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Role Of Heart Rate Variability Biofeedback In Cognitive Performance, Chronic Pain, And Related Symptoms

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DEDICATION

I want to thank my Lord and Savior, Jesus Christ. For my wife Amy and kids Audrey, Will, and Cashel, thank you for all your love and support. For my parents Jim and Maureen for always guiding and praying. To my siblings and family everywhere, thank you for your continued support. Thank you to my Dissertation Committee. To my Epidemiology & Biostatistics cohort and Exercise Science cohort for all the fun times and late nights studying. Thank you to Sabrina Karim and Samantha Truman for providing feedback on this document. *1 James 2-8*.

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ABSTRACT

Over-modulation of the sympathetic nervous system and reduced heart rate variability (HRV) are commonly overlooked components of pain, poor cognition (decreased attention, recall, and cognitive processing), depression, stress, and fatigue. HRV Biofeedback (HRVB) training induces HRV coherence to balance the autonomic system. Paced breathing (~6 breaths/minute) increases HRV coherence. This randomized, controlled intervention trial tested the hypothesis that HRVB would improve HRV coherence, pain (severity, interference, and catastrophizing), cognitive performance, and reduce depressive, stress, and fatigue symptoms and pain medication use in veterans. Participants were randomized to previously established HRVB or control protocols. Each participant completed a Baseline Assessment, 6 weekly training sessions, a Post-training Assessment, a Booster training session and Assessment (1-month post-training), and a Follow-up Assessment (2-months post-training). Outcomes included: 15-minute resting HRV recordings (HRV Coherence Ratio), Brief Pain Inventory (severity, intensity), Pain Catastrophizing Scale, pain medication use, Paced Auditory Serial Addition Test (PASAT), Hopkins Verbal Learning Test-Revised (HVLT-R), Psychomotor Vigilance Task (PVT), Beck Depression Index-II (BDI-II), Perceived Stress Scale, and Multidimensional Fatigue Inventory. To date, 85 patients completed Baseline Assessment, 63 completed Post-training Assessment, and 50 completed the

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entire protocol. Patients in the HRVB group had elevated HRV Coherence Ratios at the Follow-up Assessment relative to baseline (0.17±.02 vs. 0.45±0.08, p<0.001), whereas no differences were observed among controls (0.17±0.02 vs. 0.19±0.03, p=0.55). Compared to baseline scores, the Follow-up Assessment resulted in a reduction in Pain Interference scores (5.67 ± 0.19 vs 4.69 ± 0.37 p=<0.01) and an improvement in Mean Reaction Time (431.59 ± 17.32 vs 407.50 ± 17.71, p=0.04). No statistically significant differences were noted among controls. The intervention was received, a statistically significant increase in the HRV Coherence Ratio was observed in the intervention group over time, whereas no changes were seen in the control group. Those in the intervention group improved their reported pain and depression symptoms, reduced non-steroidal anti-inflammatory medication use and reaction time as compared to the control group. Non-pharmacological therapies that improve pain, cognition, and depression would benefit veterans. HRVB is a valid, quantifiable, easily-implemented intervention. Results from mixed effects statistical models testing study hypotheses indicate the potential benefit of HRVB in this trial.

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PREFACE

The views expressed in this document are those of the author and do not reflect the official position of the U.S. Army Medical Department Center and School, U.S. Army Medicine, Department of the Army, Department of Defense, or the U.S. Government.

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LIST OF ABBREVIATIONS

ANS..... Autonomic Nervous System

BDI..... Beck Depression Inventory

HRV ..... Heart Rate Variability

HRVB..... Heart Rate Variability Biofeedback

HVLT.....Hopkins Verbal Learning Test

IBI .....Inter-beat Interval

LTF ..... Lost-to-Follow-up

MFI.....Multidimensional Fatigue Inventory

NSAID..... Non-Steroidal Anti-Inflammatory Drug

OTC ..... Over-the-Counter

PASAT .....Paced Auditory Serial Addition Test

PCS .....Pain Catastrophizing Scale

PFC..... Pre-Frontal Cortex

PIS ..... Pain Interference Score

PNS .....Parasympathetic Nervous System

PS .....Pain Severity

PSS.....Perceived Stress Scale

PTSD ..... Posttraumatic Stress Disorder

PVT .....Psychomotor Vigilance Test

RSA ..... Respiratory Sinus Arrhythmia

SNS .....Sympathetic Nervous System

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CHAPTER 1

INTRODUCTION AND SPECIFIC AIMS

1.1 INTRODUCTION

Heart rate variability (HRV) has repeatedly been used to characterize current health status and to predict future outcomes.[1] Wide variation in heart rate throughout each day is reflective of a higher level of resilience and ability of the human body to respond to both internal and external stresses. Conversely, minimal variation of heart rate has been tied to inflexibility of the autonomic nervous system (ANS) to respond to stresses.[2] Reduced HRV has been associated with cardiac death[3], chronic pain,[4, 5] mental health disorders,[3, 6] along with reduced cognitive function.[6 7, 8] Over time, this may lead to chronic health issues which may cost billions of dollars annually in direct and indirect costs.[9, 10] It is estimated that by the year 2030, crude (age-unadjusted) prevalence of cardiovascular disease will make up 40.5% of the United States adult population (age 18+ years) with around $818 billion in direct healthcare cost and around $276 billion indirectly due to loss of productivity.[10] The ANS plays a role in cardiac function. Therefore, if cardiac autonomic function is poor, then heart failure and death may result,[3] thus leading to a shortened life expectancy, fewer productive years of employment, and a low quality of life.

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As a result of ANS dysfunction, decreased HRV has been associated with chronic pain,[4, 11] and with decreased cognitive performance,[4, 12] as well as prolonged recovery in those who sustain concussion.[5] Chronic pain is associated with changes in cognitive performance.[13] Chronic pain has been defined as pain lasting more than three months. Approximately one-fourth of the general population seeks treatment for chronic pain through their primary care providers.[14, 15] While both pharmacologic (i.e., acetaminophen, nonsteroidal anti-inflammatories, and opioids) and nonpharmacologic treatments are provided to treat pain and other conditions, opioid prescriptions have been provided to millions of people across the United States to treat pain.[16] In 2012 approximately 25 million US adults noted having pain during the 2012 National Health Interview Survey.[17]

According to the Veterans Administration, the Department of Defense, and the Centers for Disease Control and Prevention, more than 200,000 people died between 1999 and 2016 due to prescription opioid overdose.[16] The prevalence of opioid prescriptions has risen among veterans from 18.9% to 33.4% between 2004 and 2012.[18] This rise in prescription prevalence increased nearly 77%.[18] Deaths in 2016 were five times that of opioid related deaths in 1999.[19] As concern of the opioid epidemic[18] grows due to potential for addiction to medications and unintended consequences, safe, non-addictive alternatives are needed that can be used anywhere, under circumstances that may reduce injury and illness. HRVB will be evaluated here as a potentially safe, non-addictive intervention in a randomized controlled trial to determine if it is effective at restoring autonomic

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balance by decreasing pain and improving cognitive function and psychological well-being among veterans.

This dissertation included three aims within a unique population and source of data. The first chapter provides the introduction and specific aims. Chapter 2 provides the background information, rationale for the proposed specific aims and defines the study population. Each of the three specific aims utilized a population of United States military veterans over the age of 18 who have chronic pain and are registered patients of the William J Bryce (WJB) Dorn Veterans Health Administration in Columbia, South Carolina. This document is formatted with Chapter 3 describing the methods, Chapter 4 describing the results for the outcomes, and Chapter 5 providing discussion for the outcomes.

SPECIFIC AIM 1: HRVB AND CHRONIC PAIN

HRVB is thought to be a safe, effective, non-habit-forming intervention to reduce pain[4, 20-23]. This involves coaching a participant to breathe about 6 breaths per minute. When using paced breathing, also referred to as resonance frequency breathing, through the technique of HRVB, studies have shown a balancing or entrainment of the ANS referred to as HRV coherence.[24] HRV coherence enhances the parasympathetic vagal tone thus allowing the body to establish ANS homeostasis in those with increased sympathetic activity.[24] Paraphrasing Porges, homeostasis is a dynamic regulation within a functional range for living systems to maintain internal states.[2] With the application of biofeedback, participants have

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been shown to improve HRV, improve sleep, cognitive function, and reduce pain.[4, 24]

This randomized controlled intervention trial examined the efficacy of HRVB to reduce pain (severity, interference, and catastrophizing), improve cognitive function, and reduce reported symptoms of depression, stress, and fatigue among U.S. military veterans with chronic pain utilizing volunteer veterans at the WJB Dorn Veteran's Health Administration in Columbia, SC. Two arms were used where a control group was compared with an HRVB intervention group. First, we examined if receipt of the intervention (HRVB) was successful in the Intervention group by assessing outcomes of HRV parameters using a linear mixed model with group, time, group by time interactions. Next, the primary dependent variables were pain severity (PS), Pain Interference Score (PIS), and Pain Catastrophizing Scale (PCS). These measures were reported using a linear mixed model with a group, time, group by time interaction. Lastly, we evaluated pain medication usage. This was categorized based on the type of medication (i.e. Non-Steroidal Anti-Inflammatory Drug, Opioid, etc.) evaluated using a linear mixed model with the same group, time, group by time interaction. Socio-demographic (i.e. gender, race, income, education, etc.) baseline differences were examined for confounding; any differences that existed were controlled for in the regression models.

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The research aims and hypotheses for HRVB and Pain were:

1.1.1 Quantify the changes in HRV time and frequency domain measures among the Baseline, Post-Training, and Follow-up Assessments using biofeedback. ***Hypothesis***: *HRV will improve in the intervention group through the receipt of HRVB over time as compared to baseline.*

1.1.2 Evaluate changes in pain resulting from improvement in HRV. ***Hypothesis:*** *Improvements in HRV scores and coherence will result in a decrease in pain severity and intensity which will be measured from Pain Severity Score (PS) and Pain Interference Score (PIS) over time as compared to baseline.*

1.1.3 Elucidate differences in pain catastrophizing and in pain medication use. ***Hypothesis:*** *There will be a decrease in the Pain Catastrophizing Score (PCS) and a reduction in pain medication use using HRVB over time as compared to baseline.*

SPECIFIC AIM 2: HRVB AND COGNITIVE PERFORMANCE

Reduced HRV has been associated with poor health outcomes, indicative of reduced resilience in responding to physical and psychological stress,[25] and diminished cognitive function.[4] With the application of biofeedback, participants have been shown to improve cognitive function.[4]

This study used the same veteran population described above from Columbia, SC. Dependent variables were cognitive function outcomes as

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measured separately by the Paced Audio Serial Addition Test, the Hopkins Verbal Learning Test-Revised, and the Psychomotor Vigilance Test.

The research aim and hypothesis for HRVB and Cognitive Performance was:

1.2.1 Quantify the changes in Paced Audio Serial Addition Test (PASAT), Hopkins Verbal Learning Test-Revised (HVLT), and Psychomotor Vigilance Test (PVT) reaction time and total number of lapsed (missed) response measures between Baseline, Post-Training, and Follow-up Assessments through the use of HRVB. ***Hypothesis***: *The number of correctly added pairs of PASAT numbers will increase, the mean HVLT score for the number of words correctly recalled will increase, the PVT reaction time will improve, and the total number of PVT lapses will decrease in the intervention group through the receipt of* HRVB.

SPECIFIC AIM 3: HRVB, DEPRESSION, FATIGUE, AND PERCEIVED STRESS

Stress has been linked to negative changes in health such as elevated blood pressure and heart rate, increased inflammation, changes in the immune system and nervous system, along with depression, and anxiety.[25] Stress has been associated with developing illness from viral infections such as the common cold or influenza.[26] Increased psychological stress has been associated with lower HRV. HRVB can help reduce depressive symptoms, anxiety, and stress.[25] HRVB has been suggested to improve symptoms of depression,[27-40] stress, [25, 41-43] and fatigue.[44,45]

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This study assessed subjectively-reported depression, perceived stress, and fatigue in U.S. military veterans with chronic pain utilizing the same veteran population as previously described for aims 1 and 2. The primary dependent variable was self-reported depression, quantified using the Beck Depression Inventory-II (BDI). Depression was assessed using a linear mixed model with a group, time, group by time interaction. A second outcome was perceived stress score (PSS). A third outcome was self-reported fatigue using the MFI. Separate analyses were conducted to assess for General Fatigue, Mental Fatigue, Physical Fatigue, Reduced Activity, and Reduced Motivation utilizing the same linear mixed model described previously.

The Research aim for HRVB, Depression, Stress, and Fatigue was:

1.3.1 Elucidate differences in depression, perceived stress, and fatigue. ***Hypothesis:*** *There will be a decrease in the Becks Depression Inventory (BDI), less perceived stress, and a decrease in the general fatigue, mental fatigue, physical fatigue, less reduced activity, and less reduced motivation through receipt of the intervention HRVB.*

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CHAPTER 2

BACKGROUND

2.1.1 Heart Rate Variability and Biofeedback

The human heart rate is the pace at which the heart responds to stimuli throughout the day. This is driven by signals from the ANS[46-48] which is comprised of two drivers: the sympathetic (action) and parasympathetic (rest) systems.[2] The ANS is a network of neurological signals sending and receiving messages from the brain and other organs. Neural control for both sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) originate in the brainstem. The sympathetic system primarily responds to stimuli external to the body with the mobilization of metabolic resources while the parasympathetic system primarily responds to changes within the body to maintain homeostasis, allowing for rest and recovery.[2] Heart rate fluctuates continuously by adjusting to stresses from the surrounding environment. These rate alterations are also referred to as oscillations.[1, 48] Respiratory sinus arrhythmia (RSA) is the change in HR that occurs with each breath; the heart rate accelerates with inspiration and slows with exhalation.[2, 20] Messages transferred via efferent vagal pathways promote parasympathetic control and are thought to decrease inflammation, improve gas exchange in the lungs, and promote resilience and resonance.

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HRV measurements can be obtained to assess the balance in the SNS and PNS through short-term or long-term (24-hour) recordings of heart rate. The recordings produce variables in time domain[49] and frequency domain[50] that may assist in determining health status. Normative values of these heart rate variables have been established in children[51, 52] and adults[53] using standard bandwidths,[8] as introduced by McCraty.[7]

As described by Jarvelin et al., in an electrocardiogram, the peak of a normal QRS complex is the R wave. The distance from one R-wave to the next R-wave is a time interval and will vary from beat-to-beat. Variation in the distance between successive heart beats over time is called HRV and may provide objective findings.[54-56] The R-R interval has also been referred as N-N (normal-to-normal).[54] Changes in or lack of changes in variation may be reflective of both psychological as well as physical stimuli placed upon the human body and how well the ANS reacts to the stimuli.[57] Essentially, the greater the variation, the better one is able to respond, thus exhibiting better overall health.[56, 58] Anything that affects the ANS such as psychophysiological stress or recovery of the ANS should be evaluated as it relates to HRV[54]. Such things that influence HRV include age,[59, 60] fat mass,[52] gender,[59, 60] cardiorespiratory fitness,[61] physical fitness,[52] health,[59] medication,[59] circadian changes,[46] and smoking.[59]

As noted by Lehrer et al.,[62] the field of psychotherapy evolved out of necessity during World War II where physicians were the primary provider of psychological care. Over time as the field of psychology and later behavioral psychology developed, deep breathing and muscle relaxation techniques were

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found to be beneficial in treating individuals with anxiety, sleeping difficulty, headaches, and high blood pressure.[62] These techniques emphasized the use of abdominal breathing for breathing retraining.[62] Hyperventilation has been attributed to the use of thoracic muscles during breathing and Lehrer et al. noted that many authors have cited the use of thoracic breathing as being associated with both emotional difficulties and complaints of the body.[62] While relaxation techniques may attenuate SNS activity and feelings of anxiety and frustration, during the 1980s and 1990s, Russian scientists were exploring the use of resonant frequency breathing to provide more flexibility within the PNS.[62] Hyperventilation involves an increase in breathing rate often accompanying stressful events, whereas controlled breathing at a rate of around 6 breaths per minute leads to an increase in positive emotion[62, 63] as well as increased HRV. Changes in HRV has been attributed to changes in health.[5] Increased variability is associated with improved health[39] whereas decreased HRV has attributed to decline in health. Decreased HRV has been associated with depression as well as with the use of antidepressant medication.[41] HRV has been evaluated in adults to monitor outcomes after significant events and even predict outcomes over several decades. Since the 1970s, examples include congestive heart failure,[64] post myocardial infarction, alcoholism, and diabetic neuropathy.[46]

When synchronization between the heart, lungs, and brain is reached, HRV coherence develops.[24] HRV coherence can be achieved using a paced-breathing technique called resonance frequency breathing.[24] Each person has a unique frequency in which parasympathetic control is promoted and HRV coherence is

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achieved, which usually occurs at ~6 breaths per minute (or 0.1 Hz). [20, 36, 65] Coherence refers to oscillations (heart rate and respiration) that occur at the same frequency. When resonance frequency breathing is achieved, oscillations in heart rate and respiration appear, are in phase, and HRV coherence is maximized.[7] McCraty et al refer to HRV coherence as "an optimal psychophysiological state".[66] This frequency maximizes efficiency of gas exchange in the lungs, may lower blood pressure, improve depression and anxiety, decrease pain, improve athletic performance[20] and increase HRV.[9] As quoted by Swanson et al. "Increased HRV is synonymous with parasympathetic tone or vagal tone".[9] Reduced HRV has been associated with poor health outcomes and is indicative of reduced resilience in responding to physical and psychological stress. Those with positive affect (positive thought processes) performed better with HRVB in cognitive tests suggesting that positive thoughts influence the benefit of HRVB[67] which is consistent with other investigators who have stated that negative thoughts can drive negative results and conversely with positive thoughts and outcomes.[68] Porges notes that this technique influences the parasympathetic nervous system through activation of the nerve fibers which regulate blood pressure and heart rate.[69] HRVB is a non-pharmacological treatment in the reduction of chronic pain,[4] has influenced vagal activity,[65] and inhibits spinal column pain pathways.[4] HRVB has been shown to improve anxiety,[37-39, 70-72] improve sleep and cognition with decrease in stress and pain,[4, 21-23, 39, 73-75] decrease blood pressure,[76, 77] depression,[32-41] insomnia,[78] heart disease,[9, 79] asthma,[80-82] and posttraumatic stress disorder (PTSD)[8, 36, 83]

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2.1.2 HRV, HRVB and Chronic Pain in Veterans:

Pain has been labeled as the fifth vital sign in the past few decades, has been used as a subjective measurement, and appears to be noted with more frequency in the news. Pain not only interferes with activities of daily living and quality of life,[84-86] it is one of the leading reasons for primary care visits.[87, 88] Treatment for pain has led to stronger, more potent, and potentially addictive medications to be prescribed in higher quantity and in frequency to the point that the world is facing an opioid epidemic.[89, 90] Despite the increase in treatments, pain appears to be worsening globally, not improving. Chronic pain is defined as pain that lasts longer than three months[14, 15] and has been shown to disrupt sleep, cognitive function, increase fatigue and depression. It is thought that each year, over 100 million people seek treatment for chronic pain in the US resulting in medical costs near $635 billion both directly and indirectly.[91] Of those taking opioid narcotics for chronic pain, upwards of 60% may be prone to abuse.[92] In 2015, it was estimated over 2 million Americans had a prescription pain medication abuse disorder while nearly 600,000 used heroin.[93] The average annual cost for opioid rehabilitation with methadone is approximately $4,700 per patient.[94]

Military recruits are medically screened out of the general population and tend to be healthier than the general population[95] whether the individual was drafted or volunteered. Veterans comprise approximately 10% of the US population.[96] During their time in service, military personnel have access to comprehensive health care[95] with routine maintenance and care provided for exposure to both combat related and non-combat related injuries and illness.[95]

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However, following military service, veterans tend to report higher chronic pain than the general population.[97-100]

Among age-matched veterans and nonveterans, those who have provided military service tend to express higher chronic health and psychological concerns than nonveterans.[99] Among some of the symptoms, veterans who deployed for the Persian Gulf War (1990-91) have a higher prevalence of abdominal pain,[101-103] and pain in the joints relative to veterans that did not deploy during that time[101-107] and higher prevalence of arthritis,[98, 108-112] backpain,[103-105, 111] fibromyalgia,[109] and headache[102, 106] in veterans relative to nonveterans. This is most striking among those engaged in conflicts in Iraq and Afghanistan and has been shown to interfere with activities of daily life (ADLs).[113, 114]

Pain in veterans has been associated with physical and mental problems.[4] Opioid and opioid receptor binding medications are standard for use in chronic pain and have been associated with physical or psychological side-effects ranging from constipation, nausea, and intolerance to the medication, as well as addiction.[115] Opioid prescriptions are more likely to be prescribed for pain to veterans with mental health conditions than to veterans without mental health conditions.[116]

A relative increase of 76.7% in opioid prescriptions among veterans increased between 2004 and 2012 from 18.9% of all veteran outpatients to 33.4%.[117] This increased usage of opioids has the potential to alter cognitive performance. In a study by Sinnot et al.,[29] between 2000 and 2007, low back pain prevalence rate increased 4.8% as compared to diabetes 4.4%, hypertension

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4.1%, and depression 3.8% among VA users. The rate in number of individuals with low back pain rose from 10,955 to 15,205 per 100,000 Veterans Administration (VA) users.[29] Quality of life relating to health among active duty men has been reported by Barret et al., to be more likely to be physically limited from activity, report pain, and report inadequate rest as compared to men who have no military service.[113] Further, the authors note active duty men to be five times more likely to have pain and limited activity for 14 or more days as compared to men with no military service.[113] Orthopedic injuries leading to limited physical activity and chronic joint symptoms may be associated with increased prevalence of arthritis among veterans as compared to nonveterans.[108]

Pain has been associated with changes in HRV[23, 39] and with changes in memory.[30] In a study of older adults by van der Leeuw et al., women, African Americans, and those with fewer years of education were more likely to have pain interference or severe pain.[118] Pain severity was found to produce more disability, especially beyond the age of 65.[84] It is conceivable that a reduction in pain may also facilitate improvement in memory. HRVB has been shown in studies to be an effective tool in reducing pain in veterans.[4] Therefore, HRVB may be effective at improving both pain and memory.

2.1.3 HRV, HRVB, and Cognitive Function in Veterans

According to the Centers for Disease Control and Prevention (CDC), it is estimated that over 16 million people in the U.S. have some form of cognitive impairment (more than twice the population of New York City) and over 10 million

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family members provide care for these individuals.[119] Cognitive impairment may range from mild to severe in which changes may be noted in difficulty concentrating, trouble remembering or learning.[119]

Working memory is believed to correspond to activity within the prefrontal cortex (PFC).[120] In times of stress, the PFC may be bypassed or taken offline allowing the amygdala to take over and respond to threats, then return to PFC control when the threat subsides for deliberate and conscientious behavior.[121] This inhibitory control is associated with executive function, emotional control, along with working memory.[121] Normally, the amygdala can be associated with fear or response to threats. When the PFC is online and working appropriately, while it may not suppress fear, it may help to remember strategies to contend with fear.[55] Thayer et al. suggest that when the PFC goes offline, more energy is mobilized by the amygdala to be able to respond to perceived threats and a decrease in HRV has been noted.[55] Cognitive performance and the PFC have been linked with HRV.[122] An intact, activated PFC with vagally-mediated HRV demonstrated increased executive function, increased correct answers, and faster reaction times in several studies with HRVB.[122-124]

In a study by Stricker and colleagues, memory impairment was more likely in those with PTSD.[125] Among veterans of the Persian Gulf War (1990-1991), those with PTSD performed more poorly than those without PTSD in tests measuring attention, learning, and memory.[126] In a prospective cohort of over 1,200 active duty U.S. Army Soldiers of the Iraq conflict (2003-2005), study participants conducted pre- and post-deployment assessments. Those who

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deployed were found to display more tension and confusion, decreased sustained attention, decreased verbal learning, decreased visual-spatial memory, yet exhibited increased reaction time.[127] In a stratified, retrospective cohort of over 181,000 male veterans without dementia, participants were followed from 1997-2007. The 7-year cumulative incidence rate (CIR) for dementia among those participants with PTSD had a CIR of 10.6% as compared to those without PTSD with a CIR of 6.6%. Those with PTSD had nearly 2-fold incident dementia utilizing Cox proportional hazard models.[128]

Weiner et al. noted that a decline in memory and learning was found in those with chronic back pain[129] and chronic pain was associated with changes in memory and emotional decision-making tasks.[30, 130] Cognitive functions are thought to change in accordance with chronic pain, in which pain may be a distraction from required attention leading to poor cognitive outcomes.[131] It is also believed that education may be protective in preventing cognitive decline and influences neuropsychological performance.[132-136]

In a quasi-experimental study design of 37 male Norwegian sailors, upon completion of eight weeks of basic training, participants were transferred into a training program for another eight weeks. Assignment to fitness training versus a fitness detraining was based on their follow-on duty assignment. Those who maintained fitness training continued three hours per week of physical fitness whereas those in the detrained group went on-board ship for service. Those in the fitness trained group demonstrated higher HRV, faster reaction time in executive

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functions, and provided more correct answers in an N-back test, recalling numbers previously seen.[122]

In another study by Hansen et al., 53 Norwegian male sailors provided a 5-minute baseline HRV recording. HRV categories were split with the median of RMSSD. The high HRV group demonstrated faster mean reaction time, fewer errors, and more correct answers than the low HRV group.[124]

Prinsloo et al, reported using a randomized HRVB and control group study in 18 male participants with work-related stress. Upon enrollment, participants were stratified randomly based on age initially and then later randomly allocated to either the HRVB or control group. Participants were taught how to use an electronic handheld biofeedback device, to follow a wave form with inhalation and exhalation using time-domain metrics rather than true resonance frequency breathing. Baseline recordings were obtained including blood pressure and heart rate. This was followed by a five-minute Stroop task (responding to squares and color words in different colors), a five-minute rest period, and finally the ten-minute HRVB intervention. Those in the HRVB group made fewer mistakes and improved reaction time as compared to the control group.[123]

In a cross-sectional study of middle-aged male twins in the Emory Twin Studies from the Vietnam Era Twin Registry, participants remained on the Emory campus, provided 24-hour leisurely ambulatory HRV recordings, and conducted BDI and cognitive testing. HRV was positively associated with verbal memory.[137] Twin HRV recordings of less than 18 hours were excluded. Sutarto and colleagues

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reported among thirty-six operators randomly allocated into HRVB or control group, participants were provided five-weekly HRVB sessions of 30-50 minutes each. Improvement in attention and memory were noted in recipients of HRVB.[138]

2.1.4 HRV, HRVB, and Depression in Veterans

In the U.S. in 2012, direct cost of $300 billion was spent on mental health.[139] In the Department of Veteran's Affairs in 2010, over 110,000 primary care visits had new incidence of depression in veterans.[140] The veteran population comprises approximately 18 million people of the U.S. population[141] and major depression in veterans is estimated to be between 12-30%.[142] A recent publication by Liu et al. reported depression prevalence among U.S. military veterans increased from 9% (2007-2008) to over 14% (2015-2016) based on a sample from the National Health and Nutrition Examination Survey (NHANES) and over 16% of veterans reported having little energy over half the days in a two-week period.[139]

Arnsten and Goldman-Rakic described that the PFC may go off-line when under stress for survival purposes however when sustained, this may be not be conducive for society as the PFC helps with executive control and inhibition[143] This sustained off-line process can lead to psychological disorders to include depression, anxiety, and PTSD.[144] What's more is that reduced HRV is connected with depression.[32, 144, 145] Reduced HRV has been reported with depression in both healthy and unhealthy populations[146-148] and it has been improved through the use of HRVB.[35, 36, 40, 41, 146, 149] In a randomized controlled trial of 38 participants (ages 18-70 years) with unexplained somatic complaints, HRVB training over the course of 10 weekly sessions helped resolve depressive symptoms as early as 5 weeks

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after treatment.[35] Depression has been associated with chronic pain,[29, 30] concussions,[27, 28] cardiovascular risks,[150] and is observed in children with anxiety.[31] Depression has been associated with heart failure and improved HRV in heart failure patients[146] has demonstrated improved survival[151] and better outcomes.[152] However, one study suggested the direction for the development of depression was due to reduced HRV, whereas in the presence of antidepressants, depression reduced HRV.[153]

2.1.5 HRV, HRVB, and Stress in Veterans

In a review by Subhani et al.,[154] stress is believed to be associated with impairment of memory,[155] and changes in cognitive health[156] possibly resulting in atrophy of the PFC and hippocampus.[157] As the PFC has been connected to attentional endurance, changes in executive function may displayed.[158] The link between the PFC and the heart may reside in both direct and indirect pathways which control the heart rate via the vagus nerve. This PFC-cardiac connection effects the PNS and SNS as well as influence baroreceptors to modulate HRV. [158] This interaction with the baroreceptors has been associated with increased mental workload and cognitive demand.[158-160] Cognitive function can be impaired by chronic psychological stress.[123, 161-163] Chronic stress has been associated with major depression and PTSD, especially in military veterans.[142] PTSD in veterans ranges from 6-31% as compared to 6-12% of the U.S. population.[142] As women in the military in past conflicts may have been relegated to nursing or clerical roles, more recent conflicts have exposed women to greater combat intensity.[142] Since past medical studies have examined combat-related stress in male veterans, this

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new dynamic may be considered in future studies including more women. The World Health Organization has referred to stress as a nonpsychotic mental health disorder[164] and even provided a diagnostic classification code for this. Chronic psychological stress has been associated with reduced HRV.[123, 165-168] Some occupations demand intense mental focus and workload such as air traffic controllers, pilots, and surgeons. Utilizing the National Aeronautics and Space Administration Task Load Index (NASA-TLX), subjective mental load has been measured and has demonstrated correlation of HRV to both reduced attention and mental fatigue.[158] When time-on-task was recorded, lower HRV was found with longer tasks requiring sustained vigilance and attention.[158] HRVB is believed to help reduce stress.[41-43] Prinsloo et al., reported participants in an HRVB group felt more relaxed and alert.[123] Slowed breathing with the abdomen has been found to increase HRV and reduce anxiety in musicians.[43] Pregnant women who completed HRVB training reported reductions in stress compared to women who did not receive HRVB.[42]

2.1.6 HRV, HRVB, and Fatigue in Veterans

Fatigue is experienced by many people, but they often find it difficult to describe. Persson and Bondke Persson described fatigue as subjective and vague but provided three characteristics: develops gradually, while different than weakness is relieved by rest, lasting more than six months.[169] Smets et al. describe fatigue as one of the most commonly reported symptoms in cancer patients and that fatigue is a symptom often relieved via convalescence.[170] Schiehser et al. depict fatigue as being a multi-faceted entity with physical and

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mental components, involving alterations in motivation, initiating and sustaining tasks, and may be associated with trauma such as traumatic brain injury, depression, and anxiety.[171] Fatigue is often a symptom described by healthy people after being sleep restricted, after physical exertion, or in post-surgical patients[172]. Fatigue is associated with outcomes of the Psychomotor Vigilance Task, even among those who are not injured.[173] While fatigue is a common concern expressed to medical providers, it can also be a precursor to diseases or disorders.[172] Fatigue is experienced in approximately 38% of community dwellers and the prevalence of fatigue lasting more than six months in the general population may range from 2-11% at any given time.[174] HRV is reduced with fatigue[175] and has been noted to be lower due to both mental effort and workload associated with fatigue.[166, 176, 177] Difficulty with concentration and memory comprise mental fatigue, is common with concussion[173] and in workload.[178] Mental effort and HRV power have been found to be inversely related[126], and relationships between HRV, mental workload, and mental fatigue have been reported.[176, 179] Reduced HRV has been reported following physical or cognitive challenges as well.[180] HRVB has demonstrated improvement in both fatigue and in depression.[44] Reduced motivation to initiate activity may be described in those who report feeling fatigued along with depression.[172] A study found improved motivation among police officers who received HRVB. [45] A separate study found improvement in four of five fatigue subscales after HRVB. Improvements were reported in general fatigue, mental fatigue, physical fatigue, and reduced activity; however, improvements were not observed in reduced motivation.[44]

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In summary, HRV has been shown to be reduced in those with poor health and health outcomes whereas increased HRV has been associated with better health outcomes. Veterans have suffered disproportionately relative to the general population. Veterans have worse health outcomes, report more pain, and use more pain medication relative to the general population. Veterans have worse cognitive performance, depression, stress, and fatigue relative to the general population. HRVB has been shown to improve HRV, both in the general population and in veterans, and HRVB has been shown to improve health outcomes. Results from this analysis provide evidence that HRVB can improve HRV, decrease pain severity and interference, reduce the number of non-steroidal anti-inflammatory drugs used, decrease reaction time, and decrease depression.

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CHAPTER 3

METHODS AND MATERIALS

Project Design

This study was a randomized sham-controlled pilot intervention trial using a standardized HRVB protocol for the intervention group and a sham condition for the control group of chronic pain patients over a 16-week intervention period. This study was approved by the WJB Dorn Veteran's Administration Institutional Review Board as well as the University of South Carolina Institutional Review Board. The study was funded by the Veterans Affairs Office of Research and Development (Grant number: I01BX007080) and was registered as a clinical trial (NCT 02426476).

The design of this study included four assessments over a 16-week period (Appendix A, Figure A1). The initial visit included informed consent as well as a Baseline Assessment that included depression, stress, and fatigue questionnaire data, a 15-minute resting HRV recording, computer-based cognitive assessments, and saliva sample collection. Upon completion of informed consent, participants were randomized into one of two groups: HRVB intervention group or a control group. Each participant returned for weekly training visits over a period of six weeks. Participants returned on week seven for a Post-training Assessment which

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repeated the same measurements as the Baseline Assessment. A month later, participants returned for a booster training session and a third assessment. This Booster Assessment included the same questionnaire data and a 15-minute resting HRV recording. The fourth and final assessment was one month after the booster, at week 16. This final Follow-up Assessment repeated the same questionnaire, HRV recording, cognitive assessment, and saliva collection as the first two assessments (Appendix Figure A.1.).

Study Population

The target population consisted of veteran patients attending the WJB Dorn Veterans Administration Medical Center (DVAMC) who were: English literate, ≥18 years old, of any race, ethnicity, or sex who met other inclusion and exclusion criteria. Patients were recruited initially from the Dorn VAMC Pain Clinic and later from other clinics such as Rehabilitative Medicine, Rheumatology, Primary Care, and Physical Therapy. IRB approved brochures along with flyers were placed in approved public areas around DVAMC so that volunteers could contact research coordinators. The results presented in this dissertation represent data from a preliminary sample of study participants collected from June 2016 to February 2019. Eligibility was checked using a telephone screen when the veteran expressed interest in participation in the study. A chronic pain screen was performed using the Pain Screening Questionnaire (Vanderbilt University Medical Center, Center for Quality Aging, Nashville, TN). Pain was assessed with the following questions: 1.) Do you have pain anywhere right now? 2.) Does pain ever keep you from sleeping at night? 3.) Does your pain ever keep you from

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participating in activities/doing things you enjoy? 4.) Do you have pain every day? If a caller identified "yes" to questions 1-3 or to question 4, then they were determined to have chronic pain. Further eligibility was checked through VA medical records.

Exclusions targeted medications or medical conditions that could potentially bias measures of HRV or the outcomes, or conditions that would preclude protocol compliance. The following exclusion criteria (assessed by self-report and medical record review) were applied: a) history of arrhythmias requiring medication and/or hospitalization, including supraventricular tachycardia or atrial fibrillation; b) Veterans with a pacemaker or automatic implantable cardioverter-defibrillator; c) history of an acute coronary syndrome, revascularization, thrombolytic or other therapy related to ischemic heart disease; d) uncontrolled hypertension (systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg), however those with well-controlled hypertension with no change in medication in six months were not excluded; e) history of heart transplant or cardiovascular surgery within one year; f) receiving beta-adrenergic antagonists (beta-blockers); g) receiving non-dihydropyridine calcium channel blockers; h) those receiving a renin-angiotensin-aldosterone system antagonist were eligible if medication profile and blood pressure were stable; i) New York Heart Association class 3 or 4 congestive heart failure; j) history of seizure disorder or use of antiseizure or anticonvulsant medication; k) cognitive impairment such as dementia, or a history of acquired neurocognitive deficit, or central nervous system or neurological disorder (e.g., Gulf War Syndrome); l) moderate or severe head injury or stroke; m) evidence of

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active substance abuse or dependence (alcohol or tobacco use was not an exclusion and this data was collected during the questionnaire); n) life history of bipolar, psychotic, panic or obsessive-compulsive disorder (history of depression was not an exclusion).

Upon enrollment, participants signed informed consent and a Health Insurance Portability and Accountability Act (HIPAA) medical release which were kept on file and a copy was provided to the participant with instructions on how to disenroll or contact the Prinicpal Investigator (PI) should they choose to do so. A remuneration of $20 per visit was provided ($200 for completing the protocol). Later, to increase recruitment and retention, supplement funding was provided which included $30 per visit and $10 for travel ($400 max for completing the study).

Randomization

Assignment to either the HRVB treatment or control group was conducted using a permuted block randomization procedure with a block size of 4 and without stratification prior to Baseline Assessment. For example, in each block, permutations could result in six different combinations such as 1-1-2-2, 1-2-2-1, 1-2-1-2, 2-1-2-1, 2-2-1-1, or 2-1-1-2. The treatment assignment was determined before anyone was enrolled and placed in each enrollment packet where it was kept in a confidential location. This was a single-blind study in which only the HRVB trainer knew the group assignment of each participant. Participants were blinded to their group assignment. At the completion of the Follow-up Assessment, those in the control group were made aware that they had not received the intervention

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and were offered a single “cross-over training” as an unpaid training visit to receive the HRVB training just as the intervention group.

Intervention Group Training

HRVB training was conducted by a certified trainer following a previously established, standardized protocol adopted by the Biofeedback Certification Institute of America (BCIA).[4, 181] Participants in the Intervention group completed a Baseline Assessment followed by six weekly training sessions. HRVB training was provided by a trainer on a dual-screen in which both the trainer and the participant could visual HRVB changes in real-time. The trainer informed participants about the connection between resonant frequency breathing and heart rate which was reinforced with coaching to find the resonant frequency of breathing. Each weekly HRVB training session consisted of a 25-minute resting period that included coaching and biofeedback training. Participants were encouraged to “relax” during their training sessions, without using their cell phones or falling asleep. HRVB training involved two main components. The first was to assist the participant to paint a positive mental image of something that truly makes them happy and guide their thoughts to a peaceful, reduced-stress environment. The next portion of the training included instruction to adjust breathing rate and pattern. Participants were taught to perform “belly-breathing” using diaphragmatic breathing, allowing the abdomen to distend to allow for the full use of the diaphragm. Participants were taught to breathe deeply in through the nose and out through pursed lips, using the diaphragm and belly in a manner that the shoulders do not rise and fall. The use of good posture without slouching and the use of transitioning breathing

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between the peak and valley of each breath (inhalation and exhalation) were taught. The trainer coached the participants to slow their breaths to about six breaths per minute, allowing for the synchronization of heart rate oscillations with respiration. This allowed the participant to achieve a state of “HRV coherence”. This state could be directly observed on the biofeedback computer monitor by the participant and the biofeedback coach. The synchronization of the heart rate and breathing was observed as an increase of heart rate oscillations during inhalation and a decrease in heart rate oscillations during exhalation. This is also referred to as zero phase between heart rate and breathing.

For home practice, participants were provided a portable plethysmograph (emWave2® hand-held personal stress reliever, HeartMath, Boulder Creek, CA) or the use of a mobile-application (app) for smart phones (InnerBalance®) of their preference for home practice and use between weekly HRVB training sessions. Participants were encouraged to use this device for at least 15 minutes per day between each weekly training session. Participants were instructed to use the device at times of high-stress such as frustration, when preparing for sleep, or simply when time was available each day. During subsequent training visits, participants were asked how many minutes they practiced on average each day and this self-reported information was documented, and files summarizing practice time were downloaded from the portable emWave and mobile phone app for later analysis.

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Intervention Group Assessments

Four assessments were made. The first was during the baseline visit. The Post-training Assessment was conducted during the 8th week, the Booster Assessment was conducted in the 12th week, and the Follow-up Assessment in week 16. Questionnaire data was obtained first. Next, while participants were seated in a comfortable position, HRV measurements were conducted over a 15-minute resting period using non-stimulating nature scenes without any text, images would change every 40 seconds as participants practiced focusing their attention, resonant frequency breathing, and positive imagery. Third, cognitive testing was conducted followed by saliva collection.

Control Group Training

To control for the laboratory environment or other potential placebo effects, control group participants used the very same training equipment as the intervention group however without any HRVB training. During the weekly training clinic visits, control participants had HRV and respirations recorded for 15 minutes, but no active training, coaching, or biofeedback was provided. Neither heart rate nor breathing information was displayed on the monitor during the control group sessions. Participants were instructed to “relax” without using cell phone or falling asleep. Control-group participants were provided with a stress-squeeze ball to use for home practice. They were encouraged to practice relaxing at home daily for at least 15 minutes and encouraged to use the issued stress-ball while relaxing.

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Control Group Assessments

Control group participants attended the same four Baseline, Post-training, Booster, and Follow-up Assessments with the time separation and duration as the intervention participants. Questionnaire data was collected. During the passive 15-minute HRV recording period, subjects viewed the same static, relaxing nature scenes on the computer monitor as were presented to the HRVB intervention group for assessments. They sat quietly while passively observing non-stimulating nature scenes without any text. These images changed every 40 seconds. Cognitive tests were conducted followed by saliva collection.

HRV Outcomes

Each resting HRV outcome was measured at the four assessments (Baseline, Post-training, Booster, and Follow-up) in a standardized manner. HRV recording was conducted in an office setting with dimmed lights. Nature slides were viewed at each of the assessments during the recording. At baseline, the participants were asked to relax. At subsequent assessments, the participants in the HRVB group were instructed “Do what you have been trained to do”. No other instructions or biofeedback was provided. HRV data was collected with two electrodes to the left forearm and one to the right. Respirations were monitored using a Piezo-respiratory transducer. Both groups completed a 15-minute resting HRV recording with an Acquire ECG encoder.

Inter-Beat Intervals (IBI) files were exported and processed according to established guidelines (Appendix A, Figure A.2).[182] Kubios software (Kuopio,

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Finland) was used to de-artifact raw data and perform a fast Fourier transformation of the HRV power spectrum for each data file. Time-domain HRV measures: mean heart rate, SDNN (standard deviation of heart rate N-N intervals) [54], RMSSD (the square root of the mean squared difference of successive N-N intervals), and frequency-domain variables: (Very Low Frequency (VLF), Low Frequency (LF), High Frequency (HF) power, Total Power, and Coherence Ratio) were calculated. The HRV coherence ratio was obtained by identifying the maximum peak in the 0.04 Hz to 0.26 Hz HRV range, calculating the integral in a window 0.030 Hz wide centered on the highest peak in that region ('peak power', usually ~0.1 Hz), then calculating the total power of the entire spectrum. The HRV Coherence Ratio (as described by McCraty) was quantified as: peak power / (total power – peak power). The frequency range of 0.04-0.26 Hz was selected because it is the range within which HRV coherence (i.e. cardiorespiratory entrainment) occurs.[7, 8, 58, 66]

Questionnaire Outcomes

A structured, self-administered questionnaire was used to obtain sociodemographic (age, race, ethnicity, sex, body mass index, education, income, marital status), and lifestyle information (pain medication use, alcohol, caffeine consumption, tobacco use, circadian preference, employment status) (Appendix Figure A.3.). Information obtained from the patient's medical record included chronic pain condition with diagnosis. Symptoms of: pain (BPI),[183, 184] depression (BDI),[185] stress (PSS),[186] and fatigue (MFI),[170, 172] were obtained at all four assessments. Higher scores on each symptom questionnaire corresponded to

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increased symptom severity. Symptoms were scored in accordance with the original documentation accompanying each instrument.

Pain Outcomes

Pain was assessed using two instruments: Brief Pain Inventory (BPI)[184] and the Pain Catastrophizing Score (PCS).[187] Originally the BPI was designed for cancer patients by the World Health Organization and has since been used in many research and clinic settings.[183, 188] The BPI has been used for its reliability and validity in many languages and used in pain studies.[183, 188] The Brief Pain Index has been validated as an effective gauge for those who have pain related to malignant and nonmalignant disorders.[184, 189] This self-reported questionnaire for pain severity ranges with a pain-free score of 0 to worst pain of 10. Reliability and validity have been demonstrated.[183, 190-192] Negative emotion and physical inactivity are subscales of the BPI.[193] Pain interference was evaluated using the BPI with a scale of 0-10 in which 0 is no interference and 10 complete interference.[184, 194]

Pain was also assessed using the PCS.[187] The PCS explores factors that impact pain through catastrophizing, was developed from literature for catastrophic thinking as it relates to experiencing pain, is written at the sixth-grade level and performed in 5 minutes or less. Thirteen items are summed to provide a total score for the PCS with a range from 0-52. After reflecting on painful experiences, the PCS provides three subscales to assess helplessness, magnification of problems and pain, and rumination. The PCS has been shown to have internal consistency

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with alpha coefficients for total PCS 0.87, rumination 0.87, magnification 0.66, and helplessness 0.78.[187]

Cognitive Outcomes

The PASAT is used to assess processing speed, attention, working memory and is influenced by fatigue[195]. Strongly correlated with education, PASAT has demonstrated repeatability and tends to decrease score with increased age[195]. Standardized options for PASAT exist with 29, 50, or 60 summed pairs[195, 196]. Spoken at three second intervals from a recording, numbers were read aloud. The participant summed the last two spoken numbers provided by the researcher. The total score of correct responses was summed for a maximum score of 29.

The Hopkins Verbal Learning Test-Revised (HVLT-R) is a tool used to measure verbal and working memory as well as executive functioning through immediate and delayed recall of terms.[197] HVLT utilizes a list of words that the participant hears and then repeats when all 12 have been provided verbally. It is scored on a scale of 0-36 in which 0 indicates no correct responses and 36 is the max in which all responses were correct.[197] As noted, the list of words has three themes such as items of clothing, tools, occupations, etc., heard three separate times. At each of the three assessments (Baseline, Post-training, and Follow-Up), the participant is provided a different set of words to recall after hearing them. Visualization of the words is not provided. This test can ascertain immediate recall from an auditory stimulus.

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The Psychomotor Vigilance Test (PVT) is a 10-minute timed test in which a participant reacts to a stimulus on a computer screen. The stimulus varies in time between 2-10 seconds in between the stimuli. The red dot remains on the screen for 1 second[198] and the reaction time is measured in milliseconds. The shorter the reaction time, the faster the response. A response time more than 500ms is a lapse or missed response which may be suggestive of sleep deprivation or inability to sustain concentration.

Depression, Stress, & Fatigue Outcomes

Depression was measured using the Beck Depression Inventory-II (BDI). BDI was established by Beck et al. in the 1960s referencing many psychological publications of the time.[199] This was updated in 1978 as the BDI-IA[200, 201] and in 1996 as the Beck Depression Inventory-II.[200, 201] Normative variables have been established for male military veterans with chronic pain which may assist in assessing those who have more physical complaints than what is considered to be normal and possibly decrease confounding.[201] The BDI is a 21-item self-reported questionnaire to elucidate the severity of depression experienced by the reporter following diagnostic criteria established in 1994 by the Diagnostic and Statistical Manual of Mental Disorders (4th Edition) (DSM-IV).[201] Cutoffs have been standardized: 0–9 indicates normal, 10–18 indicates mild depression, 19–29 indicates moderate depression, and 30–63 indicates severe depression.[202, 203] This test has excellent reliability (Cronbach alpha:0.92),[185] and has been validated to separate depressed from non-depressed individuals.[204] Reported levels in

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depression/mood were assessed at each of the four previously stated assessments through the use of the BDI-II.

Stress was evaluated using the Perceived Stress Scale (PSS).[26, 186] This tool was first developed in 1983[186] has since been adapted for participants to answer questions in a way that causes them to consider different aspects of their lives and qualify how stressful and messy they feel their lives may be. Once a 14-item questionnaire, this questionnaire now has a 10-item negative and 4-item positive component. PSS is a self-reported questionnaire where individuals can rate their stress. Reliability and validity have been demonstrated.[79, 186, 205] Each question is based on a 5-point score ranging from (0) to (4) or "never" to "very often". [206] The PSS has been widely used and has been validated in numerous languages and populations. It presents data representing the degree to which the participant feels out-of-control, feels life is unpredictable, and feels overloaded by external factors.[186] Seven positive items are reverse-scored and then all questions are summed. [186] Reported levels in perceived stress were assessed through the PSS at each of the four previously stated time assessments.

Fatigue was assessed using the Multi-dimensional Fatigue Inventory (MFI). The MFI provides insight to motivation, physical activity, mental and general fatigue. Its 20 questions have demonstrated internal consistency and external validity.[170, 172] Changes in fatigue and energy level were assessed exploring differences in the MFI at each of the previously stated four assessments.

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Statistical Analysis

All statistical analyses were performed using SAS 9.4 (SAS Institute. Inc., Cary NC.) Descriptive characteristics of participants were summarized between intervention and control groups. Analysis included demographic and lifestyle variables comparing between groups using the Student t test for normally distributed continuous variables, the Wilcoxon exact test for non-normally distributed continuous variables or Fisher's exact test of independence for discreet variables. Continuous outcomes were compared between groups. To compare the main outcomes of interest (HRV coherence, PS, PIS, PCS, pain medication usage, PASAT, HVLT, PVT, BDI, PSS, and MFI) with group, time, and group by time interaction, linear mixed models were utilized after adjusting for demographics and/or lifestyle variables.

The process of randomization reduces the possibility of confounding between groups. To ensure this was effective, potential confounders were evaluated to determine if they were equally distributed among the intervention and the control groups. While randomization should remove potential confounding variables, demographic characteristics and outcomes measures were evaluated using bivariate comparisons between the two groups. Comparisons of categorical variables such as gender, race, and income were made between groups of baseline sociodemographic, comorbid health diagnoses, and lifestyle choices using Fisher's Exact test (PROC FREQ in SAS). Due to small cell counts, American Indian and Other races were combined with African American into one category named "Minorities". Normality of distribution of continuous variables such

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as age were evaluated (PROC UNIVARIATE in SAS). As depression can impact other variables such as pain, the BDI was considered *a priori* as a possible confounder for pain outcomes.

To be included in the study, baseline characteristics had to be provided by participants, resulting in limited missing baseline data. Missing data was assumed to be missing-at-random and was therefore ignored. Variables in which less than 10% of the population contributed to one category were removed from the analysis. No veterans in this study were prescribed stimulant medication at baseline and therefore this was not included in the analysis. Sleep apnea was also not diagnosed among participants in this study at baseline and was not included in the analysis. Medication type and frequency of usage was provided by the participant in each of the assessment questionnaires. The following medication classes were included in the analysis: non-steroidal anti-inflammatory drugs (NSAIDs), opioids, over-the-counter pain medications (OTC), musculoskeletal relaxants, sleep aids (sedatives, hypnotics), anxiolytics, and anti-depressants. None of the medications were normally distributed at baseline and therefore were logged and then back transformed for interpretability. The following comorbid diagnosis were found at baseline and included in the analysis: hypertension (HTN), cancer, depression, anxiety, post-traumatic stress disorder (PTSD), chronic headaches, diabetes, metabolic syndrome, and chronic fatigue. These data were gathered from DAVMC medical records.

A repeated measures mixed effects model (PROC MIXED in SAS) was used to evaluate the effects of group (HRVB vs. sham), time, and group by time

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interaction. The following covariance matrices were considered: unstructured (UN), compound symmetric (CS), and heterogeneous compound symmetric (CSH) and the smallest Akaike Information Criterion (AIC) was selected for the final model. In the HRVB intervention group, one-tailed p-values were used for *a priori* directional hypotheses to determine the effectiveness of the HRVB intervention. Based on previous literature, the benefit of HRVB was expected to demonstrate positive effects and a directional change, therefore statistical significance was assessed utilizing one-tailed p-values to interpret results for specific comparisons in the intervention group. As there was no beneficial effect expected in the control group, the use of *a priori* directional hypotheses were not employed and were reported using two-tailed p-values. Pre-determined contrasts were made comparing Baseline Assessment with the Post-training Assessment, and Follow-up Assessment. To assess treatment sustainability, the Post-training Assessment data were compared to the Follow-up Assessment. If baseline variables were statistically significantly different ($p<0.05$), then they were considered as possible confounders. Differing baseline demographic covariates were kept in the final model when the parameter estimates changed by ≥10%. This was applied until all statistically significant differing baseline covariates were checked. Statistically significant covariates were retained in the model without regard to the effect of the parameter estimate.

HRV was compared between groups and assessments using least square (LS) means for the following HRV measures: SDNN, RMSSD, VLF power, LF power, HF power, and HRV Coherence Ratio. Normality was checked using PROC

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UNIVARIATE. As the HRV variables were not normally distributed at baseline, each variable was logged and then back transformed for interpretability. HRV Coherence Ratio was calculated as previously cited by McCraty.[7] In the linear mixed model, with group, time, group by time interaction, the best (lowest) AIC was found using the unstructured (UN) matrix. For the SDNN and RMSSD outcome, the same linear mixed model was used using the heterogeneous compound symmetry (CSH) covariance matrix as it provided the best AIC. For the VLF outcome, the same linear mixed model was used using the UN matrix. And for the LF and HF outcomes, the same linear mixed model was used using compound symmetry (CS) matrix. Results were back-transformed from the logged LS Means Estimates.

Outcomes for all pain variables (PS, PIS, and PCS) were reported using LS Means Estimates using the already described linear mixed model above. The PS outcome was reported using the CSH covariance matrix as it provided the best AIC while adjusting for depression and race. The PIS outcome was reported using the CSH covariance matrix as it provided the best AIC while adjusting for pain interference as PIS was different between groups at baseline. PCS outcome was reported using the CS covariance matrix as it provided the best AIC while adjusting for depression.

The following pain medication variables were assessed: NSAIDs (i.e. piroxicam, meloxicam), opioids (i.e. morphine, oxycodone), OTC (i.e. aspirin, BC powder), musculoskeletal relaxants (i.e. cyclobenzaprine, methocarbamol), sleep aids (i.e. zolpidem, eszopiclone), anxiolytics (i.e. diazepam, alprazolam), and anti-

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depressants (i.e. fluoxetine, paroxetine). None of the pain medication was normally distributed at baseline when assessing using Proc Univariate. All reported medications were log transformed and then back-transformed for interpretability using the same linear mixed model already described. All medication results were reported as the back-transformed logged LS Means Estimates. NSAID outcomes were found to have the best AIC using the CSH covariance matrix. Opioid, OTC, sedatives, musculoskeletal, sleep, and anti-anxiety medications were found to have the best AIC using the CS covariance matrix. Anti-depressant medication outcomes were found to have the best AIC using the UN covariance matrix.

For cognitive outcomes, PASAT and HVLT were assessed using the same linear mixed model, reported as LS Means Estimates, and were found to have the best AIC using the CS matrix while adjusting for race. For the PVT cognitive outcomes (reaction time and lapses), in a review of literature, due to wide ranging results with the mean or median reaction time, multiple authors have recommended using the reciprocal of the mean reaction time.[207-209] Emphasis was placed on the reciprocal of the mean reaction time. Outcomes of the reciprocal mean reaction time were assessed utilizing the same linear mixed models as described above with LS Means Estimates. The best AIC was found using the CSH covariance matrix while adjusting for race and then back-transformed for interpretability. As the number of lapses were not normally distributed, the number of lapses were log transformed using LS Means Estimates and then back-transformed for interpretability. The best AIC was found using the UN covariance matrix while adjusting for race.

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Depression (BDI) outcome was analyzed using the already established linear mixed model and reported using LS Means Estimates. The best AIC was found using the CS covariance matrix while adjusting for baseline depression as they were different between groups at baseline. Stress (PSS) outcome was reported using LS Means Estimates and the best AIC was found using the CSH covariance matrix while adjusting for race and depression. Fatigue (MFI) outcomes were reported using the five subcomponents of fatigue using LS Means Estimates from the already described linear mixed model. General fatigue was reported with the best AIC found using the CS covariance matrix while adjusting for race. Mental fatigue was found to have the best AIC with the CS matrix while adjusting for depression. Physical fatigue was found to have the best AIC using the CS matrix while adjusting for race. Reduced activity was found to have the best AIC using the CS matrix while adjusting for race and pain. Reduced motivation was found to have the best AIC using the CS matrix while adjusting for pain.

To test the effect size of the change in outcome measurements between Baseline to Post-training Assessment and Baseline to Follow-up Assessment, Cohen's D was calculated using the following formula: Cohen's D = (M2-M1)/SD_{pooled}.

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CHAPTER 4

RESULTS

4.1 Overall Characteristic Results

A total of 85 United States military veterans were enrolled in the study, 63 completed the Post-training Assessment, 54 achieved the Booster Assessment, and 50 accomplished the Follow-up Assessment (59% completion). Attrition by intervention group demonstrated no statistically significant differences (Figure A.4, Consort Flow Diagram). Demographic (Table 4.1) and comorbid variables (Table 4.2) at baseline are displayed. Most demographic characteristics were equally proportioned. Participants were mostly male (66%), college educated (73%), and non-smokers (85%) (Table 4.1). Age was similar between groups; the average age (± standard error of the mean) for the HRVB intervention group was 54 ± 11 years and was 55 ± 12 in the control group. Race was the only baseline characteristic that exhibited statistically significant differences between groups (Caucasian: 37% in intervention vs 63% in control group, p=0.04, Table 4.1). Race was viewed as a potential confounder and considered as such in the statistical analyses. The amount of time it took for participants to complete this study due to cancellation of appointments or rescheduling was evaluated within both groups.

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With no missed appointments or rescheduling, the study should have been completed in 112 days. Completion of the study protocol took on average 123 ± 21 days and no statistically significant differences were observed between groups among protocol completers (124 days for intervention group, 121 days for control group, p=0.54, Table 4.1). Evaluation of medical records at baseline was conducted of comorbid diagnoses as possible confounders (Table 4.2) however there were no statistically significant differences in comorbid diseases between the groups. Baseline scores for pain interference, depression (BDI), and race were statistically significantly different between groups. Further analysis was conducted among those who completed the study relative to those who were lost-to-follow-up (LTF). Of the 85 participants in the study, 9 were still active at the time of this analysis, 50 completed the study, and 26 were LTF. The 9 active participants were removed from completion status analysis. Among those who completed the study, the average age in years was 57±9.9 compared to those who were LTF were 50±11.6 (p=0.01, Table 4.14). No other differences in demographics or comorbidities were found between those who completed the study and those who were LTF.

4.2 HRV Results

Least Square Means (LS Means) HRV Coherence Ratios increased between baseline and post-training within the intervention group (0.17 ± 0.02 at baseline versus 0.41 ± 0.07 at post-training, p=<0.01, Table 4.3) and between post-training and follow-up with in the intervention group (0.41 ± 0.07 at post-training versus 0.45 ± 0.08 at follow-up, p=<0.03). The control group did not exhibit

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any improvement between baseline and post-training (0.17 at baseline versus 0.18 post-training, p=0.61) nor post-training to follow-up (0.18 at post-training versus 0.18 at follow-up, p=0.94). Statistical significance was found in the group by timepoint interaction for the HRV Coherence Ratio (p=<0.01). LS Means HRV Coherence Ratios in the intervention group also were elevated at follow-up relative to baseline (0.17 ± 0.02 at baseline versus 0.45 ± 0.08 at follow-up, p=<0.01, Table 4.4). Figure 4.1 displays the HRV Coherence Ratio for each of the timepoints.

LS Means SDNN was found to increase in both groups between baseline and post-training and only in the control group between baseline and follow-up. RMSSD and VLF increased only in the control group between baseline and post-training (Tables 4.3 and 4.4). LF increased in both groups when comparing post-training and follow-up to baseline (Figure 4.2) (Tables 4.3 and 4.4). HF increased in the control group from baseline to post-training (Tables 4.3 and 4.4).

4.3 Pain Results

Decreases in PS were observed among the intervention group while adjusting for race and depression with a reduction at post-training as compared to baseline (5.67 ± 0.25 at baseline versus 5.24 ± 0.27 at post-training, p=0.023, Table 4.5) and decreases were also observed between Baseline and Follow-up Assessment (5.67 ± 0.25 at baseline versus 5.13 ± 0.31 at follow-up, p=0.03, Table 4.6). The group by time interaction also revealed statistically significant findings, p=0.04 (Tables 4.5 and 4.6) and displayed in Figure 4.3.

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Baseline scores for pain interference were statistically significantly different between groups. Decreases in PIS were observed among the intervention group while adjusting for pain at baseline with a reduction at post-training as compared to baseline (5.67 ± 0.19 at baseline versus 4.74 ± 0.24 at post-training, p=<0.01, Table 4.5) and decreases were also observed between Baseline and Follow-up Assessment (5.67 ± 0.19 at baseline versus 4.69 ± 0.37 at follow-up, p=<0.01, Table 4.6). The group by time interaction also revealed statistically significant findings (p=<0.01, Tables 4.5 and 4.6, Figure 4.4).

Decreases for PCS while adjusting for baseline depression were found in both groups from baseline to post-training and baseline follow-up: intervention group (25.56 ± 1.64 at baseline versus at post-training 22.69 ± 1.8, p=0.01 , Table 4.5) and (25.56 ± 1.64 at baseline versus at follow-up 21.00± 1.84, p=<0.01, Table 4.6) whereas for the control group (28.06 ± 1.71 at baseline versus 24.44 ± 1.80 at post-training , p=<0.01 , Table 4.5) and (28.06 ± 1.71 at baseline versus 23.87 ± 1.88 at follow-up, p=<0.01, Table 4.6) However, there was not a statistically significant group by time interaction observed (p=0.58, Table 4.6) and displayed in Figure 4.5.

Reductions in pain medication use were found in NSAIDS for the Intervention group at baseline compared to follow-up and reported in log back-transformed LS Means Estimates (1.35 ± 0.10 at baseline versus 1.12 ± 0.10 at follow-up, p=0.02, Tables 4.7 and 4.8) however was not observed in the group by time interaction (p=0.08, Table 4.8). Results for NSAID use are displayed in Figure 4.6 and for opioid use in Figure 4.7.

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4.4 Cognitive Results

Increases for PASAT score after adjusting for race at baseline were seen in both groups between baseline and follow-up: intervention group (16.9 ± 1.09 at baseline versus 20.29 ± 1.21 at follow-up, p=<0.01, Table 4.10) and control group (18.52 ± 1.07 at baseline versus 21.06 ± 1.14 at follow-up, p=0.01, Table 4.10). There was not a statistically significant group by time interaction observed (p=0.16, Table 4.10). PASAT is displayed in Figure 4.8.

Increases for HVLT after adjusting for race at baseline were seen in both groups between baseline and follow-up: intervention group (23.82 ± 0.79 at baseline versus 26.19 ± 0.93 at follow-up, p=<0.01, Table 4.10) and control group (23.92 ± 0.78 at baseline versus 26.84 ± 0.86 at follow-up, p=<0.01, Table 4.10). However, there was not a statistically significant group by time interaction observed (p=0.89, Table 4.10). HVLT is displayed in Figure 4.9.

Decrease in the back-transformed reciprocal mean reaction time while adjusting for race at baseline was observed in the intervention group between baseline and follow-up (431.59± 17.32 at baseline versus 407.50 ± 17.71 at follow-up, p=0.04, Table 4.10). However, there was not a statistically significant group by time interaction observed (p=0.90, Table 4.10). Reaction time is displayed in Figure 4.10.

Decrease in the back-transformed logged number of lapses while adjusting for race at baseline were seen in both groups between baseline and follow-up: intervention group (9.056 ± 1.16 at baseline versus 6.05 ± 1.19 at follow-up,

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p=<0.01, Table 4.10) and control group (9.054 ± 1.16 at baseline versus 6.46 ± 1.18 at follow-up, p=0.01, Table 4.10). However, there was not a statistically significant group by time interaction observed (p=0.79, Table 4.10). Number of lapses is displayed in Figure 4.11.

4.5 Depression, Stress, and Fatigue Results

Baseline scores for depression (BDI) were statistically significantly different between groups. Decrease in the BDI while adjusting for depression at baseline was found in the intervention group from baseline and post-training (21.9 ± 1.04 at baseline versus 17.66 ± 1.22 at post-training, p=<0.01, Table 4.11) and baseline to follow-up (21.9 ± 1.04 at baseline versus 16.30 ± 1.34 at follow-up, p=<0.01, Table 4.12). There was a statistically significant group by time interaction observed (p=0.03, Table 4.12). BDI is displayed in Figure 4.12.

PSS did not result in any statistically significant results while adjusting for baseline depression for either group when comparing baseline to post-training and when comparing baseline to follow-up (Tables 4.11 and 4.12). There was no statistically significant group by time interaction observed (p=0.76, 4.12). PSS is displayed in Figure 4.13.

Adjustments were made for the five categories of fatigue: General fatigue was adjusted for baseline race, mental fatigue was adjusted for baseline depression, physical fatigue was adjusted for baseline race, reduced activity was adjusted for baseline race and pain, and reduced motivation was adjusted for baseline pain. Among all of these, there were no statistically significant

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improvements for either group and no statistically significant group by time interactions. However, for the control group, there was a reported worsening of symptoms in physical fatigue with an increase from baseline to post-training (12.42 ± 0.31 at baseline versus 13.39 ± 0.35 at post-training, p=0.02, Table 4.11). General fatigue (Figure 4.14), mental fatigue (Figure 4.15), physical fatigue (Figure 4.16), reduced activity (Figure 4.17), and reduced motivation (Figure 4.18) are displayed.

Post-hoc analysis was conducted as concern for possible over-adjusting of baseline differences of dependent variable outcomes. For example, both depression and pain interference differed at baseline and were originally adjusted in the linear mixed models. When using the CSH matrix, pain interference was reanalyzed using a linear mixed model without adjusting for baseline differences. In the intervention group, comparing baseline to post-training (6.95 ± 0.35 at baseline vs 6.05 ± 0.40 post-training, p=<0.01) and baseline to follow-up (6.95 ± 0.35 at baseline vs 5.95 ± 0.46, p=<0.01) and in the control group comparing baseline to post-training (5.95 ± 0.36 at baseline vs 5.69 ± 0.40 post-training, p=0.39) and baseline to follow-up (5.95 ± 0.36 at baseline vs 5.76 ± 0.46, p=0.58).

Further analyses were performed for unadjusted depression using a CS matrix and a linear mixed model without adjusting for baseline differences. In the intervention group comparing baseline to post-training (23.95 ± 1.91 at baseline vs 20.09 ± 2.05 post-training, p=<0.01) and baseline to follow-up (23.95 ± 1.91 at baseline vs 18.59 ± 2.13 at follow-up, p=<0.01) and in the control group comparing baseline to post-training (18.41 ± 1.97 at baseline vs 18.20 ± 2.07 post-training,

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p=0.88) and baseline to follow-up (18.41 ± 1.97 at baseline vs 17.35 ± 2.17, p=0.49).

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Table 4.1. Demographics

	Total (n=85)	HRVB (n=44)	Control (n=41)	p-value
Age (years± SD)	54 ± 11	54 ± 11	55 ± 12	0.65
Gender n (%)				0.57
F (%)	28 (33)	15(34)	13 (32)	
M (%)	56(66)	29 (66)	27 (66)	
Race				0.04
Minorities (%)	53 (62)	32 (73)	21 (51)	
Caucasian (%)	32 (38)	12 (27)	20 (49)	
Education				0.65
Less Than College	23 (27)	10 (23)	13 (32)	
College	51 (60)	28 (63)	23 (56)	
Graduate School	11 (13)	6 (14)	5 (12)	
Income				0.66
Under $30,000	33 (39)	15 (34)	18 (44)	
$30,000-50,000	17 (20)	8 (18)	9 (22)	
$50,001 or more	30 (35)	18 (41)	12 (29)	
Refused	4 (5)	2 (5)	2 (5)	
Don't know	1 (1)	1 (2)	0 (0)	
Current Smoke				
Yes	13 (15)	6 (14)	7 (17)	0.66
No	72 (85)	38 (86)	34 (83)	
Smoke Cigarette Ever				0.63
Yes	35 (41)	18 (41)	17 (41)	
No	45 (53)	24 (55)	21 (51)	
Don't Know	1 (1)	1 (2)	0 (0)	
Missing	4	1 (2)	2	
Study Completion in Days ± SD	123 ± 21	124 ± 18	121 ± 23	0.54

Fisher's exact Test (2-sided) and Mantel-Haenszel Chi-Square used for categorical variables. Pooled T-test used for continuous variables. F: Female. M: Male. SD: Standard Deviation. Study Completion in Days: Total days to complete study from Baseline visit to completion of Follow-up Assessment.

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Table 4.2. Comorbidities at Baseline by Group

	Overall (n=85)	Intervention (n=44)	Control (n=41)	p-value
Hypertension				0.38
Yes (%)	38 (45)	22 (50)	16 (39)	
No (%)	47 (55)	22 (50)	25 (61)	
Cancer				0.92
Yes (%)	8 (9)	4 (9)	4 (10)	
No (%)	77 (91)	40 (91)	37 (90)	
Depression				0.91
Yes (%)	42 (49)	22 (50)	20 (49)	
No (%)	43 (51)	22 (50)	21 (51)	
Anxiety				0.26
Yes (%)	19 (22)	12 (27)	7 (17)	
No (%)	66 (78)	32 (73)	34 (83)	
PTSD				0.98
Yes (%)	31 (36)	16 (36)	15 (37)	
No (%)	54 (64)	28 (64)	26 (63)	
Diabetes				0.45
Yes (%)	24 (28)	14 (32)	10 (24)	
No (%)	61 (72)	30 (68)	31 (76)	

Fisher's exact Test (2-sided) and Mantel-Haenszel Chi-Square used for categorical variables. Pooled T-test used for continuous variables. F: Female. M: Male. SD: Standard Deviation. Study Completion in Days: Total days to complete study from Baseline visit to completion of Follow-up Assessment. PTSD: Post Traumatic Stress Disorder.

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Table 4.3: Mixed Model Analysis of HRV Outcomes Comparing Baseline vs. Post-training Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Post-Training (T2) Est μ± SE	n	Est. T2-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
HRV Coherence Ratio	A	0.17 ± 0.02	43	0.41 ± 0.07	31	*0.24 ± 0.08 (4.59, <0.01[c])*	(20.27, <0.01)
	B	0.17 ± 0.02	41	0.18 ± 0.03	32	*0.01 ± 0.17 (0.51, 0.61[d])*	(6.62, <0.01)
	Est A-B±SE (t, p)	*0.01 ± 0.16 (0.22, 0.82[a])*	*84*	*0.23 ± 0.11 (3.30, <0.01[b])*	*63*	n/a	(5.95, <0.01)
SDNN	A	27.5 ± 2.22	43	31.7 ± 3.24	31	*4.2 ± 0.08 (-1.63, 0.05[c])*	(0.45, 0.51)
	B	27.9 ± 2.31	41	37.6 ± 3.84	32	*9.7 ± 0.06 (-3.40, <0.01[d])*	(4.88, <0.01)
	Est A-B±SE (t, p)	*-0.4 ± 0.1 (0.13, 0.89[a])*	*84*	*-5.9 ± 0.17 (-1.18, 0.12[b])*	*63*	n/a	(0.61, 0.61)
RMSSD	A	16.9 ± 1.74	43	17.2 ± 2.32	31	*0.3 ± 0.11 (-0.18, 0.43[c])*	(0.68, 0.41)
	B	16.7 ± 1.76	41	23.4 ± 3.16	32	*6.7 ± 0.08 (-2.96, <0.01[d])*	(1.75, 0.16)
	Est A-B±SE (t, p)	*0.2* ± 0.11 *(-0.07, 0.94[a])*	*84*	-6.2 ± 0.26 (1.61, 0.05[b])	*63*	n/a	(1.51, 0.21)
VLF Power	A	265.0 ± 46.7	43	230.0 ± 46.6	31	*-35.0 ± 0.24 (0.66, 0.25[c])*	(4.65, 0.03)
	B	259.0 ± 46.9	41	429.0 ± 86.2	32	*170.0 ± 0.12 (-2.46, 0.02[d])*	(0.86,0.46)
	Est A-B±SE (t, p)	*6.0* ± 0.25 *(-0.08, 0.94[a])*	*84*	-199.0 ± 0.52 (-2.18, 0.02[b])	*63*	n/a	(4.48, <0.01)

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Table 4.3: Mixed Model Analysis of HRV Outcomes Comparing Baseline vs. Post-training Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Post-training (T2) Est μ± SE	n	Est. T2-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
LF Power	A	167.6 ± 36.8	43	442.5 ± 106	31	*274.9 ± 0.08 (-4.34, <0.01[c])*	(1.05, 0.31)
	B	170.3 ± 37.3	41	309.4 ± 74	32	*139.1 ± 0.12 (-2.69, <0.01[d])*	(11.36, <0.01)
	Est A-B±SE (t, p)	-2.7 ± 0.31 *(-0.05, 0.96[a])*	*84*	133.1 ± 0.24 (-1.06, 0.29[b])	*63*	n/a	(0.77, 0.51)
HF Power	A	81.1 ± 18.8	43	70.4 ± 17.8	31	*-10.7 ± 0.27 (0.61, 0.27[c])*	(1.61, 0.21)
	B	85.1 ± 20.2	41	155.9 ± 40.1	32	*70.8 ± 0.13 (-2.6, 0.01[d])*	(0.74, 0.53)
	Est A-B±SE (t, p)	*-4.0 ± 0.35 (0.15, 0.89[a])*	*84*	-85.5 ± 0.81 (2.19, 0.02[b])	*63*	n/a	(1.93, 0.13)

LS-Means estimates displayed as mean. Larger scores represent greater HRV Coherence SDNN: Standard Deviation of the Normal to Normal in milliseconds (ms). RMSSD: Root Mean Square of the Successive Differences in ms. VLF Power: Very Low Frequency Power in ms^2. LF Power: Low Frequency Power in ms^2. HF Power: High Frequency Power in ms^2. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Post-training Assessment. [d]2-sided comparison between Baseline Assessment and Post-training Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T2: Timepoint 2. t: test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided).

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Table 4.4: Mixed Model Analysis of HRV Outcomes Comparing Baseline vs. Follow-up Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Follow-up (T4) Est μ± SE	n	Est. T4-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
HRV Coherence Ratio	A	0.17 ± 0.02	43	0.45 ± 0.08	25	*0.28 ± 0.07 (-5.25, <0.01[c])*	(20.27, <0.01)
	B	0.17 ± 0.02	41	0.19 ± 0.03	25	*0.02 ± 0.16 (-0.60, 0.55[d])*	(6.62, <0.01)
	Est A-B±SE (t, p)	*0.01 ± 0.16 (-0.22, 0.82[a])*	*84*	*0.26 ± 0.10 (-3.75, <0.01[b])*	*50*	n/a	(5.95, <0.01)
SDNN	A	27.5 ± 2.22	43	31.1 ± 3.79	25	3.6 ± 0.09 (-1.18, 0.12[c])	(0.45, 0.51)
	B	27.9 ± 2.31	41	34.8 ± 4.27	25	*7 ± 0.08 (-2.09, 0.04[d])*	(4.88, <0.01)
	Est A-B±SE (t, p)	*-0.4 ± 0.1 (0.13, 0.89[a])*	*84*	-3.7 ± 0.19 (0.65, 0.26[b])	*50*	n/a	(0.61, 0.61)
RMSSD	A	16.9 ± 1.74	43	16.25 ± 1.93	25	*-0.65 ± 0.11 (0.36, 0.36[c])*	(0.68, 0.41)
	B	16.7 ± 1.76	41	18.96 ± 2.27	25	*2.26 ± 0.10 (-1.13, 0.26[d])*	(1.75, 0.16)
	Est A-B±SE (t, p)	*0.2* ± 0.11 *(-0.07, 0.94[a])*	*84*	-2.71 ± 0.20 (0.91, 0.18[b])	*50*	n/a	(1.51, 0.21)
VLF Power	A	265.0 ± 46.7	43	210.0 ± 55.7	25	*-54.0 ± 0.32 (0.9, 0.18[c])*	(4.65, 0.03)
	B	259.0 ± 46.9	41	408.0 ± 109	25	*154.0 ± 0.16 (-1.77, 0.08[d])*	(0.86,0.46)
	Est A-B±SE (t, p)	*6.0* ± 0.25 *(-0.08, 0.94[a])*	*84*	-198.0 ± 0.73 (1.77, 0.04[b])	*50*	n/a	(4.48, <0.01)

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Table 4.4: Mixed Model Analysis of HRV Outcomes Comparing Baseline vs. Follow-up Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Post-training (T4) Est μ± SE	n	Est. T4-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
LF Power	A	167.6 ± 36.8	43	427.8 ± 109.8	25	*260.2 ± 0.09 (-3.88, <0.01[c])*	(1.05, 0.31)
	B	170.3 ± 37.3	41	279.2 ± 72.1	25	*108.9 ± 0.15 (-2.04, 0.04[d])*	(11.36, <0.01)
	Est A-B±SE (t, p)	-2.7 ± 0.31 *(-0.05, 0.96[a])*	*84*	148.6 ± 0.24 (-1.17, 0.12[b])	*50*	n/a	(0.77, 0.51)
HF Power	A	81.1 ± 18.8	43	68.1 ± 18.7	25	*-13.0 ± 0.27 (0.61, 0.27[c])*	(1.61, 0.21)
	B	85.1 ± 20.2	41	109.0 ± 30.1	25	*23.9* ± 0.20 *(-0.97, 0.33)*	(0.74, 0.53)
	Est A-B±SE (t, p)	*-4.0 ± 0.35 (0.15, 0.88[a])*	*84*	*-40.9 ±0.62 (1.21, 0.11[b])*	*50*	n/a	(1.93, 0.13)

LS-Means estimates displayed as mean. Larger scores represent greater HRV Coherence SDNN: Standard Deviation of the Normal to Normal measured in milliseconds (ms). RMSSD: Root Mean Square of the Successive Differences in ms. VLF Power: Very Low Frequency Power in ms^2. LF Power: Low Frequency Power in ms^2. HF Power: High Frequency Power in ms^2. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Follow-up Assessment. [d]2-sided comparison between Baseline Assessment and Follow-up Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T4: Timepoint 4. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided).

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Table 4.5: Mixed Model Analysis of Pain Outcomes Comparing Baseline vs. Post-Training Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Post-Training (T2) Est μ± SE	n	Est. T2-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
Pain Severity Score#	A	5.67 ± 0.25	44	5.24 ± 0.27	31	*0.43 ± 0.21 (2.02, 0.02[c])*	(4.90, 0.03)
	B	5.93 ± 0.25	41	5.72 ± 0.26	32	*0.21 ± 0.21 (0.99, 0.32[d])*	(1.68, 0.18)
	Est A-B±SE (t, p)	*0.26 ± 0.36 (0.73, 0.47[a])*	*85*	*0.48 ± 0.38 (1.27, 0.21[a])*	*63*	n/a	(2.91, 0.04)
Pain Interference Score^	A	5.67 ± 0.19	44	4.74 ± 0.24	31	*0.93 ± 0.26 (3.53, <0.01[c])*	(5.77, 0.02)
	B	5.59 ± 0.18	41	5.33 ± 0.23	32	*0.26 ± 0.26 (0.98, 0.33[d])*	(3.74, 0.01)
	Est A-B±SE (t, p)	*-0.08 ± 0.25 (-0.31, 0.76[a])*	*85*	*0.59 ± 0.33 (1.81, 0.07[a])*	*63*	n/a	(4.40, <0.01)
Pain Catastrophizing Scale*	A	25.56 ± 1.6	44	22.69 ± 1.8	31	*2.87 ± 1.23 (2.34, 0.01[c])*	(1.55, 0.22)
	B	28.06 ± 2	41	24.44 ± 1.8	32	*3.62 ± 1.22 (2.98, <0.01[d])*	(9.52, <0.01)
	Est A-B±SE (t, p)	*2.49 ± 2.40 (1.04, 0.30[a])*	*85*	*1.75 ± 2.55 (0.68, 0.49[a])*	*63*	n/a	(0.66, 0.58)

LS-Means estimates displayed as means. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Post-training Assessment. [d]2-sided comparison between Baseline Assessment and Post-training Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T2: Timepoint 2. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided). *Adjusted for baseline depression. ^Adjusted for baseline pain. #Adjusted for baseline race and depression.

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Table 4.6: Mixed Model Analysis of Pain Outcomes Comparing Baseline vs. Follow-Up Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Follow-Up (T4) Est μ± SE	n	Est. T4-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
Pain Severity Score#	A	5.67 ± 0.25	44	5.13 ± 0.31	25	*-0.54 ± 0.28 (1.89, 0.03[c])*	(4.90, 0.03)
	B	5.93 ± 0.25	41	6.04 ± 0.30	25	*0.11 ± 0.28 (-0.41, 0.68[d])*	(1.68, 0.18)
	Est A-B±SE (t, p)	*-0.26 ± 0.36 (0.73, 0.47[a])*	*85*	*-0.91 ± 0.43 (2.11, 0.037[a])*	*50*	n/a	(2.91, 0.04)
Pain Interference Score^	A	5.67 ± 0.19	44	4.69 ± 0.37	25	*-0.98 ± 0.37 (2.65, <0.01[c])*	(5.77, 0.02)
	B	5.59 ± 0.18	41	5.40 ± 0.37	25	*-0.19 ± 0.37 (0.50, 0.62[d])*	(3.74, 0.01)
	Est A-B±SE (t, p)	*-0.08 ± 0.25 (-0.31, 0.76[a])*	*85*	*-0.71 ± 0.52 (1.38, 0.17[a])*	*50*	n/a	(4.40, <0.01)
Pain Catastrophizing Scale*	A	25.56 ± 1.64	44	21.00 ± 1.84	25	*-4.56 ± 1.33 (3.44, <0.01[c])*	(1.55, 0.22)
	B	28.06 ± 1.71	41	23.87 ± 1.88	25	*-4.19 ± 1.33 (3.15, <0.01[d])*	(9.52, <0.01)
	Est A-B±SE (t, p)	*-2.50 ± 2.40 (1.04, 0.30[a])*	*85*	*-2.87 ± 2.66 (1.08, 0.28[a])*	*50*	n/a	(0.66, 0.58)

LS-Means estimates displayed as means. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Follow-up Assessment. [d]2-sided comparison between Baseline Assessment and Follow-up Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T4: Timepoint 4. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided). *Adjusted for baseline depression. ^Adjusted for baseline pain. #Adjusted for baseline race and depression.

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Table 4.7: Mixed Model Analysis of Pain Outcomes Comparing Baseline vs. Post-training Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Post-Training (T2) Est μ± SE	n	Est. T2-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
Opioid	A	1.33 ± 0.11	43	1.42 ± 0.14	31	*0.09 ± 0.09 (0.64, 0.26[c])*	(0.01, 0.92)
	B	1.31 ± 0.35	41	1.35 ± 0.13	32	*0.04 ± 0.11 (0.41, 0.68[d])*	(1.17, 0.32)
	Est A-B±SE (t, p)	*0.02 ± 0.11 (0.17, 0.86[a])*	*84*	*0.07 ± 0.13 (0.34, 0.73[b])*	*63*	n/a	(0.72, 0.54)
Non-steroidal anti-inflammatory drug	A	1.35 ± 0.10	43	1.21 ± 0.11	31	*-0.14 ± 0.10 (1.28, 0.10[c])*	(2.43, 0.12)
	B	1.32 ± 0.10	41	1.51 ± 0.14	32	*0.19 ± 0.08 (1.51, 0.13[d])*	(2.16, 0.09)
	Est A-B±SE (t, p)	*0.03 ± 0.11 (0.22, 0.83[a])*	*84*	*-0.3 ± 0.16 (1.77, 0.04[b])*	*63*	n/a	(2.27, 0.08)
Over-the-counter	A	2.60 ± 0.33	43	2.43 ± 0.35	31	*-0.17 ± 0.15 (0.48, 0.32[c])*	(0.09, 0.77)
	B	2.72 ± 0.36	41	2.25 ± 0.33	32	*-0.47 ± 0.17 (1.35, 0.18[d])*	(0.89, 0.45)
	Est A-B±SE (t, p)	*-0.12* ± 0.19 *(0.24, 0.81[a])*	*84*	0.18 ± 0.17 (1.35, 0.09[b])	*63*	n/a	(0.88, 0.45)
Musculoskeletal	A	1.64 ± 0.15	43	1.80 ± 0.19	31	*0.16 ± 0.2 (-0.66, 0.26[c])*	(1.77, 0.19)
	B	1.47 ± 0.14	41	1.29 ± 0.13	32	*-0.18 ± 0.1 (2.42, <0.01[d])*	(0.07, 0.98)
	Est A-B±SE (t, p)	*0.17* ± 0.12 *(0.84, 0.40[a])*	*84*	0.51 ± 0.11 (2.28, 0.01[b])	*63*	n/a	(1.35,0.26)

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Table 4.7: Mixed Model Analysis of Pain Outcomes Comparing Baseline vs. Post-training Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Post-training (T2) Est μ± SE	n	Est. T2-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
Sleep	A	1.15 ± 0.07	43	1.27 ± 0.09	31	*0.12 ± 0.07 (1.38, 0.08[c])*	(0.03, 0.86)
	B	1.19 ± 0.07	41	1.02 ± 0.07	32	*-0.17 ± 0.08 (0.14, 0.89[d])*	(0.91, 0.44)
	Est A-B±SE (t, p)	-0.04 ± 0.09 *(0.39, 0.70[a])*	*84*	0.25 ± 0.10 (0.06, 0.48[b])	*63*	n/a	(0.07, 0.98)
Anti-Anxiety	A	1.44 ± 0.15	43	1.63 ± 0.19	31	*0.19 ± 0.08 (1.29, 0.10[c])*	(3.45, 0.07)
	B	1.76 ± 0.19	41	1.94 ± 0.22	32	*0.18 ± 0.08 (1.06, 0.29[d])*	(1.32, 0.27)
	Est A-B±SE (t, p)	*-0.32 ± 0.18 (1.33, 0.18[a])*	*84*	-0.31 ± 0.20 (1.09, 0.14[b])	*63*	n/a	(0.65, 0.59)
Anti-depressant	A	1.50 ± 0.12	43	1.48 ± 0.13	31	*-0.02 ± 0.09 (0.10, 0.46[c])*	(0.28, 0.60)
	B	1.31 ± 0.11	41	1.28 ± 0.12	32	*-0.03 ± 0.09 (0.28, 0.78[d])*	(0.15, 0.93)
	Est A-B±SE (t, p)	*0.19 ± 0.002 (1.13, 0.26[a])*	*84*	0.20 ± 0.11 (1.15, 0.13[b])	*63*	n/a	(1.37, 0.26)

Back-transformed logged LS-Means estimates of number of pills per day. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Post-training Assessment. [d]2-sided comparison between Baseline Assessment and Post-training Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T2: Timepoint 2. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided).

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Table 4.8: Mixed Model Analysis of Pain Outcomes Comparing Baseline vs. Follow-up Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Follow-up (T4) Est μ± SE	n	Est. T4-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
Opioid	A	1.33 ± 0.11	43	1.30 ± 0.13	25	*-0.03 ± 0.11 (0.28, 0.39[c])*	(0.01, 0.92)
	B	1.31 ± 0.35	41	1.25 ± 0.13	25	*-0.06 ± 0.11 (0.41, 0.68[d])*	(1.17, 0.32)
	Est A-B±SE (t, p)	*0.02 ± 0.11 (0.17, 0.86[a])*	*84*	*0.05 ± 0.15 (0.24, <0.41[b])*	*50*	n/a	(0.72, 0.54)
Non-steroidal anti-inflammatory drug	A	1.35 ± 0.10	43	1.12 ± 0.10	25	*-0.23 ± 0.11 (2.16, 0.02[c])*	(2.43, 0.12)
	B	1.32 ± 0.10	41	1.45 ± 0.12	25	*0.13 ± 0.09 (1.01, 0.31[d])*	(2.16, 0.09)
	Est A-B±SE (t, p)	*0.03 ± 0.11 (0.22, 0.83[a])*	*84*	-0.33 ± 0.2 (-1.15, 0.13[b])	*50*	n/a	(2.27, 0.08)
Over-the-counter	A	2.60 ± 0.33	43	2.28 ± 0.36	25	*-0.32 ± 0.17 (0.87, 0.19[c])*	(0.09, 0.77)
	B	2.72 ± 0.36	41	2.47 ± 0.39	25	*-0.25 ± 0.17 (0.64, 0.53[d])*	(0.89, 0.45)
	Est A-B±SE (t, p)	*-0.12* ± 0.19 *(0.24, 0.81[a])*	*84*	-0.19 ± 0.24 (0.36, 0.36[b])	*50*	n/a	(0.88, 0.45)
Musculoskeletal	A	1.64 ± 0.15	43	1.62 ± 0.18	25	*-0.02 ± 0.11 (0.12, 0.45[c])*	(1.77, 0.19)
	B	1.47 ± 0.14	41	1.46 ± 0.16	25	*-0.01 ± 0.11 (0.02, 0.98[d])*	(0.07, 0.98)
	Est A-B±SE (t, p)	*0.17* ± 0.12 *(0.84, 0.40[a])*	*84*	0.16 ± 014 (0.64, 0.26[b])	*50*	n/a	(1.37, 0.26)

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Table 4.8: Mixed Model Analysis of Pain Outcomes Comparing Baseline vs. Follow-up Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Follow-up (T4) Est μ± SE	n	Est. T4-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
Sleep	A	1.15 ± 0.07	43	1.17 ± 0.09	25	*0.02 ± 0.08 (0.26, 0.40[c])*	(0.03, 0.86)
	B	1.19 ± 0.07	41	1.20 ± 0.09	25	*0.01 ± 0.08 (0.14, 0.89[d])*	(0.91, 0.44)
	Est A-B±SE (t, p)	-0.04 ± 0.09 *(0.39, 0.70[a])*	*84*	-0.03 ± 011 (0.23, 0.41[b])	*50*	n/a	(0.07, 0.98)
Anti-anxiety	A	1.44 ± 0.15	43	1.35 ± 0.16	25	*-0.09 ± 0.11 (0.65, 0.26[c])*	(3.45, 0.07)
	B	1.76 ± 0.19	41	1.84 ± 0.23	25	*0.08* ± 0.10 *(0.44, 0.66[d])*	(1.32, 0.27)
	Est A-B±SE (t, p)	*-0.32 ± 0.18 (1.33, 0.18[a]))*	*84*	*-0.49 ±0.24 (1.81, 0.07)*	*50*	n/a	(0.65, 0.59)
Anti-depressant	A	1.50 ± 0.12	43	1.33 ± 0.14	25	*-0.17 ± 0.12 (1.12, 0.13[c])*	(0.28, 0.60)
	B	1.31 ± 0.11	41	1.47 ± 0.15	25	*0.16 ± 0.10 (1.01, 0.31[d])*	(0.15, 0.93)
	Est A-B±SE (t, p)	*0.19 ± 0.002 (1.13, 0.26[a])*	*84*	-0.14 ± 0.16 (0.70, 0.48[b])	*50*	n/a	(1.37, 0.26)

Back-transformed logged LS-Means estimates of number of pills per day. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Follow-up Assessment. [d]2-sided comparison between Baseline Assessment and Follow-up Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T4: Timepoint 4. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided).

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Table 4.9: Mixed Model Analysis of Cognitive Variables Comparing Baseline vs. Post-Training Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Post-Training (T2) Est μ± SE	n	Est. T2-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
PASAT+	A	16.9 ± 1.09	44	18.04 ± 1.19	31	*1.14 ± 0.91 (-1.25, 0.11[c])*	(0.22, 0.64)
	B	18.52 ± 1.07	41	17.37 ± 1.14	32	*-1.15 ± 0.90 (1.28, 0.20[d])*	(11.75, <0.01)
	Est A-B±SE (t, p)	*-1.62 ± 1.53 (1.06, 0.29[a])*	*85*	*0.67 ± 1.65 (-0.4, 0.69[a])*	*63*	n/a	(1.90, 0.16)
HVLT+	A	23.82 ± 0.79	44	24.99 ± 0.90	31	*1.17 ± 0.84 (-1.39, 0.09[c])*	(0.10, <0.75)
	B	23.92 ± 0.78	41	25.16 ± 0.86	32	*1.24 ± 0.83 (-1.50, 0.14[d])*	(8.84, <0.01)
	Est A-B±SE (t, p)	*-0.10 ± 1.11 (0.09, 0.93[a])*	*85*	*-0.17 ± 1.24 (0.14, 0.89[a])*	*63*	n/a	(0.12, 0.89)

LS-Means estimates displayed as means. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Post-training Assessment. [d]2-sided comparison between Baseline Assessment and Post-training Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T2: Timepoint 2. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided). *Adjusted for baseline depression. ^Adjusted for baseline pain. +Adjusted for baseline race. #Adjusted for baseline race and depression. § Adjusted for baseline race and pain.

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Table 4.9: Mixed Model Analysis of Cognitive Variables Comparing Baseline vs. Post-Training Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Post-Training (T2) Est μ± SE	n	Est. T2-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
Mean Reaction Time+	A	431.59 ± 17.32	44	416.32 ± 17.85	31	*-15.27 ± 0.53 (-1.15, 0.13[c])*	(0.04, 0.84)
	B	431.22 ± 16.74	41	423.37 ± 17.39	31	*-7.85 ± 0.65 (-0.60, 0.55[d])*	(2.37, 0.11)
	Est A-B±SE (t, p)	*0.37 ± 0.58 (0.01, 0.99[a])*	*85*	*-7.05 ± 0.46 (-0.28, 0.78[a])*	*62*	n/a	(0.11, 0.90)
Lapses+	A	9.056 ± 1.164	43	8.04 ± 1.18	31	*-1.016 ± 0.016 (1.00, 0.16[c])*	(0.03, 0.85)
	B	9.054 ± 1.161	41	8.004 ± 1.17	31	*-1.05 ± 0.009 (1.46, 0.15[d])*	(9.19, <0.01)
	Est A-B±SE (t, p)	*0.002 ± 0.003 (0.24, 0.81[a])*	*84*	*0.036 ± 0.01 (-0.02, 0.98[a])*	*62*	n/a	(0.23, 0.79)

Reaction time LS-Means estimates displayed in milliseconds (ms). Back-transformed logged number of lapses displayed. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Post-training Assessment. [d]2-sided comparison between Baseline Assessment and Post-training Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T2: Timepoint 2. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided). *Adjusted for baseline depression. ^Adjusted for baseline pain. +Adjusted for baseline race. #Adjusted for baseline race and depression. § Adjusted for baseline race and pain.

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Table 4.10: Mixed Model Analysis of Cognitive Variables Comparing Baseline vs. Follow-Up Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Post-Training (T4) Est μ± SE	n	Est. T4-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
PASAT+	A	16.9 ± 1.09	44	20.29 ± 1.21	25	*3.39 ± 0.94 (-3.60, <0.01[c])*	(0.22, 0.64)
	B	18.52 ± 1.07	41	21.06 ± 1.14	25	*2.54 ± 0.94 (-2.51, 0.01[d])*	(11.75, <0.01)
	Est A-B±SE (t, p)	*-1.62 ± 1.53 (1.06, 0.29[a])*	*85*	*-0.77 ± 1.68 (0.46, 0.65[a])*	*50*	n/a	(1.90, 0.16)
HVLT+	A	23.82 ± 0.79	44	26.19 ± 0.93	25	*2.37 ± 0.88 (-2.69, <0.01[c])*	(0.10, <0.75)
	B	23.92 ± 0.78	41	26.84 ± 0.86	25	*2.92 ± 0.88 (-3.21, <0.01[d])*	(8.84, <0.01)
	Est A-B±SE (t, p)	*-0.10 ± 1.11 (0.09, 0.93[a])*	*85*	*-0.65 ± 1.29 (0.51, 0.61[a])*	*50*	n/a	(0.12, 0.89)

LS-Means estimates displayed as means. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Follow-up Assessment. [d]2-sided comparison between Baseline Assessment and Follow-up Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T4: Timepoint 4. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided). *Adjusted for baseline depression. ^Adjusted for baseline pain. +Adjusted for baseline race. #Adjusted for baseline race and depression. § Adjusted for baseline race and pain.

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Table 4.10: Mixed Model Analysis of Cognitive Variables Comparing Baseline vs. Follow-Up Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Post-Training (T4) Est μ± SE	n	Est. T4-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
Mean Reaction Time+	A	431.59 ± 17.32	44	407.50 ± 17.71	25	*-24.09 ± 0.39 (-1.78, 0.04[c])*	(0.04, 0.84)
	B	431.22 ± 16.74	41	413.91 ± 17.82	25	*-17.31 ± 1.08 (-1.26, 0.22[d])*	(2.37, 0.11)
	Est A-B±SE (t, p)	*0.37 ± 0.58 (0.01, 0.99[a])*	*85*	*-6.41± 0.11 (-0.26, 0.80[a])*	*50*	n/a	(0.11, 0.90)
Lapses+	A	9.056 ± 1.164	43	6.05 ± 1.19	25	*-3.006 ± 0.026 (2.71, <0.01[c])*	(0.03, 0.85)
	B	9.054 ± 1.161	41	6.46 ± 1.18	25	*0.39 ± 0.16 (2.50, 0.01[d])*	(9.19, <0.01)
	Est A-B±SE (t, p)	*0.002 ± 0.003 (0.24, 0.81[a])*	*84*	*-0.41 ± 0.01 (0.28, 0.78[a])*	*50*	n/a	(0.23, 0.79)

Reaction time LS-Means estimates displayed in milliseconds (ms). Back-transformed logged number of lapses displayed. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and follow-up. [d]2-sided comparison between Baseline Assessment and Follow-up Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T4: Timepoint 4. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided). *Adjusted for baseline depression. ^Adjusted for baseline pain. +Adjusted for baseline race. #Adjusted for baseline race and depression. § Adjusted for baseline race and pain.

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Table 4.11: Mixed Model Analysis of Psychological Variables from Baseline vs. Post-Training Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Post-training (T2) Est μ± SE	n	Est. T2-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
BDI Score*	A	21.9 ± 1.04	44	17.66 ± 1.22	31	*-4.24 ± 1.35 (3.14, <0.01[c])*	(3.54, 0.06)
	B	21.1 ± 1.08	41	20.97 ± 1.21	32	*-0.13 ± 1.35 (0.1, 0.92[d])*	(5.73, <0.01)
	Est A-B±SE (t, p)	*0.8 ± 1.5 (-0.52, 0.6[a])*	*85*	*-3.31 ± 1.7 (1.92, 0.057[a])*	*63*	n/a	(2.42, 0.03)
Perceived Stress Score*	A	22.46 ± 0.66	44	21.72 ± 0.76	31	*-0.74 ± 0.77 (0.96, 0.17[c])*	(1.66, 0.20)
	B	23.76 ± 0.69	41	22.26 ± 0.76	32	*-1.50 ± 0.76 (1.96, 0.05[d])*	(2.83, 0.04)
	Est A-B±SE (t, p)	*-1.30 ± 0.96 (1.35, 0.18[a])*	*85*	*-0.54 ± 1.09 (0.5, 0.62[a])*	*63*	n/a	(0.38, 0.76)
General Fatigue+	A	12.51 ± 0.36	44	11.92 ± 0.42	31	*-0.59 ± 0.43 (1.36, 0.09[c])*	(0.00, 0.97)
	B	12.38 ± 0.36	41	12.37 ± 0.40	31	*-0.01 ± 0.43 (0.04, 0.97[d])*	(2.48, 0.06)
	Est A-B±SE (t, p)	*0.13 ± 0.5 (-0.25, 0.80[a])*	*85*	*-0.45 ± 0.58 (0.77, 0.44[a])*	*62*	n/a	(0.45, 0.72)

LS-Means estimates displayed as means. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Post-training Assessment. [d]2-sided comparison between Baseline Assessment and Post-training Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T2: Timepoint 2. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided). *Adjusted for baseline depression. ^Adjusted for baseline pain. +Adjusted for baseline race. #Adjusted for baseline race and depression. § Adjusted for baseline race and pain.

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Table 4.11: Mixed Model Analysis of Psychological Variables from Baseline vs. Post-Training Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Post-training (T2) Est μ± SE	n	Est. T2-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
Mental Fatigue*	A	11.08 ± 0.32	43	11.38 ± 0.38	31	*0.30 ± 0.43 (-0.71, 0.24[c])*	(1.27, 0.26)
	B	11.68 ± 0.33	41	11.97 ± 0.38	31	*0.29 ± 0.44 (-0.67, 0.50[d])*	(0.43, 0.26)
	Est A-B±SE (t, p)	*-0.60 ± 0.46 (1.3, 0.19[a])*	*84*	*-0.59 ± 0.54 (1.1, 0.27[a])*	*62*	n/a	(0.36, 0.78)
Physical Fatigue+	A	13.53 ± 0.31	44	13.23 ± 0.37	31	*-0.30 ± 0.42 (0.72, 0.24[c])*	(2.26, 0.14)
	B	12.42 ± 0.31	41	13.39 ± 0.35	31	*0.97 ± 0.42 (-2.27, 0.02[d])*	(0.89, 0.45)
	Est A-B±SE (t, p)	*1.11 ± 44 (-2.55, 0.01[a])*	*85*	*-0.16 ± 0.51 (0.31, 0.76[a])*	*62*	n/a	(1.83, 0.14)
Reduced Activity§	A	13.18 ± 0.37	44	13.21 ± 0.43	31	*0.03 ± 0.52 (-0.06, 0.48[c])*	(2.05, 0.16)
	B	12.42 ± 0.38	40	12.85 ± 0.41	31	*0.43 ± 0.53 (-0.81, 0.42[d])*	(0.40, 0.76)
	Est A-B±SE (t, p)	*0.76 ± 0.51 (-1.48, 0.14[a])*	*84*	*0.36 ± 0.59 (-0.61, 0.54[a])*	*62*	n/a	(0.41, 0.74)

LS-Means estimates displayed as means. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Post-training Assessment. [d]2-sided comparison between Baseline Assessment and Post-training Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T2: Timepoint 2. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided). *Adjusted for baseline depression. ^Adjusted for baseline pain. +Adjusted for baseline race. #Adjusted for baseline race and depression. § Adjusted for baseline race and pain.

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Table 4.11: Mixed Model Analysis of Psychological Variables from Baseline vs. Post-Training Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Post-Training (T2) Est μ± SE	n	Est. T2-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
Reduced Motivation^	A	12.39 ± 0.37	44	11.97 ± 0.44	31	*-0.42 ± 0.47 (0.88, 0.19[c])*	(0.39, 0.53)
	B	11.62 ± 0.39	41	11.98 ± 0.44	30	*0.36 ± 0.48 (-0.73, 0.46[d])*	(0.25, 0.86)
	Est A-B±SE (t, p)	*0.77 ± 0.54 (-1.41, 0.16[a])*	*85*	*-0.01 ± 0.62 (0.01, 0.99[a])*	*62*	n/a	(0.53, 0.66)

LS-Means estimates displayed as mean. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Post-training Assessment. [d]2-sided comparison between Baseline Assessment and Post-training Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T2: Timepoint 2. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided). *Adjusted for baseline depression. **^**Adjusted for baseline pain. +Adjusted for baseline race. #Adjusted for baseline race and depression. § Adjusted for baseline race and pain.

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Table 4.12: Mixed Model Analysis of Psychological Variables from Baseline vs. Follow-Up Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Follow-Up (T4) Est μ± SE	n	Est. T4-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
BDI Score*	A	21.9 ± 1.04	44	16.30 ± 1.34	25	*-5.60 ± 1.46 (3.84, <0.01[c])*	(3.54, 0.06)
	B	21.1 ± 1.08	41	20.32 ± 1.34	25	*-0.78 ± 1.47 (053, 0.59[d])*	(5.73, <0.01)
	Est A-B±SE (t, p)	*0.8 ± 1.5 (-0.52, 0.6[a])*	*85*	*-4.02 ± 1.92 (2.10, 0.037[a])*	*50*	n/a	(2.42, 0.03)
Perceived Stress Score*	A	22.46 ± 0.66	44	21.66 ± 0.82	25	*-0.80 ± 0.83 (0.96, 0.17[c])*	(1.66, 0.20)
	B	23.76 ± 0.69	41	23.35 ± 0.83	25	*-0.41 ± 0.83 (0.49, 0.62[d])*	(2.83, 0.04)
	Est A-B±SE (t, p)	*1.30 ± 0.96 (1.35, 0.18[a])*	*85*	*-1.69 ± 1.18 (1.43, 0.16[a])*	*50*	n/a	(0.38, 0.76)
General Fatigue+	A	12.51 ± 0.36	44	11.86 ± 0.45	25	*-0.65 ± 0.47 (1.40, 0.08[c])*	(0.00, 0.97)
	B	12.38 ± 0.36	41	11.85 ± 0.44	25	*-0.53 ± 0.47 (1.14, 0.26[d])*	(2.48, 0.06)
	Est A-B±SE (t, p)	*0.13 ± 0.5 (-0.25, 0.80[a])*	*85*	*0.01 ± 0.63 (-0.02, 0.99[a])*	*50*	n/a	(0.45, 0.72)

LS-Means estimates displayed. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline t and Follow-up Assessment. [d]2-sided comparison between Baseline and Post-training Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T4: Timepoint 2. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided). *Adjusted for baseline depression. ^Adjusted for baseline pain. +Adjusted for baseline race. #Adjusted for baseline race and depression. § Adjusted for baseline race and pain.

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Table 4.12: Mixed Model Analysis of Psychological Variables from Baseline vs. Follow-Up Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Follow-Up (T4) Est μ± SE	n	Est. T4-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
Mental Fatigue*	A	11.08 ± 0.32	43	11.53 ± 0.41	25	*0.45 ± 0.47 (-0.98, 0.17[c])*	(1.27, 0.26)
	B	11.68 ± 0.33	41	11.50 ± 0.42	25	*-0.18 ± 0.47 (0.38, 0.71[d])*	(0.43, 0.26)
	Est A-B±SE (t, p)	*-0.60 ± 0.46 (1.3, 0.19[a])*	*84*	*0.03 ± 0.59 (-0.05, 0.96[a])*	*50*	n/a	(0.36, 0.78)
Physical Fatigue+	A	13.53 ± 0.31	44	13.65 ± 0.40	25	*0.12 ± 0.45 (-0.25, 0.40[c])*	(2.26, 0.14)
	B	12.42 ± 0.31	41	12.80 ± 0.39	25	*0.38 ± 0.46 (-0.83, 0.41[d])*	(0.89, 0.45)
	Est A-B±SE (t, p)	*1.11 ± 44 (-2.55, 0.01[a])*	*85*	*0.85 ± 0.56 (-1.51, 0.13[a])*	*50*	n/a	(1.83, 0.14)
Reduced Activity§	A	13.18 ± 0.37	44	12.81 ± 0.47	24	*-0.37 ± 0.55 (0.62, 0.27[c])*	(2.05, 0.16)
	B	12.42 ± 0.38	40	12.82 ± 0.45	25	*0.40 ± 0.55 (-0.92, 0.36[d])*	(0.40, 0.76)
	Est A-B±SE (t, p)	*0.76 ± 0.51 (-1.48, 0.14[a])*	*84*	*-0.01 ± 0.65 (0.02, 0.98[a])*	*49*	n/a	(0.41, 0.74)

LS-Means estimates displayed as mean. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Follow-up Assessment [d]2-sided comparison between Baseline Assessment and Post-training Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T4: Timepoint 4. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided). *Adjusted for baseline depression. ^Adjusted for baseline pain. +Adjusted for baseline race. #Adjusted for baseline race and depression. § Adjusted for baseline race and pain.

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Table 4.12: Mixed Model Analysis of Psychological Variables from Baseline vs. Follow-Up Assessments

Outcome	Group A=Intervention B=Control	Baseline (T1) Est μ ± SE	n	Follow-Up (T4) Est μ± SE	n	Est. T4-T1±SE (t, p)	Group (f, p) Timepoint (f, p) Group x Timepoint (f, p)
Reduced Motivation^	A	12.39 ± 0.37	44	12.39 ± 0.48	25	*-0.002 ± 0.51 (-0.00, 0.50[c])*	(0.39, 0.53)
	B	11.62 ± 0.39	41	12.14 ± 0.49	24	*0.52 ± 052 (-0.98, 0.32[d])*	(0.25, 0.86)
	Est A-B±SE (t, p)	*0.77 ± 0.54 (-1.41, 0.16[a])*	*85*	*0.25 ± 0.69 (-0.37, 0.71[a])*	*49*	n/a	(0.53, 0.66)

LS-Means estimates displayed as mean. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between Baseline Assessment and Follow-up Assessment. [d]2-sided comparison between Baseline Assessment and Post-training Assessment. μ: Mean. SE: Standard error of the mean. T1: Timepoint 1. T4: Timepoint 4. t: t-test statistic. f: F test statistic. p: p-value. Group x Timepoint: Type 3 test of fixed effects for group by timepoint interaction term (1-sided). *Adjusted for baseline depression. ^Adjusted for baseline pain. +Adjusted for baseline race. #Adjusted for baseline race and depression. § Adjusted for baseline race and pain.

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Table 4.13 Cohen's D Estimates for Outcomes

Outcome	TP2-TP1	Pooled SD	Cohen's D1	TP4-TP1	Pooled SD	Cohen's D2
HRV Coherence	0.4464	0.6392	0.70	0.4529	0.5456	0.83
Pain Severity	-0.2319	1.0277	-0.23	-0.9600	1.4549	-0.66
Pain Interference	-4.6472	8.7967	-0.53	-5.9922	16.0202	-0.37
Pain Catastrophizing	0.5252	6.8512	0.07	-1.4800	7.5542	-0.20
Paced Auditory Serial Addition Test	2.00	5.26	0.38	0.4800	4.5249	0.11
Hopkins Verbal Learning Test	0.1613	4.8529	0.03	-0.8000	5.2144	-0.15
Beck Depression Inventory	-4.6472	8.7967	-0.53	-5.3600	8.9607	-0.60
Perceived Stress	0.5927	4.9926	0.12	-0.3600	3.8794	-0.09
General Fatigue	0.2333	3.2749	0.07	0.2833	3.3129	0.09
Mental Fatigue	0.2667	2.8426	0.09	0.1633	3.1477	0.05
Physical Fatigue	-0.0667	2.7224	-0.02	.0383	2.7707	0.01
Reduced Activity	0.1000	3.5025	0.03	-0.3982	3.2132	-0.12
Reduced Motivation	0.3381	2.7766	0.12	0.2120	3.6650	0.06

TP2-TP1: Difference score of group means between post-training and baseline, Pooled SD: Pooled Standard Deviation, Cohen's D1: Cohen's D Estimate between post-training and baseline, TP4-TP1: Difference score of group means between follow-up and baseline, Cohen's D2: Cohen's D Estimate between follow-up and baseline.

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Table 4.14. Demographics by Completion Status

	Total (n=76)	Completers (n=50)	Loss to Follow-up (n=26)	p-value
By Group				1.00
Intervention	38 (50)	25 (66)	13 (34)	
Control	38 (50)	25 (66)	13 (34)	
Age (years± SD)	55 ± 11	57 ± 9.9	50 ± 11.6	0.01
Gender n (%)				0.63
Female (%)	26 (35)	19 (38)	7 (27)	
Male (%)	49 (65)	30 (60)	19 (73)	
Race				0.62
Minorities (%)	47 (62)	32 (64)	15 (58)	
Caucasian (%)	29 (38)	18 (36)	11 (42)	
Education				0.14
Less Than College	20 (26)	15 (30)	5 (19)	
College	47 (62)	27 (54)	20 (77)	
Graduate School	9 (12)	8 (16)	1 (4)	
Income				0.31
Under $30,000	31 (41)	18 (36)	13 (50)	
$30,000-50,000	15 (20)	12 (24)	3 (12)	
$50,001 or more	25 (33)	15 (30)	10 (38)	
Refused	4 (5)	4 (8)	0 (0)	
Don't know	1 (1)	1 (2)	0 (0)	

Fisher's exact Test (2-sided) and Mantel-Haenszel Chi-Square used for categorical variables. Pooled T-test used for continuous variables. n: number SD: Standard Deviation.

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Table 4.15. Comorbidities at Baseline by Completion Status

	Overall (n=76)	Completers (n=50)	Loss to Follow-up (n=26)	p-value
Hypertension				0.47
Yes (%)	34 (45)	24 (48)	10 (38)	
No (%)	42 (55)	26 (52)	16 (62)	
Cancer				0.71
Yes (%)	8 (11)	6 (12)	2 (8)	
No (%)	68 (89)	44 (88)	24 (92)	
Depression				0.34
Yes (%)	35 (46)	21 (42)	14 (54)	
No (%)	41 (54)	29 (58)	12 (46)	
Anxiety				0.78
Yes (%)	17 (22)	12 (24)	5 (19)	
No (%)	59 (78)	38 (76)	21 (81)	
PTSD				0.08
Yes (%)	28 (37)	22 (44)	6 (23)	
No (%)	48 (63)	28 (56)	20 (77)	
Diabetes				0.78
Yes (%)	19 (25)	12 (24)	7 (27)	
No (%)	57 (75)	38 (76)	19 (73)	

Fisher's exact Test (2-sided) and Mantel-Haenszel Chi-Square used for categorical variables. Pooled T-test used for continuous variables. n: number SD: Standard Deviation. PTSD: Post Traumatic Stress Disorder.

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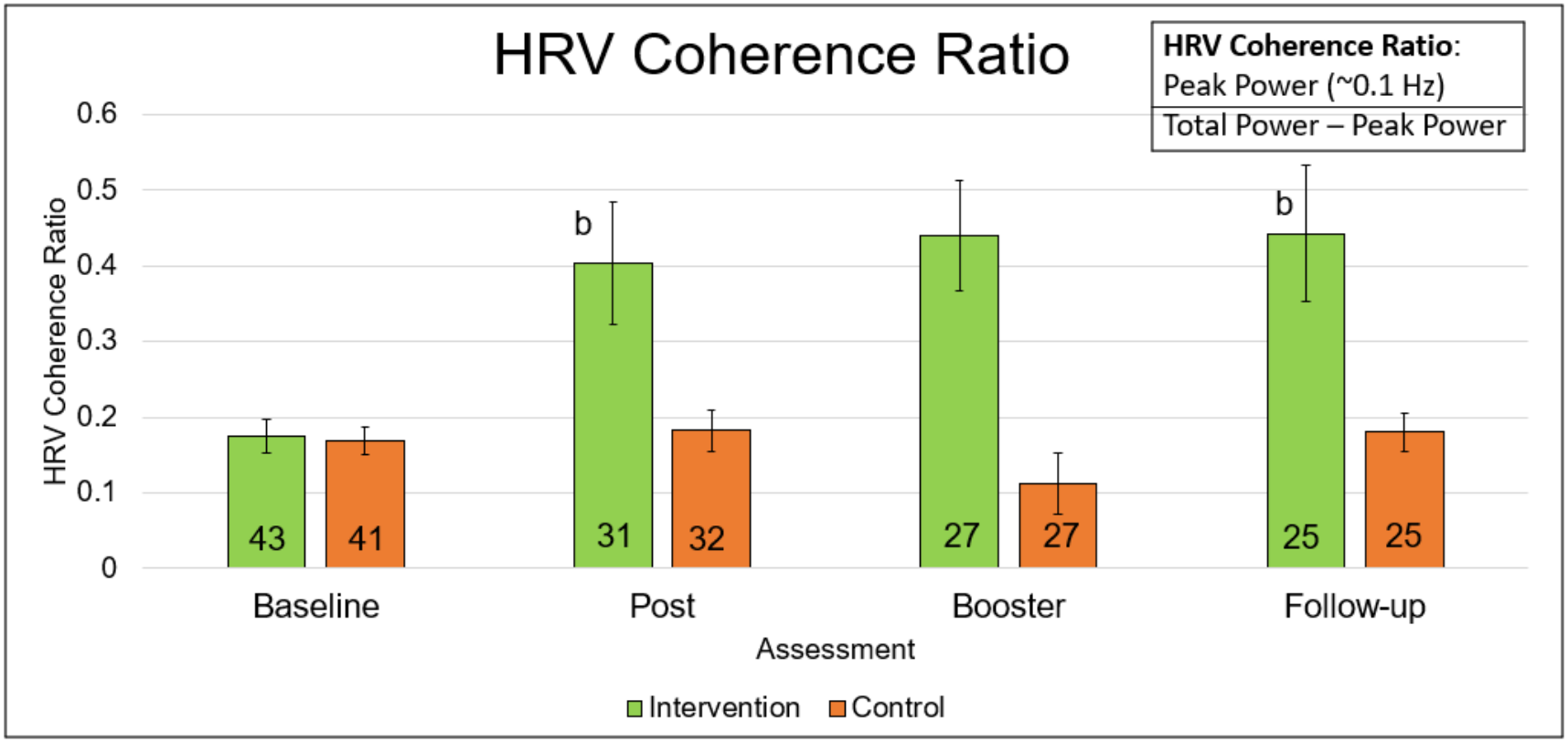

Figure 4.1. Back-transformed log HRV Coherence LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar.

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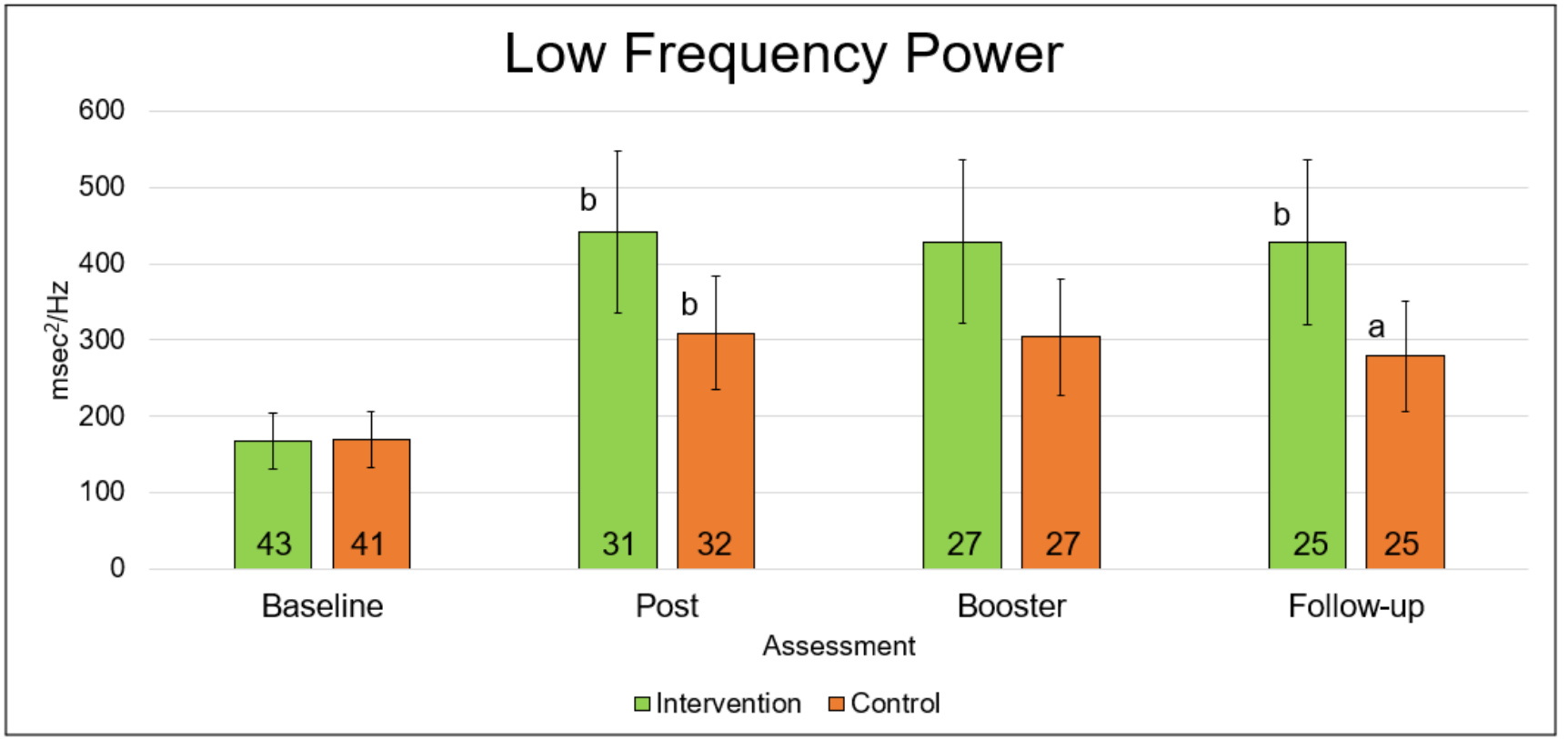

Figure 4.2. Back-transformed log LF Power LS Means ± SE msec^2/Hz by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar.

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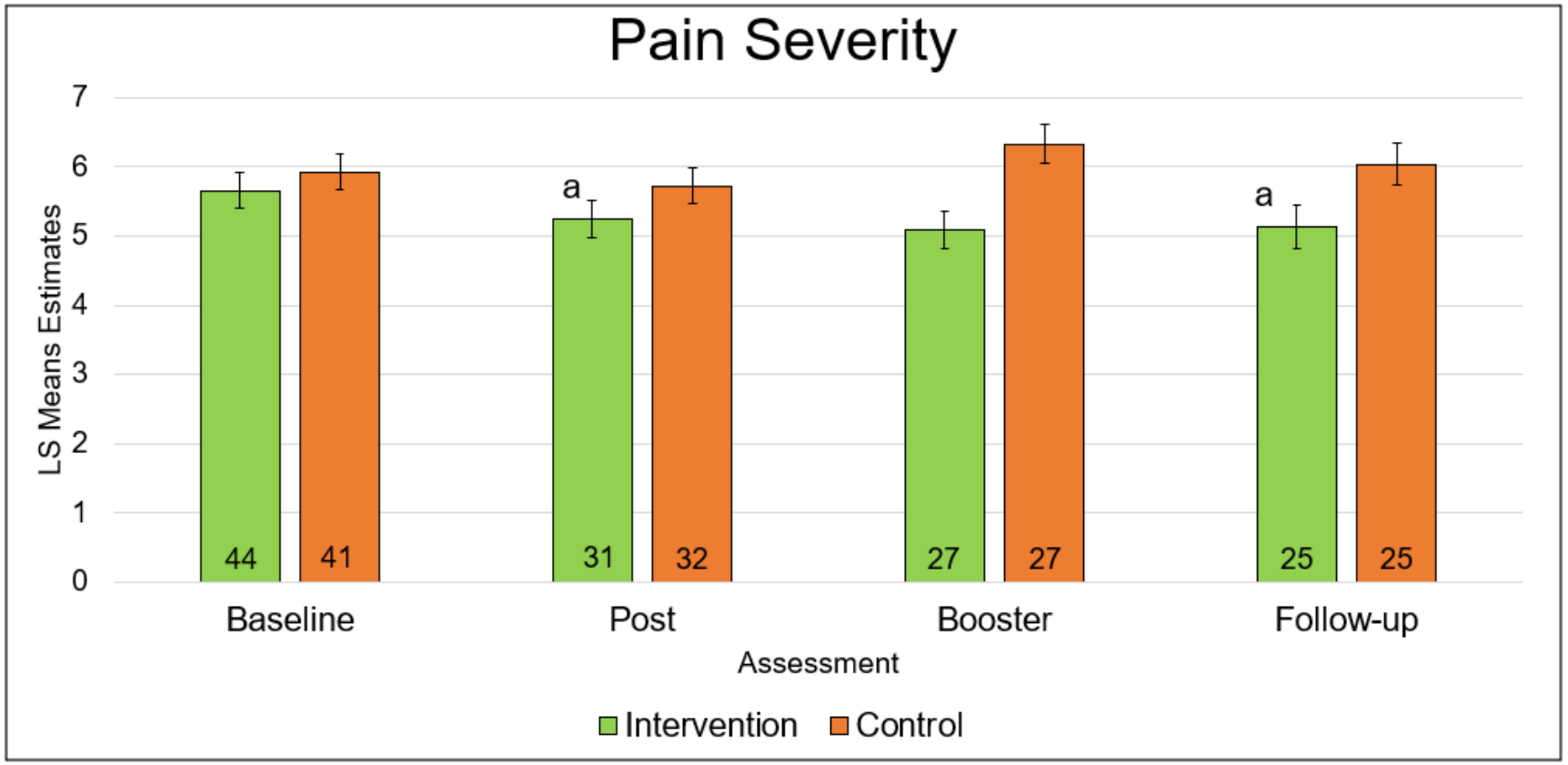

Figure 4.3. Pain Severity Score LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for race and depression at baseline.

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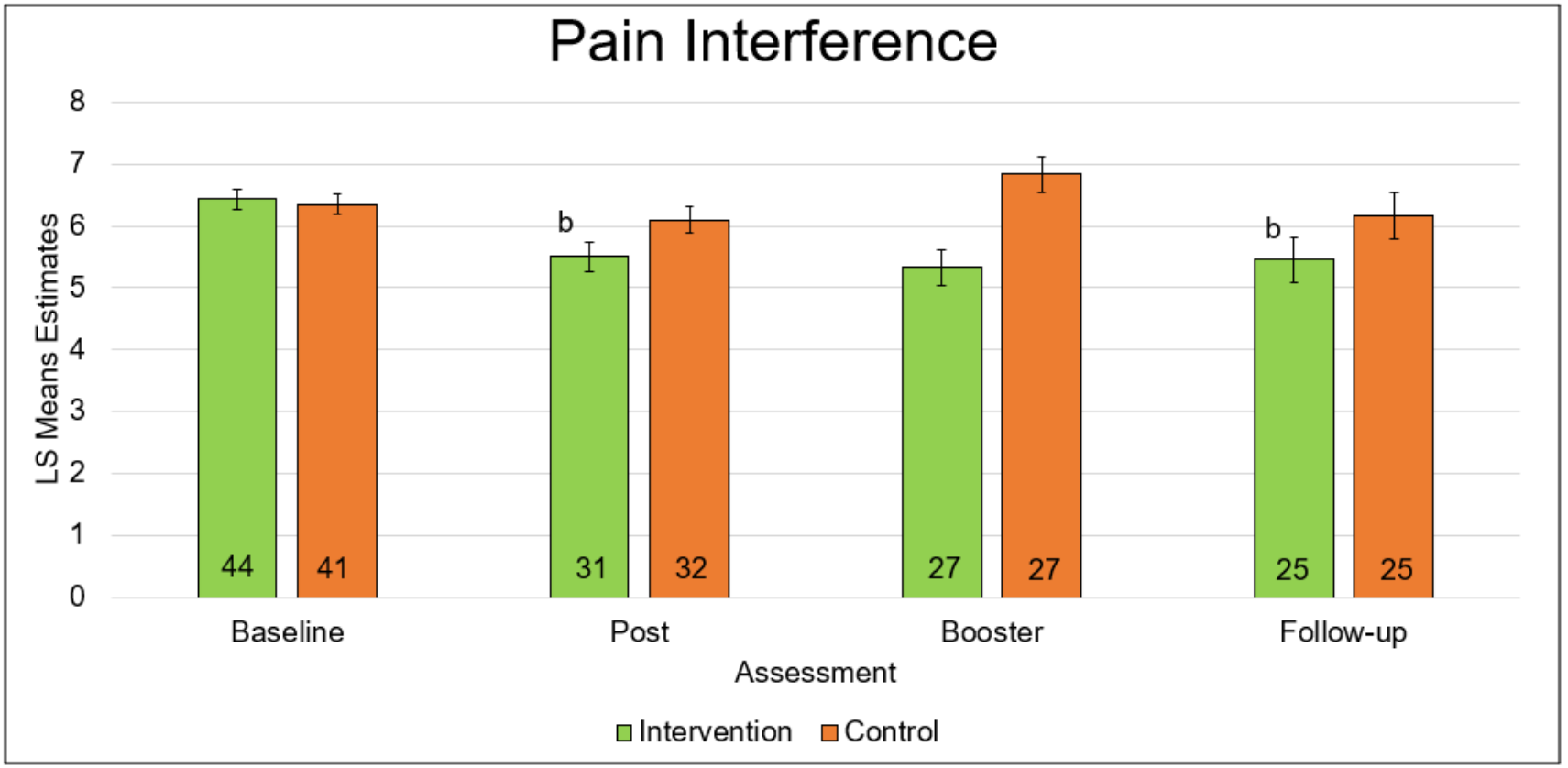

Figure 4.4. LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for pain at baseline.

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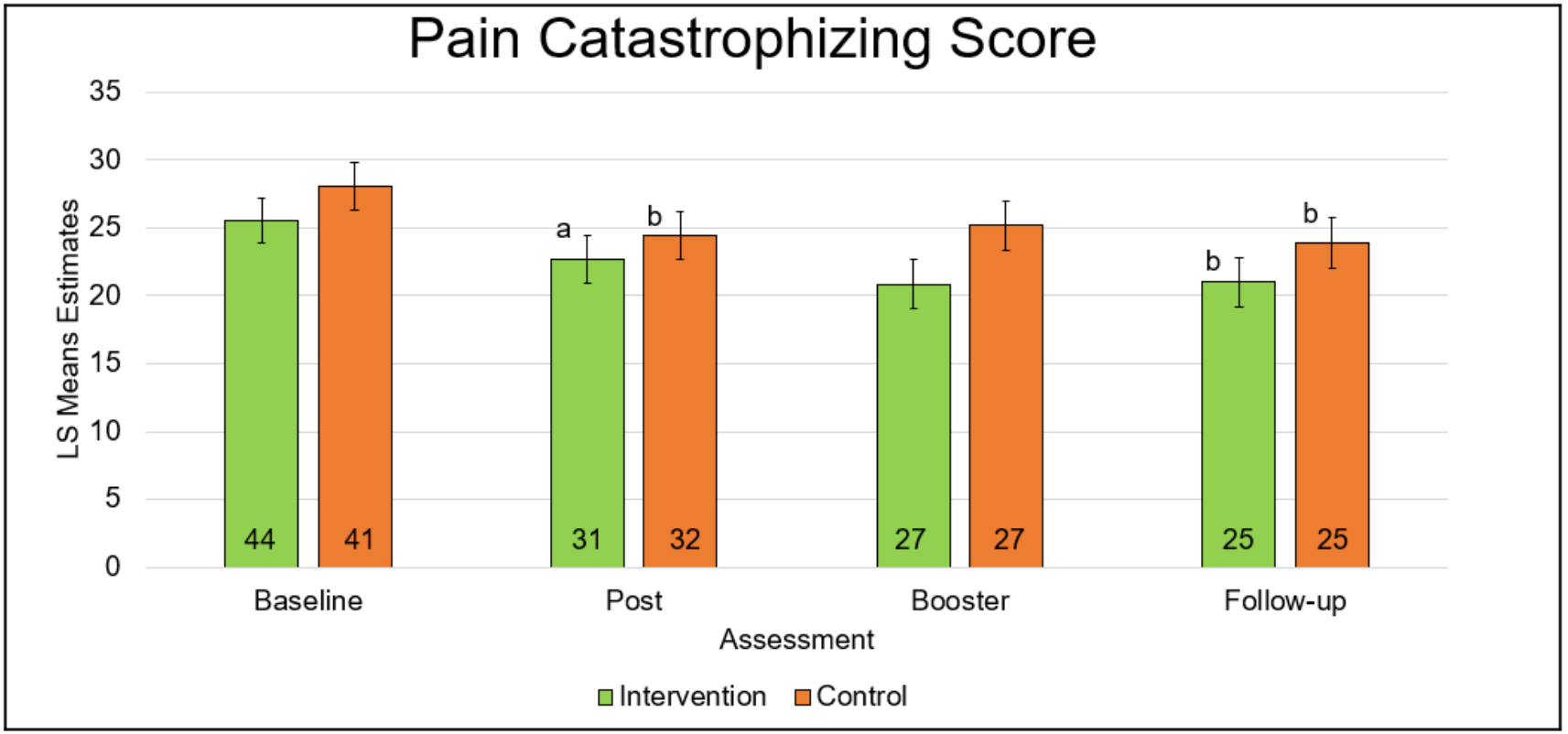

Figure 4.5. Pain Catastrophizing Score LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for depression at baseline.

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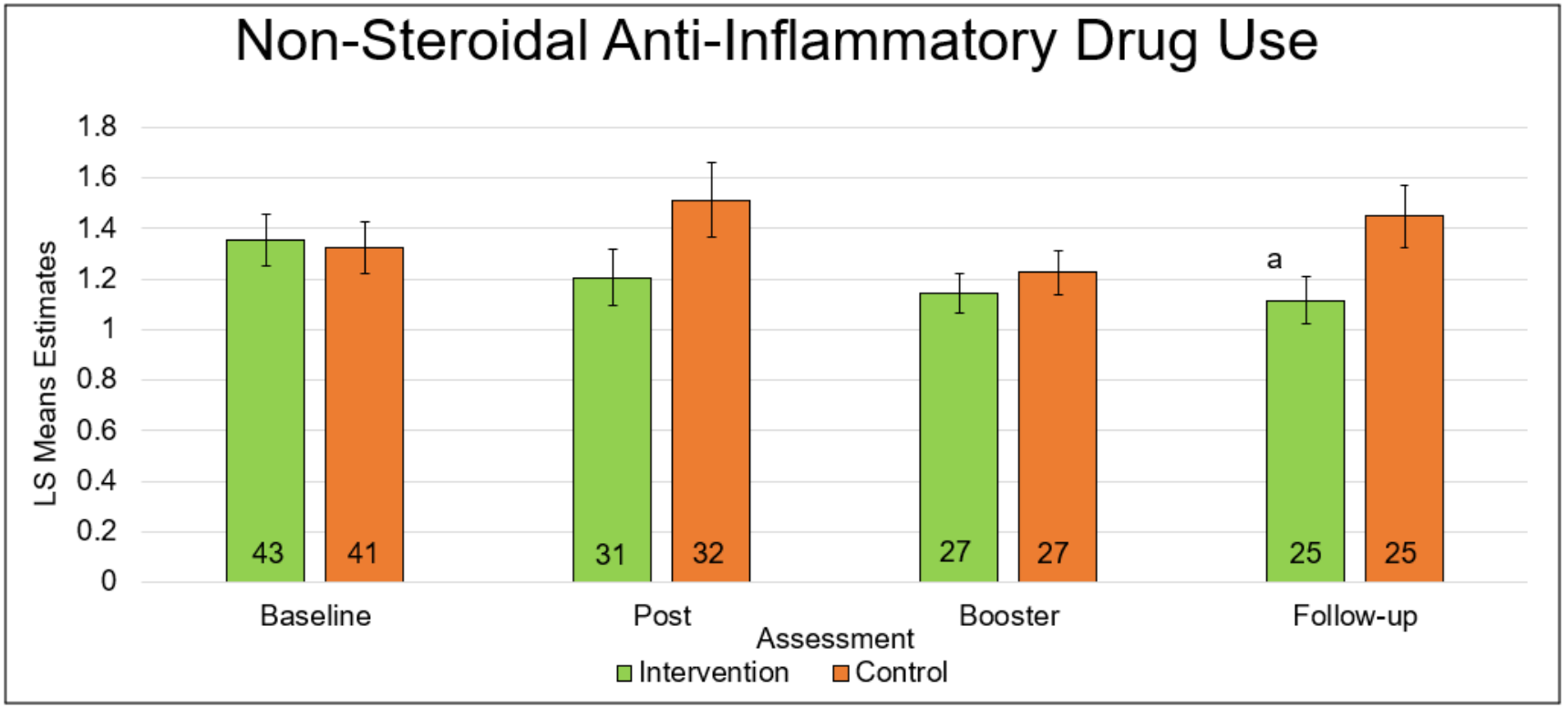

Figure 4.6. Back-Transformed non-steroidal anti-inflammatory drug use LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar.

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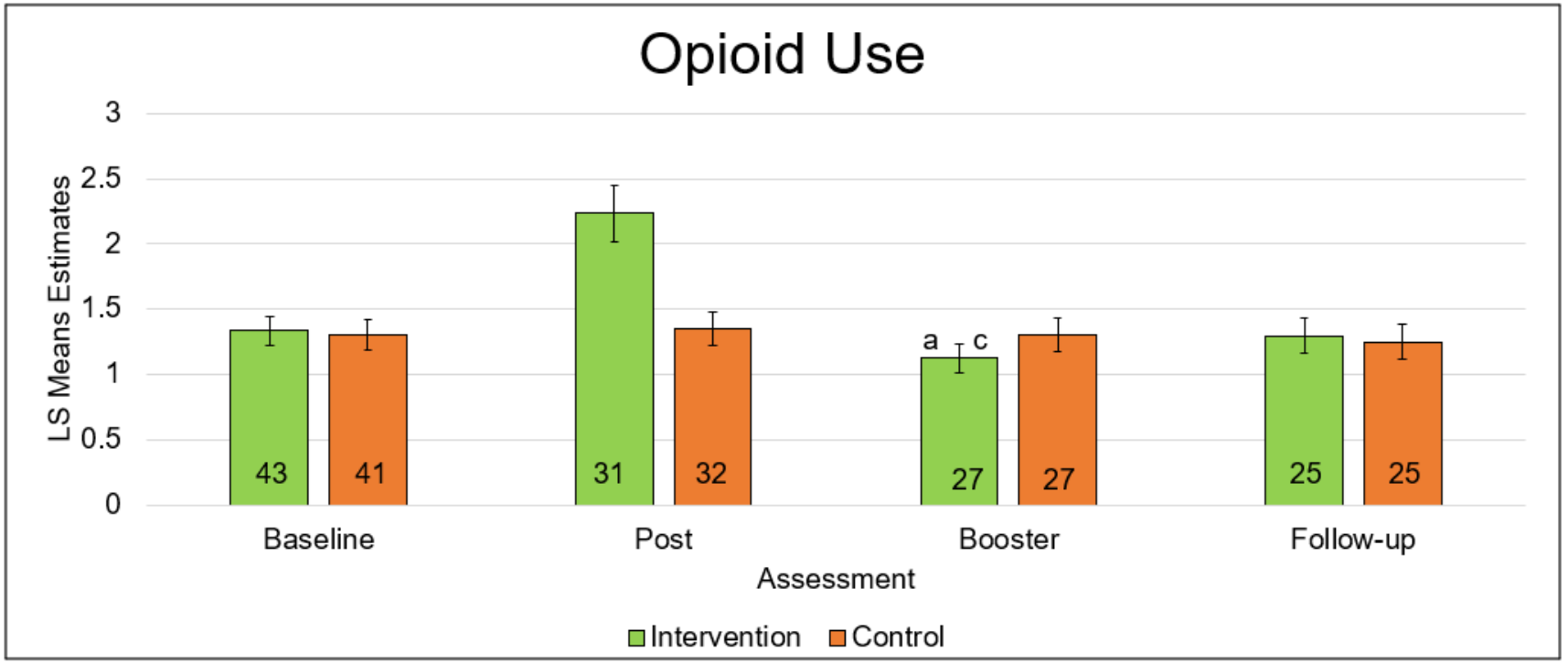

Figure 4.7. Back-Transformed Opioid LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar.

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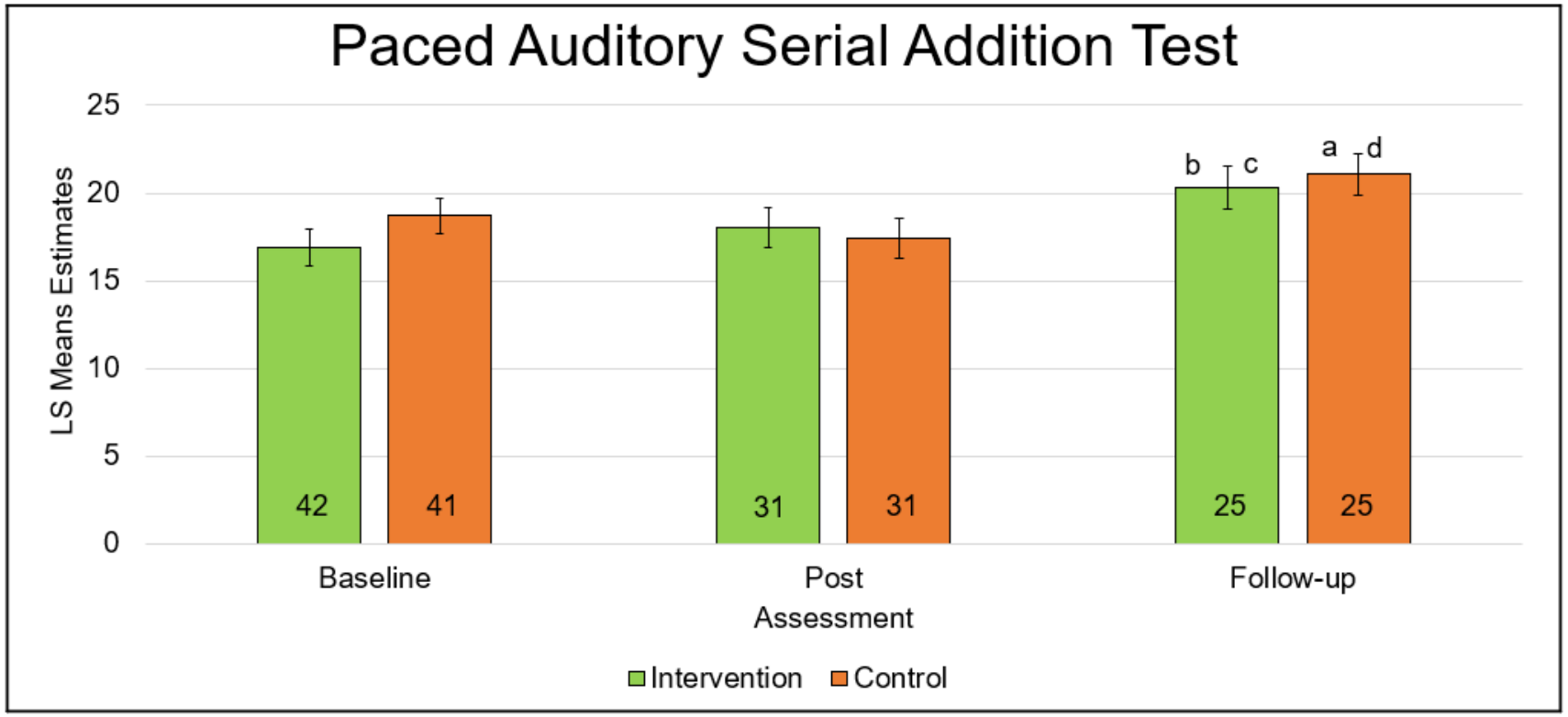

Figure 4.8. Paced Auditory Serial Addition Test LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for race at baseline.

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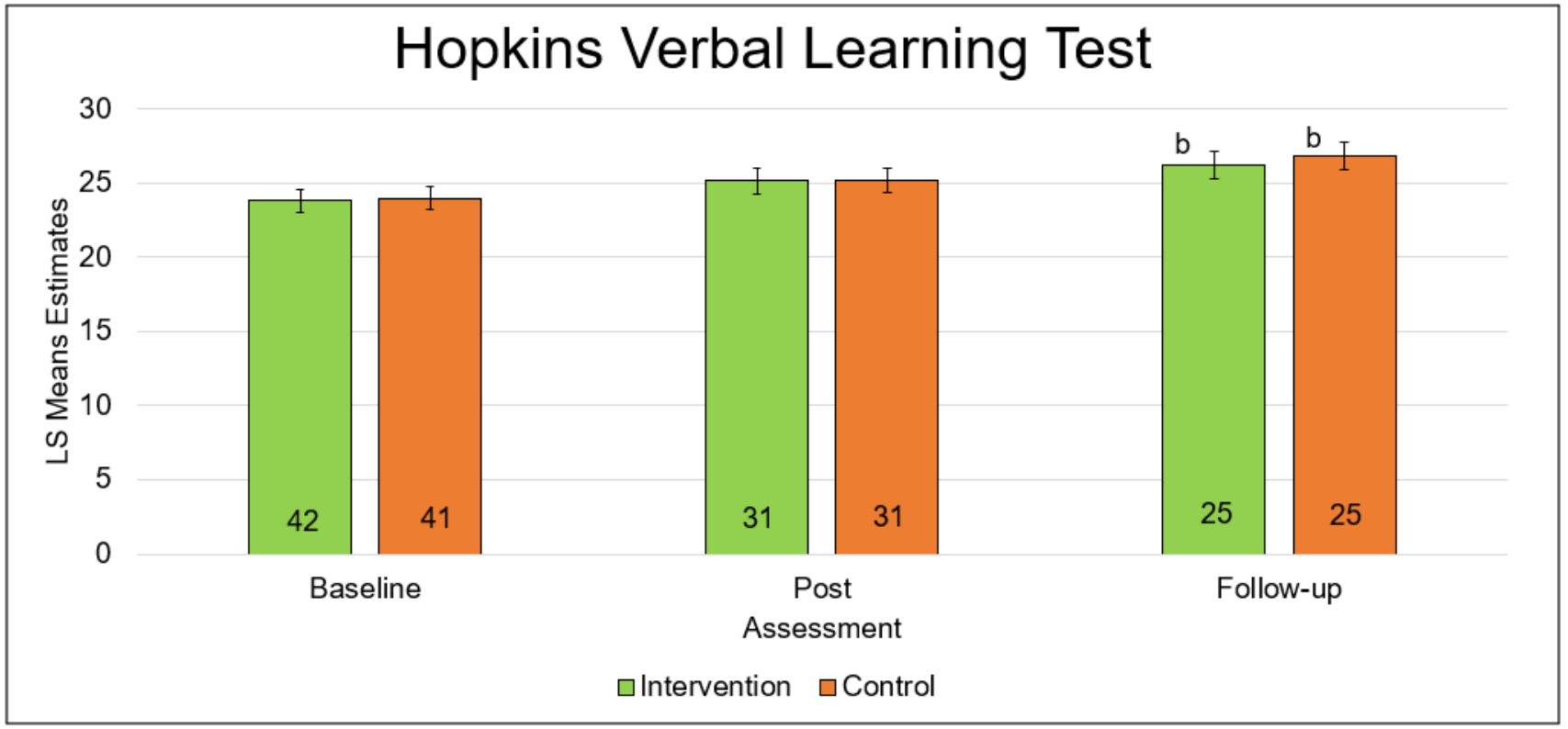

Figure 4.9. Hopkins Verbal Learning Test LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for race at baseline.

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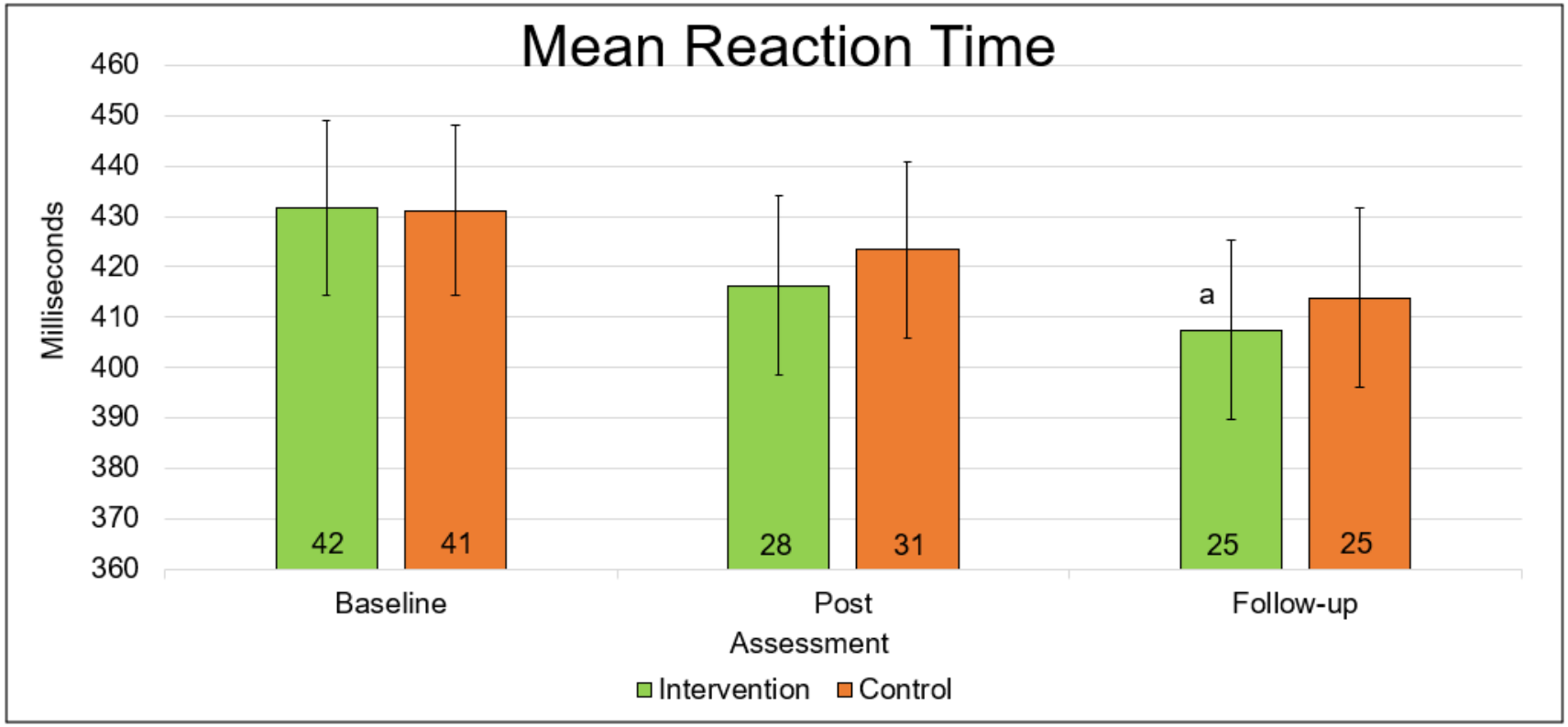

Figure 4.10. Back-transformed Reciprocal Mean Reaction Time LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for race at baseline.

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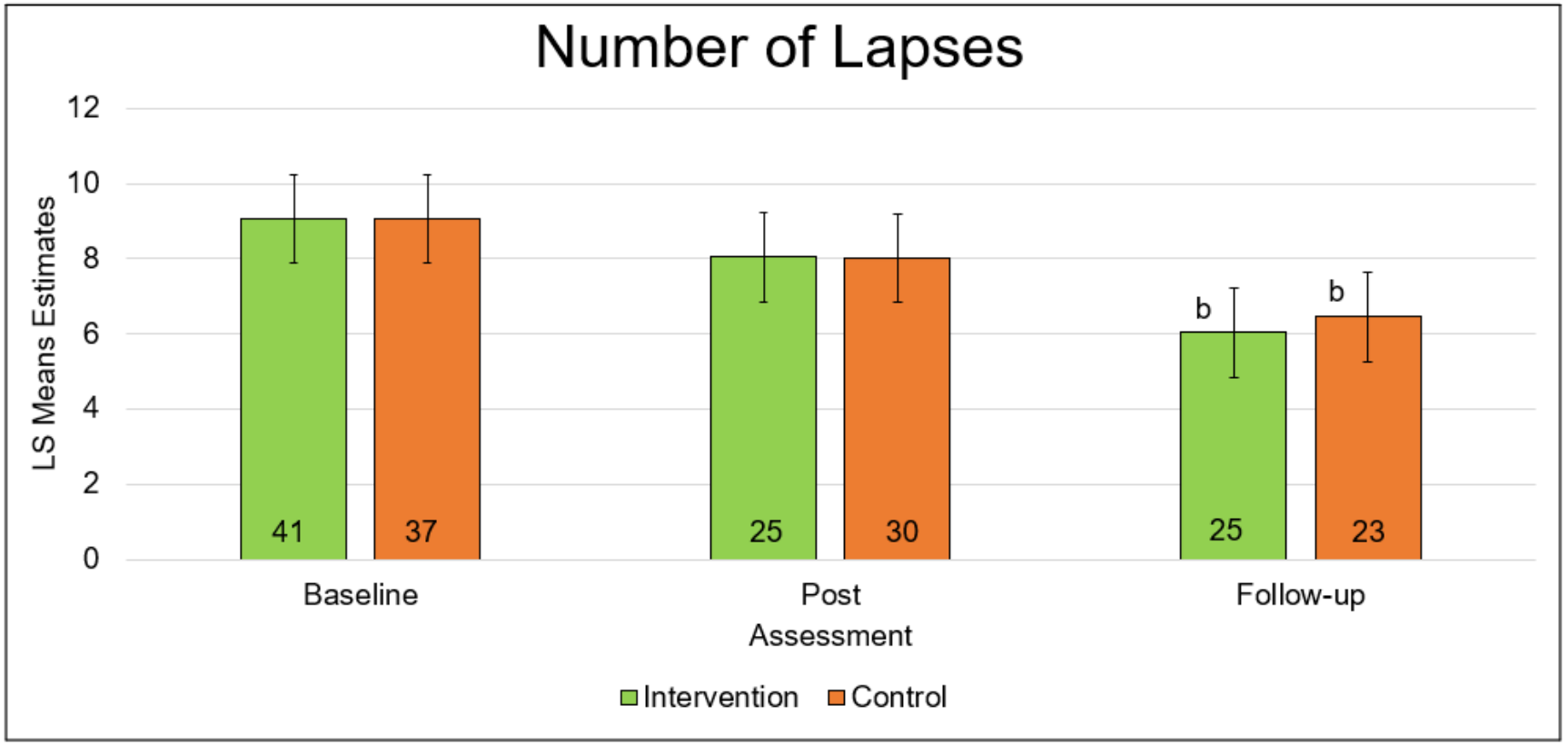

Figure 4.11. Lapses LS Means ± SE log transformed then back-transformed by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for Race at baseline.

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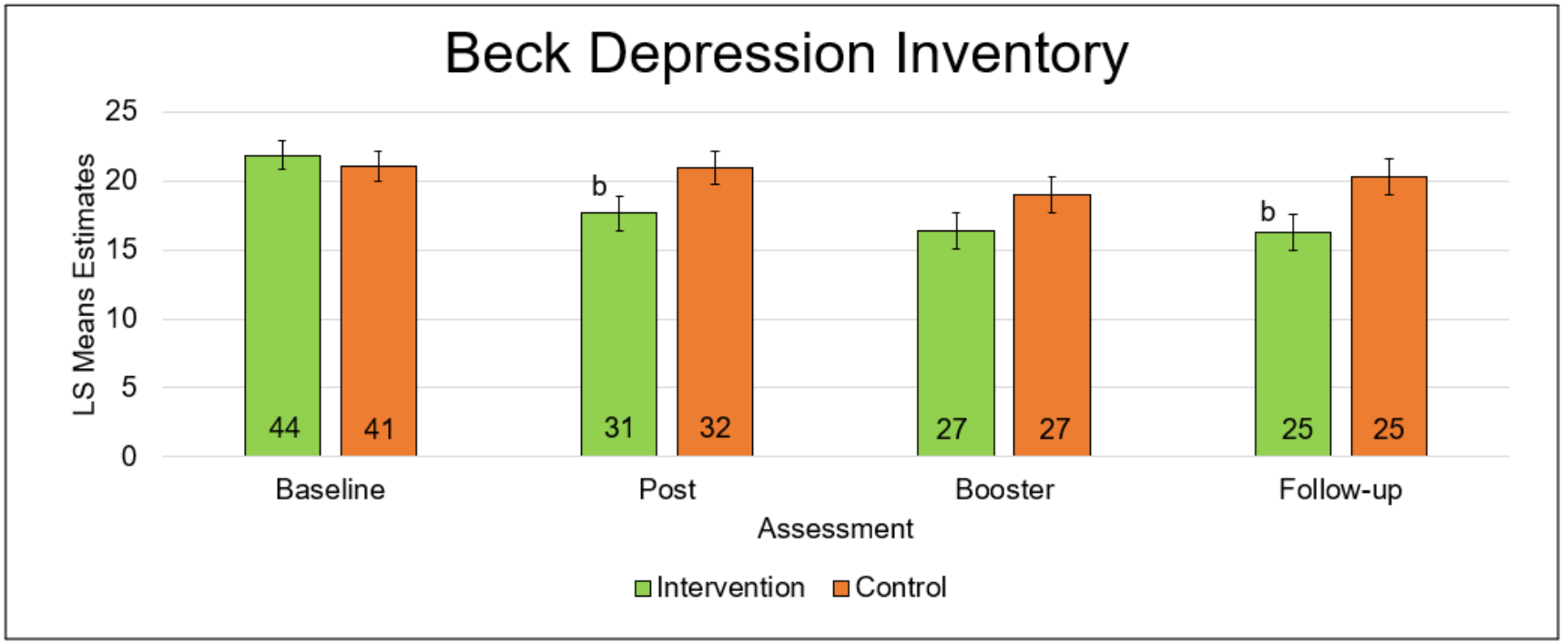

Figure 4.12. Beck Depression Inventory LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for depression at baseline.

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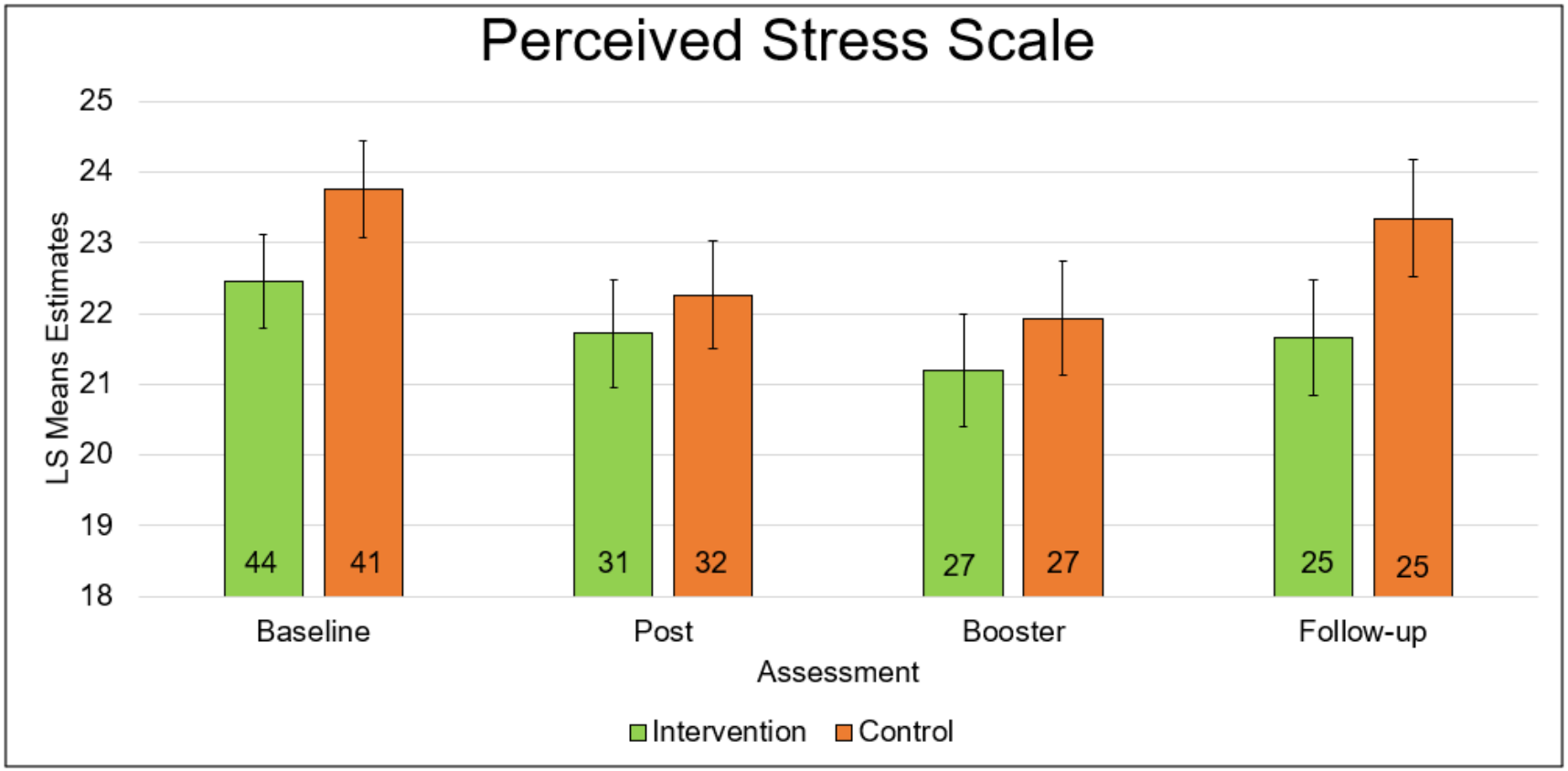

Figure 4.13. Perceived Stress Scale LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for depression at baseline.

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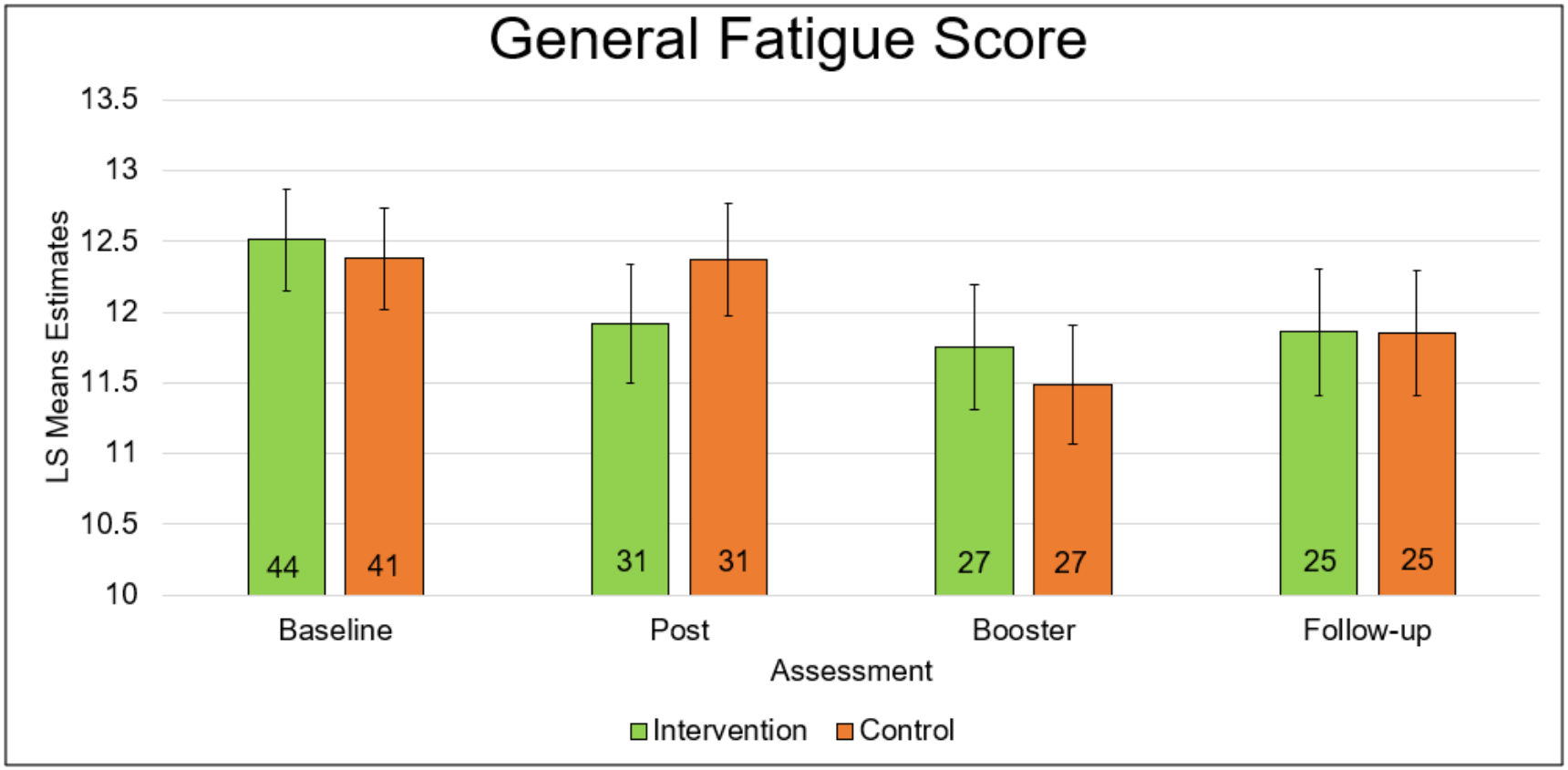

Figure 4.14. General Fatigue Score LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for race at baseline.

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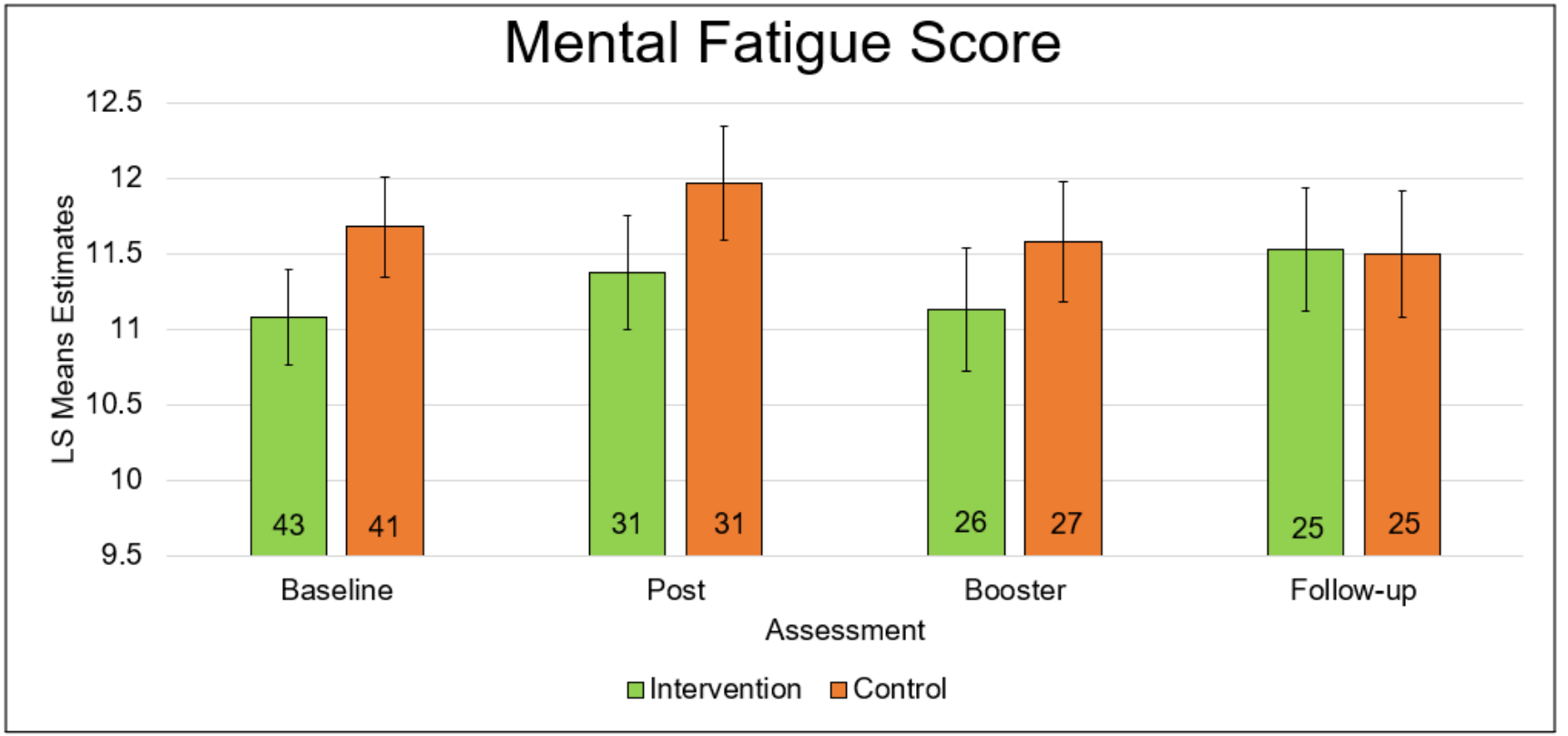

Figure 4.15. Mental Fatigue Score LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for depression at baseline.

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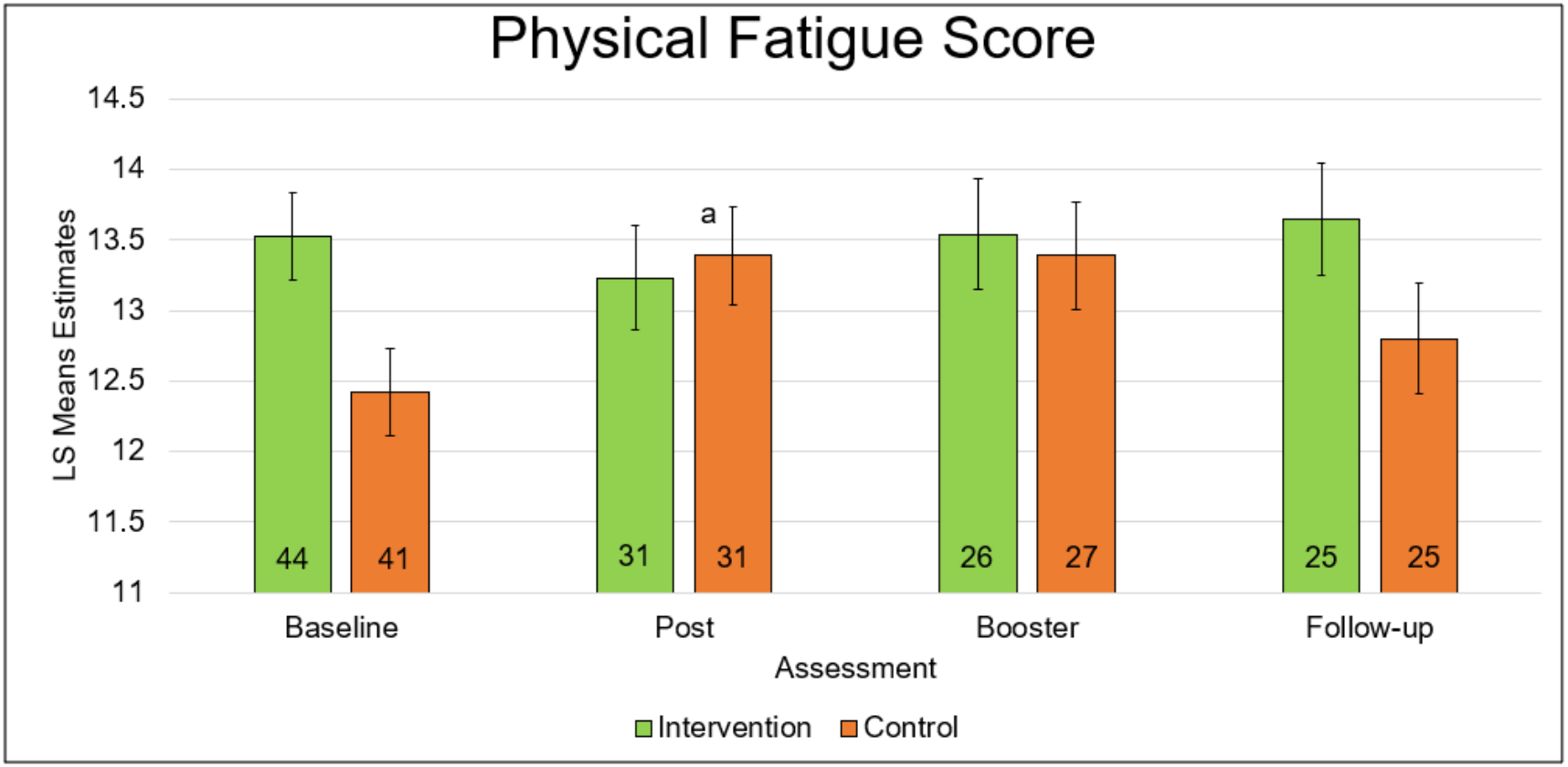

Figure 4.16. Physical Fatigue Score LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for race at baseline.

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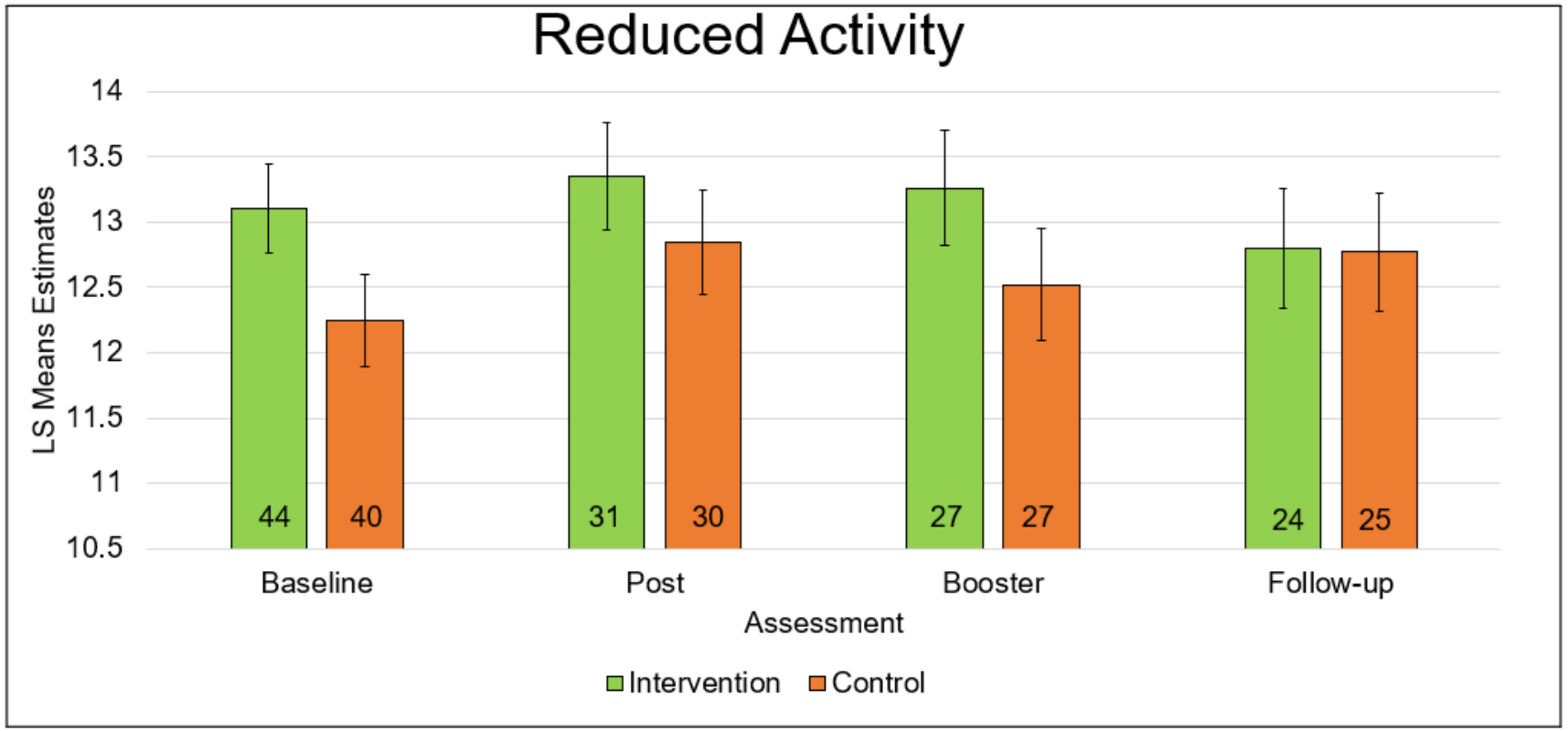

Figure 4.17. Reduced Activity LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for race and pain at baseline.

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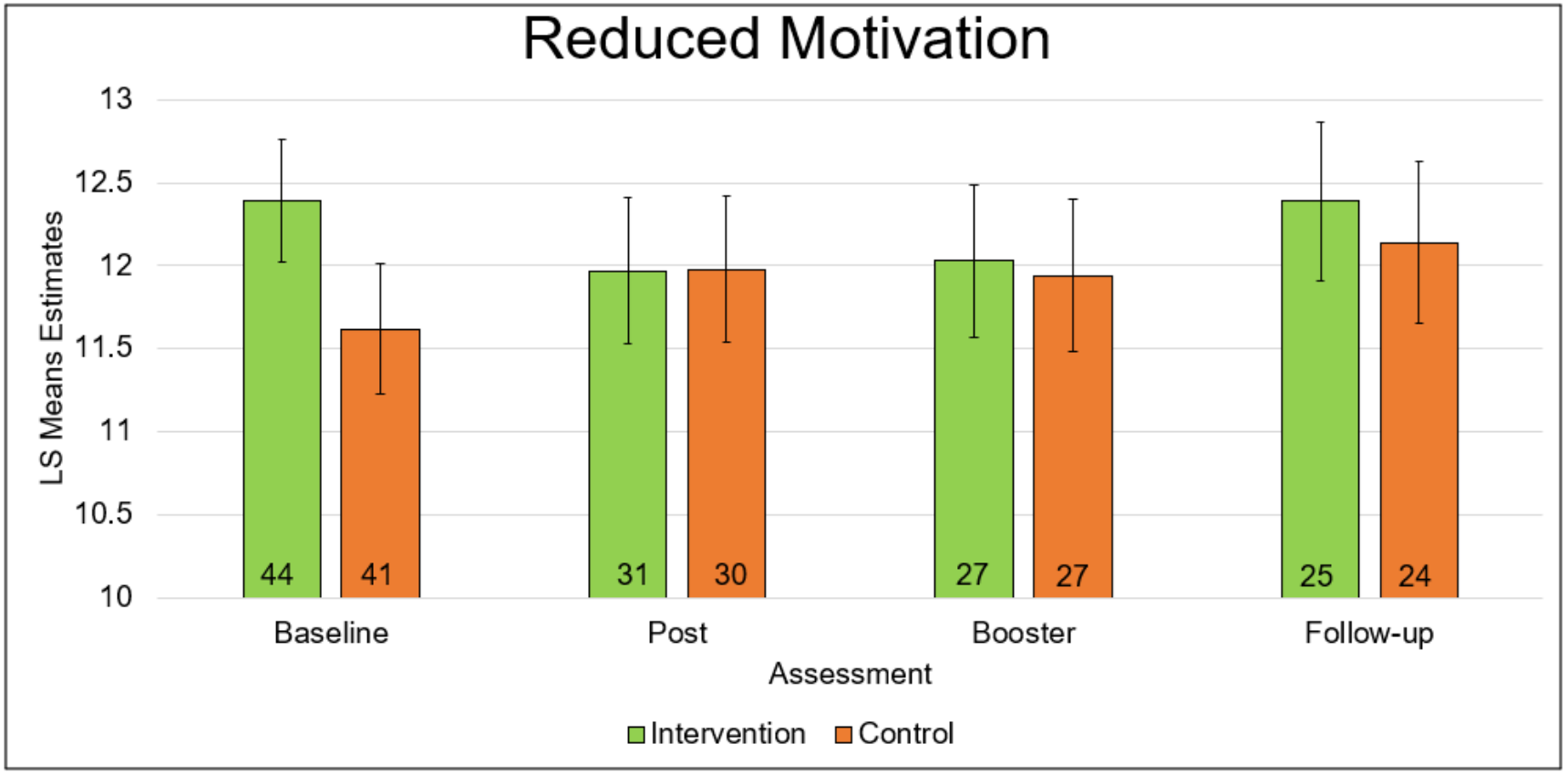

Figure 4.18 Reduced Motivation LS Means ± SE by treatment group and assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. [c]1-sided, $p < 0.05$ vs Post value in the same group. [d]1-sided, $p < 0.01$ vs Post value in the same group. n of patients within each group and assessment indicated at base of each bar. Adjusted for pain at baseline.

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CHAPTER 5

DISCUSSION

5.1 Overall Discussion

Results from this study indicate the receipt of HRVB can improve HRV coherence in veterans with chronic pain. HRV Coherence has been shown to help reduce clinical symptoms in other studies.[8] For example, in a population of human immunodeficiency viral disease (HIV) patients, HRVB helped to reduce anxiety. [210] HRVB helped improve emotional well-being and lower blood pressure in those with high blood pressure.[211] Among physicians, HRVB helped reduce stress.[212] In a group of congestive heart failure elderly patients, HRVB improved symptoms of depression.[213] In the current study, receipt of the HRVB intervention was demonstrated by a statistically significant improvement in the HRV Coherence Ratio values. Large effect estimates of the HRV Coherence Ratio were noted when comparing baseline to post-training values (d=0.7) and baseline to follow-up (d=0.83) in the intervention group (Table 4.13). This is evidence that the biofeedback technique was received and sustained over the course of the study.

Both groups had a statistically significant improvement in Low Frequency Power. Improvement in LF for those in the control group may have been due to some sham-induced relaxation that also facilitated resonant frequency breathing in that group. This may be a result of sitting in a relatively quiet, calm, supportive

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atmosphere while watching peaceful, static images of nature scenes. Improvement in LF power suggests an improvement in parasympathetic stimuli.[214] Van der Zwan et al. conducted a study to evaluate efficacy of physical activity, mindfulness meditation, and HRVB with twenty adult volunteers aged 18-40 years old in Amsterdam who reported stress with a PSS cut-off score of 17. Participants were stratified by gender and age then randomized into one of three groups. After a Baseline Assessment, five weekly training visits were conducted over 2-hours and a stair-stepped approach of intervention at home from 10-20 minutes over the five weeks. This was followed by a Follow-up Assessment. Van der Zwan et al. found no statistical differences between the three, and found all equally improved stress, anxiety, depression, and a general sense of well-being.[25] Possibly, sitting passively observing nature scenes may mimic mindful meditation in which if that is the case, it would explain why the control group in the current study also improved their LF power. An increase in HRV coherence in the current study suggests the intervention group received and benefited from HRVB and that the intervention was sustained over four months. A strength of Van der Zwan's study is the comparison of physical activity, HRVB, and meditation, however two limitations are the very small number of participants enrolled (n=20) and another is the short duration of the study. It would be interesting to see if there were any differences in the groups over a longer period with additional assessments longitudinally and to see if one group sustained benefit longer than others. A benefit of the current study is the larger sample size (n=85) between two groups and was evaluated over

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four months which demonstrated sustainability and improved duration of the HRVB intervention.

5.2 Pain Discussion

The current study demonstrated a reduction in pain severity in the intervention group relative to the control group. A small effect estimate was noted between baseline and post-training (-0.23, Table 4.13) whereas a medium effect was noted between baseline and follow-up (d= -0.66, Table 4.13). This suggests that the use of HRVB has the potential to reduce pain severity in those who experience chronic pain. Further, pain interference was also statistically significantly reduced in those who received HRVB. A medium effect size was noted from baseline to post-training (-0.53, Table 4.13) and later a small effect size from baseline to follow-up (-0.37, Table 4.13) suggesting pain that interferes with daily activities may be reduced in those who practice HRVB. This reduction in both outcomes can be attributed as a result of the benefit of HRVB. Both groups had a statistically significant reduction in pain catastrophizing scores from baseline to follow-up. When comparing group differences at follow-up, there was no statistically significant difference between the intervention group and the control group (p=0.28, Table 4.13). Small effect sizes for pain catastrophizing were also noted from baseline to post-training (0.07, Table 4.13) and baseline to follow-up (-0.20, Table 4.13) in the intervention group (Table 4.13). The reduction may not have been completely due to HRVB, another possible factor to consider is the potential for a placebo effect. In a double-blinded, randomized control trial by Kapitza et al., 42 participants between the ages 18-70 years, with chronic low back

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pain were enrolled into either an HRVB intervention or a placebo group. The participants were fitted for a machine to use at home in which the HRVB group had tailored resonance frequency breathing with feedback whereas the control group had no feedback and the device was set to about eight breaths per minute. Participants provided baseline data, 30 minutes of training at home for 15 days, follow-up at two weeks and at 3 months post intervention. A reduction in pain of approximately 25% was reported in the intervention group as compared to the control group. In the study by Kapitza, there were no dropouts, however in the current study, a loss-to-follow-up of about 33% was observed.[21]

In a separate study by Berry et. al., the use of HRV coherence biofeedback was randomly assigned in a pilot study of 14 U.S. military veterans with chronic pain allocating them to an HRVB intervention group and a placebo group. Following the Baseline Assessment, four weekly HRVB training visits were conducted prior to a Post-intervention Assessment. A greater reduction of pain was observed in the HRVB group as compared to the control group at post-intervention ($p=0.04$) and a reduction in pain from pre- to post-intervention was reported in the HRVB group ($p=<0.001$).[4] A limitation of the study is the small number of participants (n=14), along with the limited number of test outcome which used the BPI and PSS. However, similarities exist with the current study in that both populations were U.S. military veterans with chronic pain. Berry et al used four weeks of HRVB, whereas the current study prescribed six weeks Improved HRV coherence and reductions in pain were observed in the HRVB groups.

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In the present study, reductions in medication used were found only for non-steroidal anti-inflammatory drug use in the intervention group and a slight but statistically significant reduction in opioid use in the intervention group between Post-training and Booster Assessment. This reduction in opioid use occurred after an unexplained increase in opioid use post-training and most likely is an artifact. The current study included all opioids in one category. Future studies should consider quantification of morphine equivalents and comparing quantity consumed before and after HRVB intervention. While a sustained reduction in opioid use was not achieved during the current study, the use of a longer study, possibly with a larger sample size could further elucidate if HRVB leads to reductions in pain and in opioid use. As chronic opioid use has potential for side-effects, so does separation from opioid use. In opioid addiction, on average, it takes a minimum of 90 days of rehabilitation and a minimum of 12 months for methadone treatment to see limited benefit.[94] Reductions in NSAID use may indicate that HRVB benefitted pain management among participants in a relatively short period of time. The results of the current study are consistent with other studies, which have also demonstrated a reduction of pain through the use of HRVB.[4, 21-23, 39, 75] Hassett and associates assessed HRVB in a small sample (n=12) of female patients with fibromyalgia aged 18-60 years old from a rheumatology clinic utilizing ten weekly training sessions over three months with a pre- and post-assessment.[22] Participants were asked to practice for two 20-minute sessions per day and asked to refrain from caffeine or alcohol for 12 hours prior to assessments. Reductions in pain and depression were noted.[22] Hallman and colleagues included 24

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participants (22 female, 2 male) aged 25-50 years old with chronic shoulder and neck pain along with perceived stress, randomly assigned to intervention or control. Reductions in pain were found with pre- and post-intervention measurements, 10 weekly training sessions, and practice at home 15 minutes per day for 5 days per week.[39] Similarities exist with Hallman's study and the current study. Both were single-blind with an intervention and a control group. Both utilized personnel trained and credentialled in HRVB.

Multiple studies have used varying lengths of training with an HRVB trainer from 4-10 weeks and home practice of 15 to 20 minutes per day or twice a day. Improvements in HRV have been reported through receipt of HRVB however a standardized length of training and a standardized amount of home training have not been yet established. Future studies should consider what is the minimum number of training sessions required to reach HRVB coherence and what is the minimum amount of home practice required to maintain that skill.

5.3 Cognitive Discussion

The PFC has been described as having an association with HRV and inhibitory control.[215-217] High levels of HRV while resting have been associated with positive performance in executive function, cognitive flexibility, and in control of inhibition[218], however as noted by Gillie and Thayer, individual differences may be linked to cognitive performance.[215] HRVB has demonstrated improvement in cognitive performance in previous studies.[4, 7, 8, 12]

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PASAT has been used in numerous studies to assess cognitive processing, speed of information processing, measures of sustained attention, concentration, and working or immediate memory. This multifactorial test requires both information processing speed and task completion.[219] Both groups had statistically significant improvements in PASAT at follow-up. When evaluating effect estimates for PASAT, initially a small to medium effect was noted (d= 0.38, Table 4.13) from baseline to post-training, whereas a smaller effect was found from baseline to follow-up (d= 0.11, Table 4.13). The increases in both groups over time may have been due to a learning effect.

In a comprehensive review of the PASAT, numerous published comments appear to explain many of the findings in the current study. For example, the PASAT is an auditory test or can be performed visually as a paced visual serial addition test (PVSAT). In the current study, it was an auditory test. The most common reported results are the correct number of responses for each trial when multiple trials are given or as with this study the sum of the correct number of responses overall. Others have suggested reporting the number of omissions and errors.[219] Tombaugh suggests that most errors by the participant are the result of not answering as opposed to delayed answering. Some have noted that the participant may willingly skip a number to get the next one. This has been called "chunking" and is considered less taxing to the individual and could hinder identifying cognitive impairment. This may be where two numbers are summed, then they skip one or two numbers, and then resume. To overcome this, patterns could be identified and measured in "dyads" of consecutively provided correct

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answers.[219] A study examined the total number of correctly answered pairs of numbers. In some instances, participants keep track of numbers with their fingers, and differences may be present due to how the task is calculated rather than how quickly information is processed.[219] In the current study, data was not collected if people were using their fingers to keep track of the last stated number. This author did however witness some participants whispering numbers to themselves to keep track of the last heard number.

It has been suggested that due to the inherent stressful nature of the PASAT, frustration and anxiety are common even among cognitively intact individuals. With repeated exposure, a desensitization may occur, decreasing the novelty, and allowing for improved performance. Increased comfort in performing the exam may occur when anxiety reduces with repeated exposure, allowing for increased concentration which may be a possibility for the findings in the current study. Numerous authors have noted it to be unnecessarily stressful and some have even noted participants would rather have a lumbar puncture than go through the trials and tribulations of performing the PASAT.[219] To reduce negative arousal, the participant should be notified in advance that the PASAT is a stressful test and that it should be administered at the end of a neurocognitive test battery. Even though this is not a pass or fail test, some people will feel as though they failed. [219] Anecdotally, many subjects commented to this researcher of the difficulty of the PASAT and some expressed concern of having to perform it on their 2nd, 3rd, or 4th assessment having recalled their baseline experience.

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In a convenient sample of undergraduate psychology students, 95 participants were randomly assigned to a resonance frequency group (RF), a resonance frequency +1 additional breath/minute pace (RF+1), and a control group that sat quietly while conducting the PASAT. In that experiment, PASAT was used as a stressor while mood, HRV values, and blood pressure were assessed as outcomes. Systolic blood pressure remained lower and mood was more positive in the resonance frequency group relative to the controls while the resonance frequency group was not statistically different relative to the RF+1 group as the PASAT was conducted.[220]

When considering the results for the HVLT in the current study, both groups demonstrated improvement over time. If improvement had only been seen in the intervention group, then it may have resulted from the HRVB training. Since both groups improved, the results cannot be fully attributed to HRVB. Small effect sizes were observed from baseline to post-training (d=0.03) and from baseline to follow-up (d= -0.15, Table 4.13). A possible limitation of this study was that it did not measure delayed recall in which the participant would try to recall as many words as possible after a set number of minutes or after other tasks. It would be interesting to assess delayed recall in addition to immediate recall in future studies.

Several studies have suggested that executive function is a direct reflection of HRV, and as executive demands increase, participants should exhibit lower HRV.[158] However, other studies have not shown a direct correlation with increased executive demand and lower HRV.[158] Luque-Casado et al. proposed that workload, or perceived difficulty of a task, along with the amount of time spent on

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the task was more of an indicator for low HRV than the actual task itself. The National Aeronautics and Space Administration (NASA) developed a tool that was sensitive to mental workload. Using the NASA Task Load Index (NASA-TLX), Luque-Casado and colleagues evaluated subjective data of perceived mental stress through workload with objective HRV data. Twenty-four undergraduate Spanish males age 18-28 were enrolled, conducted the PVT (vigilance), N-back test (measured working memory to respond to a stimulus if it matched a stimulus two trials before), a duration discrimination task (respond if a stimulus duration was longer or shorter compared to another), and an oddball condition (indicated if an infrequent characteristic displayed during a frequent characteristic), all while recording HRV measures. The oddball task was used as a control measure. Results displayed sensitivity of HRV to sustained attention. The researchers noted that HRV varied with the demands of the tasks and that lower HRV values were observed with the N-back test. It was noted that when they compared the oddball tests with the other three, the oddball and the N-back tests had twice the number of trials (in 12 minutes) as the PVT and the discrimination test. As there were more trials over a longer time, sustained attention in the N-back provided increased workload, thus influenced HRV more so than cognitive control, perceptual processing, working memory, or the individual tasks themselves.[158] This corresponds with research conducted by Hansen, Johnsen, and Thayer which suggested that those who had high levels of HRV, performed better with increased workload as compared to those with low levels of HRV[124] and corresponds with research by Fairclough and Houston which noted that HRV reduced with longer

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time-on-tasks.[221] In the current study, HRV measurements were recorded prior to recording PASAT and HVLT measurements. As a result, the current study is not able to determine how HRV fluctuated during the PASAT and HVLT. Furthermore, as both the PASAT and HVLT are tests that require speaking, it would be nearly impossible to maintain a resonance frequency breathing rate while conducting those tests. Future studies should consider including recording HRV measurements while conducting cognitive tests which would allow for an initial resting assessment, an assessment with an increased workload during the cognitive tests, and then follow-up with a same-day post-assessment resting recording to allow for comparisons at rest, with increased workload and time-on-task, and then a period of recovery.

Although there were no differences in PASAT and HVLT outcomes between treatment groups, some of the participants did acknowledge they had a difficult time hearing the recording. Use of different speakers for the computer (both internal and external) provided the same difficulty for some participants. For continuity and consistency, the same recordings of words were used throughout this study. For future consideration, quality of recordings must be ensured, and alternate speaker systems may be used. This study did not inquire if the participant required hearing aids nor did it ensure they were wearing prescribed hearing aids at each of their visits for this study. A strength of this study is that both groups had the same list of words for the same assessment visits and a different list of words were used at each of the three assessments. Lists of words were nouns that are common in daily life and are tangible such as corn, hammer, dentist, etc. These

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are words that could be mentally visualized. Many of the veterans told this researcher they noticed a pattern of three groups which helped them to improve on the second and third trial at each of the assessment visits. The most likely reason for improvements observed in both the intervention and control group in both the PASAT and HVLT is a practice effect.

Reaction time improved in the intervention group but not in the control group. Reaction time is an aspect of cognitive processing of vigilant attention. Improvement in HRV using HRVB has the potential to synchronize neuro-cardiovascular coupling, improve blood flow, and restore cognitive processes, thereby facilitating faster reaction time in those who utilize HRVB. In the current study, the PVT was conducted over a period of 10 minutes. This sustained attention with an increased workload of varying time intervals between stimuli further illustrates the importance of HRVB in cognitive ability to maintain vigilance to respond more quickly in the intervention group compared to the control group. Impaired error processing is caused by decreased attention and reduced attention from mental fatigue.[222] When sustained attention is given to a task, mental fatigue may ensue, resulting in slower cognitive processing and increased errors. When a person recognizes they made an error, reaction time slows.[222] This has further implications for athletes, military and law enforcement members scanning for threats, and those in high risk occupations, such as airline pilots, where quick reaction to potential concerns is needed. This study did not conduct resonance frequency breathing during PVT testing, however resonance frequency breathing in the HRVB group was conducted immediately prior to conducting the cognitive

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tests. Only a couple of minutes would have lapsed between HRV measurements and moving four feet away to the computer for cognitive tests. It would be interesting to explore reaction time while performing resonance frequency breathing in future studies. A hypothesis would be that performing resonance frequency breathing during PVT testing would facilitate faster reaction times.

As it pertains to the number of lapses, both groups demonstrated reduced lapses over time. This may be explained by a learning effect or an intention to want to perform better. Furthermore, at the time of the final assessment (Follow-up), participants were exposed to two previous opportunities to gain experience and understand how the test is conducted. Former military members are likely to be competitive and want to personally demonstrate self-improvement either for self-fulfillment or to gain approval and positive affirmation from testers. This may explain why both groups demonstrated improvement over time. As noted by Prinsloo et al, often times participants sacrifice speed for accuracy or conversely sacrifice accuracy for speed.[123] It is possible those in the control group demonstrated a reduction in lapses by sacrificing speed for accuracy. However, the number of lapses has been suggested to be directly influenced by fatigue and sleep deprivation.[223] Therefore, it is conceivable that those who continued to be sleep deprived or fatigued may have been more likely to miss the visual stimuli, thus causing a lapse(s).

Psychomotor tasks and behavior are affected by time-on-task as well[158] as is seen following sleep deprivation. [198] The vigilance and reaction time components of psychomotor vigilance tasks such as learning new skills and short-term memory

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as well as fatigue and mental concentration are negatively affected by poor sleep, leading to increased time-on-task and increased lapses.[198] The PVT is a high workload test demanding vigilant attention.[198] Symptoms of sleep deprivation may be expressed as difficulty concentrating thus facilitating lapses and slower reaction times, changes in mood (stress and fatigue) and reduced motivation.[198] LF power has been highly correlated with PVT lapses.[224] In those who were sleep restricted, a correlation was found between HRV in the 0.01–0.08 Hz band and PVT lapses.[225] However, the current study found no correlation between PVT lapses and LF power in the 0.04-0.15 Hz range, however both the intervention and the control group had decreases in the number of lapses.

The 10-minute version of the PVT was used in the present study. A longer version of the PVT leads to more lapses and longer reaction time due to waning attention and monotony.[226] Lim et al[198]. note that when sleep is deprived, or subjects have prolonged wakefulness, reaction time is slower, more errors of commission are made, and is difficult for participants to stay focused on the task.[198, 223, 226] Time-on-task has been previously reported to be inversely proportional to HRV measurements. While the focus of this analysis does not pertain to sleep measurements, future studies should consider how HRVB influences sleep quality and quantity in conjunction with cognitive performance.

A quasi-experimental descriptive study was conducted among 26 male PTSD Vietnam war veterans and 21 male normal Vietnam war veterans.[227] Outcomes included learning and memory utilizing an auditory-verbal learning as well as a visuospatial information test, in addition to an intelligence quotient (IQ)

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test and arithmetic test. Those with PTSD recalled fewer words, demonstrated lower IQ than non-PTSD veterans and in those on psychoactive medications performed more poorly on the arithmetic testing than those not medicated. This study concluded that higher education may buffer development of PTSD.[227] In a separate study, Vasterling examined 961 Soldiers preparing for the war in Iraq. Those who deployed demonstrated compromised attention and visuo-spatial memory and increased tension and confusion.[127] It is unclear how many people in the current study deployed as deployment history was not gathered. Deployment history should be considered in future studies. While individual differences and experiences may be interesting to compare and could possibly confound a study, randomization in the current demonstrated effectiveness as there were no differences in PTST, anxiety, and other disorders between the HRVB and control groups.

HRVB was used in a study of PTSD veterans including ten combat veterans; five with PTSD (intervention) and five without PTSD (controls). Patients in the intervention group were provided with four weeks of HRVB training. Attention and immediate memory were both statistically and clinically significant, with an increase in learned words in the HRVB group and a small decrease in words learned in the control group.[8]

In summary, the PASAT, a measure of speed, attention, and the working memory component of executive function, demonstrated both groups improved. The HVLT, a measure of executive function, verbal and working memory, and to a lesser degree, attention, demonstrated both groups improved. The PVT, a

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measure of sustained vigilance, demonstrated an improvement in the HRVB intervention group. As both HVLT and PASAT have the potential for a learning effect, this may explain why an improvement was seen in both groups. An improvement was noted in the HRVB intervention group but not in the control group for the PVT which demonstrates the receipt of HRVB lead to an improvement in reaction time. Furthermore, stress loads in PASAT and HVLT may be higher than in PVT and attenuated benefits from the HRVB intervention. Future studies should evaluate in finer detail the cognitive functions and stress load of each of these tests while recording HRV measurements in a resting state, during task performance, and then followed by a resting state after testing to evaluate how much HRV changes from rest to stress and then how quickly, if at all, HRV returns to pretesting levels. As time-on-task is a crucial matter for cognitive function tests, the PASAT and HVLT were conducted over the course of about 4 minutes each, whereas the PVT was conducted over 10 minutes. If longer versions of the PASAT and HVLT were conducted over 10 minutes for example, it would be hypothesized that those in the HRVB intervention group would demonstrate a significant improvement over and above those in the control group. Lastly, it would be hypothesized those in the HRVB intervention group who conduct resonant frequency breathing during the PVT would demonstrate less reduction in HRV during testing, would demonstrate decreased reaction time, and would result in a fewer number of lapses of the PVT as compared to the control group.

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5.4 Depression, Stress, and Fatigue Discussion

In the present study, HRVB training improved depression symptoms immediately following the training and was evident two months later at the Follow-up Assessment. Medium effect sizes were observed from baseline to post-training (-0.53, Table 4.13) and from baseline to follow-up (-0.60, Table 4.13). This finding is consistent with previous studies, all of which that had fewer participants. Improvement in depression was reported by Windthorst and colleagues in a study among 28 women with chronic fatigue and refractory depression who were randomized into an HRVB or a graded exercise training group. HRVB was provided for 10 training sessions and a reduction in both depressive symptoms and fatigue was reported over a five-month period.[44] Another study reported improvements in major depressive disorder (MDD) in eight participants over a 10 week period.[40] To the author's knowledge, the current study is the largest randomized controlled study of US military veterans to show a statistically significant improvement in depression due to HRVB.

There is a growing acceptance in the Western world for the benefits that can be derived from alternative stress-reducing therapies.[25, 228] Van der Zwan and colleagues conducted a randomized HRVB trial among 76 individuals 18-40-years old. Outcomes included measures of depression, anxiety, and stress. The interventions entailed 20 minutes of daily exercise, meditation, or HRVB for five weeks. The largest effects were found with physical activity/exercise. Depression did not improve in the HRVB group. There were no statistically significant group differences for any of the outcomes. Small but statistically significant

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improvements in psychological well-being were observed among the HRVB group. However, on average, those in the physical activity group exercised longer than the other groups spent in their intervention (meditation, HRVB), therefore protocol compliance differed.[25] In the current study, protocol compliance was the same between groups and depression was improved in the intervention group indicating HRVB was successful at reducing depression in the intervention group.

In a study of 32 female college students (ages 18-25 years) with MDD, HRVB was compared with treatment as usual (TAU), or a non-depressed control group. [41] MDD can be defined as a unipolar depressive disorder displaying five of nine symptoms most days over the course of two weeks: (depressed mood, loss of interest/pleasure, weight or appetite change, insomnia/hypersomnia, psychomotor retardation or agitation, loss of energy or fatigue, impaired concentration or indecisiveness, worthlessness or guilt, thoughts of death or suicidal ideation/attempt).[229-231] Randomization for those with depression occurred into the HRVB+TAU or the TAU group. Five weekly HRVB training sessions were administered, and participants were encouraged to practice 15-20 minutes per day 4-5 times per week. HRV measurements did not improve in the TAU (medication) group alone relative to HRVB+TAU. However, greater increases in HRV were found with HRVB+TAU (psychotherapy) and greater decreases in BDI scores among those with MDD compared to those without MDD.[41]

Karavidas conducted an open-label research study in which all 11 participants with MDD age 25-58 received HRVB training with 10 weekly sessions and encouraged to practice twice daily for 20 minutes each. A decrease in

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depression severity and total BDI scores was noted in the group. A very large effect size (d=3.6) was noted in the Hamilton Depression Scale with a reduction in depression and statistically significant reduction in BDI from baseline to sessions 4, 7, and 10.[40] Consistent with the present study, BDI was reduced through the use of HRVB. A limitation of the study by Karavidas is the small number of participants. In comparison to the current study, nearly eight times as many participants were enrolled as with Karavidas' study. A strength of the above study is the encouragement to practice HRV twice a day for 20 minutes as compared to 15 minutes in the current study and ten training visits were conducted compared to six in the current study. It would be interesting to see if effect sizes were even more improved in the current study by either increasing the number of sessions or to increase the frequency and duration of home training visits.

Zucker et al. conducted HRVB in a randomized pilot study of 38 people diagnosed with PTSD (ages 18-60), comparing HRVB and progressive muscle relaxation with a 4-week post-intervention follow-up and practicing 20-minutes per day averaging 5-6 practices per week. These participants were in a residential facility for substance abuse. A group by time interaction was found for improvements in SDNN. While no group by time interaction was found for PTSD symptom tests, reductions were found in PTSD symptoms in both groups from pre- to post-intervention. A reduction in BDI was found when it was used categorically; over 94% of the intervention group reduced in severity one category (mild depression=0-13, moderate= 14-19, and sever 29-63).[36] Consistent with the current study, a decrease in depression was noted, however in the current study

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an increase in SDNN was not found in the HRVB group. While Zucker et al did find a reduction in PTSD symptoms, the current study did not observe a statistically significant reduction in stress in the intervention group. As it pertains to practice time, the current study recommended 15 minutes per day each day. It also is noteworthy that those with current substance abuse were excluded from the current study. Upon completion of any substance abuse rehabilitation program, potential participants had to remain sober for at least six months prior to being able to enroll. Substance abuse and withdrawal have direct implications on HRV measurements.[232-234]

No statistical differences in perceived stress were noted between groups in the current study, and small effect sizes were observed between baseline to post-training as well as baseline to follow-up respectively (d= 0.12 and -0.09, Table 4.13). There are several published studies pertaining to stress and HRVB among veterans focusing on PTSD patients that reported improvements in stress.[36, 235-237] Of the 85 participants who enrolled in this study, 38 were diagnosed with PTSD at baseline and they were equally distributed between the two groups. Perceived stress may be due to situations in the lives of the participants that are either chronic or may have occurred just prior to conducting the assessments. For example, a participant may have received the intervention and demonstrated improvement in HRV coherence, however due to both chronic and acute situational stressors, the participant may not have felt that their stress level had improved. Anecdotally, there was one specific participant in the intervention group that did just this. Her HRV coherence significantly improved, however chronically, she was providing

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care for her elderly mother while acutely, a 2-year-old niece she had previously provided care for died of congenital birth defects during this study. Consideration should be given to evaluate the composition of perceived stress in future studies.

In a study by Ratanasiripong and researchers, HRVB was conducted with 60 second-year baccalaureate nursing students in Thailand comparing a control group with an intervention group over five weeks. As they entered their clinical training, those who received HRVB demonstrated essentially no change in stress level, although a reduction in anxiety was observed relative to the control group.[238]

Similar to perceived stress, no statistically significant improvements were noted in general fatigue or the fatigue subscales in the present study, and small effect sizes were also noted among the fatigue assessments (Table 4.13). Smets and coauthors describe fatigue as a normal feeling resulting from physical exertion such as with exercise or due to insufficient sleep. While fatigue may be a symptom, Smets suggests that it could be a precursor to other disease outcomes and could also be analyzed as an outcome for treatments.[172] The benefit of a multidimensional inventory to measure fatigue as compared to a single dimension, is that one person could feel mentally alert while being physically tired or a person could feel mentally tired but express physical stamina.[172] Analyses of the five components of the MFI showed improvement in all five fatigue categories (general, mental, physical, activity, and motivation) after HRVB.[44] As the follow-up was observed at five months post-intervention, it may be that fatigue takes a longer period of time to recover. In the current study, fatigue was measured up to four

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months after Baseline Assessment. Future studies should consider at least five months of follow-up to ascertain if fatigue takes longer to recover.

5.5 Strengths and Limitations

As this is a randomized control trial, one study strength of this design is reduced confounding and selection bias. Differences noted between the groups at baseline were by chance alone. Another strength of this study is that subjects were screened for exposure to biofeedback. An assessment of HRV was made at baseline prior to HRVB exposure. Changes in HRV between the assessments were found to be causally related to HRVB training thus supporting the hypothesis that improvement in HRV can improve pain severity, pain interference, the need for non-steroidal anti-inflammatory drug use, as well as reaction time, and depression.

A limitation of this study is that it only included US military veterans ages 18+ and therefore may not be generalizable to all populations. Information bias could have resulted if participants had difficulty either recalling past information or were indecisive in how to respond to a question. Furthermore, information bias may have resulted if a participant decided not to answer (refused) a question (i.e. income) or may have been magnified if, despite the confidentiality imposed by the study protocol, they felt that information provided in this study may negatively impact their financial compensation from the VA. Efforts were made to ensure completeness of all questionnaires at the time they were completed and then, using a neutral demeanor, participants were asked if the blank answer they

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provided was what they meant to provide. Staff were trained on how to transcribe and code variables for accuracy and they performed a 10% audit of data at various times. Interviewer bias was minimized by ensuring participant information was coded. Participants were blinded to which group they were randomly enrolled and upon completion, and the control group was offered the opportunity to receive the HRVB training. Another limitation of this study was that participants who volunteered may have differed from those who did not volunteer to participate. A large limitation of this study due to the length of time involved over four months, was loss-to-follow-up. Attempts were made to encourage participants to continue to remain enrolled and when a participant decided to voluntarily disenroll or to not make any more appointments, research staff inquired as to the reasoning to help in the final analysis. Over 500 veterans were screened prior to enrollment. Of these, many were not eligible due to uncontrolled hypertension or due to either a beta-blocker or calcium channel blocker medication. This precluded participation among some patients, yet exclusion of these patients helped prevent introduction of other biases. Those who were younger were more likely to be lost-to-follow-up rather than those who were older. Otherwise, no differences were noted among those who completed the study versus those who were lost-to-follow-up in the demographics or comorbid diseases (Tables 4.14 and 4.15).

A limitation of the PASAT has been noted with regional rates of diction. Those with language or speech difficulties may have been placed at a disadvantage and geographical or cultural speech patterns also may have influenced PASAT outcomes.[219] For example, this study was performed in the

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southeastern United States where some people may naturally speak with a slower cadence. This could be weighed against the fact that the study sample was comprised of former members of the military that grew up and served across the US and the globe. However, Tombaugh notes that obtaining low scores on the PASAT does not confirm pathology of the neurological system. Differences were not observed in PASAT outcome between groups. In the present study, improvements were found in both the HRVB group and the control group in the PCS, PASAT, HVLT, and the number of Lapses in the PVT. This may be due to a learning effect or that these tests may not be the best tests for this veteran population.

In conclusion, HRVB is a safe, easily implemented, non-pharmacological technique that can be used virtually anywhere and can help in the self-regulation of symptoms such as pain and depression. Through the use of HRVB, HRV coherence improved, pain severity and pain interference decreased, a reduction in NSAID use was observed, depression decreased, and reaction time improved in the intervention group relative to the control group. Larger studies conducted at multiple sites should be conducted to further determine the efficacy of HRVB among those with pain related symptoms in both veterans and the general population.

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APPENDIX A

SUPPLEMENTAL MATERIALS

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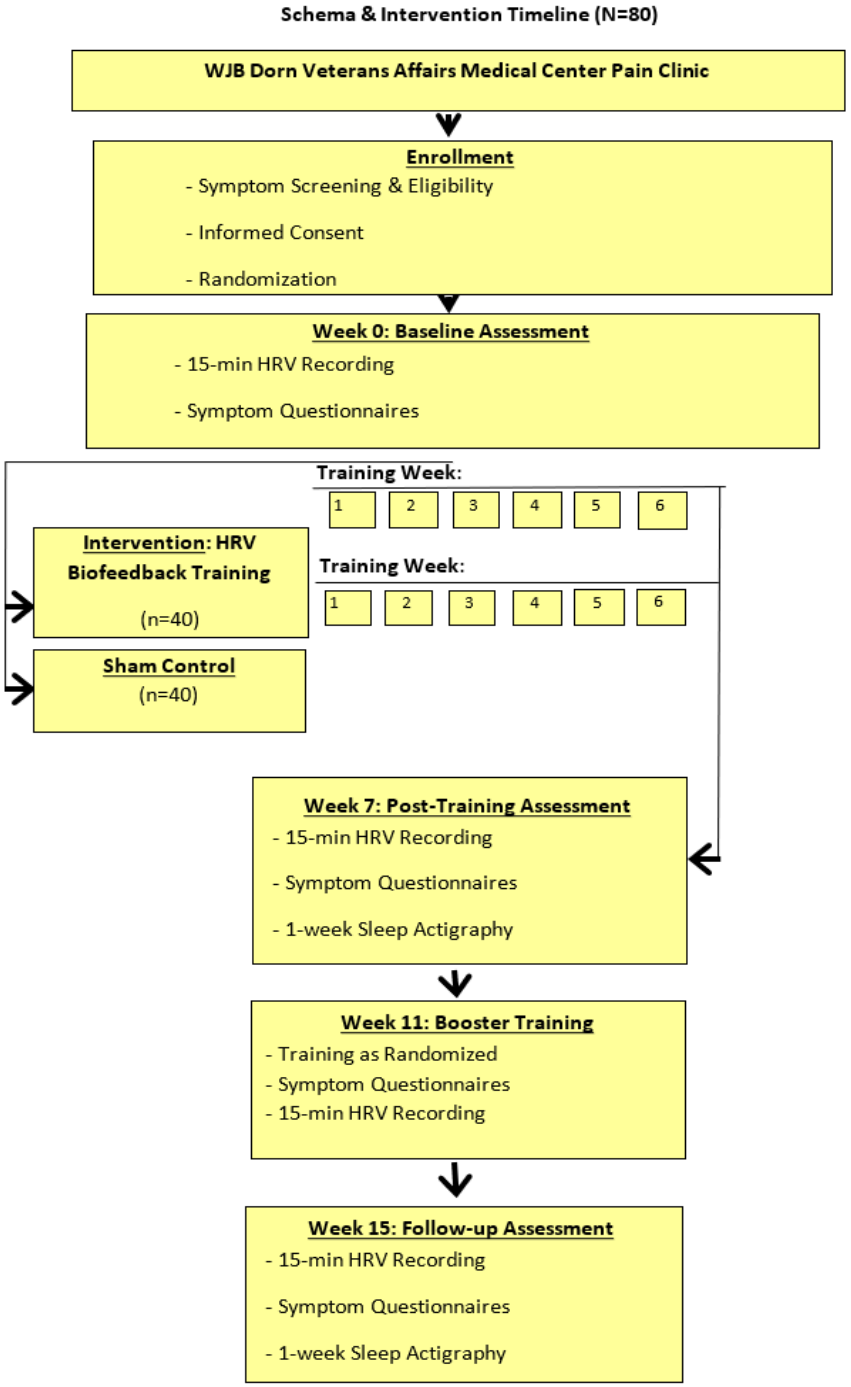

Figure A.1: 16-Week Study Timeline

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Extraction of HRV Coherence values using Kubios:

1. Open the interbeat interval (ibi) file in Kubios

2. Apply artifact correction to highest level (Very Low, Low, Medium, etc) that does not alter the waveform from previous level. Do not use Custom.

3. Record all data values of interest from Time- and Frequency-Domain screens.

4. On "Analysis Options, Frequency Bands" window, change the LF Band (blue) upper limit and the HF Band (yellow) lower limit both to 0.26Hz.

5. Note Peak Frequency in the LF range (which you have now set to be from 0.04Hz to 0.26Hz).

6. Set LF lower and upper limits to values that are +/- 0.015 Hz around the peak frequency in the range from 0.04Hz to 0.26Hz. For example, if LF Peak between 0.04Hz and 0.26Hz is 0.085Hz, change LF Band lower limit to 0.070Hz and upper limit to 0.10Hz. Note: Do not set LF lower limit less than 0.04Hz or the upper limit greater than 0.26Hz.

7. Record the power (ms2) in the LF Band as "Coherence".

8. From this value and the values collected from the Frequency-Domain table in Step 3 above, calculate the Coherence ratio as: Coherence/Total Power-Coherence.

Figure A.2: Instructions to calculating HRV Measures

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QUESTIONNAIRE

1. Sociodemographic Information (SDI)
2. Brief Pain Inventory (BPI)
3. Perceived Stress Scale (PSS)
4. Beck Depression Index II (BDI)
5. Occupation (OCC)
6. Munich Chronotype Questionnaire (MCTQ)
7. Pittsburgh Sleep Quality Index (PSQI)
8. Multidimensional Fatigue Inventory (MFI)
9. Pain Catastrophizing Scale (PCS)
10. Brief Cope Questionnaire (BCQ)
11. Social Support (SS)

Figure A.3 Participant Questionnaire

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INSTRUCTIONS: Read carefully each question and answer each by circling the answer of by filling in the blank. If you have a question, please ask the research staff person administering this survey.

ID: _____ Date: _____ Session: _____ Start Time: _____

1.0 INDIVIDUAL CHARACTERISTICS

1.1 Age: _____Years

1.2 Height (feet, inches): _____

1.3 Weight (pounds): _____

1.4 Sex:

[1] Male
[2] Female

1.5 What is your ethnic group?

[1] Hispanic or Latino
[2] Not Hispanic or Latino
[7] Refuse
[9] Don't know

1.6 What is your racial group?

[1] American Indian or Alaska Native
[2] Asian
[3] Native Hawaiian or Other Pacific Islander
[4] Black or African American
[5] White
[6] Other (Specify: _____)
[7] Refuse
[9] Don't know

1.7 What is the highest grade or year of school that you have completed? (Circle Answer)

1 2 3 4 5 6 7 8 / 9 10 11 12 / 13 14 15 16 / 17 18 19+
Grade School / High School / College / Graduate or Technical

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1.8 Which income level in the following list comes closest to the total income for your family before taxes in the last year?

[1] under $10,000
[2] $10,000 up to $30,000
[3] $30,000 up to $50,000
[4] $50,000 up to $75,000
[5] $75,000 up to $100,000
[6] $100,000 or more
[7] Refuse
[9] Don't know

1.9 Do you currently smoke cigarettes?

[1] Yes [2] No

1.10 If no, have you ever smoked? (At least 5 packs in your entire life)

[1] Yes [2] No [9] Don't know

1.11 How many **packs** of cigarettes do you currently smoke **each day**, on the average? (1 pack = 20 cigarettes)

Number of Packs per Day: _____
(Enter 0 if you are a nonsmoker)

1.12 How many **years** have you smoked?

Number of Years: _____ (Enter 0 if you are a nonsmoker)

1.13 Do you currently use any of the other tobacco products listed below? (Circle all that apply).

[1] yes, cigars
[2] yes, pipes
[3] yes, chewing tobacco
[4] yes, snuff
[5] no

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1.14 Are you exposed to the smoke from other people's cigarettes, pipes, or cigars on a daily basis while at home or at work? (Circle all that apply).

[1] Yes, at home only
[2] Yes, at work only
[3] Yes, at home and at work
[4] No

1.15 How many days per week do you drink alcoholic beverages, on the average?

Days per week: _____ (Enter zero if none).

1.16 About how many drinks do you consume on days when you drink, on the average?
(Note: A drink is 1 can or bottle of beer, or 1 glass of wine or wine cooler, or 1 cocktail, or 1 shot of liquor).

Number of drinks _____ (Enter zero if none).

1.17 How many caffeinated beverages do you drink per day, on the average? (Enter 0 if none).

[1] Coffee: _____
[2] Tea: _____
[3] Chocolate (Cocoa): _____
[4] Soda Pop (Soft Drinks, Cola): _____
[5] Other: _____ (Specify): _____
[9] Don't Know

1.19 Was there a time in the past 12 months when you needed to see a doctor but could not because of cost?

[1] Yes
[2] No
[7] Don't know/not sure
[9] Refused

2.0 PAIN

2.1 Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

[1] Yes [2] No

2.2 Please indicate the areas that hurt the most by circling the appropriate numbers (circle all that apply).

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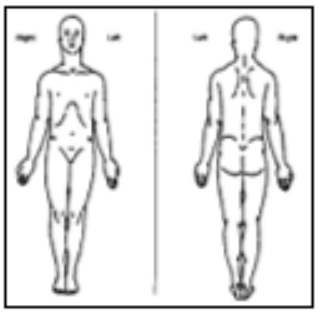

[1] Arm and/or hand [2] Leg and/or foot [3] Head and/or neck [4] Chest

[5] Abdomen [6] Pelvis [7] Back [8] Buttock

2.3 Please rate your pain by circling the one number that best describes your pain at its **worst** in the last 24 hours.

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]

No Pain Pain as bad as you can imagine

2.4 Please rate your pain by circling the one number that best describes your pain at its **least** in the last 24 hours.

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]

No Pain Pain as bad as you can imagine

2.5 Please rate your pain by circling the one number that best describes your pain on the **average**.

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]

No Pain Pain as bad as you can imagine

2.6 Please rate your pain by circling the one number that tells how much pain you have **right now**.

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]

No Pain Pain as bad as you can imagine

2.7 What treatments or medications are you receiving for your pain?

_____

_____

2.8 In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much **relief** you have received.

[0%] [10%] [20%] [30%] [40%] [50%] [60%] [70%] [80%] [90%] [100%]

No Relief Complete Relief

2.9 Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

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A. General Activity

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]

Does not interfere Completely Interferes

B. Mood

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]

Does not interfere Completely Interferes

C. Walking Ability

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]

Does not interfere Completely Interferes

D. Normal Work (includes both work outside the home and housework)

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]

Does not interfere Completely Interferes

E. Relations with other people

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]

Does not interfere Completely Interferes

F. Sleep

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]

Does not interfere Completely Interferes

G. Enjoyment of life

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]

Does not interfere Completely Interferes

Instructions: We would like some information about medications and treatments you currently receive. Please place an X in the appropriate column. If you answer yes, please enter number of pills you take per day, on average. Otherwise, leave it blank.

Do you take any of the following over-the-counter **pain medications**?

Name of Medication	Yes	No	Average number of pills per day	Name of Medication	Yes	No	Average number of pills per day
Aspirin, Baby Aspirin				Ascriptin A/D			
Anacin				BC Powder			
Arthritis Pain Formula				Buffered Aspirin			
Ascriptin				Bufferin			

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Cama				Enteric-Coated Aspirin			
Ecotrin				Excedrin			
Acetaminophen (Tylenol)				Aleve			
Ibuprofen				Advil			
Other: _____				Other: _____			

Do you take any of the following prescription strength **non-steroidal anti-inflammatory drugs (NSAIDs)**?

Name of Medication	Yes	No	Average number of pills per day	Name of Medication	Yes	No	Average number of pills per day
Diclofenac (Voltaren)				Meloxicam (Mobic)			
Piroxicam (Feldene)				Ketoprofen (Orudis)			
Other: _____				Other: _____			

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Do you take any of the following **opioid or narcotic medications**?

Name of Medication	Yes	No	Average number of pills per day	Name of Medication	Yes	No	Average number of pills per day
Codeine				Oxycodone (OxyContin)			
Fentanyl (Duragesic)				Hydrocodone (Lortab, Vicodin)			
Hydromorphone (Dilaudid)				Oxycodone (Percocet)			
Morphine (MS Contin)				Tramadol (Ultram)			
Other:				Other:			

Do you take any of the following **muscle relaxers**?

Name of Medication	Yes	No	Average number of pills per day	Name of Medication	Yes	No	Average number of pills per day
Cyclobenzaprine (Flexeril)				Methocarbamol (Robaxin)			
Metaxalone (Skelaxin)				Tizanidine (Zanaflex)			
Baclofen (Lioresal)				Other: _____			

Do you take any of these **medications**?

Name of Medication	Yes	No	Average number of pills per day	Name of Medication	Yes	No	Average number of pills per day
Sertraline (Zoloft)				Fluoxetine (Prozac)			
Citalopram (Celexa)				Paroxetine (Paxil)			
Amitriptyline (Elavil)				Nortriptyline (Pamelor)			
Desipramine (Norpramin)				Duloxetine (Cymbalta)			
Venlafaxine (Effexor)				Milnacipran (Savella)			
Escitalopram (Lexapro)				Bupropion (Wellbutrin/Zyban)			
Trazodone (Desyrel)				Mirtazapine (Remeron)			
Gabapentin (Neurontin)				Pregabalin (Lyrica)			
Alprazolam (Xanax)				Diazepam (Valium)			
Lorazepam (Ativan)				Clonazepam (Klonopin)			
Zolpidem (Ambien)				Eszopiclone (Lunesta)			
Doxepin (Silenor)				Butalbital, (Fioricet)			
Methylphenidate (Ritalin, Concerta)				Dextroamphetamine (Dexedrine)			
Dextroamphetamine Amphetamine (Adderall)				Other: _____			

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Please indicate whether you have received any of the following treatments? (Circle your response).

Treatment	Never	Not in the past month	Less than once a week	Once or twice a week	Three or more times a week	Daily
Working with a psychologist	[0]	[1]	[2]	[3]	[4]	[5]
Meditation or relaxation training (not this study)	[0]	[1]	[2]	[3]	[4]	[5]
Yoga	[0]	[1]	[2]	[3]	[4]	[5]
Exercise	[0]	[1]	[2]	[3]	[4]	[5]
Physical therapy	[0]	[1]	[2]	[3]	[4]	[5]
Surgery (e.g., lumbar fusion, discectomy)	[0]	[1]	[2]	[3]	[4]	[5]
Steroid injection for pain	[0]	[1]	[2]	[3]	[4]	[5]
Nerve burning procedure	[0]	[1]	[2]	[3]	[4]	[5]
Electronic pain device	[0]	[1]	[2]	[3]	[4]	[5]
Acupuncture	[0]	[1]	[2]	[3]	[4]	[5]
Spinal manipulation or chiropractic care	[0]	[1]	[2]	[3]	[4]	[5]
Massage therapy	[0]	[1]	[2]	[3]	[4]	[5]
Other: _____	[0]	[1]	[2]	[3]	[4]	[5]

We would like some information about your medical history. Please place an **X** in the appropriate column.

Have you ever been told by your doctor that you have any of the following conditions?	Yes	No
Asthma		
Irritable Bowel Syndrome		
Fibromyalgia		
Chronic Fatigue Syndrome		
Any Sleep Disorder (e.g., insomnia, obstructive sleep apnea)		
Pre-Diabetes or Diabetes		
Chronic or Frequent Headaches		
Chronic Symptoms of Concussion or Traumatic Brain Injury (TBI)		

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3.0 STRESS

The questions in this scale ask you about your feelings and thoughts **during the last month**. In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.

0 = Never 1 = Almost Never 2 = Sometimes 3 = Fairly Often 4 = Very Often

3.1	In the last month, how often have you been upset because of something that happened unexpectedly?	[0]	[1]	[2]	[3]	[4]
3.2	In the last month, how often have you felt that you were unable to control the important things in your life?	[0]	[1]	[2]	[3]	[4]
3.3	In the last month, how often have you felt nervous and "stressed"?	[0]	[1]	[2]	[3]	[4]
3.4	In the last month, how often have you felt confident about your ability to handle your personal problems?	[0]	[1]	[2]	[3]	[4]
3.5	In the last month, how often have you felt that things were going your way?	[0]	[1]	[2]	[3]	[4]
3.6	In the last month, how often have you found that you could not cope with all the things that you had to do?	[0]	[1]	[2]	[3]	[4]
3.7	In the last month, how often have you been able to control irritations in your life?	[0]	[1]	[2]	[3]	[4]
3.8	In the last month, how often have you felt that you were on top of things?	[0]	[1]	[2]	[3]	[4]
3.9	In the last month, how often have you been angered because of things that were outside of your control?	[0]	[1]	[2]	[3]	[4]
3.10	In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	[0]	[1]	[2]	[3]	[4]

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4.0 MOOD

Instructions: Please read each group of statements carefully, and then pick out **the one statement** in each group that best describes the way you have been feeling during **the past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Items 4.16 (Changes in Sleeping Pattern) and 4.18 Changes in Appetite.

4.1 Sadness [0] I do not feel sad. [1] I feel sad much of the time. [2] I am sad all the time. [3] I am so sad or unhappy that I can't stand it.	**4.6 Punishment Feelings** [0] I don't feel I am being punished. [1] I feel I may be punished. [2] I expect to be punished. [3] I feel I am being punished.
4.2 Pessimism [0] I am not discouraged about my future. [1] I feel more discouraged about my future than I used to be. [2] I do not expect things to work out for me. [3] I feel my future is hopeless and will only get worse.	**4.7 Self-Dislike** [0] I feel the same about myself as ever. [1] I have lost confidence in myself. [2] I am disappointed in myself. [3] I dislike myself.
4.3 Past Failure [0] I do not feel like a failure. [1] I have failed more than I should have. [2] As I look back, I see a lot of failures. [3] I feel I am a total failure as a person.	**4.8 Self-Criticalness** [0] I don't criticize or blame myself more than usual. [1] I am more critical of myself than I used to be. [2] I criticize myself for all my faults. [3] I blame myself for everything bad that happens.
4.4 Loss of Pleasure [0] I get as much pleasure as I ever did from the things I enjoy. [1] I don't enjoy things as much as I used to. [2] I get very little pleasure from the things I used to enjoy. [3] I can't get any pleasure from the things I used to enjoy.	**4.9 Suicidal Thoughts or Wishes** [0] I don't have any thoughts of killing myself. [1] I have thoughts of killing myself, but I would not carry them out. [2] I would like to kill myself. [3] I would kill myself if I had the chance.

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4.5 Guilty Feelings	4.10 Crying
[0] I don't feel particularly guilty.	[0] I don't cry any more than I used to.
[1] I feel guilty over many things I have done or should have done.	[1] I cry more than I used to.
[2] I feel quite guilty most of the time.	[2] I cry over every little thing.
[3] I feel guilty all of the time.	[3] I feel like crying, but I can't.

4.11 Agitation	4.17 Irritability
[0] I am no more restless or wound up than usual.	[0] I am no more irritable than usual.
[1] I feel more restless or wound up than usual.	[1] I am more irritable than usual.
[2] I am so restless or agitated that it's hard to stay still.	[2] I am much more irritable than usual.
[3] I am so restless or agitated that I have to keep moving or doing something.	[3] I am irritable all the time.
4.12 Loss of Interest	**4.18 Changes in Appetite**
[0] I have not lost interest in other people or activities.	[0] I have not experienced any change in my appetite.
[1] I am less interested in other people or things than before.	[1a] My appetite is somewhat less than usual.
[2] I have lost most of my interest in other people or things.	[1b] My appetite is somewhat greater than usual.
[3] It's hard to get interested in anything.	[2a] My appetite is much less than before.
	[2b] My appetite is much greater than usual.
	[3a] I have no appetite at all.
	[3b] I crave for food all the time.
4.13 Indecisiveness	**4.19 Concentration Difficulty**
[0] I make decisions about as well as ever.	[0] I can concentrate as well as ever.
[1] I find it more difficult to make decisions than usual.	[1] I can't concentrate as well as usual.
[2] I have much greater difficulty in making decisions than I used to.	[2] It's hard to keep my mind on anything for very long.
[3] I have trouble making any decisions.	[3] I find I can't concentrate on anything.
4.14 Worthlessness	**4.20 Tiredness or Fatigue**
[0] I do not feel I am worthless.	[0] I am no more tired or fatigued than usual.
[1] I don't consider myself as worthwhile and useful as I used to.	[1] I get more tired or fatigued more easily than usual.
[2] I feel more worthless as compared to other people.	[2] I am too tired or fatigued to do a lot of things I used to do.
[3] I feel utterly worthless.	[3] I am too tired or fatigued to do most of the things I used to do.

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4.15 Loss of Energy [0] I have as much energy as ever. [1] I have less energy than I used to have. [2] I don't have enough energy to do very much. [3] I don't have enough energy to do anything.	**4.21 Loss of Interest in Sex** [0] I have not noticed any recent change in my interest in sex. [1] I am less interested in sex than I used to be. [2] I am much less interested in sex now. [3] I have lost interested in sex completely.
4.16 Changes in Sleeping Pattern [0] I have not experienced any change in my sleeping pattern. [1a] I sleep somewhat more than usual. [1b] I sleep somewhat less than usual. [2a] I sleep a lot more than usual. [2b] I sleep a lot less than usual. [3a] I sleep most of the day. [3b] I wake up 1-2 hours early and can't get back to sleep.	

5.0 OCCUPATION

INSTRUCTIONS: Read carefully each question and answer each by circling the answer of by filling in the blank. If you have a question, please ask the research staff person who is administering this questionnaire.

Your Domestic Situation:

5.1 Are you *(Circle one)*: [1] Married/Living with a partner
[2] Separated/Divorced
[3] Widowed
[4] Single

5.2 If married or living with partner, on average, how many hours per week does your partner work in paid employment? _____ Hours

If "0" hours, is your spouse/partner: __ retired
__ unemployed

5.3 What is your partner's usual work pattern? (Circle one)

[1] Daytime - no shifts
[2] Rotating shifts with nights
[3] Rotating shifts without nights
[4] Permanent nights
[5] Other *(Please specify)*: _____

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5.4 How many people live in your household? _____

5.5 How many of these need to be cared for by you? _____

5.6 Which of the following age groups are represented in your household excluding yourself ?

(circle all that apply)

[1] 0 to 5 years
[2] 6 to 12 years
[3] 13 to 18 years
[4] 19 to 24 years
[5] 25 to 60 years
[6] 60 years +

5.7 Do you work now?

[1] No → Currently [2] Retired
[3] Unemployed
↓
Go to the question 6.0

[4] Yes → Continue to the next question

5.8 Present job title: _____

5.9 How long have you worked at the job you entered above? _____ Years

5.10 Circle the type of industry or profession in which you currently work:

[1] Agriculture, Forestry, & Fishing
[2] Mining
[3] Construction
[4] Manufacturing (plants, factories, or mills assembling parts & products)
[5] Transportation, Communications, Electric, Gas, or Sanitary
[6] Wholesale Trade (agents or brokers in buying & selling merchandise)
[7] Retail Trade (selling merchandise for personal or household consumption)
[8] Finance, Insurance, or Real Estate
[9] Services (hotel, repair, amusement, health, legal, engineering & other professional services, education, membership organizations)
[10] Public Administration (Federal, State, local, & international government)
[11] Other: Specify_____

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5.11 On average, how many hours do you work each week excluding overtime?

_____hours _____minutes _____

5.12 What is your usual work schedule? (Check one)

[1] Days → **Go to the question 5.15**
[2] Evenings (2nd) shifts
[3] Permanent nights
[4] Rotating shifts with nights
[5] Rotating shifts without nights
[6] Other (please specify): _____

5.13 How long in your lifetime have you worked evenings or night shifts?

_____Years (enter 0 if none)

5.14 How does your partner feel about you working shifts? (Circle one)

Extremely unsupportive	**Fairly unsupportive**	**Quite indifferent**	**Fairly supportive**	**Extremely supportive**
[1]	[2]	[3]	[4]	[5]

Your shift details:

5.15 How long have you worked in your present shift system? _____ years _____months

5.16 How regular is the shift system you work? (Please circle one)

[1] **REGULAR** i.e., a fixed schedule that is repeated when the cycle of shifts finishes, even if occasional variations occur to meet special requests.

[2] **IRREGULAR** i.e., the schedule does not cycle or repeat in any regular manner and individual preferences are not taken into account.

[3] **FLEXIBLE** i.e., individuals concerned are consulted about their preferred duty hours before the schedule is drawn up.

	None	**Not very much**	**A fair amount**	**Quite a lot**	**Complete**
5.17 To what extent do you feel you have control over the specific shifts that you work?	[1]	[2]	[3]	[4]	[5]

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5.18 To what extent do you feel you have control of the specific start and finish times of the shifts you work? [1] [2] [3] [4] [5]

If you are working days or if you do not work please go to 6A.0

IF you working nights or irregular shifts please go to 6B.0

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6A.0 SLEEP/WAKE HABITS

6A.1 I have a regular work schedule (this includes being a housewife or househusband): [1] Yes [2] No

6A.2 If "Yes", how many days per week? [1] [2] [3] [4] [5] [6] [7]

Please complete all of the following sections, regardless of whether you are working on a regular basis or not. Use a 24 hour clock (military time). For example, 23:00 instead of 11:00PM

Workdays

6A.3 Image 1: I go to bed at _____ o'clock.

Image 2: Note that some people stay awake for some time when in bed!

6A.4 Image 3: I actually get ready to fall asleep at _____ o'clock.

6A.5 Image 4: I need _____ minutes to fall asleep.

6A.6 Image 5: I wake up at _____ o'clock.

6A.7 [1] with an alarm clock [2] without an alarm clock

6A.8 Image 6: After _____ minutes I get up.

Free Days

6A.9 Image 1: I go to bed at _____ o'clock.

Image 2: Note that some people stay awake for some time when in bed!

6A.10 Image 3: I actually get ready to fall asleep at _____ o'clock.

6A.11 Image 4: I need _____ minutes to fall asleep.

6A.12 Image 5: I wake up at _____ o'clock.

6A.13 [1] with an alarm clock [2] without an alarm clock

6A.14 Image 6: After _____ minutes I get up.

6A.15 Comments: Please leave a comment if you currently have NO possibility of freely choosing your sleep times (e.g. because of pet(s), child(ren) etc.). Provide other information as desired:

_____

_____

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6B.0 SLEEP/WAKE HABITS

Note: This instrument is for shift workers only. Complete either 6A or 6B but not both.

The following questions concern your sleep- and wake behavior on work days and free days. Please answer them with regard to your current shift schedule, i.e. not all combinations have to be filled out! Also, please reply with regard to the current season (i.e., the last 6 weeks). Please try to answer all questions, even when an answer seems difficult! Spontaneous answers are often the best. Please use a 24 hour clock (military time). For example, 23:00 instead of 11:00PM

How to fill out the Munich ChronoType Questionnaire:

Image 1:	The time when you went to bed.
Image 2:	Note that some people stay awake for some time when in bed!
Image 3:	The time when you "decided" to sleep, i.e. closed your eyes or turned off the lights.
Image 4:	Minutes you usually spent of average on falling asleep.
Image 5:	Time when you woke up.
Image 6:	Minutes to get up.
Alarm:	Indicate whether you used an alarm or not (NO, if you woke up before the alarm signal went off).
Between two shifts:	Please indicate your sleep times between two shifts.
Between two free days after a given shift:	Please indicate your sleep times between two free days after a given shift block (i.e., 2 free days after 4 days of morning shift in a row).

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Between two Morning Shifts

6B.1	I go to bed at _____ o'clock.	(Image 1)
	Note that some people stay awake for some time when in bed!	(Image 2)
6B.2	I actually get ready to fall asleep at _____ o'clock.	(Image 3)
6B.3	I need _____ minutes to fall asleep.	(Image 4)
6B.4	I wake up at _____ o'clock.	(Image 5)
6B.5	[1] with alarm [2] without alarm	
6B.6	I get up after _____ minutes.	(Image 6)
6B.7	I usually take a nap: [1] Yes [2] No	
6B.8	If "Yes", I take a nap from _____ o'clock to _____ o'clock.	
6B.9	There are particular reasons why I **cannot** freely choose my sleep times on morning shifts: [1] Yes [2] No	
6B.10	If "Yes": [1] Child(ren)/pet(s) [2] Hobbies [3] Others, for example:	
6B.11	_____	

Between two free days after Morning Shifts

6B.12	I go to bed at _____ o'clock.	(Image 1)
	Note that some people stay awake for some time when in bed!	(Image 2)
6B.13	I actually get ready to fall asleep at _____ o'clock.	(Image 3)
6B.14	I need _____ minutes to fall asleep.	(Image 4)
6B.15	I wake up at _____ o'clock.	(Image 5)
6B.16	[1] with alarm [2] without alarm	
6B.17	I get up after _____ minutes.	(Image 6)
6B.18	I usually take a nap: [1] Yes [2] No	
6B.19	If "Yes", I take a nap from _____ o'clock to _____ o'clock.	
6B.20	There are particular reasons why I **cannot** freely choose my sleep times on morning shifts: [1] Yes [2] No	
6B.21	If "Yes": [1] Child(ren)/pet(s) [2] Hobbies [3] Others, for example:	
6B.22	_____	

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Between two Evening Shifts

6B.23 I go to bed at _____ o'clock. (Image 1)

Note that some people stay awake for some time when in bed! (Image 2)

6B.24 I actually get ready to fall asleep at _____ o'clock. (Image 3)

6B.25 I need _____ minutes to fall asleep. (Image 4)

6B.26 I wake up at _____ o'clock. (Image 5)

6B.27 [1] with alarm [2] without alarm

6B.28 I get up after _____ minutes. (Image 6)

6B.29 I usually take a nap: [1] Yes [2] No

6B.30 If "Yes", I take a nap from _____ o'clock to _____ o'clock.

6B.31 There are particular reasons why I **cannot** freely choose my sleep times on morning shifts:

[1] Yes [2] No

6B.32 If "Yes": [1] Child(ren)/pet(s) [2] Hobbies [3] Others, for example:

6B.33 _____

Between two free days after Evening Shifts

6B.34 I go to bed at _____ o'clock. (Image 1)

Note that some people stay awake for some time when in bed! (Image 2)

6B.35 I actually get ready to fall asleep at _____ o'clock. (Image 3)

6B.36 I need _____ minutes to fall asleep. (Image 4)

6B.37 I wake up at _____ o'clock. (Image 5)

6B.38 [1] with an alarm clock [2] without an alarm clock

6B.39 I get up after _____ minutes. (Image 6)

6B.40 I usually take a nap: [1] Yes [2] No

6B.41 If "Yes", I take a nap from _____ o'clock to _____ o'clock.

6B.42 There are particular reasons why I **cannot** freely choose my sleep times on morning shifts:

[1] Yes [2] No

6B.43 If "Yes": [1] Child(ren)/pet(s) [2] Hobbies [3] Others, for example:

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6B.44 _____

Between two Night Shifts

6B.45 I go to bed at _____ o'clock. (Image 1)

Note that some people stay awake for some time when in bed! (Image 2)

6B.46 I actually get ready to fall asleep at _____ o'clock. (Image 3)

6B.47 I need _____ minutes to fall asleep. (Image 4)

6B.48 I wake up at _____ o'clock. (Image 5)

6B.49 [1] with alarm [2] without alarm

6B.50 I get up after _____ minutes. (Image 6)

6B.51 I usually take a nap: [1] Yes [2] No

6B.52 If "Yes", I take a nap from _____ o'clock to _____ o'clock.

6B.53 There are particular reasons why I **cannot** freely choose my sleep times on morning shifts:

[1] Yes [2] No

6B.54 If "Yes": [1] Child(ren)/pet(s) [2] Hobbies [3] Others, for example:

6B.55 _____

Between two free days after Night Shifts

6B.56 I go to bed at _____ o'clock. (Image 1)

Note that some people stay awake for some time when in bed! (Image 2)

6B.57 I actually get ready to fall asleep at _____ o'clock. (Image 3)

6B.58 I need _____ minutes to fall asleep. (Image 4)

6B.59 I wake up at _____ o'clock. (Image 5)

6B.60 [1] with an alarm clock [2] without an alarm clock

6B.61 I get up after _____ minutes. (Image 6)

6B.62 I usually take a nap: [1] Yes [2] No

6B.63 If "Yes", I take a nap from _____ o'clock to _____ o'clock.

6B.64 There are particular reasons why I **cannot** freely choose my sleep times on morning shifts:

[1] Yes [2] No

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6B.65 If "Yes": [1] Child(ren)/pet(s) [2] Hobbies [3] Others, for example:

6B.66 _____

7.0 SLEEP

The following questions relate to your usual sleep habits during the past week *only*. Your answers should indicate the most accurate reply for the *majority* of days and nights in the past week. Please answer all the questions.

7.1 At approximately what time of day do you usually feel your best?

[5] 5:00 a.m. - 8:00 a.m.
[4] 8:00 a.m. - 10:00 a.m.
[3] 10:00 a.m. - 5:00 p.m.
[2] 5:00 p.m. - 10:00 p.m.
[1] 10:00 p.m. - 5:00 a.m.

7.2 One hears about "morning types" and "evening types." Which one of these types do you consider yourself to be?

[6] Definitely a morning type
[4] Rather more a morning type than an evening type
[2] Rather more an evening type than a morning type
[0] Definitely an evening type

7.3 During the past month, when have you usually gone to bed?

Usual bed time [USE MILITARY TIME, e.g., 24:00 = midnight] _____

7.4 During the past month, how long has it usually taken to you to fall asleep each night?

Number of minutes_____

7.5 During the past month, when have you usually gotten up in the morning?

[USE MILITARY TIME, i.e. 24:00 = midnight] _____

7.6 During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

Hours of sleep per night_____

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For each of the next few questions, indicate how often you have trouble sleeping because of the following situations.

7.7 How often have had trouble sleeping because you…

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
7.7a. Cannot get to sleep within 30 minutes	[1]	[2]	[3]	[4]
7.7b. Wake up in the middle of the night or early morning	[1]	[2]	[3]	[4]
7.7c. Have to get up to use the bathroom	[1]	[2]	[3]	[4]
7.7d. Cannot breath comfortably	[1]	[2]	[3]	[4]
7.7e. Cough or snore loudly	[1]	[2]	[3]	[4]
7.7f. Feel too cold	[1]	[2]	[3]	[4]
7.7g. Feel too hot	[1]	[2]	[3]	[4]
7.7h. Had bad dreams	[1]	[2]	[3]	[4]
7.7i. Have pain	[1]	[2]	[3]	[4]
7.7j. Other reason Please describe:	[1]	[2]	[3]	[4]

7.8 During the past **week**, how would you rate your sleep quality overall?
[1] Very good
[2] Fairly good
[3] Bad
[4] Very bad

7.9 How often have you taken medicine (prescribed or "over the counter") to help you sleep?
[1] Not during the past month
[2] Less than once a week
[3] Once or twice a week
[4] Three or more times a week

7.10 How often have you used alcohol to help you to sleep?
[1] Not during the past month
[2] Less than once a week
[3] Once or twice a week
[4] Three or more times a week

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7.11 How often have you had trouble staying awake while driving, eating a meal, or engaging in social activities?

[1] Not during the past month
[2] Less than once a week
[3] Once or twice a week
[4] Three or more times a week

7.12 How much of a problem has it been for you to keep up enough enthusiasm to get things done?

[1] No problem at all
[2] Only a very slight problem
[3] Somewhat of a problem
[4] A very big problem

7.13 How frequently have you ever been told by *your spouse, partner, or roommate* that you do any of the following while you are sleeping?

	No spouse	Never	Sometimes	Often	Always
7.13a. Loud snoring	[0]	[1]	[2]	[3]	[4]
7.13b. Long pause between breaths while asleep	[0]	[1]	[2]	[3]	[4]
7.13c. Legs twitching or jerking while you sleep	[0]	[1]	[2]	[3]	[4]
7.13d. Episodes of disorientation or confusion during sleep	[0]	[1]	[2]	[3]	[4]
7.13e. Other restlessness while you sleep Describe_____	[0]	[1]	[2]	[3]	[4]

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8.0 FATIGUE

Instructions:

By means of the following statements we would like to get an idea of how you have been feeling **lately**.

There is, for example, the statement:

"I FEEL RELAXED"

If you think that this is **entirely true**, that indeed you have been feeling relaxed lately, please, place an **X** in the extreme left box; like this:

yes, that is true ☒1 ❑2 ❑3 ❑4 ❑5 **no, that is not true**

The more you **disagree** with the statement, the more you can place an **X** in the direction of "no, that is not true". Please do not miss out a statement and place only one **X** in a box for each statement.

8.1	I feel fit.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.2	Physically, I feel only able to do a little.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.3	I feel very active.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.4	I feel like doing all sorts of nice things.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.5	I feel tired.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.6	I think I do a lot in a day.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.7	When I am doing something, I can keep my thoughts on it.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.8	Physically I can take on a lot.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.9	I dread having to do things.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.10	I think I do very little in a day.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.11	I can concentrate well.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.12	I am rested.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.13	It takes a lot of effort to concentrate on things.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.14	Physically I feel I am in a bad condition.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.15	I have a lot of plans.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.16	I tire easily.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.17	I get little done.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.18	I don't feel like doing anything.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.19	My thoughts easily wander.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8.20	Physically I feel I am in an excellent condition.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true

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9.0 COPING WITH PAIN

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0– not at all 1– to a slight degree 2– to a moderate degree 3– to a great degree 4– all the time

When I'm in pain…

9.1 _____ I worry all the time about whether the pain will end.

9.2 _____ I feel I can't go on.

9.3 _____ It's terrible and I think it's never going to get any better.

9.4 _____ It's awful and I feel that it overwhelms me.

9.5 _____ I feel I can't stand it anymore.

9.6 _____ I become afraid that the pain will get worse.

9.7 _____ I keep thinking of other painful events.

9.8 _____ I anxiously want the pain to go away.

9.10 _____ I keep thinking about how much it hurts.

9.11 _____ I keep thinking about how badly I want the pain to stop.

9.12 _____ There's nothing I can do to reduce the intensity of the pain.

9.13 _____ I wonder whether something serious may happen.

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10.0 COPING

The following statements deal with ways in which you may cope with a serious medical problem in your life. Of course, different people deal with things in different ways, but we are interested in how you've tried to deal with it. Each item says something about a particular way of coping. Use these response choices. Try to rate each item separately in your mind from the others. Make your answers as true FOR YOU as you can:

1 = Not at all 2 = A little Bit 3 = A medium amount 4 = A lot

10.1 I've been trying to work on other activities to take my mind off things. _____

10.2 I've been concentrating my efforts on doing something about the situation I'm in. _____

10.3 I've been saying to myself "This isn't real." _____

10.4 I've been using alcohol or other drugs to make myself feel better. _____

10.5 I've been getting emotional support from others. _____

10.6 I've been taking action to try to make the situation better. _____

10.7 I've been giving up trying to deal with it. _____

10.8 I've been refusing to believe that it has happened. _____

10.9 I've been saying things to let my unpleasant feeling escape. _____

10.10 I've been getting help and advice from other people. _____

10.11 I've been using alcohol or other drugs to help myself get through it. _____

10.12 I've been trying to see it in a different light, to make it seem more positive. _____

10.13 I've been criticizing myself. _____

10.14 I've been trying to come up with a strategy about what to do. _____

10.15 I've been getting comfort and understanding from someone. _____

10.16 I've been giving up to attempt to cope. _____

10.17 I've been looking for something good in what is happening. _____

10.18 I've been making jokes about it. _____

10.19 I've been doing something to think about it less, such as going to movies, watching TV, reading, day dreaming, sleeping, or shopping. _____

10.20 I've been accepting the reality of the fact that it has happened. _____

10.21 I've been expressing my negative feelings. _____

10.22 I've been trying to find comfort in my religion or spiritual beliefs. _____

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10.23 I've been trying to get advice or help from other people about what to do. _____

10.24 I've been learning to live with it. _____

10.25 I've been thinking hard about what steps to take. _____

10.26 I've been blaming myself for things that happened. _____

10.27 I've been praying or meditating. _____

10.28 I've been making fun of the situation. _____

11.0 SUPPORT

We are interested in how you feel about the following statements. Read each statement carefully. Indicate how you much you agree or disagree with each statement.

	Very Strongly Disagree	Strongly Disagree	Mildly Disagree	Neutral	Mildly Agree	Strongly Agree	Very strongly Agree
11.1 There is a special person who is around when I am in need	[1]	[2]	[3]	[4]	[5]	[6]	[7]
11.2 There is a special person with whom I can share my joys and sorrows	[1]	[2]	[3]	[4]	[5]	[6]	[7]
11.3 My family really tries to help me	[1]	[2]	[3]	[4]	[5]	[6]	[7]
11.4 I get the emotional help and support I need from my family	[1]	[2]	[3]	[4]	[5]	[6]	[7]
11.5 I have a special person who is a real source of comfort to me	[1]	[2]	[3]	[4]	[5]	[6]	[7]
11.6 My friends really try to help me	[1]	[2]	[3]	[4]	[5]	[6]	[7]
11.7 I can count on my friends when things go wrong	[1]	[2]	[3]	[4]	[5]	[6]	[7]
11.8 I can talk about my problems with my family	[1]	[2]	[3]	[4]	[5]	[6]	[7]
11.9 I have friends with whom I can share my joys and sorrows	[1]	[2]	[3]	[4]	[5]	[6]	[7]
11.10 There is a special person in my life who cares about my feelings	[1]	[2]	[3]	[4]	[5]	[6]	[7]
11.11 My family is willing to help me make decisions	[1]	[2]	[3]	[4]	[5]	[6]	[7]
11.12 I can talk about my problems with my friends	[1]	[2]	[3]	[4]	[5]	[6]	[7]

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11.13 Have you had a major life event that has created significant stress in your life **NOW**?

a. Assault/robbed	[1] Yes	[2] No
b. Divorce/separation	[1] Yes	[2] No
c. Serious marital problems	[1] Yes	[2] No
d. Major financial problem	[1] Yes	[2] No
e. Serious housing problems	[1] Yes	[2] No
f. Serious illness or injury	[1] Yes	[2] No
g. Job loss or serious difficulties at work	[1] Yes	[2] No
h. Legal problems	[1] Yes	[2] No
i. Loss of confidant	[1] Yes	[2] No
j. Other: (*Please specify*)	[1] Yes	[2] No

_____

End Time: _____

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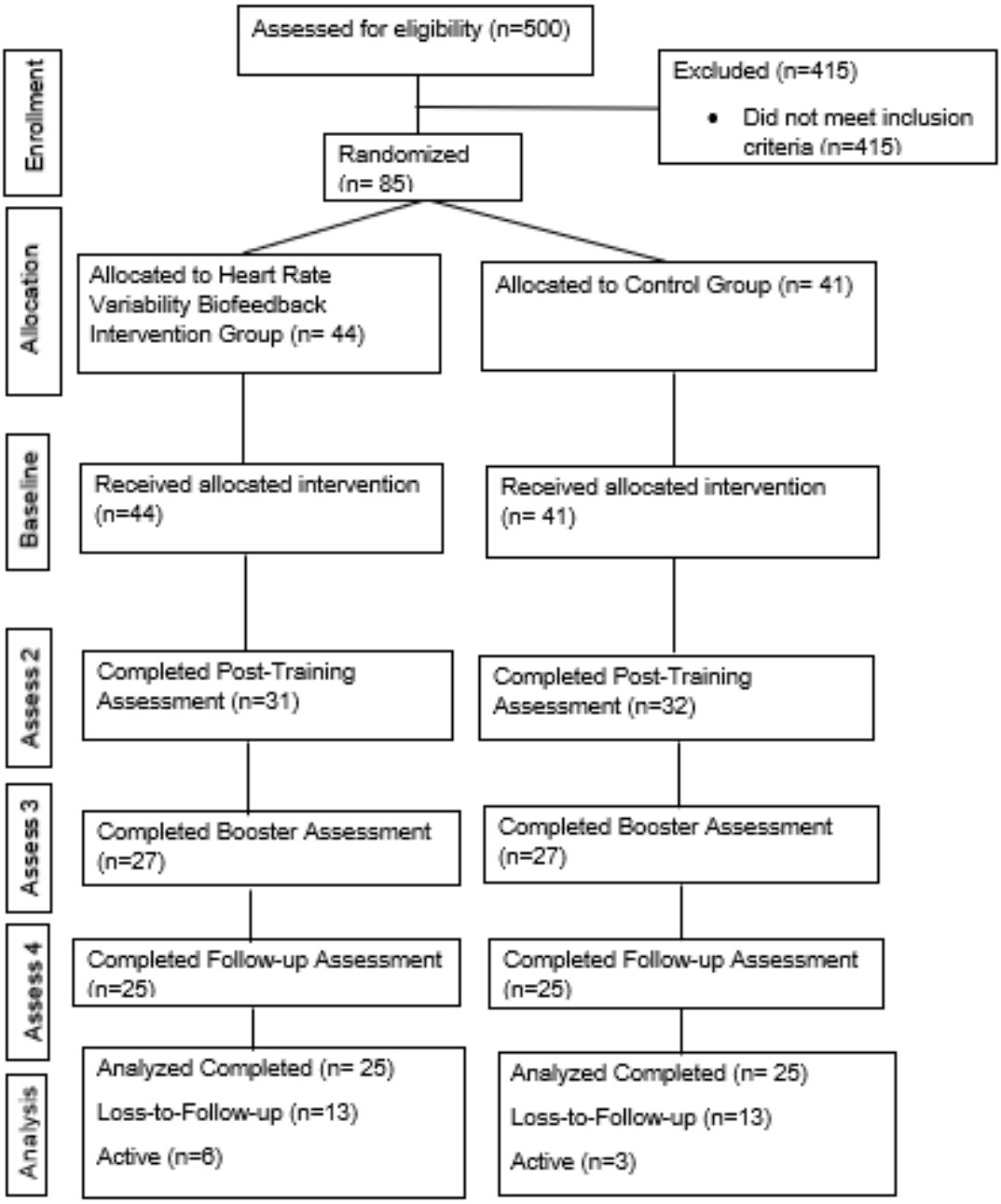

Figure A.4: CONSORT Flow Diagram

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