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Effect of Heart Rate Variability Biofeedback on Sleep

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ABSTRACT

Healthy amounts of sleep is vital for normal human functions such as daily learning, memory, emotional state and cardiovascular function. Studies conducted previously have shown sleep deprivation to be associated with increases in sympathetic activity contributing to autonomic nervous system (ANS) dysregulation. HRV biofeedback (HRVB) training induces HRV coherence, a condition that maximizes HRV and facilitates autonomic and cardiorespiratory homeostasis. This randomized, controlled, intervention trial will test the hypothesis that HRVB can improve HRV coherence and increase overall sleep quality. Patients are randomized to previously established HRVB or sham protocols (n=40 each, total planned enrollment N=80). Each participant completes 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). Wrist actigraphy is used to obtain continuous rest/activity recordings 24-hours per day over three 1-week periods coinciding with the baseline, post-treatment, and follow-up assessments. Subjective sleep symptoms are included at each assessment using the Pittsburg Sleep Quality Index (PSQI). Outcomes include: 15-minute resting HRV recordings (HRV Coherence Ratio), as well as subjective (total PSQI and sleep quality scores) and quantitative sleep measures (actigraphic sleep onset latency, duration, efficiency, wake after sleep onset). To date, 85 patients completed their baseline assessment; 63 completed their post-training assessment, and 50 completed the entire protocol. In preliminary analyses, HRVB

patients had elevated mean (±SD) HRV Coherence Ratios at the post-training assessment relative to baseline (0.11±.02 vs. 0.27±0.05, n=43, p<0.001), whereas no differences were observed among controls (0.10±0.02 vs. 0.12±0.02, n=41, p=0.97). Compared to baseline scores PSQI Global Score was reduced at Post Assessment (12.3±0.5 vs 11.1±0.6 n=31, p=0.02) and at Follow-up Assessment (12.3±0.5 vs 10.3±0.9 n=25, p<0.001); no differences among controls. Compared to baseline scores Sleep Duration elevated at Post Assessment (436±15 vs 465±19 n=23, p=0.03) and at Follow-up Assessment (436±15 vs 479±19 n=21, p=0.02); no differences among controls. Preliminary results indicate receipt and persistence of intervention among HRVB participants to date. Results show evidence of Subjective (PSQI) and Objective (Duration) sleep improvements. HRVB is a valid, quantifiable, easily-implemented procedure; and previous research suggests that HRVB can improve overall sleep quality.

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CHAPTER 1

INTRODUCTION AND SPECIFIC AIMS

Poor sleep quality can lead to insomnia, fatigue, cognitive disturbance, and depression.[1,2] Overall quality of sleep in the United States has taken a toll with 50% of people age 55 years and older reporting problems with their routine sleep schedule.[3] Sleep has shown to be vital for functions such as development of physiological systems, learning, memory, emotional state, cardiovascular and metabolic function and cellular toxin removal.[4] Epidemiological studies have identified associations between short sleep duration (less than ~7 hours per 24-hour period) and chronic diseases such as diabetes, obesity, depression, hypertension, cardiovascular disease, stroke, cancer, and all-cause mortality, with at least some studies showing the elderly being particularly susceptible.[1,2,5–7] Diminished or reduced heart rate variability (HRV), the variation of heart rate over time, has been linked to cardiovascular disease, decreased immune system function, diabetes, poor sleep quality, and premature death.[8,9] However, improving an individual's HRV with biofeedback (HRV-B) can elicit improvements in depressive symptoms, chronic pain, immune system function, overall autonomic nervous system (ANS) function, and sleep issues.[10–12]

HRV-B is a technique used to increase an individual's HRV through a non-invasive, nonpharmacological paced breathing exercise. Subjects trained in HRV-B

perform slow, paced diaphragmatic breathing to achieve HRV coherence. While in coherence, one can observe waveforms from breathing that are synchronized with the rise and fall of the heart rate. As one inhales the heart rate increases and the heart rate decreases with exhalation. An individual achieving HRV coherence typically reports feelings of joy, resilience, mindfulness, and hope. This technique is typically taught by a trained coach and uses visual feedback through a computer screen to achieve the resonant frequency of breathing. The resonant frequency is the breathing rate needed to acquire a sinusoidal waveform of increasing and decreasing heart rate that is synchronized with the breath, usually at a frequency of ~5-6 breaths per minute, that corresponds with a state of HRV coherence.[8,13] HRV coherence is a normal physiological state that amplifies HRV.[13] During sleep, parasympathetic nervous system activity dominates, HRV is heightened, specifically during non-rapid eye movement (NREM) sleep, and HRV coherence likely occurs naturally due to cardiorespiratory coupling, which heightens heart rate variability.[14,15] While sleeping, we breathe at a slower rate, in particular during NREM sleep. During REM sleep ~5-7 breaths per minute are taken and the ANS exhibits sympathetic dominance.[16,17] Once the resonant frequency of breathing is achieved, individuals will begin to improve their own HRV by being in coherence on demand, which in turn can help them self-regulate to improve symptoms of stress, anxiety, fatigue or depression that have been associated with low HRV, by bringing balance to the ANS. The restorative properties of sleep also are likely associated with the cardiorespiratory coupling that occurs naturally during sleep.[18]

It is important to understand the role HRV-B can play in improving an individual's overall sleep quality. Low HRV has been found to be associated with

reduced sleep quality.[19] If HRV-B can improve sleep quality, then, a relatively simple, but effective technique can be implemented among individuals with sleep disturbances. Thus, previous studies have shown that HRV-B may serve as a useful alternative treatment among individuals suffering from insomnia or other sleep disorders.[7,9,19–21]

This study used data collected from Veterans patients with chronic pain participating in a study conducted at the Wm. Jennings Bryan Dorn Veterans Affairs Medical Center (DVAMC). Data collection included questionnaires to obtain information on psychometric outcomes including pain, stress, depression, fatigue, sleep quality, cognitive function, as well as sociodemographic data and other potential confounding factors. Eligible participants included DVAMC patients above the age of 18, who were English literate and are currently experiencing chronic pain.

In this randomized, sham-controlled, behavioral intervention trial, data collected from June 2016 to February 2019 was included in this analysis. The target sample size was to enroll 80 Veterans with chronic pain currently being treated at Dorn Veterans Affairs Medical Clinic. Eligible Veterans who were willing to participate provided written informed consent, after which they were enrolled and randomized into the HRV-B intervention or sham group. Participants completed a 16-week intervention. Veterans were randomized after consent and assigned to the treatment group or the control group. If randomized into the control group Veterans completed a 16-week sham protocol that did not include any HRV-B. At baseline, a 15-minute resting HRV recording was obtained, and sleep was assessed via a questionnaire and one week of wrist actigraphy. During weeks 1-7, the intervention group was given HRV-B via a trained and qualified coach. Participants engaged in weekly sessions that included their respirations being

monitored, their heart rate observed via a photoplethysmography (PPG) and were instructed to breathe a 5-6 breathes per minute. During this instruction the form of inhalation and exhalation was critiqued and corrected, if needed. The control group received sham training where their pulse and respirations are monitored while they passively view static nature slides on a computer screen. They are instructed to 'just relax' and picture themselves in a state of relaxation within the images. After the 6 weekly training sessions, subjects were reassessed using the same outcome measurements. On week 12, subjects received a HRVB 'booster' training session, had their HRV measured, and completed the questionnaire again. However, they do not receive a sleep actigraphy monitor. The final follow-up visit occurred on week 16, and all outcomes were measures one last time. The Pittsburg Sleep Quality Index (PSQI) and wrist actigraphy are previously validated sleep measures..[22]

Statistical analysie examined the relationship between sleep quality and HRV using generalized linear mixed models for repeated measures (PROC MIXED in SAS). This study tested the hypothesis that HRV-B training will improve sleep quality (total PSQI score and sleep quality subscore), and actigraphic sleep efficiency, sleep onset latency, wake after sleep onset and sleep duration compared to the sham control group. The primary objective of this study was to determine if HRV-B can improve overall sleep quality via wrist actigraphy and perceived sleep quality among DVAMC patients with chronic pain.

The specific aims of this study were to:

1. Determine if a 6-week regimen of HRV-B training improves subjective sleep symptoms (Pittsburg's Sleep Quality Index's Global Sleep Score) relative to a sham control group.

2. Determine if a 6-week regimen of HRV-B training improves objective sleep measures (Sleep duration, Sleep efficiency, Sleep onset latency, wake after sleep onset) relative to a sham control group.

CHAPTER 2

BACKGROUND

Autonomic Nervous System

The ANS is involved in many bodily functions including energy metabolism, regulation of the cardiovascular system and makes significant contributions to overall physiological homeostasis. This system operates without our conscious, voluntary control.[23] Within this branch of the nervous system are two divisions, the sympathetic and parasympathetic nervous systems. The sympathetic nervous system (SNS) controls the "fight -or- flight response. When activated it can increase heart rate, dilate pupils, slow down digestive activity, and inject adrenaline into the bloodstream. This system allows the body to be prepared to conduct strenuous physical activity by delivering oxygenated blood to the tissues that need it, predominately the skeletal muscles. Furthermore, the parasympathetic nervous system (PNS) allows the body to rest and recover from all things related to daily living.[23] The PNS dominates during quiet, resting conditions. The overall role of the PNS is for individuals to converse and store energy and continue regulation of bodily functions just as urine production, digestion and recovery.[23] Sympathetic dominance can be seen from stressors of daily life.

Parasympathetic dominance can be seen while being involved in relaxing activities and especially while sleeping.

Sleep-related changes in ANS has been investigated and reported. During sleep, a reduction in sympathetic activity, during non-rapid eye movement stage of sleep, has been shown using interbeat intervals (IBI).[20] Whereas, during REM sleep sympathetic activity spikes back towards waking period levels.[20] It has also been reported that an increase in HR and blood pressure (BP) during REM sleep occur, indicating increased levels of sympathetic influence.[20] Another study in fibromyalgia patients showed that pain from this disease increases sympathetic activity causing these patients overall sleep efficiency and overall quality to be significantly reduced.[24] Over-stimulation of the SNS causes an imbalance of the ANS which can result in restlessness and overall poor sleep quality due to sympathetic dominance. Rebalancing the ANS through HRV-B may lead to improvement to overall sleep quality.[24]

Sleep

The physiological function of sleep is not entirely understood. Human physiology is driven by what are called circadian rhythms, which are generated centrally in the hypothalamus and synchronized to the ambient light-dark cycle via the retina, optic nerve, and suprachiasmatic nuclei.[4] Sleep is a cyclical process that is essential to human functionality. While we sleep, we have increased protein formation and synthesis. This restoration involves parasympathetic dominance. The circadian rhythm maintained by the hypothalamus keeps a bodily schedule of gland secretion for sleep regulating hormones like melatonin. There is also a homeostatic sleep rhythm of the sleep-wake

cycle. This cycle acts as a counter or a balance to when and how long we sleep.[25] The circadian rhythm for sleep is primarily responsible for when an individual generally goes to sleep and wakes up. However, this may not always be followed, such as someone who works the night shift or stays up late to complete a task. Sleep-wake homeostasis works to effectively be a timer of sleep regardless of when you normally sleep.[25] Sleep-wake homeostasis will remind the body it needs to rest after a certain amount of time through the use of an endogenous chemical, primarily adenosine. Essentially, it makes the desire to sleep greater the longer we have been awake and ultimately the likelihood of falling asleep increases. Sleep-wake processes work bidirectionally in that the longer one remains asleep, the more likely an individual will awaken. The sleep-wake cycle can take precedent for someone who generally goes to sleep late and wakes up late. If this individual were to go to bed much earlier after a long day, they may not wake up as late as they normally would because the likelihood of sleeping into double digit hours is reduced due to this mechanism.[25]

Sleep stages can be divided into NREM and rapid-eye-movement (REM) sleep.[2,26] REM periods can last from 10 minutes up to 1-hour long. The average person will cycle through these stages of sleep four to five times per night. NREM is thought to be helpful for rebuilding the body whereas REM is thought to be focused on the brain. Previous studies have shown that deprivation of REM sleep can lead to hallucinations, short-term personality changes and paranoia.[2]

The relationship between autonomic dysfunction and disrupted sleep has not been thoroughly examined. Studies conducted previously have shown that sleep deprivation can cause an increase in sympathetic ANS activity.[27] During sleep is a good time to

assess ANS function as the heart rate is primarily under PNS control.[27] Cardiovascular autonomic control plays a crucial part in the integrity of sleep quality. Tobaldini also concluded that analysis of HRV can play a key role in being a non-invasive tool for providing information on autonomic changes that would lead to sleep disturbances.[28]

Sleep deprivation throws off the ANS creating an asymmetry of PNS and SNS activity. By increasing a sympathetic dominance over the parasympathetic system an imbalance of the system is created leading to a lack of flexibility to respond to emotional challenges such as stress on a regular basis.[27] The restorative properties of deep sleep are related to the resonance frequency of breathing, cardiorespiratory coupling, and parasympathetic dominance that typically occur during non-rapid eye movement (NREM) and slow-wave sleep.[14] In a study conducted on shift working nurses, those working the night shift had autonomic dysregulation as compared to the day shift nurses during their sleep periods. Measurement of HRV coherence during sleep may serve as an indicator of ANS dysfunction within individuals.[14]

HRV & HRV-B

HRV is the variability between consecutive heartbeats. By recording the time between individual heartbeats, the IBI can be used for measuring HRV.[18,29,30] Variation in the IBI is controlled by the SNS and PNS portions of the ANS. Respiratory sinus arrhythmia (RSA) is the variation in heart rate that occurs during one respiratory cycle. The RSA is characterized by an increase in sympathetic activity when inhaling, which increases heart rate, and parasympathetic activity when exhaling, which decreases the heart rate.[31] Practice with HRV is designed to strengthen baroreflexes which ultimately

will improve the ANS balance of parasympathetic and sympathetic activity.[32] Individuals with anxiety, high stress, sleep issues, chronic pain, and depression have been shown to have diminished HRV.[18,29,32] In previous studies, HRV-B has demonstrated an ability to alleviate symptoms of both mental and physical disorders involving the ANS.[33]

HRV-B is conducted through individual training using a paced breathing exercise. HRV-B is an interactive procedure whereby participants engage in training to increase their HRV in real time. HRV-B is a complementary technique that can be used in unison with other non-pharmacological techniques such as yoga, cardiorespiratory activity, and meditation.[9] When introducing HRV-B to a new patient, trainers instruct them to breathe deeply with their stomach, also called belly breathing, and regulate their breathing rate at 5-6 breaths per minute, which is at 0.1 Hz. By doing this consistently participants learn how to increase their parasympathetic activity which concurrently reduces sympathetic activity.

Pharmacology interventions are available for sleep issues, but non-pharmaceutical approaches are desirable. HRV-B is a valid technique that may improve autonomic function. Previous studies have shown HRV-B to positively impact overall sleep quality. A case study by a medical provider in a combat zone reported improved sleep after using a portable biofeedback device.[12] Another study used HRV-B in a randomized controlled trial study design in Amsterdam. This study compared HRV-B with other stress relief strategies and found improvements in overall sleep quality after a 5-week HRV-B training including home practice.[9] Additionally, a randomized clinical trial conducted by Sakakibara et al. found that HRV-B training increased PNS activity during sleep.[33] This result was found by analyzing HRV-B during sleep and observing an increase at follow-

up that the high-frequency component of HRV, the component associated with PNS activity, was heightened.[33] This experimental epidemiological randomized control trial sought to examine the relationship between sleep quality and HRV-B.

HRV, HRV-B & Sleep

The HRV of an individual is a useful measure of an individual's autonomic health. By measuring HRV, we can determine the overall health of the ANS. Reduced HRV indicates overstimulation of the SNS and dominance over the PNS. Increased HRV shows a balance between the two systems or even parasympathetic dominance.

While we sleep the expectation is for HRV to increase due to parasympathetic dominance, which is required to begin the physiological restoration that occurs while sleeping. This increased parasympathetic dominance allows the body to conduct the growth and repair previously stated. Also, this parasympathetic dominance is important for restful uninhibited sleep. However, if the PNS is unable to obtain dominance due to sympathetic dominance sleep disturbances can begin to arise. The inability to sleep through the night or inability to fall asleep can be experienced due to the SNS dominance. Sleep can be thought of like a seesaw effect. While sympathetic activity increases during the REM cycle, which will increase BP and improve blood flow to the brain, parasympathetic dominance does not occur. Likewise, when parasympathetic dominance is occurring during NREM, the restorative properties of sleep occur.[25]

HRV-B can play a critical role in addressing sympathetic nervous system dominance that plagues many individuals. HRV-B could be used to tame sympathetic nervous system dominance during an individual's daily life. Balancing this during the

waking periods allows an individual to have parasympathetic dominance during sleep periods. We theorize, an increase in an individual's HRV during waking periods and sleep periods can show an improvement in autonomic health. This improvement could lead to an overall improvement in an individual's sleep patterns.

Characterization of Sleep

Wrist actigraphy can be used to measure a person's sleep and wake cycle as well as a subject's rest/activity rhythms. An actiwatch measures activity through means of a piezo-electric accelerometer that is set to record the integration of intensity, amount and duration of movement in all directions. This study used Motionlogger WatchWare version 1.99.5.1 for actigraphy analysis (AMI, Ardsley,NY). The actiwatch device has a maximum sampling frequency of 32 Hz and will record all movements above a g-force of 0.05g.[34] These actiwatches are useful for recording objective measures on an individual's sleep and is rapidly developing as a significant asset for measuring sleep quality and assessing sleep disorders. A research assistant manually identifies the beginning and end of each sleep interval, which is then used to obtain sleep summary measures.[35]

Wrist actigraphy has been validated in numerous studies.[36] Esbensen et al. aimed to validate wrist actigraphy within a pediatric down syndrome population. Using wrist actigraphy, compared against the gold standard polysomnography, this study validated the watches results suggesting the data from them is sensitive in measuring duration and efficiency.[36] Another pediatric study used wrist actigraphy on children with atopic dermatitis and validated their results with the questionnaires completed.[37] Wrist

actigraphy as a tool to quantify sleep quality is a cheaper, less invasive, more accessible and valid option to researchers and participants.

Many sleep variables can be considered within a given sleep interval. However, some of the most important objective measures identified are: amount of sleep (sleep duration), the amount of time asleep compared to total time in bed (sleep efficiency), how long does it take for you to fall asleep once you are attempting to fall asleep (sleep onset latency) and finally the amount of minutes spent awake during the sleep period (wake after sleep onset). An individual's sleep duration is a measure of the length of time spent sleeping each night.[38] Sleep duration is calculated by creating a down interval that is set by determining the point of sleep beginning and the point in which sleep ends. The down interval is determined by the research assistant processing the accelerometers (AMI, Ardsley, NY). An individual's sleep efficiency is the ratio of the total time spent asleep compared to the total amount of time spent in bed.[38] Sleep efficiency is calculated with the following equation (100*Sleep Duration (O-O Duration)). The O-O Duration is calculated with a sub-interval of the Down Interval that estimates the true sleep period. It represents the time from sleep Onset (as defined by the sleep latency) to sleep Offset (the end of the last sleep episode in the Down Interval). Thus, an O-O interval represents the Down Interval minus the sleep latency and any terminal wake in the down interval.[39] Essentially, sleep onset latency is the period between where the research assistant sets the beginning of sleep and where the software begins the O-O interval. Wake after sleep onset refers to the period of wakefulness occurring during the O-O interval.[38] Wake after sleep onset is calculated by adding the total minutes of wakefulness that occurs during the

O-O interval. Typically, these measures can categorize the participants as poor, average and good sleepers.

A score of 85% or greater is considered to be good sleep efficiency.[40] A score of 75 and below is considered poor sleep. A score between 75 and 85 is considered average sleep.[40] Sleep duration greater than 420 minutes is considered good sleep. Sleep duration less than 360 minutes is considered poor sleep. Sleep duration between good sleep and poor sleep is considered average.[40] Sleep onset latency (SOL) and wake after sleep onset (WASO) are expected to decrease for sleep improvement.[41] An increase in efficiency and duration into the good range is expected for improved sleep. Using wrist actigraphy data, insomnia may be defined using the following cut-off values: sleep onset latency >12 minutes, total sleep time <440 minutes, WASO >25 minutes, sleep efficiency <92%.[7,42]

The Pittsburg Sleep Quality Index was developed at the University of Pittsburg and is currently the most used sleep inventory questionnaire available. Subjective measures of sleep can be obtained using the PSQI questionnaire.[40] It refers to usual sleep habits over the past 30 days. The PSQI also has subsections that allow it to take into account days at work and days away from work.[22] In the PSQI questionnaire, there are 19 questions, composed of 7 subscales, that create a total overall score. The PSQI generally takes around 5-10 minutes to complete, offering a quick and accurate way to assess an individual's overall sleep quality.[43] The validity of the PSQI has been tested in a multitude of studies each of which have found the PSQI to be consistent and internally valid.[44–46]

CHAPTER 3

METHODS

In this study, a previously approved, standardized HRV-B intervention protocol was used to deliver the HRV-B intervention. Data from the intervention group were compared to a sham control group over the 16-week intervention period. The Dorn VA institutional review board approved this study. All participants gave informed consent prior to participation. The Veterans Affairs Office of Research and Development funded this study (Grant number: I01BX007080). This study was prospectively registered (clinical trial number NCT02426476).

The experimental design included four assessments over a 16-week study period (Appendix A, Figure A1). The initial visit (baseline) occurred on the same day of consent and included a 15-minute resting HRV recording, and a symptom questionnaire. Subjects were sent home with an actiwatch for a 1-week sleep outcome assessment. The following six weeks involved group specific training. On the seventh week, after six training visits post-training took place, remeasuring of all outcomes measured at baseline took place. One-month post-training, a booster assessment occurred that included a 15-minute HRV recording and symptoms questionnaire, although no wrist actigraphy was measured. Finally, one month after the booster was a follow-up assessment. Saliva was collected at the conclusion of each assessment, excluding the booster assessment, and

stored in a freezer at -80°C.

Eligibility, Participants, and Recruitment

The study population was comprised of Veteran patients experiencing chronic pain who lived in the Columbia, South Carolina area. Flyers with pull tabs advertising the study were distributed around Dorn Veterans Affairs Medical Center (DVAMC). Subjects were recruited who were: English literate, ≥18 years old, of any race, ethnicity, or sex meeting inclusion and exclusion criteria. Additionally, eligibility was checked, patients were telephoned to ascertain interest in the study and perform the chronic pain eligibility screen (Pain Screening Questionnaire, Vanderbilt University Medical Center, Center for Quality Aging, Nashville, TN). The pain screening instrument assessed pain using 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 participating in activities/doing things you enjoy? 4.) Do you have pain every day? Chronic pain was determined to be present if the patient answered yes to questions 1-3, or to question 4 alone. Recruitment targeted patients in the Pain Clinic, and the Rehabilitative Medicine and Rheumatology and primary care department at the DVAMC. Initially, participation in the study included ten reimbursements ($20 per visit or $200 total for protocol completion), and towards the end of the study, supplemental funding was provided to increase recruitment and retention, and $30 per visit was offered along with a $10 travel reimbursement ($400 total).

Veterans were excluded if their participation would not be appropriate from a safety standpoint; if they had a health condition or medication use that could bias their

HRV measures; or if they were considered cognitively incapable of completing the protocol. The following exclusions were applied: a) history of arrhythmias requiring medication and/or hospitalization, including supraventricular tachycardia or atrial arrhythmias (e.g., 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), although patients with well-controlled hypertension (no change in medications for 6 months) were not be excluded; e) history of heart transplant or cardiovascular surgery within 1 year; f) Veterans receiving beta-adrenergic antagonists; g) Veterans receiving non-dihydropyridine calcium channel blockers; h) Veterans receiving an antagonist of the renin-angiotensin-aldosterone system were eligible if their medication profile was stable; i) Veterans with 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 (e.g., 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 active substance abuse or dependence (alcohol or tobacco use was not an exclusion, Veterans will be asked to report their use via questionnaire); n) life history of bipolar, psychotic, panic or obsessive-compulsive disorder (history of depression will not be an exclusion).

Random Allocation to Conditions

Random assignment to the 6-week HRV-B treatment or sham intervention group was performed prior to the baseline assessment using a permuted block randomization

procedure, with a block size of 4 and no stratification. Thus, for example, assuming 20 patients are to be assigned either to sham (S) or biofeedback, and two patients will be assigned each to the (S) treatment and two to the biofeedback by randomly selecting one of six possible permutations of the two treatments in blocks of four. The treatment assignment was determined before any patient was enrolled into the study and the documentation and assignment of each patient was kept confidential. This was a single-blinded study and only the HRV-B trainer was aware of group assignment. Research participants were blinded to their group assignment of each participant. At the conclusion of the study, sham participants were told that they would be offered a "cross-over training" after completion of their protocol. If interested, sham participants were provided with one session of HRV-B training in the same manner as the intervention group.

Intervention

Participants in the two intervention arms both received an introduction to the study including reimbursement, the study timeline, and the process of data collection. The HRV-B training consisted of a 15-minute resting period that included an HRV recording, and a 25-minute period of biofeedback training and coaching. Participants were fitted with HRV monitoring equipment and were instructed to sit quietly for 15 minutes in a relaxed posture, viewing a series of neutral nature scenes on a computer monitor without any text or stimulating or confrontational content, changing at 40-second intervals. Patients were instructed to 'just relax', or 'take it easy' during this time. The HRV-B portion of the training involved a trained and qualified biofeedback coach to instruct the participant on two primary techniques. The first was to paint relaxing

imagery into the participant's mind and help guide them to thoughts that were stress-free, and they found relaxing in their day to day lives. The second part was to adjust the breathing pattern as well as the rate. This involved instructions such as diaphragmatic breathing (aka "belly breathing") with the abdomen to have full use of the diaphragm, breathing deeply through the nose and out through pursed lips, to use good posture while breathing, avoiding slouching, and including a good transition between inhaling and exhaling. Through coaching, participants were able to slow their breathing to ~6 breaths per minute which over time synchronized their heart rate oscillations with their breathing, ultimately allowing the participant to get into a state of 'HRV coherence'. This state could be visualized by the patient on the computer monitor using the biofeedback equipment. The synchronization observed was the increase of the heart rate oscillations during inhalation and a decrease in heart rate oscillations during exhalation (i.e., zero phase between breathing and heart rate). Home practice was administered for a minimum of 10 minutes daily. The participant was issued an Emwave 2 device or an attachment that took advantage of the Innerbalance phone application. Instructions on when to practice the intervention technique was described as times of high stress, feelings of frustration or when attempting to go to sleep at night. Intervention group practice minutes were recorded via download from the device used as well as self-report on average time practiced per day over a 1-week period, at each training session. Sham participants were asked how much time they practiced with the squeeze ball and relaxed per day over a 1-week period, at each training assessment.

Patients in the sham condition used the same training equipment as the intervention group however they were asked to 'just relax' or 'take it easy' for the

duration of the training session. Rather than given biofeedback, control participants were given nature slide videos to watch for the duration of the training session. No heart rate information was displayed on the screen and there was no mention of heart rate or breathing during the sham session. A stress squeeze ball was issued to the participant and used during training. If a question about this arose, they were instructed to 'relax and keep a clear mind'. Otherwise, no instruction, coaching or biofeedback was provided to the participant. Home practice was administered for a minimum of 10 minutes daily, same as the intervention group. The stress squeeze ball was recommended for use while relaxing for the minimum time period.

HRV Measures

Resting physiological measures were recorded for 15 minutes at baseline. The use of an autonomic testing system to precisely determine HRV at the four time periods (baseline, post-training, booster, follow-up assessments). Testing was performed in a standardized, recognized, and quantified manner that is non-invasive. Recording occurred in a comfortable office setting with lights dimmed. During recording the participants viewed nature slides and were asked to relax at baseline and in later assessments instructed, "Do what you have been trained to do". HRV data was obtained via dry electrode wrist straps on both forearms of the participant, one on the right forearm and two on the left forearm. Respiration was also monitored via a Piezo-respiratory transducer. This data was later processed by a research assistant.

Software integrated into the HRV physiological monitoring system ran on a laptop computer was used to complete the processing of HRV data to get time domain

outcomes (SDNN, RMSSD), frequency outcomes (very low frequency, low frequency and high frequency) and HRV Coherence Ratio. Processing began by de-artifacting raw data and a 5-minute period was selected to calculate the power spectrum of HRV for each patient (Appendix A, Figure A2). This provided data for frequency (VLF, LF, HF power, peak frequency, peak frequency power) and time-domain HRV measures (heart rate mean and standard deviation, NN50, pNN50, RMSSD). From these values HRV coherence is calculated using previously acquired measures as well as new ones obtained by adjusting the frequency bands and using the coherence equation (High_Frequency_Peak_Power / (Total Power – High_Frequency_Peak_Power). The HRV Coherence Ratio is estimated by calculating the ratio of power in the LF peak to the remainder of power in the spectrum without the LF peak.[29,47]

Sleep Outcome Measures

The Pittsburgh Sleep Quality Index was used to measure the subjective perception of sleep disturbances and sleep quality over the course of the past month. The PSQI consists of 19 individual questions, addressing seven components of sleep: (a) subjective sleep quality, (b) sleep latency, (c) sleep duration, (d) habitual sleep efficiency, (e) sleep disturbances, (f) use of sleeping medications, and (g) daytime dysfunction (Appendix A, Figure A3, A4 & A5). Each component receives a score between 0 and 3. The global PSQI score is calculated by the summation of each individual component, for a total score of 21. A score above five is indicative of poor sleep quality.[9,43]

Wrist actigraphy is a validated method that was used to provide a quantitative means by which sleep disruption could be assessed. The participant was instructed to

wear the watch consistently for 7 nights unless the watch was to be in jeopardy of getting wet (i.e., showering, swimming, washing dishes. Weekly monitoring was performed at baseline, post-training, and at the 8-week follow-up assessment using a standardized protocol. AMI motionloggers (AMI, Ardsley, NY, with built-in ambient multiple spectrum light sensor, event marker, digital watch, and off-wrist detection capability) were used in this study. Watches were worn on the non-dominant wrist, recording activity and light exposures at 1-minute intervals. Each participant was provided with the wrist-worn accelerometers immediately following their baseline visit, which was returned one week later at their first training visit. The second sleep actigraphy period was initiated on the sixth training visit and completed at the post-training assessment. After the follow-up assessment, rest/activity monitors were mailed back with a stamped, pre-addressed box to be returned through the United States Postal Service. Participants were provided with a sleep log and asked to manually record their sleep and wake times each day while wearing the watch.

Actigraphy data were processed using the manufacturer's software after downloading the data from the AMI motionloggers to a computer. Data was processed using ActionW 2.7 to calculate sleep duration, sleep efficiency, sleep onset latency and wake after sleep onset. The beginning of sleep was set for each day taking into consideration the participants sleep log, activity levels and light exposure levels (Appendix A, Figure A6). Likewise, the end of the sleep period was set using the same considerations. This process was completed for each of the nights a participant wore the watch. If less than three days was recorded for any given participant, the data was considered incomplete and was not processed or used in the analysis. The manufacturer's

software was used to calculate outcomes of interest during each sleep period. The sleep variables used in this study included: sleep duration, sleep onset latency, sleep efficiency and wake after sleep onset.

Statistical Analysis

All statistical analyses were performed using statistical analysis software computer program (SAS version 9.4, Cary, NC). The independent variable of interest for analysis is the change in HRV between the baseline assessment and follow-up assessment. The group effect, the time effect and the group by time effect in the mixed analysis was also of interest.

The effectiveness of randomization was checked to be sure all potential confounders are equally distributed between both groups. Randomization makes observable baseline differences unlikely, however, outcome measures and demographic characteristics were evaluated whether differences in the groups occurred using bivariate comparisons between treatment and control groups at baseline. Due to the small frequency of American Indian and "Other" races in this study, the African American, American Indian and Other participants were combined into one classification named "Minorities." Four individuals refused to provide race status and were not included in the frequency count for race. Group comparisons of baseline sociodemographic, lifestyle choices and comorbid ailments were performed using Fisher's Exact test for categorical variables such as sex, race and income status (PROC FREQ in SAS). For variables such as age, the normality of the distribution was checked using PROC UNIVARIATE. Because of the effects depression can have on an individual's sleep the Beck's

Depression Index (BDI) was considered as a possible confounder for all outcomes of interest.[48] During the analysis baseline scores of BDI were adjusted for in the models based on an *a priori hypothesis.*

Normally distributed data then had a test of homogeneity, F-test, to look at the equality of variances. If the variances were equal, the pooled t-test was used and if the variances were unequal the Satterthwaite t-test was used. If data was determined to be not be normally distributed, a nonparametric test, the Wilcoxon signed rank test, was used. Variables found to be statistically significantly different at baseline were considered as a possible confounder along with baseline BDI scores.

By group and timepoint means were calculated for each assessment for the following HRV outcome measures: SDNN, RMSSD, VLF, LF, HF and HRV Coherence Ratio. PROC UNIVARIATE was used to check each variable for normality.

Next, to test the effect of HRV-B relative to controls, linear mixed models for repeated measures (PROC MIXED in SAS) was used to assess the effects of intervention group, time, and the interaction between group and time. Two-tailed p-values were used to check baseline group comparisons as well as the Group by Time interaction term, and changes in outcomes over time in the control group. The *a priori* directional hypotheses was not applied to the control group due to no expectation of a beneficial effect. One-tailed p-values were used for *a priori* directional hypotheses on HRV-B intervention effectiveness. One-tailed p-values were used in all assessments of statistical significance due to an expectation of a directional change, based on previous literature stating the positive effects of HRV-B on the outcomes of interest. The following covariance matrix

structures were evaluated: compound symmetric, unstructured, and heterogeneous compound symmetry, and the minimum Akaike Information Criterion (AIC) was used to select the covariance matrix to be used in subsequent models. Each outcome was evaluated separately. Demographic covariates that differed at baseline were retained in the final model if inclusion changed the parameter estimate for the Group by Time interaction by ≥10%. This was done until all covariates that were statistically significantly different at baseline were checked. Covariates that were statistically significant in the model also were retained, regardless of the effect to the parameter estimate. The baseline score for depression (BDI) was evaluated as an *a priori* confounder for sleep. Adjusted (least squares or LS) means were computed for each group and assessment period. In addition to the overall Group by Time interaction, the following contrasts were used to test *a priori* hypotheses concerning the intervention effect: baseline versus post-training assessment, baseline versus follow-up assessment, and, to assess treatment sustainability, post-training assessment versus follow-up assessment.

For the PSQI Global score, this outcome was dichotomized as "good" and "poor" sleepers using the cut point score of 5.[43] This cut point has a sensitivity of 89.6% and specificity of 86.5% for identifying individuals with sleep issues. The PROC FREQ procedure in SAS was used to obtain the proportion of "good" and "poor" sleepers for each group and assessment timepoint.

Finally, Cohen's D was calculated to test effect size of the change in outcome measures from baseline to post-training and baseline to follow-up assessment in the intervention group. The following formula was used to calculate Cohen's D: Cohen's d

$= [(M_2 - M_1) / SD_{pooled}]$. The SD_{pooled} was calculated using the following formula: $SD_{pooled} = [\sqrt{((SD_1^2 + SD_2^2) / 2)}]$.

Missing data on baseline characteristics was limited since participants had to provide this information to be included in the study. Missing outcome data was ignored in the linear mixed model under the missing-at-random assumption.

CHAPTER 4

RESULTS

Amongst the 85 patients who completed the baseline assessment, 63 further completed the post-training assessment, 54 completed the booster assessment and 50 completed the follow-up assessment (59%). The rate of attrition by group was similar and showed no statistically significant differences. Demographic and outcome variables at baseline are shown in Table 4.1. Using randomization, equal proportions were obtained for most demographic variables. Participants were primarily male (66%), College educated (73%) and non-smokers (85%) (Table 4.1). The average age (± standard error of the mean) for the intervention group was 54 ± 10 and 55 ± 12 in the control group. Aside from race, there were no differences of baseline characteristics by group (White: 37% in intervention group vs. 63% in control group, p=0.04, Table 4.1). This potential confounder was considered when developing the final model. Due to cancellation and rescheduling within both groups, an analysis of length of time to complete the study by group was conducted. Without missed appointments, the study protocol could have been completed in 112 days. On average the study protocol took 123 ± 21 days. There was no difference between the groups in mean study completion time among those who completed the protocol (124 days for the intervention group and 121 days for the control group, p=0.54, Table 4.1). Comorbid diagnoses from medical records at baseline were evaluated as potential confounders (Table 4.1).

Mean HRV Coherence improved at the post-training assessment in the intervention group compared to the baseline assessment (0.11 at baseline vs. 0.41 at post-training, p=<0.01, Table 4.3). There was no improvement found in the control group at post-training compared to the baseline assessment (0.10 at baseline vs. 0.08 at post-training, p=0.67). The Group by Timepoint interaction term for the HRV Coherence Ratio was statistically significant (t:4.21, p= <0.01). Mean HRV Coherence is improved at follow-up assessment in the intervention group compared to baseline (0.11 at baseline vs. 0.45 at follow-up, p=<0.01, Table 4.4). Figure 4.1 displays the improvement of the intervention group in HRV Coherence. Figure 4.1 shows a persistence effect with a significant improvement from baseline to post-training, but no significant changes are observed from post-training to follow-up assessment.

Improvements in PSQI Global Score were observed, with a reduction at post-training compared to the baseline assessment, in the intervention group (~12 at baseline vs. ~11 at post-training, p=0.02, Table 4.2). From baseline to the follow-up assessment of the study declines in PSQI Global Score were observed, in the intervention group. (~12 at baseline vs. 10 at follow-up p=<0.01). There were no noteworthy effects observed for the control group. Figure 4.2 displays the mean PSQI Global Score by group and timepoint. Reductions in the PSQI Global Score, relative to baseline, for the intervention group were found at post and follow-up assessments whereas no improvement is observed in the control group, Figure 4.2. No significant differences were observed between the post and follow-up assessment in either group for PSQI Global Score.

Improvements in sleep duration were observed between baseline and post-training assessments, in the intervention group (~421 minutes at baseline vs 453 minutes at post assessment, p=0.03, Table 4.3). Improvements for sleep duration were also observed between baseline and follow-up assessments, in the intervention group (~ 421 minutes of sleep per night at baseline vs. ~458 minutes of sleep per night at follow-up, p=<0.01, Table 4.4). The group by time interaction was significant for sleep duration between baseline and follow-up assessments (t=1.83, p=0.04). Figure 4.3 shows an increase in minutes slept per night for the intervention group at each assessment, however this is not observed in the control group.

There were no significant differences between baseline and post assessments or baseline and follow-up assessment for Sleep Efficiency, in either the intervention or control group (Table 4.3 and 4.4). Figure 4.4 displays a reduction in sleep efficiency however it was not found to be statistically significant.

There were no significant differences, for the intervention group, between baseline and post assessments or baseline and follow-up assessment for Sleep Onset Latency, in either the intervention or control group (Table 4.3 and 4.4). However, the control group did have an increase in sleep onset latency of ~2 minutes, Figure 4.5.

There were no significant differences, for the intervention group, between baseline and post assessments or baseline and follow-up assessment for Sleep Onset Latency, in either the intervention or control group (Table 4.3 and 4.4). Figure 4.6 displays a modest increase for both groups in the minutes awake once sleep onset has

begun (WASO). Although a small noticeable difference is observed neither group saw a statistically significant increase.

Using the PSQI, a clinical cut point of 5 is used to determine if an individual is a "Good sleeper" or "Poor Sleeper".[43] In Table 4.5 the frequency of good sleepers, as classified by the PSQI Global Score, is displayed by group and timepoint. There is an observable increase in the proportion of individuals below the clinical cut-point from baseline to post assessment for the intervention group (4.7% vs. 12.9%). The booster and follow-up assessments, for the intervention group, also had a greater proportion of individuals below the cut-point of 5 compared to baseline however, they were slightly lower than the post assessment (Booster- 11.1%, Follow-up-12%). The control group had an increase in the proportion of individuals below the clinical cut-point of 5 from baseline to post assessment (2.4% vs. 6.3%). However, there is a reduction in the booster and follow up compared to the minor improvement seen at the post assessment (Booster- 3.7%, Follow-up- 4%).

Cohen's D effect size estimate was calculated for the intervention group. This test was calculated between baseline and post assessment as well as baseline and follow-up assessment. Excluding coherence, at post assessment all outcome variables saw a small effect size ($d < 0.3$). Coherence scores experience a large effect ($d = 0.87$). Comparing the change from baseline to follow-up assessment coherence had a large effect ($d = 1.01$). PSQI and sleep duration had medium effects (PSQI $d = 0.47$, sleep duration $d = 0.42$). The remaining sleep outcomes, sleep onset latency, sleep efficiency, and wake after sleep onset, had small changes ($d < 0.3$).

A table for comparisons between post and follow-up assessments was not created nor reported due to proc mixed analysis not showing any statistically significant data.

Table 4.1: Baseline Characteristics by Group

	Overall (n=85)	Intervention (n=43)	Sham (n=41)	p-value
Gender				0.57
F (%)	28 (33)	15(34)	13(32)	
M (%)	56(66)	29 (66)	28 (66)	
Race				0.04
Minorities (%)	49 (53)	30 (61)	19 (39)	
Caucasian (%)	32 (38)	12 (37)	20 (63)	
Age mean ± SD	54 ± 11	54 ± 10	55 ± 12	0.65
Education				0.65
≤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
$30,000 or less	33 (39)	15 (34)	18 (44)	
$30,000-$50,000	17 (20)	8 (18)	9 (22)	
$50,000 or more	30 (35)	18 (41)	12 (29)	
Refuse	4 (5)	2 (5)	2 (5)	
Don't know	1 (1)	1 (2)	0 (0)	
Study Completion In Days ± SD	123 ± 21	124 ± 18	121 ± 23	0.54
Current Smoke				0.66
Yes	13 (15)	6 (14)	7 (17)	
No	72 (85)	38 (86)	34 (83)	
Ever Smoke Cigarette				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)	
Hypertension				0.31
Yes (%)	38 (45)	22 (50)	16 (39)	
No (%)	47 (55)	22 (50)	25 (61)	
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)	
Sleep Disorder				0.83
Yes (%)	26 (31)	13 (30)	13 (32)	
No (%)	59 (69)	31 (70)	28 (68)	
Diabetes				0.45
Yes (%)	24 (28)	14 (32)	10 (24)	
No (%)	61 (72)	30 (68)	31 (76)	

Fisher's exact Test (2-sided) 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.

Table 4.2: Mixed model analysis of outcome 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 (t, p) Timepoint (t, p) Group x Timepoint (t, p)
HRV Coherence Ratio	A	0.11 ± 0.02	43	0.27 ± 0.05	31	*0.16 ± 0.07* *(3.99, <0.01[c])*	(4.64, <0.01)
	B	0.10 ± 0.02	41	0.12 ± 0.02	32	*0.2 ± 0.16* *(0.78, 0.43[d])*	(2.59, <0.01)
	Est A-B±SE ***(t, p)***	*0.01 ± 0.21* *(0.15, 0.88[a])*	*84*	*0.15 ± 0.11* *(3.36, <0.01[b])*	*63*	n/a	(3.08, <0.01)
SDNN	A	27 ± 3	43	32 ± 3	31	*5 ± 0.1* *(1.51, 0.07[c])*	(0.7, 0.24)
	B	28 ± 3	41	37 ± 4	32	*9 ± 0.1* *(3.15, <0.01[d])*	(2.05, <0.01)
	Est A-B±SE ***(t, p)***	*-1 ± 0.1* *(-0.12, 0.91[a])*	*84*	*-5 ± 0.1* *(-1.15, 0.13[b])*	*63*	n/a	(0.68, 0.25)
RMSSD	A	17 ± 2	43	17 ± 2	31	*0.9 ± 0.1* *(0.16, 0.44[c])*	(0.79, 0.21)
	B	17 ± 2	41	23 ± 3	32	*6 ± 0.08* *(2.96, <0.01[d])*	(1.33, 0.08)
	Est A-B±SE ***(t, p)***	*0.9* ± 0.2 *(0.07, 0.47[a])*	*84*	-6 ± 0.2 (-1.73, 0.04[b])	*63*	n/a	(-0.9, 0.18)
VLF Power	A	265 ± 51	43	230 ± 50	31	*-35 ± 0.2* *(-0.66, 0.26[c])*	(2.17, 0.02)
	B	259 ± 51	41	429 ± 92	32	*170 ± 0.1* *(2.42, <0.01[d])*	(0.81,0.29)
	Est A-B±SE ***(t, p)***	*6* ± 0.3 *(0.08, 0.47[a])*	*84*	-199 ± 0.6 (-2.05, <0.01[b])	*63*	n/a	(-2.15,0.02)

Table 4.2: Mixed model analysis of outcome 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 (t, p) Timepoint (t, p) Group x Timepoint (t, p)
LF Power	A	168 ± 37	43	443 ± 106	31	*275 ± 0.08* *(4.34, <0.01[c])*	(1.02, 0.15)
	B	170 ± 37	41	309 ± 74	32	*139 ± 0.1* *(2.69, <0.01[d])*	(3.37, <0.01)
	Est A-B±SE ***(t, p)***	-2 ± 0.3 *(-0.05, 0.48[a])*	*84*	134 ± 0.2 (1.06, 0.15[b])	*63*	n/a	(1.29, 0.1)
HF Power	A	81 ± 19	43	70 ± 18	31	*-11 ± 0.3* *(-0.61, 0.27[c])*	(1.27, 0.27)
	B	85 ± 20	41	156 ± 40	32	*71 ± 0.1* *(2.6, <0.01[d])*	(0.86, 0.10)
	Est A-B±SE ***(t, p)***	*-4 ± 0.3* *(-0.15, 0.44[a])*	*84*	-86 ± 0.8 (-2.19, 0.02[b])	*63*	n/a	(-1.18, 0.12)
PSQI Global Score	A	12 ± 0.4	43	11 ± 0.6	31	*-1 ± 0.5* *(-2.06, 0.02[c])*	(2.19, 0.02)
	B	13 ± 0.5	41	12 ± 0.6	32	*-1 ± 0.5* *(-1.8, 0.07[d])*	(2.12, <0.01)
	Est A-B±SE ***(t, p)***	*-0.9 ± 0.7* *(-1.42, 0.16[a])*	*84*	*-1 ± 9* *(-1.31, 0.10[b])*	*63*	n/a	(0.21, 0.42)
Sleep Duration	A	421 ± 24	37	453 ± 25	23	*32 ± 16* *(1.97, 0.03[c])*	(0.56, 0.29)
	B	431 ± 28	33	445 ± 29	24	*14 ± 16* *(0.89, 0.38[d])*	(1.46, 0.06)
	Est A-B±SE ***(t, p)***	*-10 ± 22* *(-0.43, 0.67[a])*	*70*	*8 ± 26* *(-0.32, 0.37[b])*	*47*	n/a	(0.77, 0.22)

Table 4.2: Mixed model analysis of outcome 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 (t, p) Timepoint (t, p) Group x Timepoint (t, p)
Sleep Efficiency	A	79 ± 3	37	78 ± 3	23	*-1 ± 1* *(-0.89, 0.19[c])*	(1.34, 0.09)
	B	76 ± 3	33	75 ± 3	24	*-0.3 ± 1* *(-0.21, 0.84[d])*	(0.56, 0.37)
	Est A-B±SE ***(t, p)***	*4 ± 2* *(1.56, 0.12[a])*	*70*	*3 ± 3* *(1.01, 0.16[b])*	*47*	n/a	(-0.49, 0.31)
Sleep Onset Latency	A	11 ± 2	37	13 ± 2	23	*2 ± 0.1* *(1.45, 0.08[c])*	(0.1, 0.46)
	B	10 ± 2	33	13 ± 2	24	*3 ± 0.1* *(2.06, 0.04[d])*	(1.76, 0.02)
	Est A-B±SE ***(t, p)***	*1 ± 0.1* *(0.32, 0.75[a])*	*70*	*0.05 ± 0.2* *(-0.17, 0.43[b])*	*47*	n/a	(-0.43, 0.34)
Wake After Sleep Onset	A	82 ± 10	37	91 ± 10	23	*9 ± 7* *(1.34, 0.10[c])*	(0.96, 0.17)
	B	97 ± 11	33	99 ± 11	24	*2 ± 7* *(0.32, 0.75[d])*	(0.88, 0.26)
	Est A-B±SE ***(t, p)***	*-15 ± 9* *(-1.6, 0.12[a])*	*70*	*-8 ± 10* *(-0.79, 0.22[b])*	*47*	n/a	(0.72, 0.24)

LS-Means estimates displayed as mean. Larger scores represent greater HRV Coherence, Sleep Duration and Sleep Efficiency. Greater scores of PSQI Global Score, Sleep Onset Latency and Wake After Sleep Onset display more severe symptoms. SDNN: Standard Deviation of the Normal to Normal. RMSSD: Root Mean Square of the Successive Differences. VLF Power: Very Low Frequency Power. LF Power: Low Frequency Power. HF Power: High Frequency Power. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between baseline assessment and post-training. [d]2-sided comparison between baseline assessment and post-training. 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). *Adjusted for baseline depression.

Table 4.3: Mixed model analysis of outcome variables comparing Baseline vs. Post-Training 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 (t, p) Timepoint (t, p) Group x Timepoint (t, p)
HRV Coherence Ratio	A	0.11 ± 0.02	43	0.27 ± 0.05	25	*0.16 ± 0.01* *(5.13, <0.01[c])*	(4.81, <0.01)
	B	0.10 ± 0.02	41	0.12 ± 0.02	25	*0.02 ± 0.16* *(-1.0, 0.32[d])*	(2.19, <0.01)
	Est A-B±SE ***(t, p)***	*0.01 ± 0.21* *(0.15, 0.88[a])*	*84*	*0.15 ± 0.11* *(3.36, <0.01[b])*	*50*	n/a	(4.21, <0.01)
SDNN	A	27 ± 3	43	31 ± 3	25	*4 ± 0.9* *(1.51, 0.07[c])*	(0.7, 0.24)
	B	28 ± 3	41	35 ± 4	25	*7 ± 0.07* *(3.15, <0.01[d])*	(2.05, <0.01)
	Est A-B±SE ***(t, p)***	*-1 ± 0.1* *(-0.12, 0.91[a])*	*84*	-4 ± 0.2 (-1.15, 0.13)	*50*	n/a	(-0.1, 0.32)
RMSSD	A	17 ± 2	43	16 ± 2	25	*-1 ± 1* *(0.16, 0.44[c])*	(0.8, 0.21)
	B	17 ± 2	41	19 ± 2	25	*2 ± 0.1* *(2.96, <0.01[d])*	(1.3, 0.08)
	Est A-B±SE ***(t, p)***	*0.9 ± 0.2* *(0.07, 0.47[a])*	*84*	-3 ± 0.2 (-1.73, 0.04)	*50*	n/a	(-0.14, 0.44)
VLF Power	A	265 ± 51	43	211 ± 49	25	*-54 ± 0.2* *(-0.66, 0.26[c])*	(2.17, 0.02)
	B	259 ± 51	41	413 ± 96	25	*154 ± 0.1* *(2.42, 0.01[d])*	(0.8, 0.29)
	Est A-B±SE ***(t, p)***	*6 ± 0.3* *(0.08, 0.47[a])*	*84*	-202 ± 0.6 (-2.05, 0.02)	*50*	n/a	(-2.56, 0.02)

Table 4.3: Mixed model analysis of outcome variables comparing Baseline vs. Post-Training 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 (t, p) Timepoint (t, p) Group x Timepoint (t, p)
LF Power	A	168 ± 37	43	428 ± 110	25	*260 ± 0.08 (4.34, <0.01[c])*	(1.02, 0.15)
	B	170 ± 37	41	279 ± 72	25	*109 ± 0.1 (2.69, <0.01[d])*	(3.37, <0.01)
	Est A-B±SE (t, p)	*-2 ± 0.3 (-0.05, 0.48[a])*	*84*	149 ± 0.7 (1.06, 0.15)	*50*	n/a	(1.08, 0.14)
HF Power	A	81 ± 19	43	68 ± 19	25	*-13 ± 0.3 (-0.61, 0.27[c])*	(1.3, 0.11)
	B	85 ± 20	41	109 ± 30	25	*24* ± 0.1 *(2.60, <0.01[d])*	(0.9, 0.27)
	Est A-B±SE (t, p)	*-4 ± 0.3 (-0.15, 0.44[a])*	*84*	*-41 ±0.8 (-2.19, 0.02)*	*50*		(-0.39, 0.35)
PSQI Global Score	A	12 ± 0.6	43	10 ± 0.7	25	*-2 ± 0.6 (-3.55, <0.01[c])*	(2.19, 0.02)
	B	13 ± 0.6	41	13 ± 0.7	25	*-0.5 ± 0.6 (-0.88, 0.38[d])*	(2.12, <0.01)
	Est A-B±SE (t, p)	*-1 ± 0.8 (-1.25, 0.8[a])*	*84*	*-3 ± 1 (-2.81, <0.01[b])*	*50*	n/a	(-1.98, 0.02)
Sleep Duration	A	421 ± 24	37	458 ± 26	21	*37 ± 17 (2.20, 0.02[c])*	(0.56, 0.29)
	B	431 ± 28	33	423 ± 30	20	*-7 ± 18 (-0.42, 0.68[d])*	(1.46, 0.06)
	Est A-B±SE (t, p)	*-10 ± 22 (-0.43, 0.67[a])*	*70*	*35 ± 26 (1.33, 0.09[b])*	*41*	n/a	(1.83, 0.04)

Table 4.3: Mixed model analysis of outcome variables comparing Baseline vs. Post-Training 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 (t, p) Timepoint (t, p) Group x Timepoint (t, p)
Sleep Efficiency	A	79 ± 3	37	78 ± 3	21	*1 ± 2 (-0.65, 0.26[c])*	(1.34, 0.09)
	B	76 ± 3	33	76 ± 3	20	*0.06 ± 2 (0.04, 0.97[d])*	(0.56, 0.37)
	Est A-B±SE (t, p)	*4 ± 2 (1.56, 0.12[a])*	*70*	*3 ± 3 (0.96, 0.17[b])*	*41*	n/a	(-0.48, 0.32)
Sleep Onset Latency	A	10.6 ± 2	37	11.7 ± 2	21	*1 ± 0.1 (0.77, 0.22[c])*	(0.1, 0.46)
	B	10.1 ± 2	33	10.3 ± 2	20	*0.2 ± 0.1 (0.89, 0.38[d])*	(1.76, 0.02)
	Est A-B±SE (t, p)	*1 ± 0.1 (0.32, 0.75[a])*	*70*	*1 ± 0.2 (0.14, 0.44[b])*	*41*	n/a	(-0.10, 0.46)
Wake After Sleep Onset	A	65 ± 12	37	75 ± 16	21	*10 ± 0.1 (0.82, 0.21[c])*	(0.87, 0.19)
	B	83 ± 18	33	81 ± 20	20	*-2 ± 0.1 (0.66, 0.52[d])*	(1.28, 0.11)
	Est A-B±SE (t, p)	*-18 ± 0.2 (-1.39, 0.17[a])*	*70*	*-6 ± 0.3 (-0.34, 0.37[b])*	*41*	n/a	(0.68, 0.25)

LS-Means estimates displayed as mean. Larger scores represent greater HRV Coherence, Sleep Duration and Sleep Efficiency. Greater scores of PSQI Global Score, Sleep Onset Latency and Wake After Sleep Onset display more severe symptoms. SDNN: Standard Deviation of the Normal to Normal. RMSSD: Root Mean Square of the Successive Differences. VLF Power: Very Low Frequency Power. LF Power: Low Frequency Power. HF Power: High Frequency Power. [a]2-sided comparison between groups. [b]1-sided test between groups. [c]1-sided comparison between baseline assessment and post-training. [d]2-sided comparison between baseline assessment and post-training. 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). *Adjusted for baseline depression.

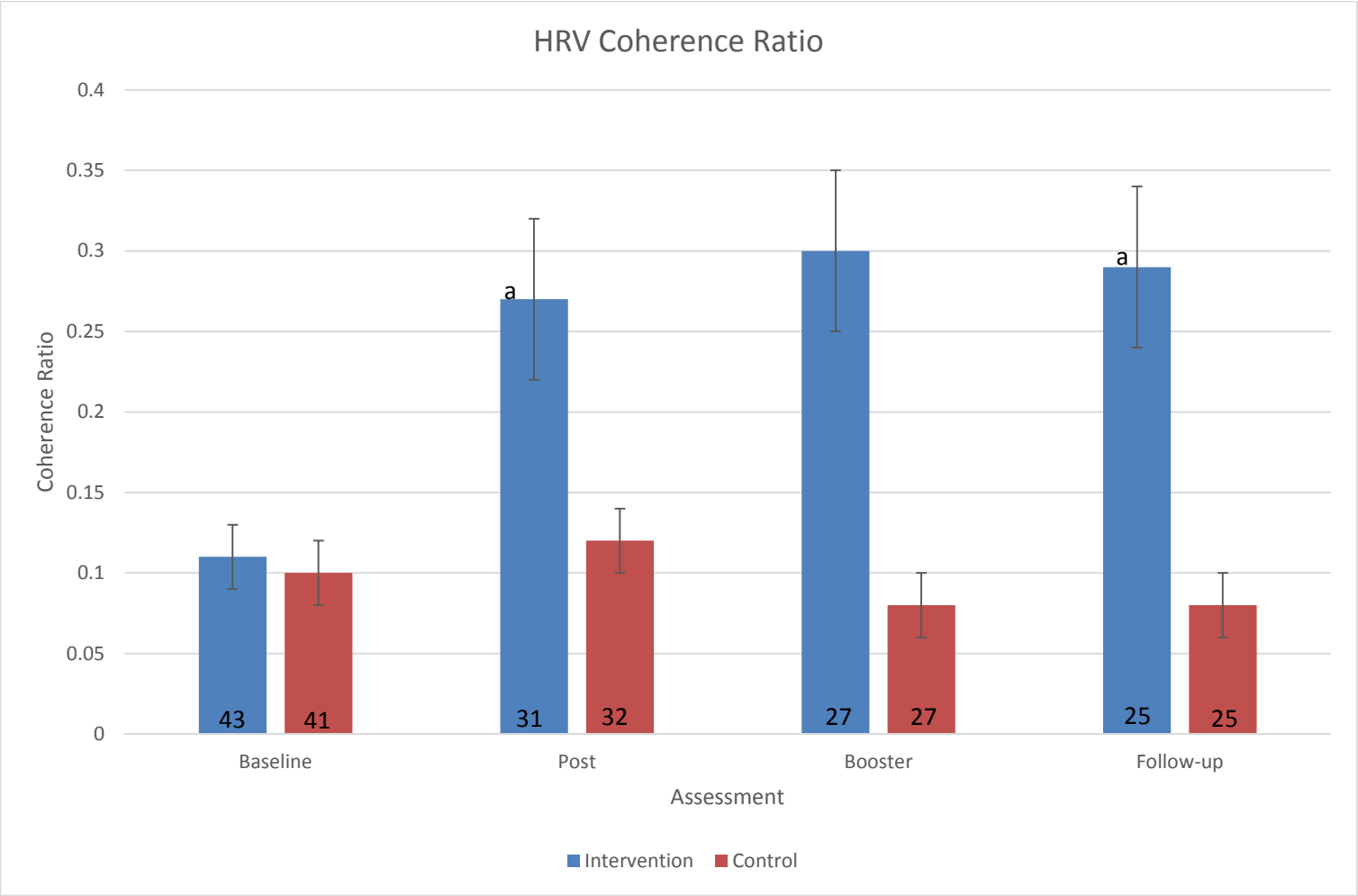

Figure 4.1: LS Means Estimates of HRV Coherence Levels by Group and Timepoint. LSMeans ± SE by treatment group and Assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. n of patients within each group and assessment indicated at base of each bar.

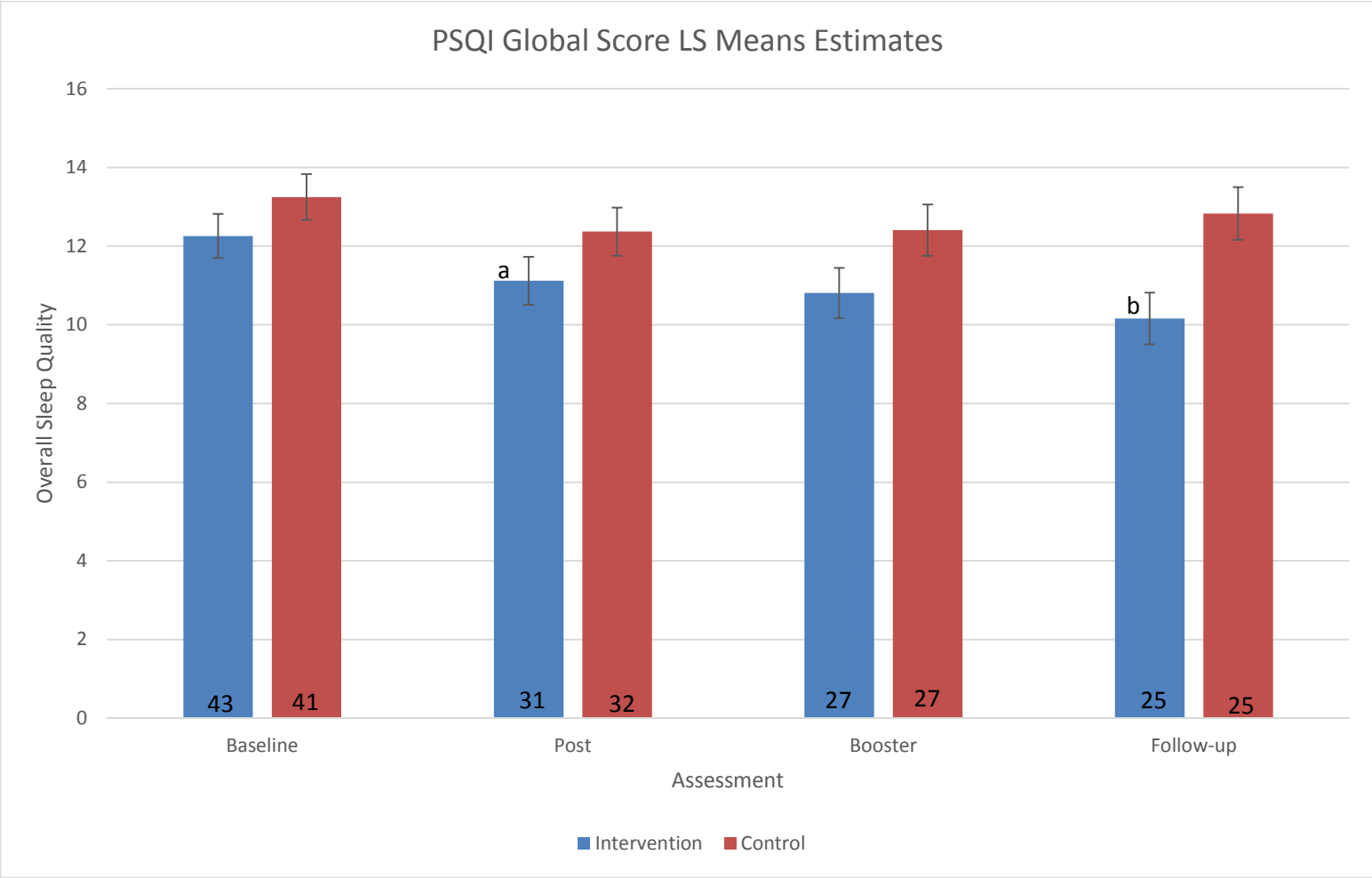

Figure 4.2: LS Means Estimates of Pittsburg Sleep Quality Index – Global Score by Group and Timepoint. LSMeans ± SE by treatment group and Assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. [b]1-sided, $p < 0.01$ vs Baseline value in the same group. N of patients within each group and assessment indicated at base of each bar. Adjusted for baseline depression.

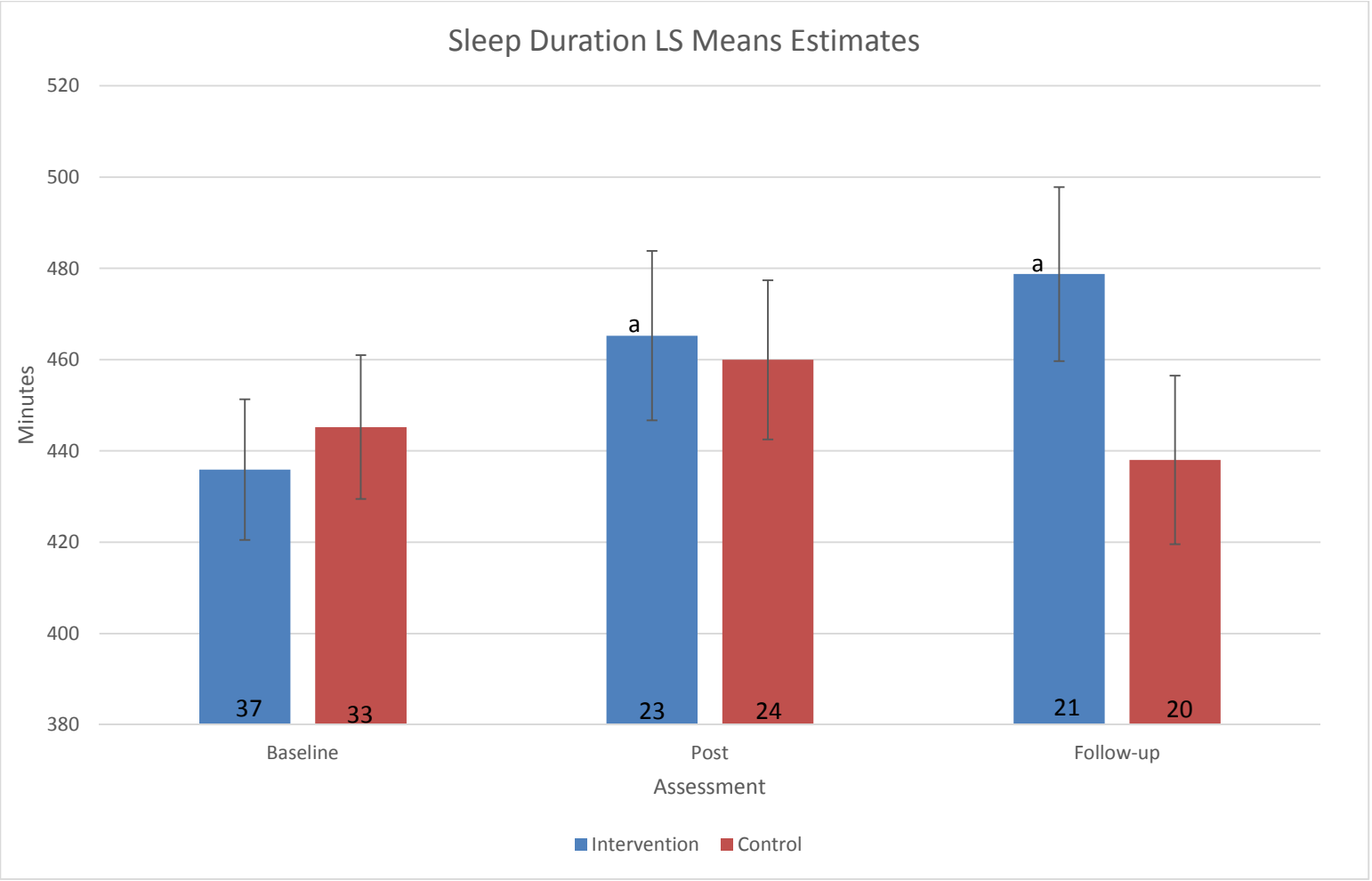

Figure 4.3: LS Means Estimates of Sleep Duration by Group and Timepoint. LSMeans ± SE by treatment group and Assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. N of patients within each group and assessment indicated at base of each bar. Adjusted for race.

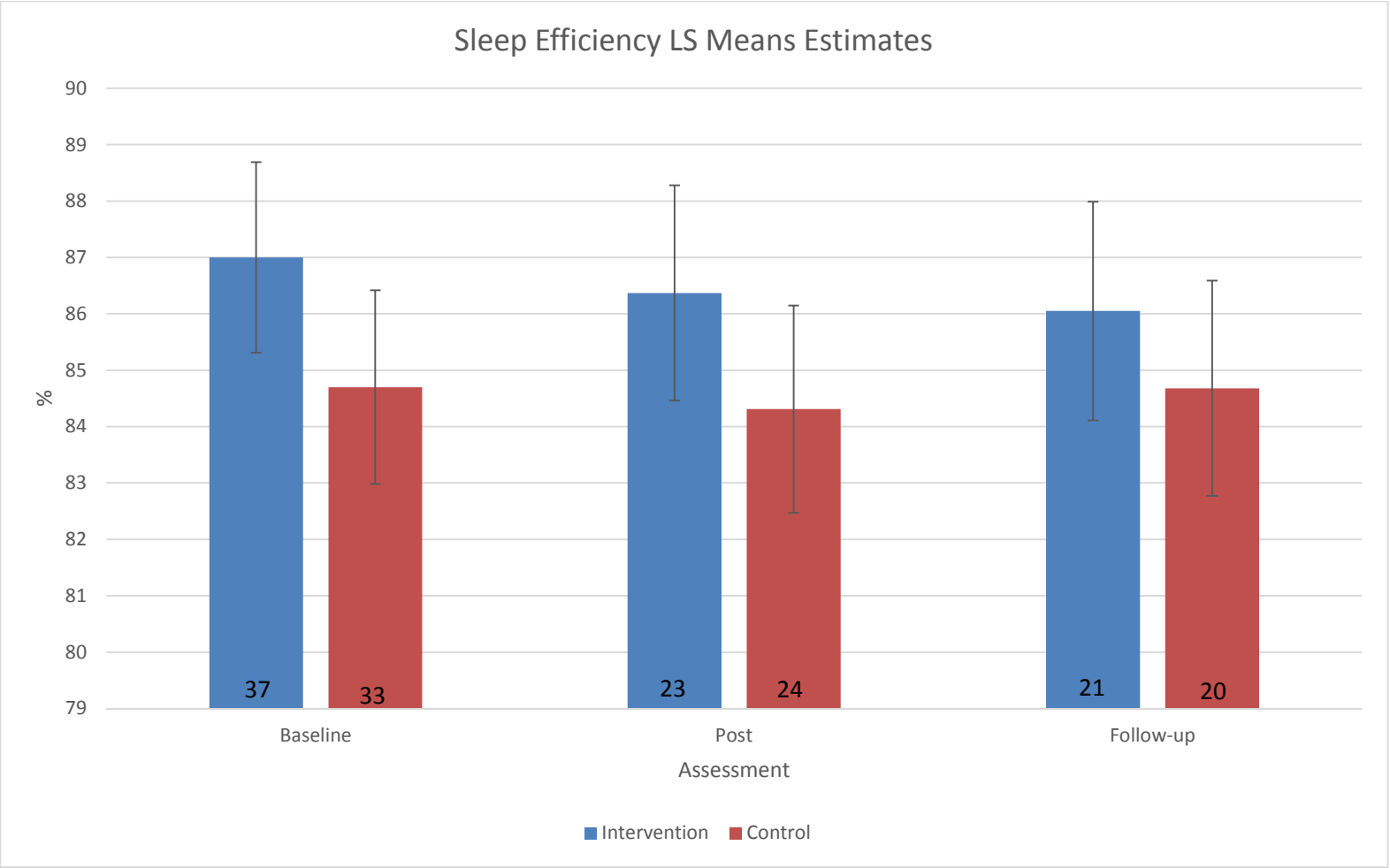

Figure 4.4: LS Means Estimates of Sleep Efficiency by Group and Timepoint. LSMeans ± SE by treatment group and Assessment. [a]1-sided, $p < 0.05$ vs Baseline value in the same group. N of patients within each group and assessment indicated at base of each bar. Adjusted for race.

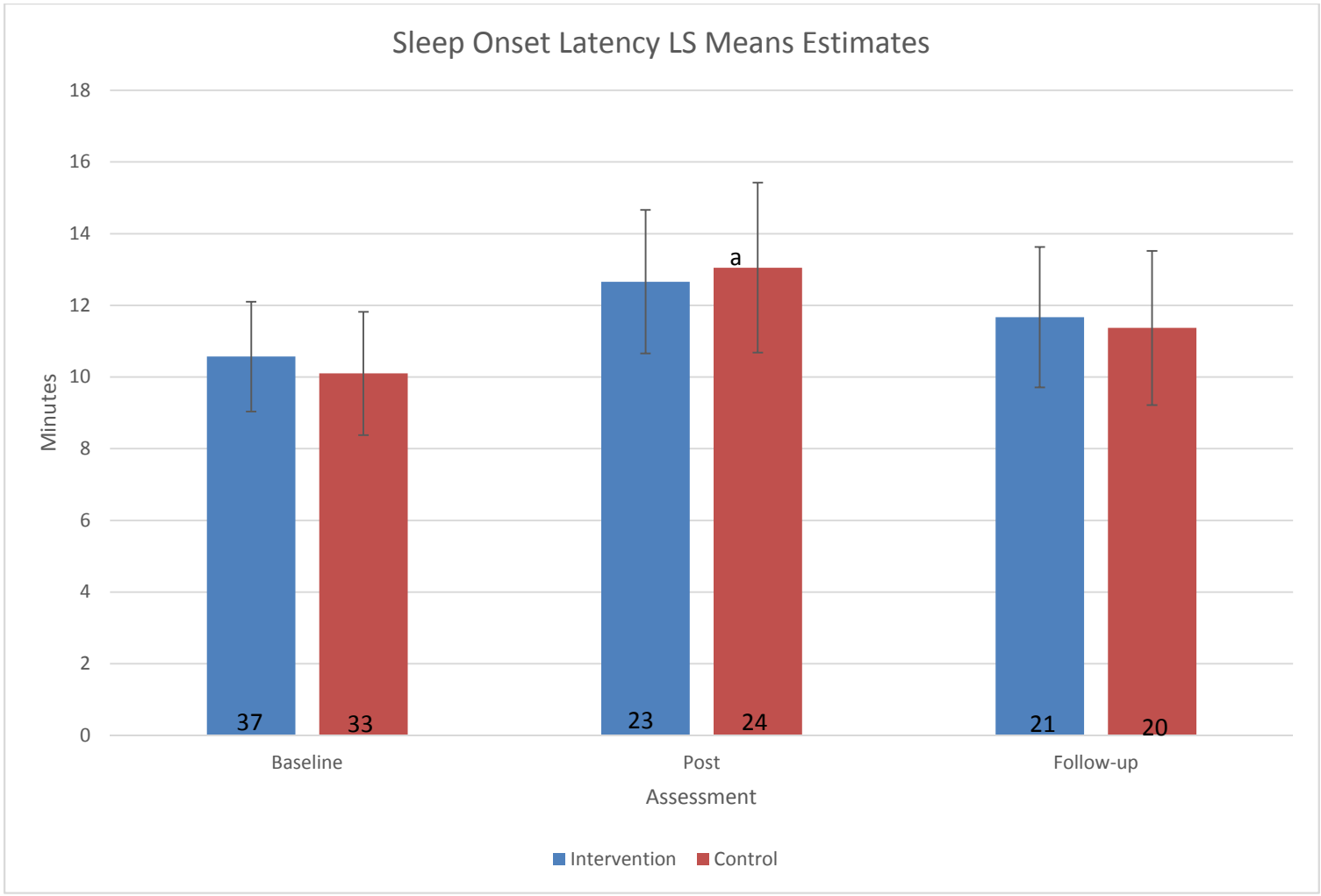

Figure 4.5: LS Means Estimates of Sleep Efficiency by Group and Timepoint. LSMeans ± SE by treatment group and Assessment.
[a]LSMeans compared to Assessment 1 (1-sided, $a < 0.05$). Adjusted for baseline depression and race.

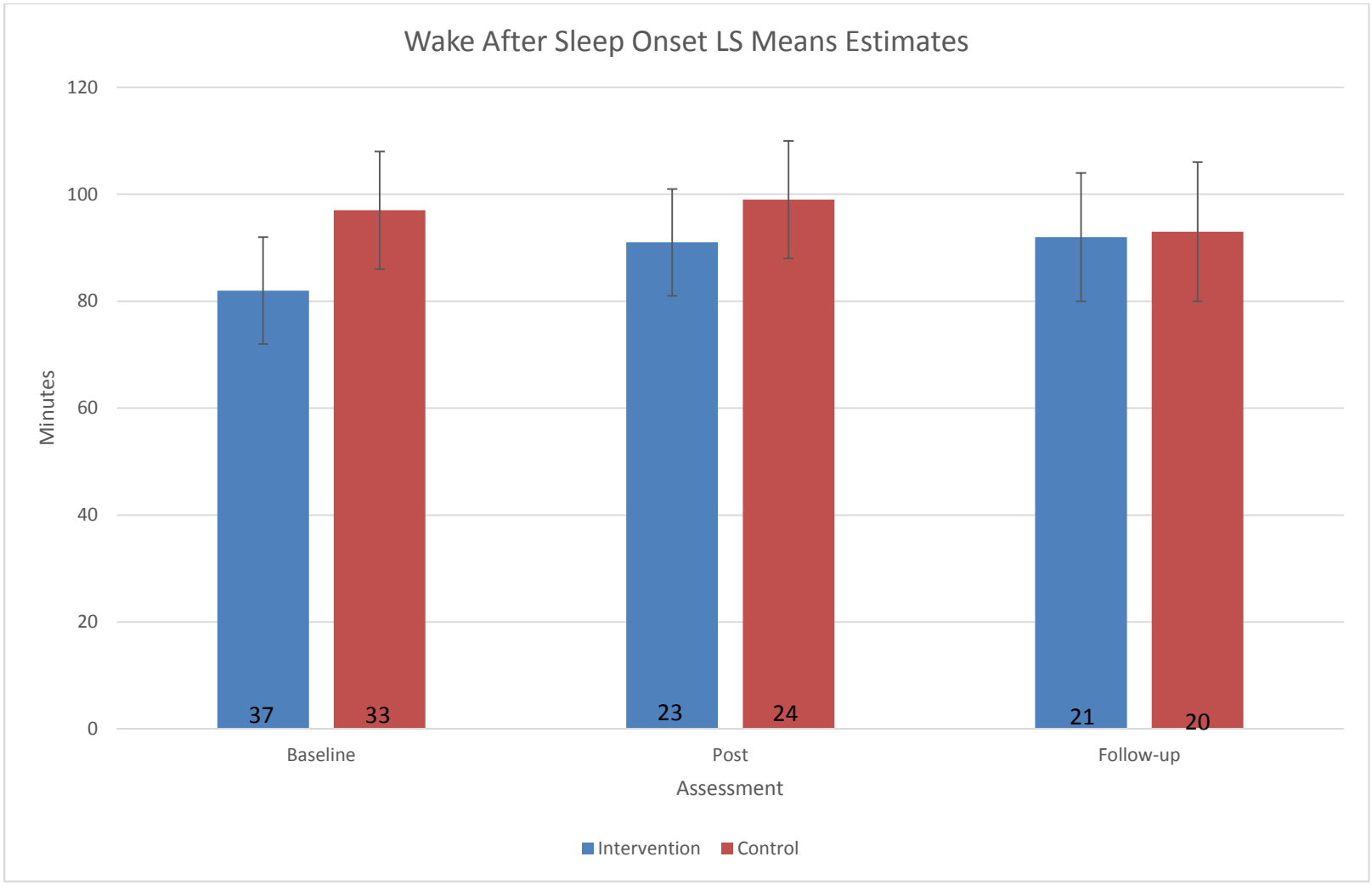

Figure 4.6: LS Means Estimates of Wake After Sleep Onset by Group and Timepoint. LSMeans ± SE by treatment group and Assessment. Adjusted for race.

Table 4.4: Proportion of Participants with good Sleep Quality by Group and Timepoint

Outcome	Group	Baseline		Post-Training		Booster		Follow-up	
		%	n	%	n	%	n	%	n
PSQI	Intervention	4.7	2/43	12.9	4/31	11.1	3/27	12.0	3/25
	Control	2.4	1/41	6.3	2/32	3.7	1/27	4.0	1/25

[a] PSQI ≤5 is considered to good sleep quality. PSQI: Pittsburg Sleep Quality Index. n is the total number of participants to complete the questionnaire within each group. 2/43: This represents the number of participants below the cut point compared to everyone who completed the questionnaire. i.e. 2/43 shows 2 participants scored at 5 or below out of 43 participants who completed the questionnaire at baseline for the intervention group.

CHAPTER 5

DISCUSSION

Sleep is a vital function of the physiological process that every human being partakes in each night. Literature has stated a loss of sleep is associated with impairments to our attention, memory functioning, and increases of irritability and emotional volatility.[26,27] Minkel et al reported in 2012 one night of sleep loss increases the subjective reports from participants of stress, anxiety, and anger responses towards low stress situations.[49]

The prevalence of sleep disorders among veterans has continually increased since the year 2000.[50] Veterans dealing with sleep insomnia and symptoms related to reduced or inefficient sleep can see quality of life decline as well as adverse health outcomes that can lead to shorten life span.[2,4,7,24] Medication usage often can be highly ineffective and costly to the consumer. Further, a plethora of chronic diseases have been found to be associated with poor sleep quality, such as, Diabetes, Cardiovascular disease, Obesity, and depression.[51–55]

Balance of the ANS is paramount in the function of sleep. During the NREM stage of sleep, the PNS becomes dominant over the SNS allowing for the body to complete restorative processes. Parasympathetic dominance is considered to be important for achieving restorative sleep.[14] The potential benefits of HRV-B can have in restoring balance to the ANS may be valuable in that it is a non-pharmacological approach to the problem, it is cheap, easy to do and can be done on an as needed basis.

Previous studies have shown HRV-B can lead to improvements to overall sleep quality.[8,9,21]

This study is one of a few to investigate the role HRV-B on improving sleep outcomes among Veterans with chronic pain. The improvement of HRV coherence ratios from baseline to the follow-up assessment indicates successful implementation of the training protocol among intervention group participants. Of the 5 outcomes that were assessed, improvements among the PSQI Global Score and sleep duration were statically significant. The PSQI improvement is indicative of intervention group members feeling as if they are sleeping better, longer and more efficiently through the night. The duration of sleep improved by an average of ~40 minutes for individuals within the HRV-B group by the follow-up assessment, the conclusion of the study. However, the improvements in sleep quality that were subjective in nature from the PSQI were not reflected in the other objective measures from the actiwatch data. Sleep efficiency, sleep onset latency and wake after sleep onset did not show statically significant changes from baseline to the post-training or follow-up assessments.

Among some studies that used HRV-B to mitigate the symptoms of poor sleep quality, one compared the breathing technique to physical activity and a control group (n=75). Physical activity showed a reduction in the PSQI Global score. The HRV-B group also showed an equivalent decline in the PSQI Global score.[9] Another study completed by Laborde et al. found that slow paced breathing done for 30 days each evening led to improvements in subjective sleep quality scores (n=64).[21] Improvements in sleep related to HRV coherence also were found by a case report (n=1) completed on an active military member in a combat zone who suffered from sleep deprivation due to

job stressors and used a portable biofeedback device for a total of 8 weeks. At the conclusion of his training, the individual reported improved sleep quality as well as reductions in depression, anxiety and sleep insomnia with practice prior to bed.[12] A study conducted on cancer patients, primarily breast cancer, showed reductions in sleep symptoms after a maximum of 6 HRV-B training visits (n=29).[56] Due to the restricted sample sizes of the studies previously completed, interpreting the results can be difficult. These few studies, however, are consistent with much of the literature with the effects HRV-B can have in improving the overall sleep quality of an individual suffering from sleep insomnia. The results from the previous studies mention as well as this current pilot study would suggest HRV-B is a promising intervention that can be easily implemented to mitigate the symptoms of sleep insomnia as well as be a possible treatment option for the issue.

Insomnia is common among individuals with chronic pain as it can cause sympathetic overactivation.[26] This current pilot study showed evidence of marked improvements in the HRV Coherence Ratio up to 2 months post-training, suggesting increased parasympathetic activity during sleep with decreases sleep-disrupting sympathetic activity that may have occurred due to the pain stimulus. These improvements were seen from baseline to follow-up, and no difference was found between the post-training assessment and the follow-up assessment. This suggests a persistence of the HRV-B training effect and underscores the ability for these individuals to improve their sleep and maintain that improvement through the duration of their time spent in the study. This improvement is vital for the restorative properties of sleep to occur which was hypothesized to improve sleep quality. The improvement in PSQI from

baseline to follow-up assessment suggests that the increases in sleep duration were manifested as improvements in sleep quality. The improvement of over 40 minutes in the intervention group in the intervention group shows individuals improving from just over 7 hours of sleep to ~ a full 8 hours of sleep each night. This improvement being attributed to HRV-B can possibly show evidence of individuals struggling to get a full night of sleep can receive some relief by simply implementing this simple breathing protocol to acquire some extra sleep their body may require. The lack of evidence of improvement in sleep efficiency, sleep onset latency and wake after sleep onset may be attributed the sample size, thus the acquisition of more participants may bolster those trends in the data. Although a rise in the proportion of individuals below the cut point of 5 on the PSQI Global score increases, this can be seen due primarily to sparse data. However, the shams did not exhibit this pattern of change. It is possible the individuals who experienced improvements in sleep quality were more engaged in the home practice prior to bedtime. The increased levels in coherence levels prior to sleep could have reduced the sympathetic dominance prior to rest and improved sleep function. Further investigation is required to discern what specific characteristics, if any, allowed these individuals to improve as they did where other intervention participants did not. This improvement could be attributed to: increased home practice, superior ability in the technique, belief in the technique to be effective or improved self-regulation mechanics while partaking in day to day life. Evaluation of practice time was outside the scope of this analysis.

Limitations of this study do exist. The sample size for this study was limited to 50 participants at follow-up whereas the recruitment goal was 80. The study population

was limited in that only Veterans of the United states military were eligible. Further, Veterans also had to qualify by having chronic pain to be eligible. This may have limited generalizability. In addition, over 500 participants were screen for eligibility, however, the population could have become selective due to high prevalence of uncontrolled high blood pressure, an exclusion criterion, and excluding medications, such as beta blockers used to control high blood pressure. These exclusion criteria did remove many otherwise eligible participants, however, it was necessary because blood pressure and these medications can have direct effects on the measurement of HRV.

There were also several strengths to the study. The protocol used was one that had been tested and used in several other studies. This study used trainers with over a decade of experience and multiple licensing and certifications in biofeedback education. The equipment used in this study was one of the better equipment setups available to administer HRV-B. The study design mitigated potential confounding due to randomization. The study design also used a 2-arm intervention which allowed for comparison to a control group.

In conclusion, HRV-B is a nonpharmacological, easy to learn, easy to use technique, capable of being administered as needed for self-regulation of sleep disturbances and various other symptoms. The results displayed from this pilot study provide evidence that HRV-B can mitigate or improve sleep quality issues. Larger, multisite studies are needed to further evaluate the efficacy of HR-B among patients with chronic pain or related symptoms.

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APPENDIX A
SUPPLEMENTAL MATERIALS

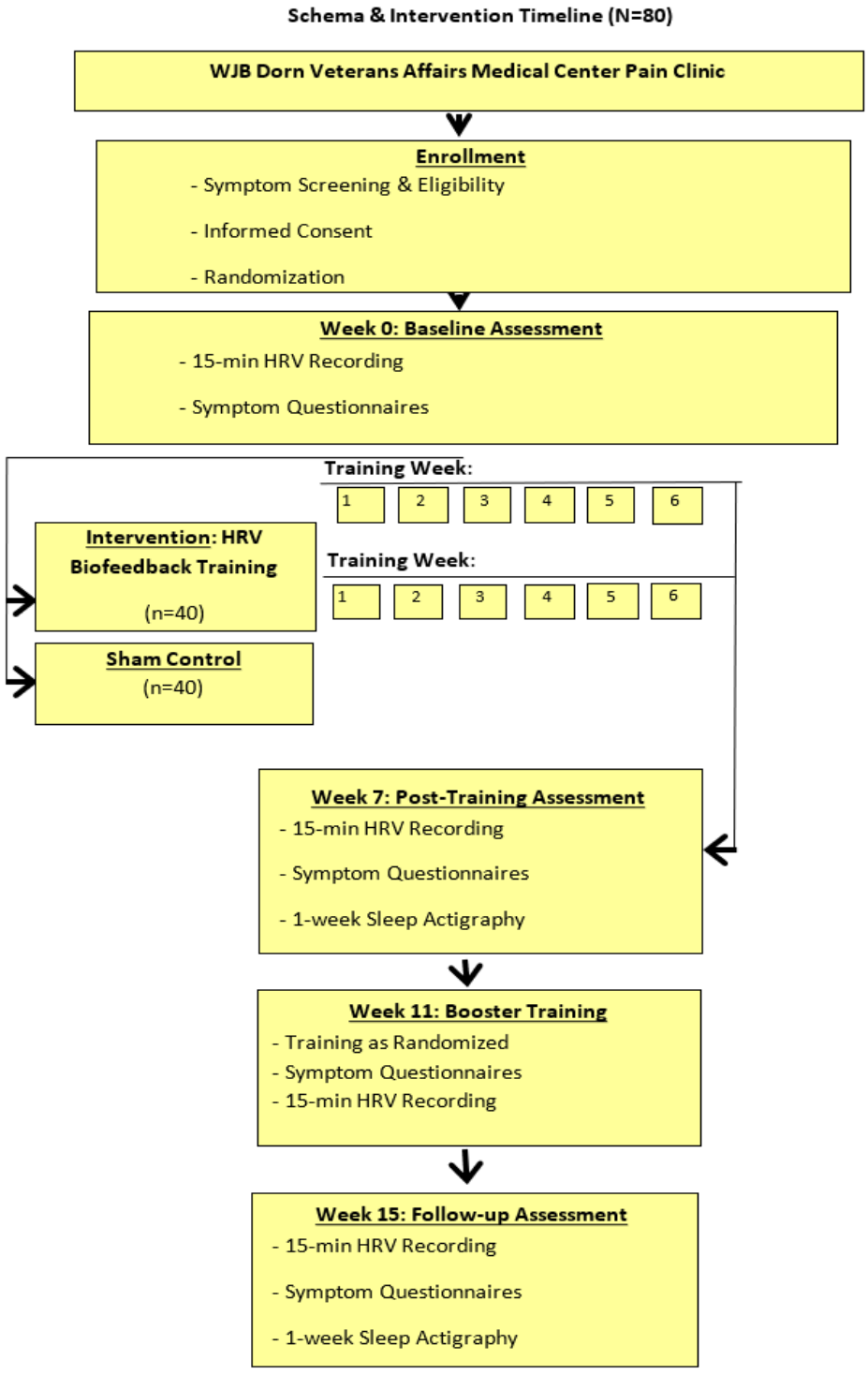

Figure A.1: 16-Week Study Timeline

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

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_____

Figure A.3: Page 1 of 3 of the PSQI questionnaire

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

Figure A.4: Page 2 of 3 of the PSQI questionnaire

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]

Figure A.5: Page 3 of 3 of the PSQI questionnaire

Time-Log

Subject Time-log Form: Please record the times you go to bed, the times you wake-up and the times you turn the light off (below the log). For example, if you go to bed at 11:30 in the night, put 11: 30 PM.

Day	Time wake-up	Time turn light off	Time to bed	Comments/Concerns
1st Day				
2nd Day				
3rd Day				
4th Day				
5th Day				
6th Day				
7th Day				

Figure A.6: Subject Time Log for Sleep Actigraphy