Title:

High-resolution, Relational, Resonance-based, Electroencephalic Mirroring (HIRREM) for Pre-Hypertension: A Randomized, Controlled Clinical Trial

Abstract:

Background: Hypertension, high blood pressure, is the most important risk factor for cardiovascular and cerebrovascular disease in the United States of America, and thus the leading identifiable cause of death and disability from heart disease and stroke. Most patients with hypertension do not have an identifiable etiology, and are classified as having primary hypertension. Evidence suggests that even modest levels of blood pressure below the traditional thresholds for diagnosing hypertension, pre-hypertension, are associated with increased cardiovascular risk, and predict transition to hypertension. However, evidence-based therapies targeted for those with pre-hypertension are lacking. Chronic stress, with associated autonomic dysregulation, and hyperarousal has been implicated as a potential causal factor for primary hypertension, but effective noninvasive, non-drug interventions are needed.

High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM®) is a closed-loop, allostatic, acoustic stimulation neurotechnology that uses software-guided algorithmic analysis to identify and translate selected brain frequencies into audible tones to support real-time self-optimization of brain activity. Pilot data shows that the use of HIRREM is associated with reduced symptoms of traumatic stress and anxiety, and improved autonomic cardiovascular regulation across heterogeneous cohorts, as well as reduced blood pressure in a small series with comorbid hypertension. This study will evaluate the use of HIRREM for those with pre-hypertension in a randomized clinical trial.

Objective: The primary objective of this pilot study is to evaluate whether the addition of acoustic stimulation linked to brain activity (HIRREM), as compared to the addition of acoustic stimulation not linked to brain activity (ambient nature sounds), to continued current care, will reduce systolic and diastolic blood pressure (BP) in patients with blood pressure levels that place them in the category of pre-hypertension.

Methods: This will be a randomized, single site, controlled, pilot clinical trial, enrolling up to 24 men and women, aged 18 or older, who have not been previously diagnosed with hypertension, and who have documented blood pressures that place them in the category of pre-hypertension (systolic BP 120-139, and/or diastolic BP 80-89), have no known cardiovascular disease, or other medical conditions associated with likelihood for development of hypertension, and who are not taking medications for management of blood pressure. Participants will be randomly assigned to receive 8-16 sessions of either acoustic stimulation linked to brain activity (HIRREM and continued current care, HCC), or acoustic stimulation of ambient nature sounds not linked to brain activity (nature sounds and continued current care, NCC), over a maximum of 4 weeks. Both groups will continue their other current care throughout. There will be pre- and post-intervention data collection to include physiological outcomes (BP, HR, and measures of autonomic cardiovascular regulation), as well as symptom inventories for insomnia (Insomnia Severity Index, ISI; Pittsburgh Sleep Quality Index, PSQI; and the Epworth Sleepiness Score, ESS), depression (Center for Epidemiological Studies- Depression Scale, CES-D), anxiety

(Generalized Anxiety Disorder-7, GAD-7), traumatic stress (PTSD Checklist-Civilian, PCL-C), stress (Perceived Stress Scale, PSS), and a quality of life measure (EuroQol Five Dimensions Questionnaire, EQ-5D), as well as drop stick reaction testing, and dynamometry for grip strength. Measures will be collected at an enrollment visit (V1), and the intervention will begin 1-14 days thereafter. BP and heart rate (HR) recording will be repeated prior to the start of the 7th session. Post-intervention data collections will be obtained at 1-7 days (V2), 4-6 weeks (V3, primary outcome), and 12-14 weeks (V4) following completion of the intervention. The primary outcome will be differential change in the systolic and diastolic BP from V1 to V3. Following V4, those in the NCC group will be offered the opportunity to cross over to receive a course of HCC, and will continue to be followed for data collections at 1-7 days (V5), 4-6 weeks (V6), and 12-14 weeks (V7) after completing their crossover HIRREM sessions. We will utilize linear mixed models (LMMs) to contrast longitudinal changes in systolic and diastolic blood pressure between the HCC and NCC groups. Mean contrasts will be used to compare the changes in blood pressures between groups from V1 to V3, our primary test of efficacy. Additional mean contrasts will be constructed to evaluate the consistency of any benefit of HIRREM through subsequent visits beyond V3. Comparisons of changes in all secondary outcomes will be assessed in a similar fashion.

Importance: This study will explore the use of HIRREM for pre-hypertension, a condition now lacking evidence-based therapies to manage and prevent progression to overt hypertension, in a randomized, controlled clinical trial. The primary outcome of change in blood pressure is a practical, objective physiological parameter. The study will confirm feasibility of a controlled trial using acoustic stimulation interventions in this population, and provide estimates of effect size, which might justify larger controlled trials. A positive result would suggest that HIRREM might have benefit as a noninvasive, non-drug alternative for initial management of pre-hypertension. This, over and above the potential beneficial effects of acoustic stimulation not tied to brain activity, or the impact of interacting with the study personnel and the study environment. The study will also help to identify the characteristics of subgroups that might experience differential effects/benefits from HIRREM. Identification of an effective, noninvasive, non-drug therapy to reduce blood pressure in this cohort could have direct implications for reducing cardiovascular risk in large populations.

Background:

Hypertension, high blood pressure, is the most important risk factor for cardiovascular, and cerebrovascular disease, and thus the leading identifiable cause of death and disability from heart attack and stroke. Combined, these disorders cause > 800,000 deaths annually in the United States, with an estimated direct and indirect cost of over $316 billion, along with the countless lives impacted. Hypertension affects an estimated 70-80 million people in the USA, but only about half are believed to be adequately treated (Mozaffarian et al., 2016). Hypertension alone costs the nation an estimated $46 billion annually. Therapy can include an array of changes in life-style, along with medications, but additional, noninvasive, non-drug alternatives are needed.

There is accumulating evidence that even moderate levels of increased blood pressure have implications for cardiovascular risk, and for later development of overt hypertension, and there is now a formal designation for a category of pre-hypertension (James et al., 2014). Although there are evidence-based guidelines for treatment of the various stages of hypertension, the same are lacking for those in the pre-hypertension category. The prevalence of even low levels of elevated blood pressure (≥ 100-115 systolic BP) has increased in recent years. This level of blood pressure has also been associated with increased deaths, as well as decreased disability-adjusted life-years (Forouzanfar et al., 2017).

Hypertension and impaired autonomic function increases the risk of many cardiovascular disorders. Up to ninety-five percent of people with hypertension do not have a clear cut, identifiable etiology, and are classified as primary, or essential hypertension (Carretero & Oparil, 2000). Chronic stress, with associated autonomic dysregulation/hyperarousal has been implicated as a potential causal factor (Mancia & Grassi, 2014), but effective noninvasive interventions for symptoms/economic cost/alternative nondrug, noninvasive methods related to high blood pressure are lacking.

Disturbed central control of cardiovascular regulation due to chronic stress, anxiety, or other causes may result in hypertension and impaired heart rate variability (HRV). Evidence suggests a bihemispheric model of autonomic responses to traumatic stress; right side sympathetic, left side parasympathetic (Lee SW., 2014). Brain plasticity may allow severe or repeated traumatic stress to cause persisting imbalance, and accumulation of allostatic load, resulting in autonomic dysregulation, inflexibility, and reduced adaptability. This may provide a potential target for allostatic therapeutic interventions intended to improve brain balance, and flexibility of brain rhythms, which could improve autonomic function, with implications for treatment of hypertension.

Impaired autonomic cardiovascular regulation has been reported among those with prehypertension, or strong family history of hypertension (Pal et al., 2011; Wu et al., 2008), and may be a predictor for development of prehypertension/hypertension (Chinagudi S, 2013). While some suggest enhanced sympathetic tone as a contributing factor (Wu et al., 2008), others report a withdrawal, or decrease of the vagal effects that help to modulate sympathetic influences (Duprez, 2008; Pal et al., 2011), or both increased sympathetic and decreased vagal tone (Pal et al., 2013). Impaired autonomic cardiovascular regulation may be a viable therapeutic target for those with prehypertension. Use of non-pharmacological strategies such as biofeedback and slow abdominal breathing, EMG-biofeedback, and

HRV-biofeedback, targeting downstream autonomic function are reportedly associated with improved autonomic function and reduced blood pressure in those with prehypertension (Chen, Sun, Wang, Lin, & Wang, 2016; Lin et al., 2012; Wang et al., 2010; Xu, Gao, Ling, & Wang, 2007). Passive listening to Indian music, along with lifestyle modifications has also been reported to lower BP and improve autonomic function in subjects with prehypertension/Stage 1 hypertension (Kunikullaya et al., 2015). Strategies that more directly target/influence central management of autonomic cardiovascular regulation may thus be expected to have beneficial effects on downstream autonomic function, as well as blood pressure in this cohort.

High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM®) was developed by Brain State Technologies, Scottsdale, AZ. It is a commercially available, noninvasive, electroencephalic-based method to facilitate client-unique relaxation and auto-calibration of cortical neural oscillations by reflecting auditory tones in near real time (Gerdes, Gerdes, Lee, & Tegeler, 2013). HIRREM uses scalp sensors to observe brain frequencies and amplitudes in real time, and software-guided algorithmic analysis to identify and translate selected brain frequencies into audible tones to support real-time self-optimization of brain activity. The audible tones are reflected back to the recipient bilaterally, simultaneously, in 4-8 milliseconds, providing an opportunity for the recipient to, figuratively speaking, listen to the song the brain is playing right now. This rapid updating regarding its pattern allows the brain a chance to auto-calibrate, self-optimize, "relax," and reset/get unstuck from what has been stuck stress/trauma response patterns. The brain electrical patterns are observed to shift independently, with no conscious, cognitive activity required, no operant conditioning, and no learner in the loop, towards improved balance and reduced hyperarousal.

The mechanism of this effect remains to be fully understood, but may involve resonance between reflected tones and oscillating brain networks, much like a musical instrument tuning itself. Functionally, it may be that this acoustic stimulation facilitates kindling of sleep in neuronal units, which had previously been stuck in the "on" position due to stress responses (Krueger, Huang, Rector, & Buysse, 2013). Better sleep is foundational for all health and healing. A key aspect of observed beneficial effects may also be related to the observed improvement in downstream autonomic function, as evidenced by increased heart rate variability and baroreflex sensitivity, apparently associated with increased dynamic range and flexibility of autonomic responses managed by the brain.

Since 2011, the HIRREM Research Program at WFSM has enrolled over 450 participants in one of 5 clinical studies to evaluate the effects and potential benefits of HIRREM. Data have shown reduction in symptoms of insomnia, depression, stress/anxiety, hot flashes, and persisting symptoms after athletic concussion, associated with the use of HIRREM (Charles H. Tegeler et al., 2017; C. H. Tegeler et al., 2012; C. H. Tegeler et al., 2016; C. H. Tegeler, Tegeler, Cook, Lee, & Pajewski, 2015) Improved autonomic cardiovascular regulation has also been observed in those receiving HIRREM, including a cohort of adolescents with Postural Orthostatic Tachycardia Syndrome (Fortunato et al., 2013; CL. Tegeler et al., 2014). In addition, correlation has been reported between high frequency electrical brain pattern asymmetry scores at baseline, and measures of autonomic cardiovascular regulation (C.H. Tegeler, Shaltout, Tegeler, Gerdes, & Lee, 2015) .

Specific Relevant Pilot Data:

Recent feasibility data demonstrated significantly reduced systolic and diastolic blood pressure, as well as improved autonomic cardiovascular regulation, and improved behavioral symptoms, associated with the use of HIRREM (Table 1 and 2, and Figure 1, below), in a series of participants self-reporting to have hypertension (Shaltout HA, 2016).

10 participants (5 female), mean age 47.2 (SD 20.1) with a resting supine blood pressure of >130/90 were enrolled in an ongoing, open label, IRB-approved feasibility study of HIRREM for diverse neurological/psychophysiological symptoms and disorders. After an initial HIRREM assessment of brain frequencies and amplitudes, baseline data collection included symptom inventories for insomnia (ISI), depression (CES-D), and anxiety (GAD-7), along with physiological and functional measures. Blood pressure and heart rate was continuously recorded while supine, with spontaneous breathing. Subjects then received 17.7 (5.9) HIRREM sessions (90-120 minutes each). Sessions consisted of 5-9 protocols, from 6-40 minutes each, with up to two sessions per day, and were received over a total of 20.1 (28.6) days, but only 10.2 (3.0) in-office days. All measures were repeated after completion of the intervention, 14.4 (15.4) days after the final HIRREM session. Analysis of autonomic cardiovascular regulation included spectral analysis for calculation of multiple standard measures of HRV (including SDRR and rMSSD), baroreflex sensitivity (BRS, HF Alpha, Sequence Up SBP, Sequence Down SBP, and Sequence ALL), and arterial pressure (systolic, SAP, diastolic, DAP, and mean, MAP). There were no dropouts among those with hypertension, and no reported serious adverse events for any of the HIRREM research studies to date.

Table 1:

Key Autonomic Cardiovascular Outcomes				
Measure (Units)	Mean Value Baseline (SE)	Mean Value Post-HIRREM (SE)	Mean Change (SE)	p value
Up SBP (ms/mmHg)	10.6 (3.0)	16.3 (3.9)	5.7 (1.3)	p = 0.001
SDRR (ms)	42 (7.1)	57 (9.7)	15.1 (7.0)	p = 0.049
SAP (mmHg)	151.7 (6.0)	136 (6.9)	-15.1 (5.5)	p = 0.018
DAP (mmHg)	97.2 (2.8)	81 (1.8)	-16.2 (3.1)	p < 0.001
MAP (mmHg)	116.5 (2.9)	100.9 (2.0)	-15.6 (4.3)	p = 0.004

Table 2:

Key Behavioral Outcomes				
Measure	Mean Value Baseline (SD)	Mean Value Post-HIRREM (SD)	Mean Change (SD)	p value
ISI	8.1 (7.2)	3.3 (3.2)	-4.8 (4.6)	p = 0.009
GAD-7	7.2 (3.8)	2.2 (2.4)	-5.0 (4.3)	p = 0.06
CES-D	14.5 (11.7)	7.1 (3.8)	-7.4 (9.8)	p = 0.07

Figure 1:

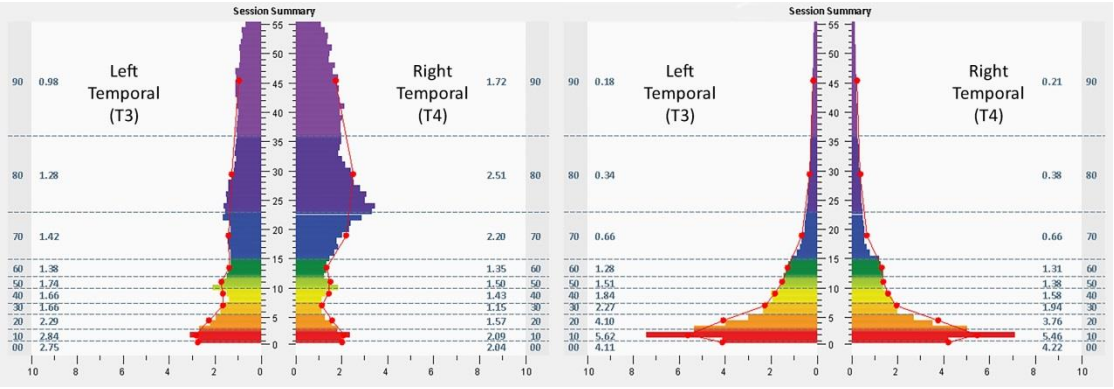


Figure Legend: FFT spectral displays from a 63 year old female participant, as an example of changes observed in electroencephalic data, with frequency (Hz, central Y axis) plotted against transformed amplitude (μv, X axis). Data represents one minute of data recorded from the T3/T4 montage with eyes closed at baseline assessment (left panel) and the penultimate minute of a protocol at the same location and eye state, in the 15th session (right panel). Note reduced hyperarousal and improved balance.

These data provide the first report of a cardiovascular benefit associated with short term use of a non-traditional, closed loop, allostatic, acoustic stimulation intervention in a cohort with hypertension, in addition to improving behavioral symptom outcome measures. Results suggest a centrally mediated effect with reduced allostatic load and improved flexibility in autonomic cardiovascular regulation, with potential impact for improved long term cardiovascular outcomes. These findings also reinforce appreciation of the brain as the organ of central command, with the implication that effective intervention for self-optimization of brain activity should have positive consequences for downstream organ function.

In addition, 18 service members (15 active duty, most from Naval Special Warfare Group Ten, 3 veterans, 1 female), median age 39.5 (range 29-50) with symptoms lasting from 2-12 years, 20.5 years (8-33) in the military, and a median of 8 deployments (2-19), were enrolled in a DoD-funded, open label, IRB-approved, pilot study of HIRREM for symptoms of military-related traumatic stress. Blood pressure and heart rate was continuously recorded while supine, with spontaneous breathing. Subjects then received 20 HIRREM sessions (17-21, 90-180 minutes each). Sessions consisted of 5-10 protocols, from 8-45 minutes each, and up to two sessions per day, were received over 12 days (11-12). All measures

were repeated on completion of HIRREM, and symptom inventories were assessed at 1, 3, and 6 months after completion. Spectral analysis was performed to calculate multiple measures of HRV and baroreflex sensitivity (BRS). There were no dropouts, or reported serious adverse events.

In addition to reduction in self-reported symptoms, and improved network connectivity on whole brain, resting MRI studies, all measures HRV and BRS measures increased, showing improved autonomic cardiovascular regulation, with increased parasympathetic influence, and SAP decreased, suggesting improved sympatho-vagal balance (Table 3, below) (Catherine Tegeler, Shaltout, Lee, & Tegeler, 2016; Charles Tegeler, Catherine Tegeler, Jared Cook, Lindsay Howard, et al., 2016; Charles Tegeler, Catherine Tegeler, Jared Cook, Sung Lee, et al., 2016).

Table 3:

Key Autonomic Cardiovascular Outcomes				
Measure (Units)	Mean Value Baseline (SE)	Mean Value Post-HIRREM (SE)	Mean Change (SE)	p value
HF Alpha (ms/mmHg)	17.61 (2.56)	27.28 (3.84)	9.67 (3.09)	p = 0.005
Up SBP (ms/mmHg)	13.06 (1.87)	21.45 (2.99)	8.39 (3.04)	p = 0.011
Down SBP (ms/mmHg)	14.43 (1.78)	22.03 (2.60)	7.61 (2.42)	p = 0.005
Sequence All (ms/mmHg)	13.75 (1.74)	21.41 (2.37)	7.66 (2.20)	p = 0.006
SDNN (ms)	50.98 (5.40)	62.97 (5.23)	11.98 (3.46)	p = 0.003
rMSSD (ms)	32.76 (4.33)	45.98 (5.33)	13.22 (3.00)	p < 0.001
SAP (mmHg)	131.26 (3.18)	125.39 (2.92)	-5.87 (1.91)	p = 0.020

While blood pressure reduction and HRV improvement in these studies could also be secondary to reduced insomnia and anxiety, it may reflect reduced sympathetic tone to blood vessels associated with reduced allostatic load. Additional studies are warranted to investigate the mechanism of the changes associated with this highly promising intervention.

Specific to pre-hypertension, which is the focus for this trial, review of participant data from the ongoing Developmental Study (IRB#00017651) identified 66 participants for whom there was V1 and V2 data, whose baseline BP readings placed them in the category of having pre-hypertension (mean systolic 127.5, diastolic 81.2, and MAP 97.0 mmHg). Participants received a mean of 16.4 HIRREM sessions, over a mean total of 22.4 days, with a mean of 9.5 days actually in the office. Although these participants had only mildly increased BP at baseline (just considered as pre-hypertension), data collection at baseline (V1), and 1-2 weeks after completion of the HIRREM intervention (V2) showed

statistically significant reductions in systolic arterial pressure (SAP, -4.5 mmHg), diastolic arterial pressure (DAP, -2.7), and mean arterial pressure (MAP, -3.7). There was also significant reduction from V1 to V2 for multiple measures of HRV (SDNN, and rMSSD), and BRS (HF Alpha, and Sequence Up, Sequence Down, and Sequence All). A subset of 28 in this cohort also had a later V3 follow up data collection. For those there was significant reduction in BP, with even larger reductions in BP (SAP, -8.6 mmHg; DAP, -5.2; MAP, -6.3), with still significant improvements in measures of BRS, and a trend for improved HRV (SDNN). These data, as yet unpublished, directly speak to the potential for meaningful reductions in BP associated with HIRREM, in spite of a potential floor effect since baseline BP levels were only in the pre-hypertension category.

Ambient nature sounds are reported to help mitigate stress, and facilitate recovery from stress-related sympathetic hyperarousal. Exposure to nature sound has been shown to facilitate reduce sympathetic activation in response to psychological stress (Annerstedt et al., 2013). While there was significant added benefit to receiving HIRREM, recent preliminary results from our placebo-controlled trial of HIRREM for moderate to severe insomnia also showed significant reduction of symptoms of insomnia for those receiving random acoustic stimulation, not linked to brainwaves (Tegeler CL, 2016). Thus, it is expected that exposure to ambient nature sounds, with accompanying exposure to the study environment, and study personnel, will have some beneficial effects in this setting.

Hypothesis:

The addition of acoustic stimulation linked to brain activity (HIRREM plus continued current care, HCC) will be associated with greater reduction in systolic and diastolic blood pressure than that seen with the addition of acoustic stimulation not linked to brain activity (nature sounds plus continued current care, NCC), among patients with pre-hypertension.

Research Design and Method:

Objectives:

Primary Objective:

The primary objective of this pilot study is to evaluate whether the addition of acoustic stimulation linked to brain activity (HIRREM, HCC), as compared to the addition of acoustic stimulation not linked to brain activity (ambient nature sounds, NCC), to continued current care for both groups, will reduce systolic and diastolic blood pressure in patients with documented blood pressure values that place them in the category of pre-hypertension.

Secondary Objectives:

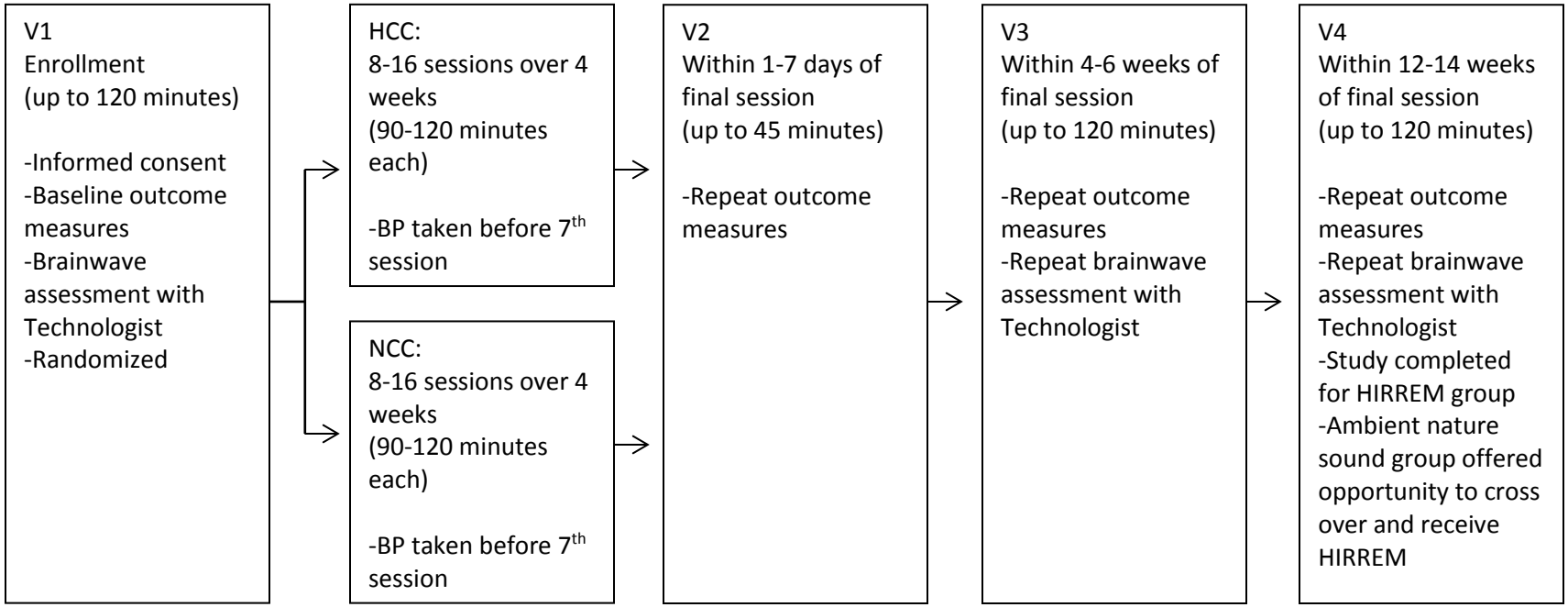
Evaluate whether the addition of acoustic stimulation linked to brain activity (HCC group), as compared to the addition of acoustic stimulation not linked to brain activity (NCC group), to continued current care, will result in greater differential changes in a variety of physiological, behavioral, and function outcome measures outlined below.

1. Autonomic nervous system functions, as manifested by heart rate, HRV, and BRS. We expect to see greater changes in autonomic activity and an improvement of sympatho-vagal balance in the HCC group. This would be reflected as changes in heart rate, and an increase of HRV and BRS parameters such as the standard deviation of the R-R interval (SDRR), rMSSD, HF alpha, and Sequence Up, Down, or All.
2. Behavioral outcomes such as insomnia (assessed by the Insomnia Severity Index, ISI; Pittsburgh Sleep Quality Index, PSQI; and the Epworth Sleepiness Score, ESS), depression (as assessed by the Center for Epidemiological Studies-Depression Scale, CES-D), anxiety (as evaluated by the GAD-7), traumatic stress (as assessed by the PCL-C), and stress (as assessed by the Perceived Stress Scale, PSS). We expect to see greater improvement in these symptom inventory scores in the HCC group.
3. Overall quality of life as evaluated using the EQ-5D measure. We hope to see greater improvement in overall quality of life scores in the HCC group.
4. Functional performance evaluated using drop stick reaction testing. We expect to see more improvement in the HCC group.
5. Functional performance evaluated by grip strength, using a hand dynamometer. We expect to see greater improvement of grip strength in the HCC group.
6. Impact on comorbidities, for example a history of TBI/concussion, PTSD, ADHD, hot flashes, migraine, or insomnia. We expect to see more reduction of symptoms in the HCC group.

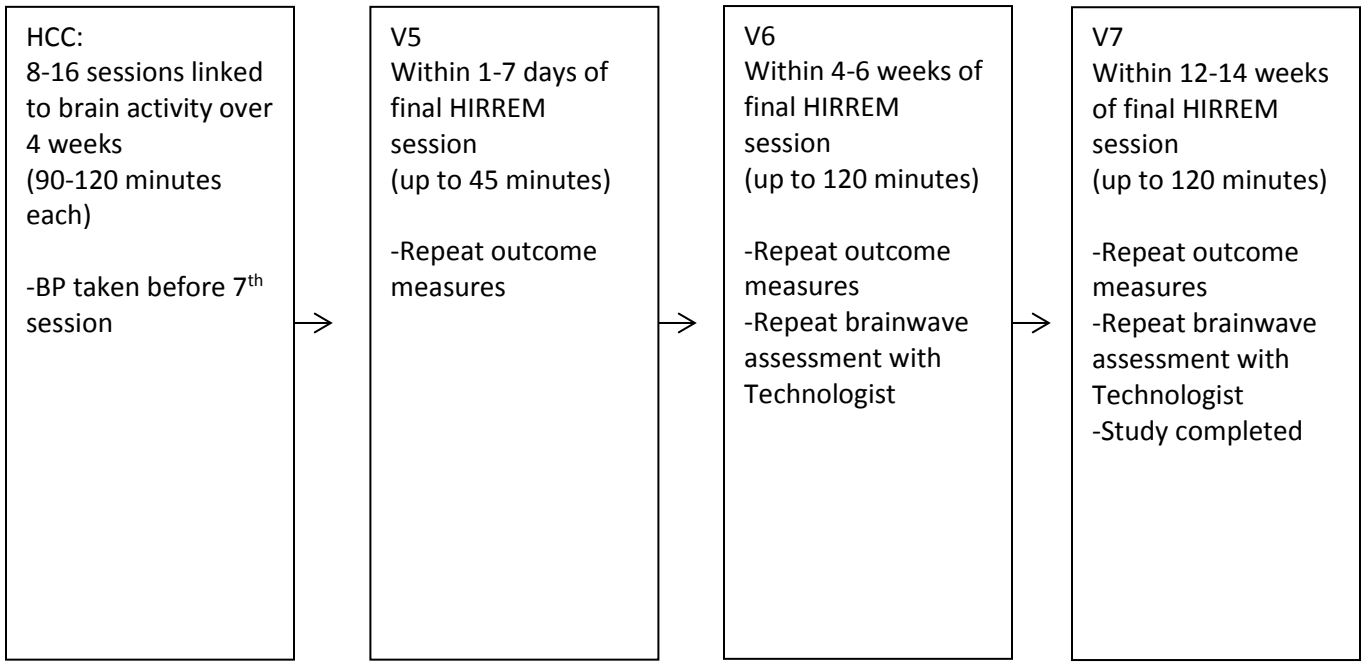
Overview:

This will be a randomized, single site, controlled, pilot clinical trial. Assuming a potential drop-out rate of 20%, up to 24 subjects will be enrolled to achieve a goal of having at least 20 subjects (10 per group) complete the study, per protocol. Patients who have blood pressures between 120-139 mm/Hg systolic, and/or 80-89 mm/Hg diastolic, as documented by their health care providers on two separate occasions, and no other exclusions, will be randomly assigned to receive either 8-16 sessions of either acoustic stimulation linked to brainwave activity (HCC), or acoustic stimulation not linked to brainwave activity (NCC), over a maximum of 4 weeks, with both groups continuing their current care throughout. There will be pre- and post-intervention data collection to include systolic and diastolic BP, and many secondary outcome measures including measures of autonomic cardiovascular regulation (continuous recording of BP and HR for calculation of measure of HRV and BRS), behavioral symptom outcomes (ISI, PSQI, ESS, CES-D, GAD-7, PCL-C, PSS), quality of life measure (QOLS), alcohol use (Audit C), and function performance measures (drop stick reaction testing, and grip strength). All measures will be collected at an enrollment visit (V1), and the intervention will begin 1-14 days later. BP and HR recordings will also be repeated prior to the start of the 7th session. Post-intervention data collections will be obtained at 1-7 days (V2), 4-6 weeks (V3, primary outcome), and 12-14 weeks (V4) following completion of the intervention. The primary outcome will be differential change in the systolic and diastolic BP from V1 to V3. Additional follow up (V4) will evaluate durability of effects. Following V4, those in the NCC group will be offered the opportunity to cross over to receive a course of HCC, and will continue to be followed for data collections at 1-7 days (V5), 4-6 weeks (V6), and 12-14 weeks (V7) after completing their crossover HCC sessions.

Pre-Hypertension Study Flow Chart



NCC Group Who Complete V1-V4 and Choose to Receive a Course of HCC



Participants/Subjects:

Adults ages 18 and older with documented blood pressure readings between 120-139 mm/Hg systolic, and/or 80-89 mm/Hg diastolic, and who meet the following inclusion criteria and are interested to participate in the study will be recruited from the community by physician referral and advertisement. Each subject must be able to provide an informed consent. Pre-hypertension will be defined by systolic BP ranging from 120-139, or a diastolic BP of diastolic pressure ranging from 80-89 mm/Hg, documented by their health care provider on two occasions, at two separate office visits. As part of the screening process, potential participants will need to provide this documentation of having BP in the target range. A prior diagnosis of hypertension, known cardiovascular disease, or other conditions associated with development of hypertension such as renovascular disease, renal failure, pheochromocytoma, aldosteronism, are not present.

Interested subjects will be informed with a more detailed description of the study, and the extent of their commitment, through phone calls or email communications. If no exclusions are apparent from initial phone or email communications, potential participants will complete an online eligibility screening form, which will be reviewed by the study team. If potential participants express continued interest in the project and have no major exclusions, and after receipt of BP documentation as noted above, they will be scheduled for an enrollment visit (V1) at which time an informed consent will be completed. As part of the informed consent process, study procedures, schedule for visits, and duration of participation will again be reviewed, and alternatives discussed, including the option to not enroll in this project, and follow up with their primary health care provider.

After informed consent is obtained, blood pressure will be obtained to confirm eligibility. Those with BP less than 120 mmHg systolic and 80 mm Hg diastolic, or greater than 140 mmHg systolic or 90 mmHg diastolic, will be considered as screening failures, and will not move on to the remaining enrollment visit activities. For those confirmed to have an eligible baseline blood pressure reading, a brief medical history will be obtained, randomization will be completed, and baseline study measures obtained, prior to the start of the intervention. Those scheduled for an enrollment visit will also be provided a copy of Appendix B, Handout to Study Participants, and/or a welcome email with details.

Inclusion Criteria:

Men and women, ≥ 18 years of age, with pre-hypertension, who have systolic BP ranging from 120-139 mm/Hg, or who have diastolic BP ranging from 80-89 mm/Hg.

Exclusion Criteria:

Blood pressure values that are outside of the range for prehypertension at the enrollment visit
Unable, unwilling, or incompetent to provide informed consent
Physically unable to come to the study visits, or to sit comfortably in a chair for up to two hours at a time
Prior diagnosis of hypertension

Ongoing need for medical treatment for hypertension, or for the use of medications commonly used for treatment of hypertension
Known cardiovascular disease
Known seizure disorder
Known or anticipated pregnancy (females of childbearing age will be tested for pregnancy prior to randomization)
Severe hearing impairment (because the subject will be using headphones during the interventions)
Ongoing need for treatment with opiate, benzodiazepine, or anti-psychotic medications, anti-depressant medications such as SSRI, SNRI, or tricyclic, and sleep medications such as zolpidem or eszopiclone
Anticipated and ongoing use of recreational drugs, alcohol, or energy drinks
Ongoing need for treatment with thyroid medications

Participants are encouraged to discuss their participation with their health care provider following completion of the study because HIRREM may alleviate some of the need for medications they were on previously. Participants are requested to abstain from using any alcohol or recreational drugs during the intervention, and for at least six weeks following sessions since use of these substances may cause reversal or cessation of the benefits of HIRREM. In addition, the participants are also advised to suspend chiropractic, cranial-sacral therapy, and bio-energy work during the intervention, and for at least six weeks following.

Number of Subjects:

As a pilot study, involving an active control condition for which we as yet have no information regarding effect size, we are not able to calculate a sample size. In order to evaluate feasibility and effect size, and allowing for up to 20% drop outs, we will arbitrarily enroll up to 24 subjects to achieve a goal of having 20 subjects complete the study per protocol (estimated 10 per group).

Number of HCC/NCC Sessions and Length of Study:

All baseline measures, along with a brainwave assessment, will be obtained during an enrollment visit (V1). The intervention will commence 1-14 days later. Participants will receive 8-16 intervention sessions over a maximum of 4 weeks. HCC or NCC sessions will be about 1.5-2 hours in length. Participants may receive two intervention sessions during a half day period. All will receive a total of 6 sessions during the first three days of the intervention period. Participants will be encouraged to complete the remainder of the intervention sessions within two-three weeks, with a maximum of four weeks to complete the sessions. If done as two sessions per half day, subject involvement will thus require 4-8 half days during the intervention period. Following the initial 6 sessions, some sessions may be arranged as singles (one per day), if needed due to schedule issues.

One to seven days after the final intervention session there will be a post-intervention data collection visit (V2). All measures will be repeated, but no brainwave assessment will be obtained. Four to six weeks after completion of the intervention, there will be a post-intervention data collection visit (V3),

with all measures repeated. Data collected at the V3 visit will comprise the primary outcome data for the study. A final data collection visit (V4) will occur 12-14 weeks after completion of the intervention, with repeat of the outcome measures, but no brainwave assessment. At V4, official study involvement is complete for those in the HCC group, while those randomized to the NCC group will be offered an opportunity to be scheduled to receive a course of HCC. Those who opt to do so will receive a course of acoustic stimulation linked to brainwaves, as described for the HCC group, and will continue to be followed for data collections at 1-7 days (V5), 4-6 weeks (V6), and 12-14 weeks (V7), as done during the initial intervention period, after completing their crossover HCC sessions.

Enrollment Visit:

Informed consent is obtained, and blood pressure is then obtained. Since all participants will have been documented to have prior blood pressure values that meet the parameters for prehypertension, and in light of variability associated with visits to the doctor, or other factors, if blood pressure values are too high, or too low on the initial measurements the potential participant will be allowed to rest for at least 3 minutes, and the blood pressure will be repeated. Those who still have blood pressure values less than 120 mmHg systolic pressure, and diastolic pressure less than 80 mmHg, and thus do not meet criteria for pre-hypertension, will be considered as screen failures. Those with blood pressure that is still higher than 140 mmHg systolic or 90 mmHg diastolic, will be also be considered as screen failures. They will not be assigned a study number, and will be excluded from further participation. Those with blood pressure values that are too high will also be advised to follow up with their medical provider. For those who meet blood pressure goals, notification of group assignment is made, and all baseline measures are collected, including a brainwave assessment. If not already completed via a REDCap link, a brief medical history form will be completed (Appendix C). The V1 visit will require about 2 hours of time.

Intervention Period:

During the intervention period, subjects will receive sessions of either acoustic stimulation linked to brainwave activity (HIRREM, HCC), or acoustic stimulation not linked to brainwave activity (ambient nature sounds, NCC), while relaxing in a zero gravity chair. Sessions last about 1.5-2 hours, and two can be done in a half day, with a short break between sessions. All subjects must receive the initial 6 sessions, two per day, on three consecutive days. Thereafter, subjects are encouraged to get the complete all sessions within 7-14 days, and in no longer than 4 weeks, without going longer than 5 days between sessions. BP and HR recordings will also be repeated prior to the start of the 7th session.

Post-Intervention Data Collection Visits:

Between 1-7 days after completion of the intervention, participants will return for a post-intervention data collection visit (V2). All measures will be repeated, but no brainwave assessment will be done. This visit will take about 45 minutes.

Between 4-6 weeks after completion of the intervention, participants will return for the primary outcome data collection visit (V3). All measures will be repeated, including a brainwave assessment. This visit will require about 120 minutes.

Between 12-14 weeks after completion of the intervention, participants will return for a final data collection visit (V4). All measures will be repeated for a final time. This will complete the official study involvement for participants in the HCC group, while those in the NCC group will be offered an opportunity to be scheduled to cross over and receive a course of HCC, and this will be discussed. This visit will take about 120 minutes.

High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM):

High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM®) is a computer-based technology created by Brain State Technologies, LLC, Scottsdale, AZ, designed to facilitate relaxation and auto-calibration of neural oscillations through reflecting back musical tones in near real time.

Brainwave Assessment:

This is the first step in the HIRREM process. It occurs during the V1 enrollment visit, and will be performed on both groups. The assessment creates a map of frequencies and amplitudes, and informs the choice of protocols for the initial HIRREM sessions. Our pilot data also suggest that this information is also useful for correlating with autonomic function (HRV and BRS), and that changes can be observed in frequencies and amplitudes from pre- to post-HIRREM. For the assessment, with the participant in a sitting position, sensors are sequentially placed over six areas of the scalp to record one minute epochs of data while the brain is at rest, or on task, with eyes open and with eyes closed. For the assessment, measurements are taken at homologous regions of the bilateral hemispheres according to the 10-20 International System at F3/F4, C3/C4, P3/P4, T3/T4, FZ/OZ, and O1/O2 with both eyes closed (EC; one minute), and eyes open (EO; one minute) conditions ("Report of the committee on methods of clinical examination in electroencephalography: 1957," 1958). For EO assessments, subjects are given standardized tasks involving numerical digit recall (F3/F4), reading silently (C3/C4), math calculations (P3/P4), listening comprehension (T3/T4), and to relax with eyes open (O1/O2). A sixth midline measurement is taken at FZ/OZ, with an EO task to count number of appearances of a specific word as they read a standardized printed passage, with additional recordings at a seventh (FP1/FP2, given standardized tasks involving numerical digit recall), and eighth (CB1/CB2, relax with eyes open) location. The reference sensors are connected at A1/A2 and linked for assessments. The data are processed to identify patterns and imbalances of frequencies and amplitudes, which are used to generate specific protocols for the initial HIRREM session. The assessment takes about 30-45 minutes to complete. An assessment will be repeated at the V3 visit to allow comparison between brain patterns at baseline, and post-intervention, between the two groups.

HIRREM/Ambient Sound Sessions:

Participants assigned to both study groups will continue their current care. The HIRREM intervention group (HCC), will also receive a course of 8-16 HIRREM sessions. Each session requires about 1.5-2 hours, and will include between 3-10 individual protocols, working with different locations on the scalp. Each protocol will typically last from 6-40 minutes. For the sessions, with the subject comfortably at rest, sitting or reclining, the sensors are placed over the specific target areas on the scalp corresponding with brain regions/lobes to be observed. Frequencies and amplitudes function are monitored in real time, and the dominant frequency within a chosen target frequency band, e.g. delta (0.5-3 Hz) is identified. The dominant frequency is assigned an auditory tone which is played back to the subject via ear phones with as little as 4-8 millisecond second delay. Thus, the subject listens to the energetic "song" being played in the brain from moment to moment, providing the brain with rapid updating about its frequencies, amplitudes, and patterns via an electronic/acoustic mirror of itself.

Some sessions will occur with eyes closed, for which the subject will be instructed to relax. Some sessions will occur with eyes open, during which the subject can read, or do other activities such as a word search, or just relax.

Although similar to methods such as neurofeedback, HIRREM uses an algorithm-based observation for the brain to view itself, which provides an opportunity for subject-unique auto-calibration, self-optimization, and movement towards a more balanced state, rather than operant conditioning designed to try to force the brain toward a standardized or ideal pattern of frequencies and amplitudes. No active, cognitive involvement by the participant is needed to accomplish this process.

The HIRREM process is individualized for each recipient, such that the specific protocols chosen, the session length, and the total number of sessions are variable. Technologists time sessions and chose protocols to facilitate an overall trend toward greater hemispheric symmetry and more optimal proportionation in frequency ranges, between and within cortical regions, based upon data from the initial assessment and the ensuing sessions (Gerdes et al., 2013). Each participant in the HCC group will receive at least 10 sessions. The final number of HIRREM sessions, which may be extended to as many as 16, will depend on continuous review of brain patterns relative to progress towards improved balance and quieting of electrical amplitudes, as well as progress and stability of self-reported status regarding symptoms such as sleep and stress.

Ambient nature sounds (NCC) were chosen as an active control because this approach may also facilitate recovery from stress-related sympathetic hyperarousal (Alvarsson, Wiens, & Nilsson, 2010). Exposure to nature sounds has been shown to facilitate reduced sympathetic activation in response to psychological stress (Annerstedt et al., 2013), which is relevant for those with hypertension, and also provides a credible control regarding the effects of expectation associated with a technological intervention, while also matching exposure to location, environment, exposure time, and staff contact for each study group.

Participants assigned to the NCC group will receive sessions in the same rooms, but will select from a variety of ambient sounds. Sessions will consist of 60-90 minutes of listening time, while in a zero gravity chair, and are intended to mirror the time, environment, eye state, and staff interaction

experienced by the HCC group. Technologists will interact with the participant during the sessions, as they would with HIRREM sessions, requesting that some portions are with eyes open, and others with eyes closed. As with the real HIRREM sessions, if eyes closed segments the participant may recline and drift to sleep, while with eyes open, they may just relax, or engage in activities such as reading, or a word search. In order to achieve comparability with the HCC group, including potential effects of exposure time to the environment and study personnel, those randomized to the NCC group will also receive between 8-16 sessions. The number of sessions for the NCC group will be randomly assigned via a second randomization, following their assignment to the NCC group.

Safety:

Evidence to date indicates that the HIRREM intervention is potentially high benefit and low risk. Based on experience reported by Brain State Technologies, garnered from provision of case management support, feedback from their clients, and feedback from the HIRREM provider community, as well as from our IRB-approved studies at WFSM (now over 450 participants to receive HIRREM), we are not aware of any serious adverse events resulting from HIRREM sessions. A few participants undergoing HIRREM have reported experiencing emotions, both positive and negative, primarily during initial sessions. These have been similar to the range of emotions one might experience in the course of everyday life events, and have been transient, resolving over a few minutes or hours, to several days. In the course of providing HCC to over 450 individuals participating in one of five IRB-approved research studies at WFSM, such mild symptoms have been estimated to occur in less than 5 percent of participants, and none have experienced prolonged or intense changes in emotional state, or required additional treatment. All HIRREM sessions are administered by Technologists who have been certified in the procedure, including guidelines for addressing emotional releases that may occur. In the event that emotional releases are prolonged or intense, individuals would be advised to see a mental health professional for additional evaluation or treatment, or if acute, will be referred to the Emergency Department. There have been no instances in the > 440 subjects participating to-date of prolonged or intense changes in emotional state. There are no anticipated risks associated with listening to ambient nature sounds.

Other Data Collection, Measures, and Process:

A series of measures will be collected at the enrollment visit (V1), as well as at three post-intervention visits for all participants.

Demographics:

Demographic information will include embedded elements to allow calculation of the Charlson Comorbidity Index Score (Charlson et al., 2008).

Autonomic cardiovascular Regulation [Blood Pressure (BP), Heart Rate (HR), Heart Rate Variability (HRV), Baroreflex Sensitivity (BRS), and Blood Pressure Variability (BPV)]:

Continuous BP and HR are acquired from noninvasive finger arterial pressure measurements and ECG for a minimum of 10 minutes in subjects lying down quietly, supine. Systolic BP and beat to beat, RR, intervals (RRI) files generated via the data acquisition system (BIOPAC acquisition system and software, Santa Barbara, CA) at 1000 Hz are analyzed using Nevrokard SA-BRS software (by Nevrokard Kiauta, d.o.o., Izola, Slovenia) for measures of BRS, HRV and BPV as follows: Frequency Method. Power spectral densities of SBP and RRI oscillations are computed by 512 points Fast Fourier Transform (FFT) and integrated over specified frequency ranges (LF: 0.04-0.15 Hz; HF: 0.15-0.4 Hz). A Hanning window is applied and the squared-coherence modulus is computed if coherence is >0.5 as reported. The square-root of the ratio of RRI's and SBP powers is computed to calculate LF, HF alpha indices, which reflect BRS (16). Power of RRI spectra in LF, HF range (LFRRI and HFRRI) are calculated in normalized units and the ratio of LFRRI/HFRRI is used as a measure of sympathovagal balance. Power of SBP spectra calculated as LFSAP is used as a measure of BPV. Sequence Method. BRS calculated by this method is based on quantification of sequences of at least three beats (n) in which SBP consecutively increases (UP sequence) or decreases (DOWN sequence), which are accompanied by changes in the same direction of the RRI of subsequent beats (n+1). The software scans the RRI and SBP records, identifies sequences, and calculates linear correlation between RRI and SBP for each sequence. If the correlation coefficient exceeds a pre-set critical value (0.85), the regression coefficient (slope) is calculated and accepted. The mean of all individual regression coefficients (slopes), a measure of sequence BRS, is then calculated for Sequence UP, DOWN and TOTAL. Time-Domain Analysis. Three time-domain parameters are used for hemodynamic variability. HRV is determined by computing the standard deviation of normal to normal intervals (SDNN), and the root mean square of successive beat-to-beat differences in R-R interval duration (rMSSD). BPV is the standard deviation of the mean arterial pressure (SDMAP).

HRV and BRS Data Processing and Interpretation:

Heart rate is measured as beat-to-beat intervals (RRI) recorded by pulse-wave recording, and will be analyzed using custom software developed by Matlab. Data can be loaded and viewed, and a subset of the data can be selected to avoid artifacts during device placement or removal. Outlier identification is performed by determining all IBIs which demonstrate a 30% difference from the mean of the previous four samples. Such outliers are removed from the data set. HRV statistics that are generated include mean, variance, SDNN, rMSSD, VLF, LF, HF, TP, LF/HF, sample asymmetry, sample entropy, and coherence ("Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996). All of the algorithms for computation of these parameters are derived from information or source code from the Physionet archive. Data are saved to Excel spreadsheets for further statistical analysis by study team members.

Blood Pressure (BP):

For evaluation of blood pressure (BP) values that will be used to qualify for participation in the study, and for analysis of the primary outcomes, BP measurements will be obtained using an automated oscillometric blood pressure device. BP will be obtained in the left arm, with the participant sitting

comfortably, and the left arm resting on a desk/table. Three samples will be obtained and the last two averaged to get the value that will be used as the reading for that visit (Kaplan NM, 2010).

Insomnia:

The severity of insomnia symptoms is measured using three self-report symptom inventories with each data collection visit (Appendix A). This includes the Insomnia Severity Index (ISI), the Pittsburgh Sleep Quality Index (PSQI), and the Epworth Sleepiness Score (ESS). The ISI is a 7 question measure, with responses from 0-4 for each question, yielding scores ranging from 0-28 (Bastien, Vallieres, & Morin, 2001; Morin, Belleville, Belanger, & Ivers, 2011). The PSQI is a 19 item inventory that assesses sleep quality over a 1-month time interval (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Items are weighted on a 0–3 interval scale. A global PSQI score is calculated by totaling the seven component scores, providing an overall score ranging from 0 to 21, where lower scores denote a healthier sleep quality. The ESS measures a person's general level of daytime sleepiness, or their average sleep propensity in daily life. The simple questionnaire is based on retrospective reports of the likelihood of dozing off or falling asleep in a variety of different situations. Rated on a 4-point scale (0-3), it evaluates their usual chances of dozing off or falling asleep while engaged in eight different activities. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24 (Johns, 1991).

Behavioral and Psycho-physiological function:

Depression:

The Center for Epidemiologic Studies Depression Scale (CES-D) is a depression scale which will help to assess this co-morbidity. CES-D is a 20-item survey assessing affective depressive symptomatology to screen for risk of depression (Radloff, 1977). Scores range from 0-60, with a score of 16 commonly used as a clinically relevant cut-off (SmarrK.L., 2003).

Anxiety:

The Generalized Anxiety Disorder-7 (GAD-7) is a seven item screening tool for anxiety that is widely used in primary care. GAD-7 is a brief, reliable and valid measure of assessing generalized anxiety disorder (Spitzer, Kroenke, Williams, & Lowe, 2006).

Traumatic Stress:

The PTSD Checklist for civilians (PCL-C), measures the American Psychiatric Association's Diagnostic and statistical manual of mental disorders (DSM-IV) Criteria B, C, & D of PTSD symptoms based on traumatic life experience related to military service. Seventeen items are rated on a Likert scale with a composite score range of 17 to 85. A score of 44 or higher correlates with probability of civilian-related PTSD (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996; FW, BT, DS, JA, & TM).

Stress:

The Perceived Stress Scale (PSS) is a ten-item psychological instrument for measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale, with answers rated from 0-4, also includes a number of direct queries about current levels of experienced stress (Cohen, Kamarck, & Mermelstein, 1983).

Quality of Life:

The Quality of Life Scale (QOLS) is a 16-item scale that was modified from a 15-item scale used in chronic disease patients. Topics include different components of daily life such as relationships, community engagement, personal fulfillment, and recreation. Each item is scaled from 1 to 7 and a sum score is calculated to represent higher levels of satisfaction in life (range is 16-112) (Carol S. Burckhardt & Anderson, 2003; C. S. Burckhardt, Woods, Schultz, & Ziebarth, 1989; Offenbächer, Sauer, Kohls, Waltz, & Schoeps, 2012).

Alcohol Intake Screening:

The AUDIT-C is a short, 3-item alcohol screening for hazardous drinkers or active alcohol use disorders. This measure consists of 3 questions to assess an individual's alcohol use. Each question has five possible answers ranging from of 0-4 with a total scoring scale of 0-12. A total score of 3 or more in women and a score of four or more in men is suggestive of hazardous drinking or active alcohol use disorders. This form is modified from the longer, 10-item AUDIT instrument (Bradley et al., 2003; Bradley et al., 2007; Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998).

Functional Measures:

Reaction Testing:

Reaction testing will be evaluated by a drop-stick, clinical reaction time apparatus. It is constructed from a meter stick covered in friction tape with gradations. The modified meter stick is fixed to a weighted rubber cylinder. The apparatus is placed between the thumb and index finger of the subject and released at a random time during a countdown. The subject catches the apparatus and the distance fallen (cm) is converted to reaction. Following two practice trials, subjects perform eight trials, and a mean distance value is used for analysis. This is repeated with a second set of 8 trials later during the enrollment visit, and the mean distance value from the second trial will be used as the baseline value. Use of the average distance from the second set of trials will be used as the baseline value so as to avoid the impact of learning effect for this test. This simple clinical measure has been evaluated by Eckner et al, and demonstrated utility in testing comparable to computerized testing methods (Eckner, Kutcher, & Richardson, 2010). Our pilot data demonstrate improved reaction testing associated with use of HIRREM for athletes with persisting post-concussion symptoms (C. H. Tegeler et al., 2016).

Grip Strength:

Grip strength will be evaluated using a hydraulic hand dynamometer (Baseline Hydraulic Hand Dynamometer). The greatest force generated during three trials will be used for analysis (Roberts et al., 2011).

Statistical Analysis:

Continuous variables will be summarized with standard descriptive statistics, such as quartiles, means, and standard deviations, while categorical variables will be summarized with percentages and frequencies. LMMs will be employed to contrast longitudinal changes in systolic and diastolic blood pressure between the HCC and NCC groups. Mean contrasts will be used to compare the changes in blood pressure between groups from V1 to V3, our primary test of efficacy. Comparisons of changes in all secondary outcomes will be assessed in a similar fashion. Assumption and computation diagnostics will be assessed for all model fits (Cheng, Edwards, Maldonado-Molina, Komro, & Muller, 2010), and model adjustments and outcome variable transformations will be made as necessary. Data will be analyzed using SAS v9.4 (SAS Institute, Inc., Cary, NC) or the R Statistical Computing Environment.

Participant Compensation:

Participants will receive up to $100 compensation for time, travel, and inconvenience related to study visits. Subjects who do not complete the entire study will receive a prorated portion of this amount ($25 per visit for completion of each of four data collection visits). Participants whose initial BP is too low to meet criteria for pre-hypertension, and are thus considered screen failures, and do not complete the rest of the at the enrollment visit, will still receive a $10 gift card as compensation for their time.

Human Subjects Protection:

Consent:

Written informed consent will be obtained by the research staff from each competent subject.

Confidentiality and Privacy:

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. Per institutional policy, all research study participants will be assigned a hospital MRN number, if none already exists. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a separate master log. The master log will be kept secure, on a separate, limited access user group on a shared network drive, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Brain State Technologies, LLC (BST) may assist with brain pattern analysis. To accomplish this, BST is be provided with the first 8 characters from the randomly generated, 36 character identifier that the HIRREM software generates for each participant's brain frequency and amplitude data, along with the participant's age and gender, which are believed important for understanding brain patterns. No other participant-specific information is provided.

Data and Safety Monitoring:

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Any collected patient identifying information corresponding to the unique study identifier will be maintained on a separate master log. The master log will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected.

Reporting of Unanticipated Problems, Adverse Events, or Deviations:

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

Appendices

A:
Insomnia Severity Index (ISI)
Center for Epidemiological Studies Depression Scale (CES-D)
Generalized Anxiety Disorder 7-Item (GAD-7)
Epworth Sleepiness Score (ESS)
PTSD Checklist for Civilians (PCL-C)
Perceived Stress Scale (PSS)
Pittsburgh Sleep Quality Index (PSQI)
AUDIT-C
Quality of Life Scale (QOLS)

B:
Handout for Study Participants

C:
Medical History/Screening Form

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