2005; Cullen et al., 2009). Therefore, this study sought to examine how biofeedback training has an impact on these three ROI's in depressed individuals.

The independent variable in this study, similar to Siepmann et al. (2008), was exposure to HRV biofeedback to Exp group versus TAU group in depressed individuals seeking therapy at the BYU counseling center. A healthy group of college students (no depression) was also used as a healthy control group. A slight modification was made in this study that all of the follow-up measurements (HRV, depression symptoms measurements, and brain scans) were done within 2 weeks upon completion of the biofeedback training. Siepmann et al. (2008) measured HRV and severity of depression symptoms in their follow-up study, the presented study added a component on fMRI imaging in it.

Why was this study unique? The presented study was unique because it served as a pilot study examining the neurological changes in depressed individuals who underwent HRV biofeedback training. While many studies have examined the association between depression and neurological change and few studies have explored the effects of biofeedback training on

depression, no research has investigated these three components together. Therefore, the presented was unique. Also, this study provided additional evidence of the efficacy of biofeedback training for depression treatment.

Methods

Participants

A total of 32 female individuals were recruited. Participation was completely voluntary. Exclusion criteria included an age less than 18 or over 25 years, use of vasoactive medications, cardiovascular disease, alcohol or drug abuse, any physiological or neurological disorders, history of electroconvulsive therapy, head injury, and MRI incompatibility. Participants were compensated $20 for each MRI scanning session and $10 for each biofeedback session. IRB approval was approved prior to beginning the study.

Within the 32 participants, a total of 21 individuals with MDD were recruited through Brigham Young University (BYU) Counseling Center consecutively. One participant with MDD was excluded in the study due to equipment errors. In total, 20 participants with MDD remained in the study. All of them met diagnostic criteria for MDD, with five reporting a history of depressive symptoms during their teen years. One of the MDD participants reported current use of medication (Prozac); however, she was in the process of weaning off this medication. Overall, half of the MDD participants was randomly assigned into the Exp group (n = 10) whereas participants received both HRV biofeedback training and treatment as usual for MDD. The other half of the group (n = 10) served as the TAU group where they only received treatment as usual for MDD without biofeedback training. Another 11 healthy individuals were recruited through BYU campus as the C_h group. One participant from the C_h group was excluded due to equipment errors. In total, 10 participants remained in the C_h group. None of them met criteria for any psychiatric disorders or reported medication use. Thus, final groups submitted for data analyses

consisted of 20 MDD participants and 10 healthy control participants. These groups did not differ by age (Exp ages $M = 20.09$, $SD = 1.81$; TAU ages $M = 20.20$, $SD = 1.47$; C_h ages $M = 20.64$, $SD = 1.29$, see Table 1).

Psychological Measures

A structured clinical interview, namely the MINI International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998) was used in this study. The M.I.N.I is one of the most widely used clinical structured diagnostic interview instrument employed by mental health professionals with good internal consistency – Cronbach's alpha equals to .66 (Sheehan et al., 1998). Thus, this study used the M.I.N.I in recruitment stage to ensure all individuals in the Exp group and TAU group met criteria for MDD, and all participants from the C_h group did not meet criteria for any disorders list on M.I.N.I.

A self-ratings depression scale, the BDI-II (Beck et al., 1996) was used to examine the severity of depression symptoms across all participants. The BDI-II consisted of 21 groups of statements where participants picked one statement in each group that best described their feeling during the past two weeks. The total score of BDI-II was 63 with 4 levels of cutoff scores. A total score between 0-13 indicated "minimal" level of depression, score between 14-19 indicated "mild" level of depression, score between 20-18 indicated "moderate" level of depression, and score between 29-63 indicated "severe" level of depression. The BDI-II has internal consistency ranges from .87 to .93 (Titov et al., 2011), one-week test-retest reliability at .93 (Beck et al., 1996), and cronbach's alpha at .93 level among college students population (Poole, Bramwell, & Murphy, 2006). Its reliability and validity have been supported (Roelofs et al., 2013).

A 45 items self-report measure for overall degree of disturbance in the course of treatment, the OQ45 (Lambert et al., 1994) was used to keep track of changing in participants' overall distress level. Each item in the OQ45 was scored on a 5-point Liket scale, from "0" never to "4" almost always. The total score of OQ45 was 150 with a cutoff score 63. A total score at or greater than 63 indicated possible clinically significant distress. Furthermore, this level of distress suggested that individuals were admitting a large number of distress symptoms in their general quality of life (Hanson & Merker, 2005). OQ45 has internal consistency ranges from .7 to .93 and test-retest reliability .78 to .84 (Hanson & Merker, 2005).

Physiological Measures

Physiological data were recorded through a biofeedback system (J&J Engineering, Poulsbo, WA). Quantification of variability that allowed us to assess how much or how little HRV was occurring included the following variables: HR, one time-domain measure: standard deviation of normal-to-normal intervals (SDNN) between adjacent heartbeat, two frequency domain measures: high frequency (HF) and low frequency (LF), and the ratio between LF and HF (LF/HF). SDNN referred to the amount of variability in heartbeat interval. It built from corresponding mean value of all the 5-minute of heartbeat interval standard deviations across time. Higher value in SDNN was associated with better health outcome. This time-domain measure was a common measure in psychophysiology which assessing HRV (DeGiorgio et al., 2010). HF HRV reflected parasympathetic activity; its value ranged between 0.15 to 0.40 Hz (Karavidas et al., 2007; Kemp et al., 2012). The higher the high frequency value, the more dominant is the parasympathetic system. LF HRV influenced by both the sympathetic and parasympathetic systems; its value ranged from 0.05 to 0.15 Hz (Karavidas et al., 2007). Lower low frequency values reflected greater influence from the sympathetic system. Since activity in

both the sympathetic and parasympathetic systems were almost always presented together, the LF/HF ratio provides an index for automatic balance between the two systems. This ratio also carried information about sympatho-vagal balance; its value ranged from 1.1 to 11.6 (Nunan, Sandercock, & Brodie, 2010).

Images Parameters

MRI data were collected on a Siemens 3 Tesla Tim MAGNETOM® Trio scanner (Erlangen, German) using a 12-channel head coil at the Brigham Young University MRI Research Facility (Provo, UT). Structural images were acquired using a standard T1-weighted MPRAGE sequence with the following parameters: 176 slices; TR = 1900 ms; TE = 2.26 ms; flip angle = 9°; field of view = 250 mm; slice thickness = 1 mm; voxel resolution = 1 ×1 ×1 mm; 1 average.

Functional images were acquired using a gradient-echo echoplanar, T2*-weighted pulse sequence with the following parameters: 39 interleaved slices; TR = 2000 ms; TE = 28 ms; flip angle 90°; field of view = 192 mm; slice thickness = 3 mm; voxel resolution = 3 × 3 × 3 mm; measurements = 180. The first 3 TRs acquired were discarded to allow for T1 stabilization.

Procedure

All participants were recruited through the BYU campus and Counseling Center. Informed consent was given prior to clinical interview. After potential participants signed the informed consent, the M.I.N.I was administered. In accordance with the purpose of this study as indicated above, all participants who met criteria for MDD were randomized into either the Exp or TAU group. Individuals without any psychopathology were assigned into the C_h group. All participants from the 3 groups were scheduled for the baseline brain scans and HRV measurements.

Baseline measurement. Each participant was asked to abstain from exercising, consuming caffeinated and tobacco products for 3 hours before testing (Gianaros et al., 2005). All participants went to the BYU MRI Research Facility for a baseline resting-state MRI measurement. Upon arrival, participants filled out a consent form specifically for MRI procedures. A verbal description and a screening form designed specifically for the MRI Research Facility were administrated to the participants. Participants were led to the fMRI scanner room and stayed on the scanner bed quietly for approximately 29 minutes. All participants were instructed to stay awake with eyes closed. They wore earplugs and were positioned carefully in the 12-channel receive-only head coil with comfortable support. The first 3 dummy scans were discarded to allow magnet stabilization. The study duration from arrival until they left the scanner room was approximately 45 minutes. After the scanning, participants' baseline HRV was measured at the BYU Counseling Center, which was about 5 minutes away from the MRI Facility.

At the BYU Counseling Center, participants were given a verbal explanation on the procedure of the HRV measurement. An online survey which includes BDI-II, OQ45, and demographic information was administrated. After that, a respiration belt was attached directly over participant's belly button for respiration data. An electrocardiography (ECG) electrode was placed on each side of the wrist for ECG signals. A ground electrode was put on the left side of the wrist, right above the ECG electrode. After all the sensors were hooked up, participants breathed with their normal day-to-day breathing rate for 10 minutes as a baseline measurement. After the baseline recording, all participants from the Exp group received their first HRV training session. The TAU and C_h groups were scheduled to come back for follow-up measurements.

1st HRV training. This training session occurs on the same day, right after the HRV baseline measurement. The purpose of the first training session was to demonstrate and teach abdominal breathing. For more detail on the procedures see Lehrer et al. (2013). In brief, participants learned diaphragmatic breathing. Participants practiced diaphragmatic breathing for 20 minutes. This breathing technique sat the stage for the following 4-week HRV training sessions. Upon finishing the first training session, participants were scheduled for their second visit and reminded to practice abdomen breathing 15 to 20 minutes a day for 4 to 5 times a week. Additionally, participants received a weekly e-mail reminding them to practice and their weekly appointment. Of note, the baseline HRV measurement and all of the following HRV training sessions lasted approximately 30 to 45 minutes each.

2nd HRV training. The purpose of the second training session was to determine participants' optimal breathing rate, i.e. the rate that got participants into the greatest oscillations of HR. At the beginning of this training session, all participants were instructed to do diaphragmatic breathing for 3 minutes then breathed at different rates, from 6.5 down to 4.5 breathes per minute (E. G. Vaschillo, Vaschillo, & Lehrer, 2006) with a change of .5 stepped down each time. Each rate of breathing lasted for 2 minutes and HRV data was recorded for each breathing rate. A visual pacer on a computer screen guided participants at each respiratory rate. Participants' optimal breathing rate was determined by the highest LF value, which was generated from the J&J program. Once participants' optimal breathing rate was determined, they were instructed to practice with a visual pacer corresponds to their target optimal breathing rate for another 3 minutes. Upon completion, participants were scheduled for three weekly 20 minutes HRV training sessions. They were also inculcated to practice 4 to 5 times a week for

three weeks, between 15 to 20 minutes a day by using visual guides that could be downloaded from the internet for free.

3rd, 4th and 5th HRV training. These three training sessions aimed to fine tune and target participants' optimal breathing rate. Participants practiced their optimal breathing rate and breathed in phase with their heart rate for 20 minutes on each of the visit. A follow-up appointment was scheduled upon completion of the 5th training session.

Follow-up measurement. All participants first received follow-up resting-state brain scans before the HRV follow-up measurement. The follow-up brain imaging appointment took approximately 45 minutes. Correspond with the baseline brain imaging appointment, a verbal description and screening form regarding the MRI scanner were given, followed by a structural, functional, and diffusion tensor imaging brain scan. After the follow-up scans, all participants went to the BYU Counseling Center for the final HRV measurement.

Similar to the baseline HRV measurement, participants from the three groups were asked to fill out an online survey first and then breathed with their normal breathing rate for 10 minutes. Data were recorded through the biofeedback system. After that, participants were debriefed. Total time commitment for the follow-up HRV measurement was approximately 30 minutes including hooking up electrodes and potential technical problems to resolve. Hence, the total time commitment for the presented study was approximately 6 weeks.

Imaging Data Processing and Analysis

Imaging data preprocessing and analysis was performed using the Analysis of Functional Neuroimages (AFNI) software (Cox, 1996). All participants' functional images were slice-time corrected. This was done to adjust for shifting in hemodynamic response in adjacent voxels due to acquisition time difference. Motion correction was performed next to realign the functional

time courses to their own first image. The processed images were smoothed and blurred across adjacent voxels to maximize functional signal-to-noise ratio. The structural scan was co-registered to the functional data in order to match functional orientation. Next, participants' structural scans were aligned through their anterior and posterior commissures (AC-PC).

All participants' structural and functional scans were normalized to the Talairach atlas (Talairach & Tournoux, 1988). Advanced Normalization Tools (ANTs, version 1.9, http://sourceforge.net/projects/advants; Klein et al., 2009; Motley & Kirwan, 2012) transformation was performed to create a template based on participants' structural scans. Next, bilateral ROIs were identified on the ANTs template and back-transformed to individual subject space. Effects of no interest were identified and removed from the functional time series. Functional time-series data were then extracted from each ROI and the pair-wise correlations were calculated between each ROI's time-series data. Resulting Pearson correlations were z-transformed and then entered into group-level repeated measure analyses of variance (ANOVA) analyses.

Analytic Strategy

All data were subjected to a 3 (Exp, TAU, C_h) × 2 (baseline, follow-up time-point) repeated measure ANOVA design. Dependent variables were the total BDI-II scores, total OQ45 scores, HRV variables, and resting-state connectivity among the ROIs. Separate repeated measure ANOVA was conducted for each dependent variable. Repeated measure ANOVA was preformed because there were two categorical groups in the independence variables: three randomized groups (Exp, TAU, C_h) and two time points conditions (baseline, follow-up) in the experiment. This 3 x 2 repeated measure ANOVA design allowed us studying the interaction

between various experimental groups and conditions by conducting a post-hoc Tukey test. Furthermore, effect size was measure by partial eta squared (η^2).

Results

Baseline Comparison

Psychological measures. Descriptive statistics showed that participants from Exp and TAU groups scored higher in both total BDI-II and total OQ45 scores in comparison with C_h group at baseline (see Table 1). Results from repeated measure ANOVAs revealed groups differences in total BDI-II scores ($F(2, 27) = 14.65$; $p < .001$; partial $\eta^2 = .52$; see Table 2) and total OQ45 scores ($F(2, 27) = 11.26$; $p = < .001$; partial $\eta^2 = .45$; see Table 2). In specific, results from post-hoc Tukey test showed no significant differences between Exp's and TAU's total BDI-II scores (Exp $M = 24.90$; TAU $M = 17.70$; $p = .31$; see Table 1) and total OQ45 scores (Exp $M = 84.20$; TAU $M = 71.10$; $p = .74$; see Table 1) at baseline. Both groups reported mild to moderate level of depression, scoring above the cutoff for clinically significant levels of distress.

Table 1

Summary of Demographic and Psychological Measures (Mean, Standard Deviation, and Range) by Groups at Baseline.

	Exp[a]		TAU[b]		C_h[c]	
N	10		10		10	
Age (years)	20.09	(1.81)	20.20	(1.47)	20.64	(1.29)
Range	18.0 – 23.0		18.0 – 23.0		18.0 – 23.0	
BDI-II[d]	24.90	(11.84)	17.70	(7.10)	3.70	(3.98)
Range	11.0 – 49.0		2.0 – 28.0		0.0 – 12.0	
OQ45[e]	84.20	(26.02)	71.10	(19.96)	32.5	(20.32)
Range	46.0 – 129.0		22.0 – 89.0		0.0 – 70.0	

Note. [a]Experimental group. [b]Treatment as usual group. [c]Healthy control group. [d]Beck Depression Inventory-II (Beck, Steer, & Brown, 1996). [e]The Outcome Questionnaire-45 (Lambert, Lunnen, Umphress, Hansen, & Burlingame, 1994).

Table 2

Repeated Measures Analysis of Variance (ANOVA) by Groups for Psychological and Physiological Measures.

		df	*MS*	*F*	*p*	*partial* η^{2f}
BDI-II[a]	Groups	2	1291.5	14.65	< .001	0.52
	Time	1	646.8	21.34	< .001	0.44
	Time*Groups	2	174.6	5.76	0.008	0.30
OQ45[b]	Groups	2	8895.7	11.26	< .001	0.45
	Time	1	1706.7	13.87	0.001	0.34
	Time*Groups	2	893.3	7.26	0.003	0.35
SDNN[c]	Groups	2	275.1	0.45	0.645	0.03
	Time	1	398.8	5.29	0.029	0.16
	Time*Groups	2	562.9	7.46	0.003	0.36
$Log_{10}LF$[d]	Groups	2	0.3	1.55	0.231	0.11
	Time	1	0.4	4.78	0.038	0.16
	Time*Groups	2	0.4	4.83	0.016	0.27
$Log_{10}HF$[e]	Groups	2	0.8	1.75	0.192	0.11
	Time	1	0.2	1.99	0.170	0.07
	Time*Groups	2	0.1	0.82	0.451	0.06
$Log_{10}LF/ Log_{10}HF$	Groups	2	0.1	2.16	0.135	0.14
	Time	1	0.2	10.50	0.003	0.29
	Time*Groups	2	0.03	2.56	0.096	0.16

Note. [a]Beck Depression Inventory-II (Beck, Steer, & Brown, 1996). [b]The Outcome Questionnaire-45 (Lambert, Lunnen, Umphress, Hansen, & Burlingame, 1994). [c]Standard deviation of normal-to-normal intervals. [d]Low frequency. [e]High frequency. [f]Patial eta-squared.

Responses from these two groups suggested that they were admitting to a large number of distress symptoms, as well as difficulties in their general quality of life. Significant differences were found between depressed participants' and healthy controls' total BDI-II scores and total OQ45 scores. Both the Exp and TAU groups reported higher depression level and clinically significant overall distress symptoms than the healthy controls. Participants from the control group reported a minimal level of depression; their total OQ45 scores were below the clinical cutoff for distress (total BDI-II scores: Exp $M = 24.90$; TAU $M = 17.70$; C_h $M = 3.70$; $p < .001$;

see Table 1; total OQ45 scores: Exp $M = 84.20$; TAU $M = 71.10$; C_h $M = 32.50$; $p < .001$; see Table 1).

Physiological measures. Since measures of physiological variables demonstrated skewed distributions, a logarithm (log_{10}) transformation was performed on the following HRV variables (LF, HF, LF/HF ratio) before a series of repeated measure ANOVAs were conducted to evaluate whether the groups (Exp, TAU, C_h) differed with regards to physiological measures at baseline. Results from repeated measure ANOVAs revealed no significant differences between groups for SDNN ($F(2, 27) = 0.45$; $p = .645$; partial $\eta^2 = .03$; see Table 2), log_{10} LF ($F(2, 26) = 1.55$; $p = .231$; partial $\eta^2 = .11$; see Table 2), log_{10} HF ($F(2, 27) = 1.75$; $p = .192$; partial $\eta^2 = .11$; see Table 2), and log_{10} LF/ log_{10} HF ratio ($F(2, 26) = 2.16$; $p = .135$; partial $\eta^2 = .14$; see Table 2) at baseline. Participants from all three groups had similar physiological measures at baseline.

Imaging data. Next, another series of repeated measure ANOVAs were performed to evaluate whether the groups (Exp, TAU, C_h) differed with regard to resting-state connectivity between each ROIs. Findings from repeated measure ANOVAs showed no significant differences between groups for all ipsilateral and bilateral ROIs at baseline (see Table 3). Overall, all three groups of participants had a similar level of resting-state connectivity at baseline. Details descriptive statistics (mean and standard deviation) for all ROIs at baseline was showed in Table 4.

Table 3

Repeated Measures Analysis of Variance (ANOVA) by Groups Between Each ROIs[a].

		df	*MS*	*F*	*p*	*partial* η^{2b}
L ACC – L Hipp	Groups	2	2.02	1.75	0.185	0.07
	Time	1	1.87	1.61	0.210	0.03
	Time*Groups	2	0.03	0.03	0.973	0.00

Table 3 (Con't)

		df	*MS*	*F*	*p*	*partial* η^{2b}
L ACC – L Amyg	Groups	2	1.71	1.53	0.227	0.06
	Time	1	1.61	1.43	0.237	0.03
	Time*Groups	2	0.02	0.02	0.980	0.00
L Hipp – L Amyg	Groups	2	1.39	1.21	0.306	0.05
	Time	1	2.05	1.78	0.188	0.04
	Time*Groups	2	0.01	0.01	0.990	0.00
R ACC – R Hipp	Groups	2	1.99	1.58	0.216	0.06
	Time	1	1.57	1.25	0.270	0.03
	Time*Groups	2	0.02	0.02	0.984	0.00
R ACC – R Amyg	Groups	2	2.05	1.81	0.174	0.07
	Time	1	1.64	1.45	0.235	0.03
	Time*Groups	2	0.01	0.01	0.987	0.00
R Hipp – R Amyg	Groups	2	1.77	1.55	0.222	0.06
	Time	1	1.90	1.66	0.204	0.03
	Time*Groups	2	0.08	0.07	0.933	0.00
L ACC – R ACC	Groups	2	1.39	1.19	0.312	0.05
	Time	1	1.69	1.46	0.133	0.03
	Time*Groups	2	0.17	0.15	0.864	0.01
L Hipp – R Hipp	Groups	2	1.50	1.13	0.332	0.04
	Time	1	2.72	2.05	0.159	0.04
	Time*Groups	2	0.11	0.08	0.921	0.00
L Amyg – R Amyg	Groups	2	1.32	1.20	0.311	0.05
	Time	1	2.19	1.99	0.165	0.04
	Time*Groups	2	0.01	0.01	0.993	0.00

Note. [a]Regions of interest. [b]Partial eta-squared. L = left; R = right; ACC = anterior cingulate cortex; Hipp = hippocampus; Amyg = amygdala.

Table 4

Summary of Correlation Coefficients (Mean, Standard Deviation) by Groups Between Each ROIs[a] at Baseline.

	Exp[b]	TAU[c]	C_h[d]	*p*-value
L ACC – L Hipp	0.19 (0.19)	0.75 (1.53)	0.12 (0.15)	0.185
L ACC – L Amyg	0.16 (0.22)	0.66 (1.42)	0.07 (0.13)	0.227
L Hipp – L Amyg	0.31 (0.12)	0.82 (1.44)	0.35 (0.19)	0.306
R ACC – R Hipp	0.20 (0.16)	0.73 (1.57)	0.15 (0.12)	0.216
R ACC – R Amyg	0.10 (0.16)	0.68 (1.44)	0.09 (0.09)	0.174

Table 4 (Con't)

	Exp[b]	TAU[c]	C_h[d]	*p*-value
R Hipp – R Amyg	0.31 (0.07)	0.83 (1.38)	0.43 (0.16)	0.222
L ACC – R ACC	0.65 (0.15)	1.11 (1.55)	0.47 (0.15)	0.312
L Amyg – R Amyg	0.30 (0.13)	0.79 (1.41)	0.35 (0.12)	0.311
L Hipp – R Hipp	0.56 (0.13)	0.95 (1.62)	0.56 (0.13)	0.332

Note. [a]Regions of interest. [b]Experimental group. [c]Treatment as usual group. [d]Healthy control group. L = left; R = right; ACC = anterior cingulate cortex; Hipp = hippocampus; Amyg = amygdala.

Follow-up Comparison

Upon finishing the study, we collected the final psychological, physiological, and imaging data from all three groups of participants.

Psychological measures. Relative to baseline, inferential statistics showed significant decreases within the Exp group, but not the TAU or the C_h group, in total BDI-II scores and total OQ45 scores at the follow-up time point (see Table 5). Results from repeated measure ANOVAs revealed within-group differences in total BDI-II scores ($F(1, 27) = 21.34$; $p < .001$; partial $\eta^2 = .44$) and total OQ45 scores ($F(1, 27) = 13.87$; $p = .001$; partial $\eta^2 = .34$; see Table 2). Details from Post-hoc Tukey test on total BDI-II scores showed that the Exp group had a significant decrease from baseline to the follow-up time point ($M_{baseline} = 24.90$; $M_{follow\text{-}up} = 12.00$; $p < .001$; see Table 5 and Figure 1). Specifically, Exp group's depression level dropped from a moderate to minimal level. Similarly, a post-hoc Tukey test on total OQ45 scores showed a significant decrease from baseline to the follow-up time point for the Exp group ($M_{baseline} = 84.20$; $M_{follow\text{-}up} = 59.00$; $p < .001$; see Table 5 and Figure 2). They had a 25-point decrease in their total OQ45 scores at the follow-up time point.

Table 5

Summary of Psychological Measures (Mean, Standard Deviation) by Groups at Two Time Points.

		Baseline	Follow-up	*p*-value
Exp[a]	BDI-II[d]	24.90 (11.84)	12.00 (10.28)	< .001
	OQ45[e]	84.20 (26.02)	59.00 (25.21)	< .001
TAU[b]	BDI-II[d]	17.70 (7.10)	12.10 (5.51)	0.239
	OQ45[e]	71.10 (19.96)	63.20 (14.44)	0.610
C_h[c]	BDI-II[d]	3.70 (3.98)	2.50 (3.26)	0.996
	OQ45[e]	32.50 (20.32)	33.60 (14.71)	0.999

Note. [a]Experimental group. [b]Treatment as usual group. [c]Healthy control group. [d]Beck Depression Inventory-II (Beck, Steer, & Brown, 1996). [e]The Outcome Questionnaire-45 (Lambert, Lunnen, Umphress, Hansen, & Burlingame, 1994).

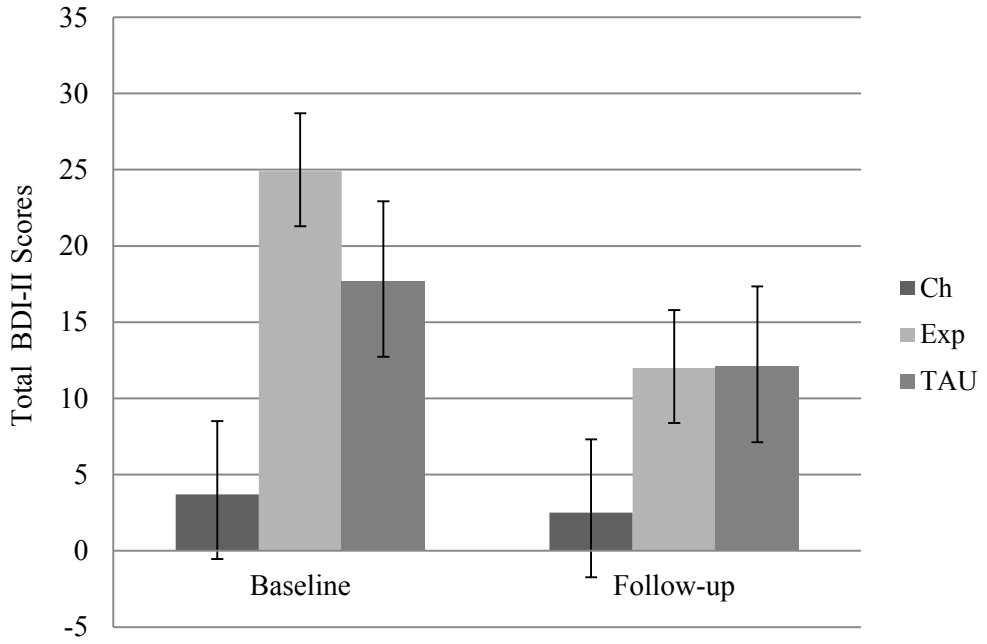

Figure 1. BDI-II total scores comparison by groups and two time points.

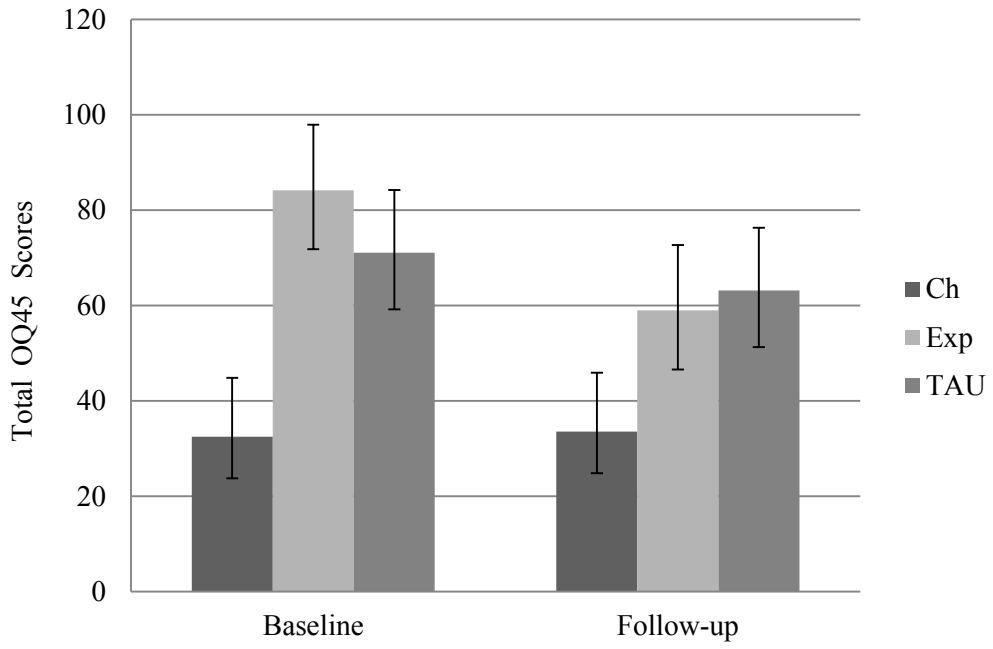

Figure 2. OQ45 total scores comparison by groups and two time points.

There were not significant differences in depression score change over time between the TAU and C_h groups TAU group's depression scores slightly shifted from a mild to minimal depression level at the follow-up time point while the health controls' depression scores remained at the minimal level (TAU's total BDI-II scores $M_{baseline} = 17.70$; $M_{follow\text{-}up} = 12.10$; $p = .239$; C_h's total BDI-II scores $M_{baseline} = 3.70$; $M_{follow\text{-}up} = 2.50$; $p = .996$; see Table 5 and Figure 1). With regard to their overall distress level, no significant differences were observed between the two time points. TAU group's OQ45 scores stayed above the clinical cutoff score at the follow-up time point while the healthy controls' OQ45 scores stayed below the clinical cutoff (TAU's total OQ45 scores $M_{baseline} = 71.10$; $M_{follow\text{-}up} = 63.20$; $p = .610$; C_h's total OQ45 scores $M_{baseline} = 32.50$; $M_{follow\text{-}up} = 33.60$; $p = .999$; see Table 5 and Figure 2).

Furthermore, finding from a Post-hoc Tukey test found no significant differences between Exp and TAU groups' total BDI-II scores at the follow-up time point; participants from

both groups reported a minimal level of depression (Exp M = 12.00; TAU M = 12.10; p = .999; see Table 5 and Figure 1). A similar result was found for Exp and TAU groups' total OQ45 scores. These two groups of participants did not have a significant difference in their overall distress level at the follow-up time point (Exp M = 59.00; TAU M = 63.20; p = .997; see Table 5 and Figure 2). Additionally, no statistical differences were observed between the depressed participants (Exp and TAU) and the C_h group with regard to total BDI-II scores (Exp M = 12.00; TAU M = 12.10; C_h M = 2.50; p = .084; see Table 5 and Figure 1). A significant difference was observed between TAU's and C_h's total OQ45 scores at the follow-up time point, with participants from the TAU group reporting a higher level of overall distress; no difference was found between Exp and C_h groups' overall distress level (TAU M =63.20; Exp M = 59.00; C_h M = 33.60; p = .110; see Table 5 and Figure 2). Both Exp and C_h groups reported an overall distress level below the clinical cutoff.

Physiological measures. Findings from repeated measure ANOVAs revealed a significant within-group difference for SDNN (F(1, 27) = 5.29; p = .029; partial η^2 = .16; see Table 2), $\log_{10}$ LF (F(1, 26) = 4.78; p = .038; partial η^2 = .16; see Table 2), and $\log_{10}$ LF/ $\log_{10}$ HF ratio (F(1, 26) = 10.5; p = .003; partial η^2 = .29; see Table 2) at the follow-up time point. Further analysis from post-hoc Tukey test showed that participants from the Exp group demonstrated 17.39 points increase for SDNN from baseline to the follow-up time point ($M_{baseline}$ = 42.93; $M_{follow\text{-}up}$ = 60.33; p = .002; see Table 6 and Figure 3). The Exp group also showed 0.48 points increase for $\log_{10}$ LF ($M_{baseline}$ = 2.74; $M_{follow\text{-}up}$ = 3.22; p = .009; see Table 6 and Figure 4) and 0.21 points increase for $\log_{10}$ LF/ $\log_{10}$ HF ratio ($M_{baseline}$ = 1.08; $M_{follow\text{-}up}$ = 1.29; p = .011; see Table 6 and Figure 6) between the two time points. All of these increases were statistically significant. However, no significant difference was observed for the Exp group with regard to

$\log_{10}$ HF; their $\log_{10}$ HF values remained at a similar level relative to baseline ($M_{baseline} = 2.56$; $M_{follow\text{-}up} = 2.59$; $p = .999$; see Table 6 and Figure 5). In addition, no significant differences were found for the TAU and C_h groups across all of the physiological variables from baseline to the follow-up time point. Results for SDNN, $\log_{10}$ LF, $\log_{10}$ HF, and $\log_{10}$ LF/ $\log_{10}$ HF ratio remained at the similar level for these two groups (see Table 6).

Table 6

Summary Physiological Measures (Mean, Standard Deviation) by Groups at Two Time Points.

		Baseline	Follow-up	*p*-value
Exp[a]	SDNN[d]	42.93 (23.07)	60.33 (26.54)	0.002
	$Log_{10}LF$[e]	2.74 (0.58)	3.22 (0.35)	0.009
	$Log_{10}HF$[f]	2.56 (0.68)	2.59 (0.58)	0.999
	$Log_{10}LF/ Log_{10}HF$	1.08 (0.11)	1.29 (0.25)	0.011
TAU[b]	SDNN[d]	50.00 (12.13)	48.51 (10.21)	0.998
	$Log_{10}LF$[e]	2.97 (0.30)	2.91 (0.31)	0.998
	$Log_{10}HF$[f]	3.02 (0.39)	2.82 (0.46)	0.644
	$Log_{10}LF/ Log_{10}HF$	1.00 (0.20)	1.03 (0.23)	0.995
C_h[c]	SDNN[d]	56.74 (16.47)	56.32 (17.87)	0.999
	$Log_{10}LF$[e]	3.15 (0.33)	3.21 (0.37)	0.997
	$Log_{10}HF$[f]	2.98 (0.42)	2.84 (0.48)	0.874
	$Log_{10}LF/ Log_{10}HF$	1.07 (0.18)	1.15 (0.19)	0.703

Note. [a]Experimental group. [b]Treatment as usual group. [c]Healthy control group. [d]Standard deviation of normal-to-normal intervals. [e] Low frequency. [f]High frequency.

Imaging data. Similar to findings from baseline comparison, results from repeated measure ANOVAs did not show any significant differences between or within groups from all ipsilateral and bilateral ROIs at the follow-up time point (see Table 3). Furthermore, no interaction was observed across all comparisons (see Table 3).

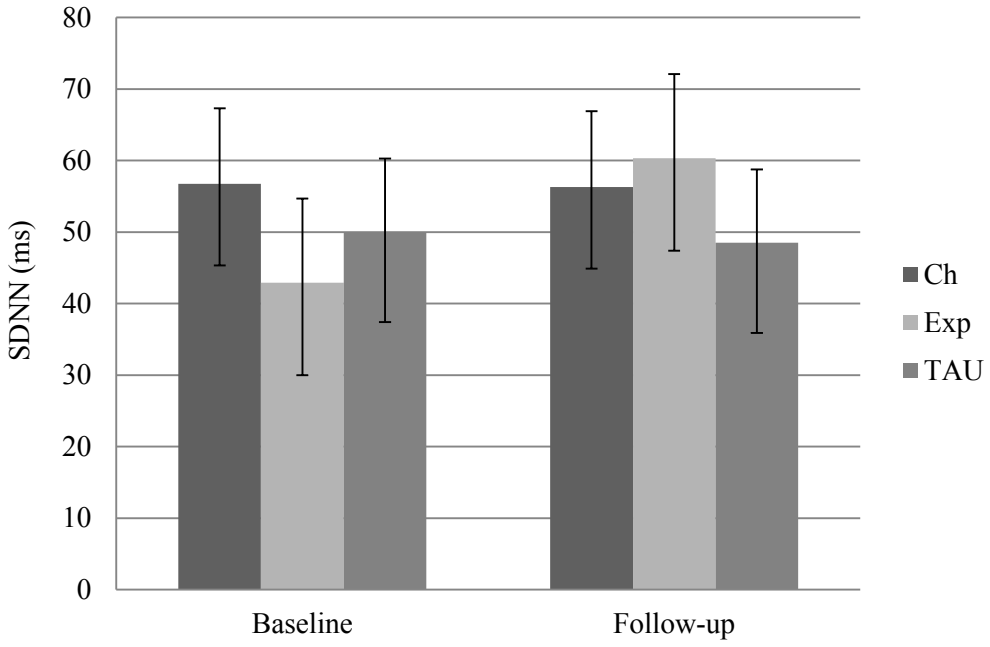

Figure 3. SDNN (ms) comparison by groups and two time points.

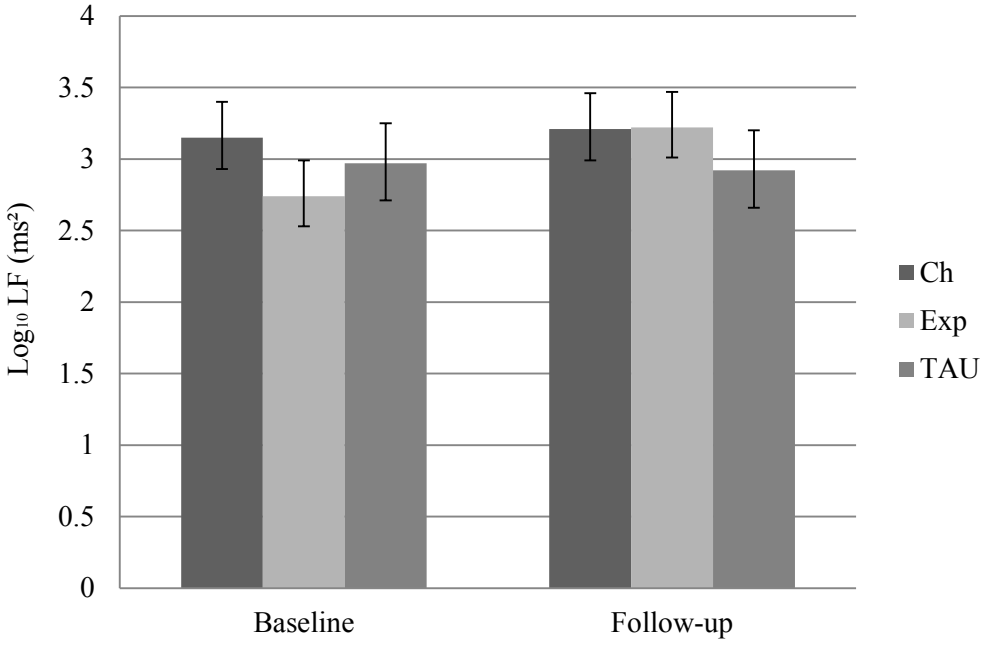

Figure 4. Log_{10} LF (ms^2) comparison by groups and two time points.

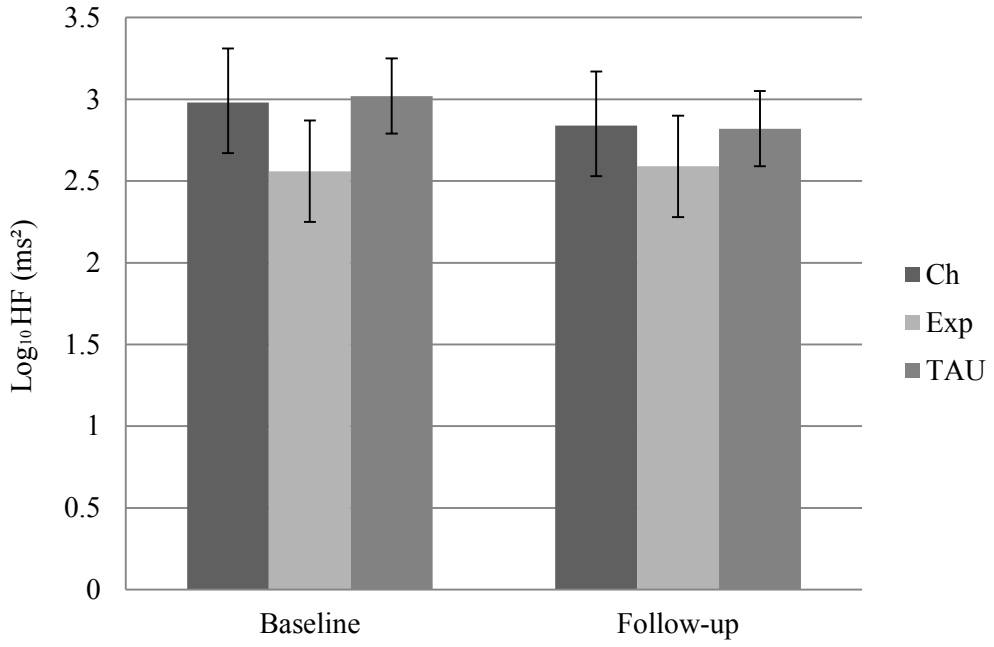

Figure 5. Log_{10} HF (ms^2) comparison by groups and two time points.

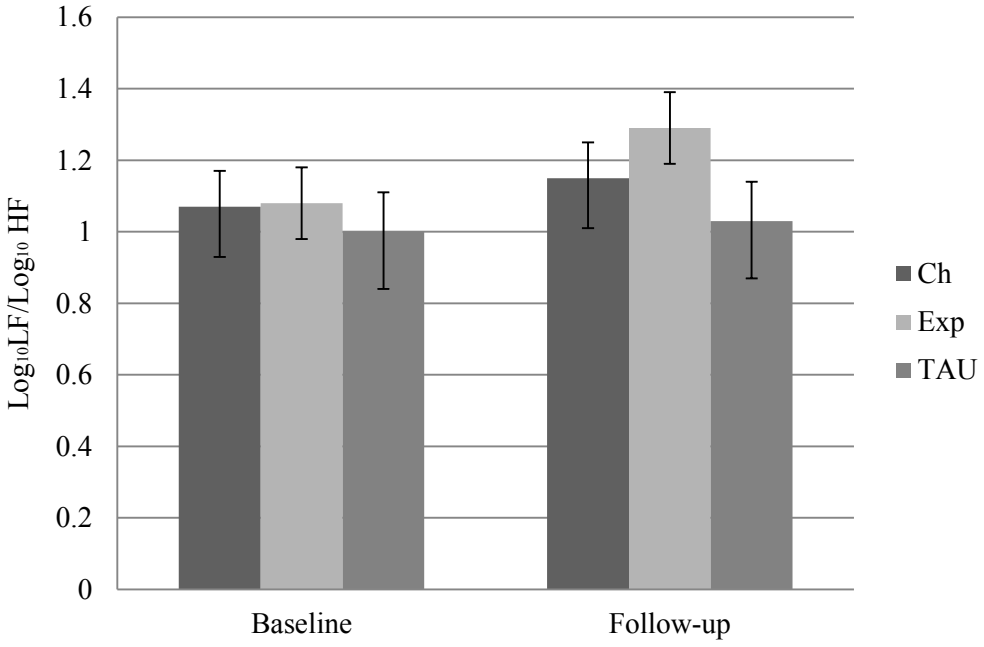

Figure 6. Log_{10} LF/ Log_{10} HF ratio comparison by groups and two time points.

Discussion

Main Findings

Since major depressive disorder (MDD) is one of the most common psychiatric illnesses in our society and causes different levels of disturbances in daily functioning (Oquendo et al., 2006), the current research sought to better understand the efficacy of an adjunct therapy option, heart-rate variability (HRV) training, for MDD and its impact on participants' resting-state connectivity. Upon finishing 5 weeks of HRV training in conjunction with traditional psychotherapy, we expected the experimental group would show significant changes in their overall distress level and depression scores between baseline and the follow-up time point. As expected, there were significant decreases in their overall distress level and depression scores. Specifically, the experimental group showed a 25-point decrease in their total OQ45 scores between the two time points. According to Lambert et al. (2004), any changes in the total OQ45 score equal or greater than 14 points are considered to be a reliable and significant change. With regard to the experimental group's depression scores, a change from a moderate to minimal depressed level was observed. Overall, we found significant improvements in the experiment group's overall distress level and depression scores at the follow-up time point after controlling for their baseline level.

Several recent studies of HRV for the treatment of major depression found similar results (Karavidas et al., 2007; Siepmann et al., 2008). These previous studies also used the total BDI-II score (Beck et al., 1996) to examine changes in depression levels before and after their experiments. Results from these previous studies found that depressed participants had a significantly decreased total BDI-II score after 6 to 10 weeks of HRV biofeedback training sessions. Together, results from the current study supported findings from existing research that

HRV training appear to be an efficacious adjunct treatment for reducing depression symptoms and the overall distress level. Furthermore, findings from the current study showed that the experimental group was significantly less distressed than the treatment as usual group at the follow-up time point. In fact, the experimental group's overall distress level had dropped to a similar level to that of the healthy control group. Existing research on HRV biofeedback and depression has mainly used two comparison groups (depressed individuals verses healthy controls) across different age groups and demographics (Kemp et al., 2012; Patron et al., 2012; Siepmann et al., 2008; Tonhajzerova et al., 2009). The current research added a new piece of information in comparing depressed individuals who went through HRV biofeedback training in conjunction with traditional psychotherapy verses those who only received psychotherapy.

Besides a reduction in psychological symptoms, we also expected the experimental group would show a significant increase in HRV functioning between the baseline and follow-up time points. Controlling for baseline levels, significant increases were observed for the following HRV variables at the follow-up time point: standard deviation of normal-to-normal intervals, low frequency values, and low frequency to high frequency ratio. By contrast, a minimal difference was noted for high frequency value. The above four variables are common and important measures in assessing HRV. Results from recent research have shown that increasing standard deviation of normal-to-normal intervals were associated with better health outcome. Since activity in both the sympathetic and parasympathetic systems are almost always presented together, we look at individuals' activity level between these two systems in a continuum. Low frequency values are in between the two spectrums, influencing by both the sympathetic and parasympathetic system. Lower low frequency values reflected greater influence from the sympathetic system. High frequency values, on the other hand, reflect parasympathetic activity.

The higher the high frequency value, the more dominant is the parasympathetic system. Findings from the experimental group suggest that individuals who went through 5 weekly HRV trainings have regained more automatic balance between their sympathetic and parasympathetic systems. A recent study found a similar result where a group of MDD patients demonstrated a significant increase on standard deviation of normal-to-normal intervals after employing 10 weeks of HRV breathing training sessions (Karavidas et al., 2007). According to a series of recent studies, increasing value in standard deviation of normal-to-normal intervals was associated with better health outcomes (Del Pozo et al., 2004; Karavidas et al., 2007; Patron et al., 2012). Of note, studies focusing on HRV measurements and depressed population demonstrated that patients with depression have attenuated HRV (Catipovic-Veselica et al., 2007; Siepmann, Joraschky, & Rebensburg, 2005).

As noted previously, the experimental group did not show a significant improvement on high frequency values upon finishing the current study. This finding was in line with a recent study which involved 6 sessions of HRV biofeedback training over two weeks (Siepmann et al., 2008). This pervious study did not find a significant change in depressed patients' high frequency values after two weeks of HRV training. In addition, their depressed patients' low frequency values and low frequency to high frequency ratio did not differ significantly from baseline to follow up. Interestingly, different from this previous study we found a significant increase in the experimental group's standard deviation of normal-to-normal intervals, low frequency values, and low frequency to high frequency ratio at the follow-up time point. These differences may be attributed to a longer period of HRV biofeedback training. The previous study had 6 HRV training sessions over two weeks while the current study had 5 weekly HRV training sessions. Together, HRV data from the current study suggests that depressed participants

have learned to increase their HRV by learning and practicing at their resonant frequency-breathing rate.

Apart from the findings above, we also expected that the experimental group would show a significant increase in resting-state connectivity across all regions of interest (ROIs) between baseline and the follow-up time point. Contrary to our original prediction, the experimental group did not have significant changes in resting-state connectivity across each ROIs after 5 weeks of HRV biofeedback training and psychotherapy. In fact, their baseline resting-state connectivity did not differ from the treatment as usual group and the health control group. These surprising results may be due to the following factors: participants' age, number of depression episodes or depression duration. Research on specific or whole brain resting-state analysis in major depression has found abnormal functional connectivity across difference networks and regions. Anand et al. (2005) found a decreasing resting-state connectivity between anterior cingulate cortex and limbic regions in patients with MDD in comparison to healthy controls. Another study found a significant reduction in depressed patients' resting-state connectivity in their prefrontal-limbic areas bilaterally relative to healthy controls (Lui et al., 2011). It was noted that these previous studies used patients who were in their late 20's or early 30's with at least 22 to 193 months of depression duration. In sum, these studies included patients who were older, with a greater number of depression episodes or longer depression duration in their studies. Another recent study that used a group of medication-free patients with a recent diagnosis of major depression and a group of age- and gender-matched controls found abnormal connectivity within an affective network, a network associated with attention and working memory, and within ventromedial visual regions in patients with depression (Veer et al., 2010). Once again, the current study did not show similar results. Two different participants' demographics were

noted when comparing the current study with this previous study: gender and age range. The previous research included both genders that were in their mid-30's while the current study only included female participants in early adulthood. Perhaps more and longer episodes of MDD in people who are older would more likely reveal deceased resting-state connectivity. Furthermore, the majority of existing research on resting state connectivity and treatment response in MDD has mostly focused on antidepressant medication and subjects who were in late adulthood (Andreescu et al., 2013; Dichter, Gibbs, & Smoski, 2015). Further exploration and collection of imaging data in HRV biofeedback training may broaden our understanding in this new area of research.

Groups Equivalence at Baseline

In light of establishing a roughly equal baseline condition, we randomized participants with MDD into either the experimental group or the treatment as usual group. We found group equivalence between these two groups' overall distress level, physiological measurement and resting-state connectivity at baseline, but not their overall depression level. Comparison between the experimental and treatment as usual groups' depression level as measured by BDI-II (Beck et al., 1996) revealed a clinical difference at baseline. Specifically, participants from the experimental group reported a moderate level of depression whereas participants from the treatment as usual group reported a mild level of depression. Upon further examination on participants' responses, it was noted that four participants from the experimental group expressed suicidal thoughts or wishes with one indicating high suicidal ideation. Contingency management had been made with these four participants' therapist right after the indication of their suicidal thoughts. The difference in self-harm thoughts may have contributed to the clinical difference on their BDI-II scores.

Relative to the depressed participants from both the experimental and treatment as usual groups, the healthy control group had significantly less distress and depression levels at baseline. These results were not surprising but were consistent with existing research findings (Liang, Lee, Chen, & Chang, 2015). Hence, we expected similar results in HRV measurements between the depressed participants and the healthy controls at baseline. Contrary to our assumption, participants from both the experimental and treatment as usual groups did not have lower HRV measurements than the healthy controls across all physiological variables at baseline. These surprising results may be due to a couple of factors. First, all participants from both experimental and treatment as usual groups were in their early adulthood with a mean age of 20 years. Furthermore, all of them were in their first episode of depression. A recent study used a group of male patients who were in their mid-20's with first-episode of major depressive disorder also found similar results when comparing the depressed patients to the healthy controls at baseline (Liang et al., 2015). This previous study did not observe any differences in their MDD patients' low frequency and high frequency values from those of the control group at baseline. It was noted that both the current study and this previous research used participants from a younger age group who were experiencing their first episode of depression. Perhaps HRV impairments are less likely to be revealed in a younger age demographic and during an early stage of depression.

Upon further review on literature focusing on HRV and depression, a majority of them included various comorbidities, longer period of depression, and a wider age range (Carney & Freedland, 2008; Kemp et al., 2012; Patron et al., 2012). A recent study investigated the relationship between HRV and depression in a group of MDD patients who were physically heathy, unmedicated, but had comorbid anxiety disorders (Kemp et al., 2012). These MDD patients were in their mid-30's and a majority of them had either generalized anxiety disorder,

panic disorder or post-traumatic stress disorder. Relative to the control group in this previous study, the MDD patients showed reduced HRV. Interestingly, the effect size was even larger among the MDD patients with comorbid anxiety disorders. Another study aimed to examine the association between depression and HRV in patients after first-time cardiac surgery (Patron et al., 2012). Compared to the non-depressed patients in this previous study, patients with depression revealed significantly lower HRV. It was noted that the depressed patients in this previous study had a mean age of 60. Comparison between the current study and these previous studies suggest that perhaps a longer depression period, with multiple episodes, and older age would more likely be associated with greater HRV impairments.

Limitations and Future Directions

There were several limitations in this study: a small sample size from each comparison group, a very selected population, and the absence of an active experimental condition in the healthy control group. The current study only included 10 participants for each comparison group. The small sample size raises concern of low statistical power which reduces chance of detecting the likelihood of a statistically significant result for a true effect. Furthermore, a small sample size study may result in overestimating of effect size and low reproducibility of results. Hence, future studies may need to increase sample size for each comparison group to increase power in detecting a true effect and to get a better estimate of effect size.

In addition, all participants in the current study were in their young adulthood and had their first episode of depression. Existing research on HRV training in conjunction with psychotherapy approach mainly included participants who were older in age and with more number of depression episodes (Karavidas et al., 2007; Siepmann et al., 2008). Future studies may consider doing a longitudinal study on this population in order to keep check on their

overall distress level, depression scores, and resting-state connectivity. In addition, the current study only included female participants. Future studies may apply the same protocol but focusing on male participants. Having more information from both genders may help us better understand whether or not there is a gender difference in HRV functioning and resting-state connectivity.

Due to funding issues, the current study only included one healthy control group who went through an active control condition. None of the healthy controls received any HRV biofeedback training. In future studies, researcher may include an active experimental condition in the heathy control group. Having a group of participants in the control condition who go through HRV biofeedback training may provide additional insight of the efficacy of HRV biofeedback training compared to depressed individuals. As previously mentioned, a higher number of HRV training sessions may also allow researchers to observe the effect of HRV biofeedback in these two populations.

Beside an additional active healthy control group, future studies may also consider adding two different comparison groups in the study: a wait list control group and a placebo group. The wait list control group will allow us to examine if people with MDD get better over time regardless of treatment effect. Comparisons between the experimental conditions and the wait list controls may also provide us additional insights regarding biofeedback HRV training efficacy. In addition to the wait list control group, we may also include a placebo group in the experimental condition. Participants from this placebo group will receive fake biofeedback training. Results from this placebo group will allow us to study placebo effect and how such effect may affect participants' HRV functioning and self-perceived distress and depression levels.

Aside from the future directions mentioned above, the current study may also compare different psychotherapy approaches in conjunction with HRV biofeedback training, in terms of

long-term effect of symptom reduction in depression and increased well-being. Numerous studies and reviews suggest that depressed patients undergoing diverse kinds of psychotherapy have better outcome than wait-list control and no-treatment patients (Lambert, 2013). Results in treating depression have shown that most psychotherapies produce similar and substantial effects and that no single approach has been found to be consistently superior (Emmelkamp, 2013). Hence, investigating and comparing the enduring effect of different kinds of psychotherapy approaches with HRV biofeedback training may provide additional insights into depression treatment efficacy and effectiveness.

Overall, despite the limitations inherent in this pilot study, HRV biofeedback training demonstrated a decrease in MDD participants' overall distress level and depression scores and an increase in heart-rate variability. This approach shows promise as an adjunctive treatment for depression.

Conclusion

In summary, this is the first study to examine impact of HRV biofeedback training on depressed population psychologically and neurologically. We utilized three comparison groups in this study to enhance our understanding. Results only partially followed predictions. HRV biofeedback training appeared to be able to reduce depressed participants' overall distress and depression level and increase their heart-rate variability. However, we did not find a significant change in their resting-state connectivity. Our findings suggest the need for additional studies on HRV biofeedback training at different stages of depression and how it might affect participants' neurologically.

References

Aizenstein, H. J., Butters, M. A., Wu, M., Mazurkewicz, L. M., Stenger, V. A., Gianaros, P. J., . . . Carter, C. S. (2009). Altered functioning of the executive control circuit in late-life depression: Episodic and persistent phenomena. *American Journal of Geriatric Psychiatry, 17*, 30-42. doi: 10.1097/JGP.0b013e31817b60af

Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clinical Psychology Review, 30*, 217-237. doi: 10.1016/j.cpr.2009.11.004

Amr, M., El-Mogy, A., Shams, T., Vieira, K., & Lakhan, S. E. (2013). Efficacy of vitamin C as an adjunct to fluoxetine therapy in pediatric major depressive disorder: A randomized, double-blind, placebo-controlled pilot study. *Nutrition Journal, 12*, 31. doi: 10.1186/1475-2891-12-31

Anand, A., Li, Y., Wang, Y., Lowe, M. J., & Dzemidzic, M. (2009). Resting state corticolimbic connectivity abnormalities in unmedicated bipolar disorder and unipolar depression. *Psychiatry Research, 171*, 189-198. doi: 10.1016/j.pscychresns.2008.03.012

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., . . . Lowe, M. J. (2005). Activity and connectivity of brain mood regulating circuit in depression: A functional magnetic resonance study. *Biological Psychiatry, 57*, 1079-1088. doi: 10.1016/j.biopsych.2005.02.021

Andreescu, C., Tudorascu, D. L., Butters, M. A., Tamburo, E., Patel, M. , Price, J., . . . Aizenstein, H. (2013). Resting state functional connectivity and treatment response in late-life depression. *Psychiatry Reasarch: Neuroimaging, 214*, 313-321.

Apelbaum, H. (2001). The effect of emg-biofeedback on female participants' major depressive disorder. *Dissertation Abstracts International: Section B: The Sciences & Engineering, 61*, 6742.

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

Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. D. (1979). Cognitive therapy of depression. *Australian and New Zealand Journal of Psychiatry, 36*, 275-278.

Beck, A. T., Steer, R. A., & Brown, G. K. (Eds.). (1996). *Beck Depression Inventory* (2nd ed.). San Antonio: The Psychological Corporation.

Beckham, A. J., Greene, T. B., & Meltzer-Brody, S. (2013). A pilot study of heart rate variability biofeedback therapy in the treatment of perinatal depression on a specialized perinatal psychiatry inpatient unit. *Archives of Womens Mental Health, 16*, 59-65. doi: 10.1007/s00737-012-0318-7

Beevers, C. G., Ellis, A. J., & Reid, R. M. (2011). Heart rate variability predicts cognitive reactivity to sad mood provocation. *Cognitive Therapy and Research, 35*, 395-403.

Blume, H. K., Brockman, L. N., & Breuner, C. C. (2012). Biofeedback therapy for pediatric headache: Factors associated with response. *Headache, 52*, 1377-1386. doi: 10.1111/j.1526-4610.2012.02215.x

Bolton, J. M., Belik, S. L., Enns, M. W., Cox, B. J., & Sareen, J. (2008). Exploring the correlates of suicide attempts among individuals with major depressive disorder: Findings from the national epidemiologic survey on alcohol and related conditions. *Journal of Clinical Psychiatry, 69*, 1139-1149.

Bremner, J. D., Vythilingam, M., Vermetten, E., Vaccarino, V., & Charney, D. S. (2004). Deficits in hippocampal and anterior cingulate functioning during verbal declarative memory encoding in midlife major depression. *The American Journal of Psychiatry, 161*, 637-645.

Brockmeyer, T., Bents, H., Holtforth, M. G., Pfeiffer, N., Herzog, W., & Friederich, H. C. (2012). Specific emotion regulation impairments in major depression and anorexia nervosa. *Psychiatry Research, 200*, 550-553. doi: 10.1016/j.psychres.2012.07.009

Butler, A. C., Chapman, J. E., Forman, E. M., & Beck, A. T. (2006). The empirical status of cognitive-behavioral therapy: A review of meta-analyses. *Clinical Psychology Review, 26*, 17-31. doi: 10.1016/j.cpr.2005.07.003

Campbell, S., Marriott, M., Nahmias, C., & MacQueen, G. M. (2004). Lower hippocampal volume in patients suffering from depression: A meta-analysis. *American Journal of Psychiatry, 161*, 598-607.

Carney, R. M., & Freedland, K. E. (2008). Depression in patients with coronary heart disease. *American Journal of Medicine, 121*, S20-27. doi: 10.1016/j.amjmed.2008.09.010

Catipovic-Veselica, K., Galic, A., Jelik, K., Baraban-Glavas, V., Saric, S., Prlic, N., & Catipovic, B. (2007). Relation between major and minor depression and heart rate, heart-rate variability, and clinical characteristics of patients with acute coronary syndrome. *Psychological Reports, 100*, 1245-1254.

Champaneri, S., Wand, G. S., Malhotra, S. S., Casagrande, S. S., & Golden, S. H. (2010). Biological basis of depression in adults with diabetes. *Current Diabetes Reports, 10*, 396-405. doi: 10.1007/s11892-010-0148-9

Ciesla, J. A., Felton, J. W., & Roberts, J. E. (2011). Testing the cognitive catalyst model of depression: Does rumination amplify the impact of cognitive diatheses in response to stress? *Cognition & Emotion, 25*, 1349-1357. doi: 10.1080/02699931.2010.543330

Cipriani, A., Santilli, C., Furukawa, T. A., Signoretti, A., Nakagawa, A., McGuire, H., . . . Barbui, C. (2009). Escitalopram versus other antidepressive agents for depression. *Cochrane Database Systematic Reviews*, CD006532. doi: 10.1002/14651858.CD006532.pub2

Cohen, H., & Benjamin, J. (2006). Power spectrum analysis and cardiovascular morbidity in anxiety disorders. *Autonomic Neuroscience, 128*, 1-8. doi: 10.1016/j.autneu.2005.06.007

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, 29*, 162-173.

Cuijpers, P., Dekker, J., Hollon, S. D., & Andersson, G. (2009). Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: A meta-analysis. *Journal of Clinical Psychiatry, 70*, 1219-1229. doi: 10.4088/JCP.09r05021

Cuijpers, P., Geraedts, A. S., van Oppen, P., Andersson, G., Markowitz, J. C., & van Straten, A. (2011). Interpersonal psychotherapy for depression: A meta-analysis. *American Journal of Psychiatry, 168*, 581-592. doi: 10.1176/appi.ajp.2010.10101411

Cuijpers, P., Huibers, M., Ebert, D. D., Koole, S. L., & Andersson, G. (2013). How much psychotherapy is needed to treat depression? A metaregression analysis. *Journal of Affective Disorder, 149* 1-13.

Cuijpers, P., van Straten, A., van Oppen, P., & Andersson, G. (2008). Are psychological and pharmacologic interventions equally effective in the treatment of adult depressive

disorders? A meta-analysis of comparative studies. *Journal of Clinical Psychiatry, 69*, 1675-1685.

Cullen, K. R., Gee, D. G., Klimes-Dougan, B., Gabbay, V., Hulvershorn, L., Mueller, B. A., . . . Milham, M. P. (2009). A preliminary study of functional connectivity in comorbid adolescent depression. *Neuroscience Letters, 460*, 227-231. doi: 10.1016/j.neulet.2009.05.022

De Maat, S. M., Dekker, J., Schoevers, R. A., & de Jonghe, F. (2007). Relative efficacy of psychotherapy and combined therapy in the treatment of depression: A meta-analysis. *European Psychiatry, 22*, 1-8.

DeGiorgio, C. M., Miller, P., Meymandi, S., Chin, A., Epps, J., Gordon, S., . . . Harper, R. M. (2010). RMSSD, a measure of heart rate variability, is associated with risk factors for SUDEP: The SUDEP-7 inventory *Epilepsy & Behavior, 19,* 78-81.

Del Pozo, J. M., Gevirtz, R. N., Scher, B., & Guarneri, E. (2004). Biofeedback treatment increases heart rate variability in patients with known coronary artery disease. *American Heart Journal, 147*, E11. doi: 10.1016/j.ahj.2003.08.013

Dichter, G. S., Gibbs, D., & Smoski, M. J. (2015). A systematic review of relations between resting-state functional-MRI and treatment response in major depressive disorder. *Journal of Affective Disorder, 172*, 8-17.

Drevets, W. C. (2001). Neuroimaging and neuropathological studies of depression: Implications for the cognitive-emotional features of mood disorders. *Current Opinion in Neurobiology, 11*, 240-249.

Drevets, W. C., Bogers, W., & Raichle, M. E. (2002). Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *European Neuropsychopharmacology, 12*, 527-544.

Elder, B. L., & Mosack, V. (2011). Genetics of depression: An overview of the current science. *Issues in Mental Health Nursing, 32*, 192-202. doi: 10.3109/01612840.2010.541588

Emmelkamp, P. M. G. (2013). Behavior therapy with adults. In M. J. Lambert (Ed.), *Handbook of psychotherapy and behavior change* (6th ed.). New Jersey: John Wiley & Sons, Inc.

Ferrari, A. J., Somerville, A. J., Baxter, A. J., Norman, R., Patten, S. B., Vos, T., & Whiteford, H. A. (2013). Global variation in the prevalence and incidence of major depressive disorder: A systematic review of the epidemiological literature. *Psychological Medicine, 43*, 471-481. doi: 10.1017/S0033291712001511

Firbank, M. J., O'Brien, J. T., Pakrasi, S., Pantoni, L., Simoni, M., Erkinjuntti, T., . . . Inzitari, D. (2005). White matter hyperintensities and depression--preliminary results from the LADIS study. *International Journal of Geriatric Psychiatry, 20*, 674-679. doi: 10.1002/gps.1342

Fitzgerald, P. B., Laird, A. R., Maller, J., & Daskalakis, Z. J. (2008). A meta-analytic study of changes in brain activation in depression. *Human Brain Mapping, 29*, 683-695. doi: 10.1002/hbm.20426

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience, 8*, 700-711. doi: 10.1038/nrn2201

Friedman, M. A., Detweiler-Bedell, J. B., Leventhal, H. E., Horne, R., Keitner, G. I., & Miller, I. W. (2004). Combined psychotherapy and pharmacotherapy for the treatment of major depressive disorder. *Clinical Psychology: Science and Practice, 11*, 47-68.

Gao, S. F., & Bao, A. M. (2011). Corticotropin-releasing hormone, glutamate, and gamma-aminobutyric acid in depression. *Neuroscientist, 17*, 124-144. doi: 10.1177/1073858410361780

Garcia-Toro, M., Medina, E., Galan, J. L., Gonzalez, M. A., & Maurino, J. (2012). Treatment patterns in major depressive disorder after an inadequate response to first-line antidepressant treatment. *BMC Psychiatry, 12*, 143. doi: 10.1186/1471-244X-12-143

Garnefski, N., & Kraaij, V. (2006). Relationships between cognitive emotion regulation strategies and depressive symptoms: A comparative study of five specific samples. *Personality and Individual Differences, 40*, 1659-1669.

Gertsik, L., Poland, R. E., Bresee, C., & Rapaport, M. H. (2012). Omega-3 fatty acid augmentation of citalopram treatment for patients with major depressive disorder. *Journal of Clinical Psychopharmacology, 32*, 61-64. doi: 10.1097/JCP.0b013e31823f3b5f

Gianaros, P. J., Derbyshire, S. W., May, J. C., Siegle, G. J., Gamalo, M. A., & Jennings, J. R. (2005). Anterior cingulate activity correlates with blood pressure during stress. *Psychophysiology, 42*, 627-635. doi: 10.1111/j.1469-8986.2005.00366.x

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*, 121-133.

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., . . . Schatzberg, A. F. (2007). Resting-state functional connectivity in major depression: Abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biological Psychiatry, 62*, 429-437. doi: 10.1016/j.biopsych.2006.09.020

Gunning, F. M., Cheng, J., Murphy, C. F., Kanellopoulos, D., Acuna, J., Hoptman, M. J., . . . Alexopoulos, G. S. (2009). Anterior cingulate cortical volumes and treatment remission of geriatric depression. *International Journal of Geriatric Psychiatry, 24*, 829-836. doi: 10.1002/gps.2290

Haby, M. M., Tonge, B., Littlefield, L., Carter, R., & Vos, T. (2004). Cost-effectiveness of cognitive behavioural therapy and selective serotonin reuptake inhibitors for major depression in children and adolescents. *Australian & New Zealand Journal of Psychiatry, 38*, 579-591. doi: 10.1111/j.1440-1614.2004.01421.x

Hallman, D. M., Olsson, E. M., 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. doi: 10.1007/s10484-011-9147-0

Hanson, W. E., & Merker, B. M. (2005). Review of OQ-45.2 (Outcome Questionnaire). In S. R. A. & B. S. Plake (Eds.), *The sixteenth mental measurements yearbook* (pp. 737-739). Lincoln, NE: Buros Institute of Mental Measurements.

Hassett, A. L., Radvanski, D. C., Vaschillo, E. G., Vaschillo, B., Sigal, L. H., Karavidas, M. K., . . . 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. doi: 10.1007/s10484-006-9028-0

Heinz, A., Smolka, M. N., Braus, D. F., Wrase, J., Beck, A., Flor, H., . . . Weinberger, D. R. (2007). Serotonin transporter genotype (5-HTTLPR): Effects of neutral and undefined conditions on amygdala activation. *Biological Psychiatry, 61*, 1011-1014. doi: 10.1016/j.biopsych.2006.08.019

Holzel, L., Harter, M., Reese, C., & Kriston, L. (2011). Risk factors for chronic depression--a systematic review. *Journal of Affective Disorder, 129*, 1-13. doi: 10.1016/j.jad.2010.03.025

Jakobsen, J. C., Gluud, C., Kongerslev, M., Larsen, K. A., Sorensen, P., Winkel, P., . . . Simonsen, E. (2012). 'Third wave' cognitive therapy versus mentalization-based therapy for major depressive disorder. A protocol for a randomised clinical trial. *BMC Psychiatry, 12*, 232. doi: 10.1186/1471-244X-12-232

Jakobsen, J. C., Hansen, J. L., Storebo, O. J., Simonsen, E., & Gluud, C. (2011). The effects of cognitive therapy versus 'no intervention' for major depressive disorder. *PLoS One, 6*, e28299. doi: 10.1371/journal.pone.0028299

Karavidas, M. K., Lehrer, P. M., Vaschillo, E., Vaschillo, B., Marin, H., Buyske, S., . . . Hassett, 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. doi: 10.1007/s10484-006-9029-z

Kemp, A. H., Quintana, D. S., Felmingham, K. L., Matthews, S., & Jelinek, H. F. (2012). Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: Implications for cardiovascular risk. *PLoS One, 7*, e30777. doi: 10.1371/journal.pone.0030777

Ketter, T. A., Kimbrell, T. A., George, M. S., Dunn, R. T., Speer, A. M., Benson, B. E., . . . Post, R. M. (2001). Effects of mood and subtype on cerebral glucose metabolism in treatment-resistant bipolar disorder. *Biological Psychiatry, 49*, 97-109.

Klein, A., Andersson, J., Ardekani, B. A., Ashburner, J., Avants, B., Chiang, M. C., . . . Parsey, R. V. (2009). Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *Neuroimage, 46*, 786-802.

Kupfer, D. J., Frank, E., & Phillips, M. L. (2012). Major depressive disorder: New clinical, neurobiological, and treatment perspectives. *The Lancet, 379*, 1045-1055. doi: 10.1016/S0140-6736(11)60602-8

Lambert, M. J. (2013). The efficacy and effectiveness of psychotherapy. In M. J. Lambert (Ed.), *Handbook of psychotherapy and behavior change* (6th ed.). New Jersey: John Wiley & Sons, Inc.

Lambert, M. J., Lunnen, K., Umphress, V., Hansen, N., & Burlingame, G. M. (1994). *Administration and scoring manual for the Outcome Questionnaire (OQ-45.1)*. Salt Lake City: IHC Center for Behavioral Healthcare Efficacy.

Lambert, M. J., Morton, J. J., Hatfield, D., Harmon, C., Hamilton, S., Reid, R. C., & Burlingame, G. M. (2004). *Adimistration and scoring manual for the OQ45-2*. Orem, UT: American Professional Credentialing Services.

Lehrer, P., Vaschillo, B., Zucker, T., Graves, J., Katsamanis, M., Aviles, M., & Wamboldt, F. (2013). Protocol for heart rate variability biofeedback training. *Biofeedback, 41*, 98-109.

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

Liang, C., Lee, J., Chen, C., & Chang, Y. (2015). Reactive heart rate variability in male patients with first-episode major depressive disorder. *Progress in Neuro-Psychoharmacology & Biological Psychiatry, 56*, 52-57.

Linden, D. E., Habes, I., Johnston, S. J., Linden, S., Tatineni, R., Subramanian, L., . . . Goebel, R. (2012). Real-time self-regulation of emotion networks in patients with depression. *PLoS One, 7*, e38115. doi: 10.1371/journal.pone.0038115

Liotti, M., & Mayberg, H. S. (2001). The role of functional neuroimaging in the neuropsychology of depression. *Journal of Clinical and Experimental Neuropsychology, 23*, 121-136. doi: 10.1076/jcen.23.1.121.1223

Lui, S., Wu, Q., Qiu, L., Yang, X., Kuang, W., Chan, R. C., . . . Gong, Q. (2011). Resting-state functional connectivity in treatment-resistant depression. *American Journal of Psychiatry, 168*, 642-648. doi: 10.1176/appi.ajp.2010.10101419

Mayberg, H. S. (2003). Positron emission tomography imaging in depression: A neural systems perspective. *Neuroimaging Clinics of North America, 13*, 805-815.

Mervaala, E., Fohr, J., Kononen, M., Valkonen-Korhonen, M., Vainio, P., Partanen, K., . . . Lehtonen, J. (2000). Quantitative MRI of the hippocampus and amygdala in severe depression. *Psychological Medicine, 30*, 117-125.

Milne, A. M., MacQueen, G. M., & Hall, G. B. (2012). Abnormal hippocampal activation in patients with extensive history of major depression: An fMRI study. *Journal of Psychiatry & Neuroscience, 37*, 28-36. doi: 10.1503/jpn.110004

Motley, S. E., & Kirwan, C. B. (2012). A parametric investigation of pattern separation processes in the medial temporal lobe. *The Journal of Neuroscience, 32*, 13076-13085.

Napadow, V., Dhond, R., Conti, G., Makris, N., Brown, E. N., & Barbieri, R. (2008). Brain correlates of autonomic modulation: Combining heart rate variability with fMRI. *Neuroimage, 42*, 169-177. doi: 10.1016/j.neuroimage.2008.04.238

Nestoriuc, Y., Martin, A., Rief, W., & Andrasik, F. (2008). Biofeedback treatment for headache disorders: A comprehensive efficacy review. *Applied Psychophysiology and Biofeedback, 33*, 125-140. doi: 10.1007/s10484-008-9060-3

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. doi: 10.1016/j.ahj.2005.03.015

Nunan, D., Sandercock, G. R. H., & Brodie, D. A. (2010). A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. *Pacing and Clinical Electrophysiology, 33*, 1407-1417.

Oquendo, M. A., Currier, D., & Mann, J. J. (2006). Prospective studies of suicidal behavior in major depressive and bipolar disorders: What is the evidence for predictive risk factors? *Acta Psychiatrica Scandinavica, 114*, 151-158. doi: 10.1111/j.1600-0447.2006.00829.x

Palomba, D., Ghisi, M., Scozzari, S., Sarlo, M., Bonso, E., Dorigatti, F., & Palatini, P. (2011). Biofeedback-assisted cardiovascular control in hypertensives exposed to emotional stress: A pilot study. *Applied Psychophysiology and Biofeedback, 36*, 185-192. doi: 10.1007/s10484-011-9160-3

Pampallona, S., Bollini, P., Tibaldi, G., Kupelnick, B., & Munizza, C. (2004). Combined pharmacotherapy and psychological treatment for depression: A systematic review. *Archives of Genearal Psychiatry, 61*, 714-719. doi: 10.1001/archpsyc.61.7.714

Papakostas, G. I. (2009). Managing partial response or nonresponse: Switching, augmentation, and combination strategies for major depressive disorder. *Journal of Clinical Psychiatry, 70 Suppl 6*, 16-25. doi: 10.4088/JCP.8133su1c.03

Patron, E., Messerotti Benvenuti, S., Favretto, G., Valfre, C., Bonfa, C., Gasparotto, R., & Palomba, D. (2012). Association between depression and heart rate variability in patients after cardiac surgery: A pilot study. *Journal of Psychosomatic Research 73*, 42-46. doi: 10.1016/j.jpsychores.2012.04.013

Patron, E., Messerotti Benvenuti, S., Favretto, G., Valfre, C., Bonfa, C., Gasparotto, R., & Palomba, D. (2013). Biofeedback assisted control of respiratory sinus arrhythmia as a biobehavioral intervention for depressive symptoms in patients after cardiac surgery: A preliminary study. *Applied Psychophysiology and Biofeedback, 38*, 1-9. doi: 10.1007/s10484-012-9202-5

Pigott, H. E., Leventhal, A. M., Alter, G. S., & Boren, J. J. (2010). Efficacy and effectiveness of antidepressants: Current status of research. *Psychotherapy and Psychosomatics, 79*, 267-279. doi: 10.1159/000318293

Poole, H., Bramwell, R., & Murphy, P. (2006). Factor structure of the Beck Depression Inventory-II in patients with chronic pain. *Clinical Journal of Pain, 22*, 790-798.

Prinsloo, G. E., Derman, W. E., Lambert, M. I., & Laurie Rauch, H. G. (2013). The effect of a single session of short duration biofeedback-induced deep breathing on measures of heart rate variability during laboratory-induced cognitive stress: A pilot study. *Applied Psychophysiology and Biofeedback, 38*, 81-90. doi: 10.1007/s10484-013-9210-0

Quintana, D. S., Guastella, A. J., Outhred, T., Hickie, I. B., & Kemp, A. H. (2012). Heart rate variability is associated with emotion recognition: Direct evidence for a relationship

between the autonomic nervous system and social cognition. *International Journal of Psychophysiology, 86*, 168-172. doi: 10.1016/j.ijpsycho.2012.08.012

Raichle, M. E., & Mintun, M. A. (2006). Brain work and brain imaging. *Annual Review of Neuroscience, 29*, 449-476. doi: 10.1146/annurev.neuro.29.051605.112819

Ratanasiripong, P., Sverduk, K., Prince, J., & Hayashino, D. (2012). Biofeedback and counseling for stress and anxiety among college students. *Journal of College Student Development, 53*, 742-749.

Roelofs, J., van Breukelen, G., de Graaf, L. E., Beck, A. T., Arntz, A., & Huibers, M. J. H. (2013). Norms for the Beck Depression Inventory (BDI-II) in a large Dutch community sample. *Journal of Psychopathology and Behavior Assessment, 35*, 93-98.

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., . . . Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *American Journal of Psychiatry, 163*, 1905-1917. doi: 10.1176/appi.ajp.163.11.1905

Segerstrom, S. C., & Nes, L. S. (2007). Heart rate variability reflects self-regulatory strength, effort, and fatigue. *Psychological Science, 18*, 275-281. doi: 10.1111/j.1467-9280.2007.01888.x

Shaffer, F., & Venner, J. (2013). Heart rate variability anatomy and physiology. *Biofeedback, 41,* 13-25.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59 Suppl 20*, 22-33;quiz 34-57.

Siepmann, M., Aykac, V., Unterdorfer, 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. doi: 10.1007/s10484-008-9064-z

Siepmann, M., Joraschky, P., & Rebensburg, M. (2005). Is autonomic cardiac control disturbed in patients with depression and coronary artery disease? *Zeitschrift fur Klinische Psychologie and Psychotherapie, 34*, 277-281.

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. doi: 10.1007/s10484-009-9077-2

Talairach, J., & Tournoux, P. (1988). *A co-planar stereotaxic atlas of the human brain*. New York: Thieme Medical.

Titov, N., Dear, B. F., McMillan, D., Anderson, T., Zou, J., & Sunderland, M. (2011). Psychometric comparison of the PHQ-9 and BDI-II for measuring response during treatment of depression. *Cognitive Behavior Therapy, 40*, 126-136.

Tonhajzerova, I., Ondrejka, I., Javorka, M., Adamik, P., Turianikova, Z., Kerna, V., . . . Calkovska, A. (2009). Respiratory sinus arrhythmia is reduced in adolescent major depressive disorder. *European Journal of Medical Research, 14 Suppl 4*, 280-283.

Uhlmann, C., & Froscher, W. (2001). Biofeedback treatment in patients with refractory epilepsy: Changes in depression and control orientation. *Seizure, 10*, 34-38. doi: 10.1053/seiz.2000.0478

van Hees, M. L. J. M., Rotter, T., Ellermann, T., & Evers, S. M. A. A. (2013). The effectiveness of individual interpersonal psychotherapy as a treatment for major depressive disorder in adult outpatients: A systematic review. *BMC Psychiatry, 13*, 1-10.

Vaschillo, E. G., Vaschillo, B., & Lehrer, P. M. (2006). Characteristics of resonance in heart rate variability stimulated by biofeedback. *Applied Psychophysiology and Biofeedback, 31*, 129-142. doi: 10.1007/s10484-006-9009-3

Vaschillo, E., Lehrer, P., Rishe, 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*, 1-27.

Veer, I. M., Beckmann, C. F., van Tol, M., Ferrarini, L., Milles, J., Veltman, D. J., . . . Rombouts, S. A. R. B. (2010). Whole brain resting-state analysis reveals decreased functional connectivity in major depression. *Frontiers in Systems Neuroscience, 4*, 1-10.

Wampold, B. E., Minami, T., Baskin, T. W., & Tierney, C. S. (2002). A meta-(re)analysis of the effects of cognitive therapy versus 'other therapies' for depression. *Journal of Affective Disorder, 68*, 159-165.

Waraich, P., Goldner, E. M., Somers, J. M., & Hsu, L. (2004). Prevalence and incidence studies of mood disorders: A systematic review of the literature. *Can J Psychiatry, 49*, 124-138.

Weissman, M. M., & Markowitz, J. C. (Eds.). (2002). *Handbook of depression*. New York, NY: Guilford Press.

Zimovetz, E. A., Wolowacz, S. E., Classi, P. M., & Birt, J. (2012). Methodologies used in cost-effectiveness models for evaluating treatments in major depressive disorder: A systematic review. *Cost Effectiveness and Resource Allocation, 10*, 1. doi: 10.1186/1478-7547-10-1