Title:

Use of High-resolution, Relational, Resonance-based, Electroencephalic Mirroring (HIRREM) for Stage 1 Primary Hypertension: A Randomized Pilot Clinical Trial

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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. Chronic stress, with associated autonomic dysregulation, and hyperarousal has been implicated as a potential causal factor for primary hypertension. Noninvasive strategies targeting central mechanisms to support brain relaxation, improve balance, and reduce hyperarousal, as potential adjunctive or alternative therapies are lacking.

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 in-office 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 pilot study will evaluate the use of HIRREM for those classified in the newly revised hypertension guidelines as being in the lower risk sub-category of Stage 1 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), to continued current care, will reduce systolic and diastolic blood pressure (BP), as compared to continued current care alone, in patients with blood pressure levels that place them in the lower risk sub-category of Stage 1 primary hypertension.

Methods: This will be a randomized, single site, pilot clinical trial, enrolling up to 24 adults, aged 18 or older, who have been diagnosed with primary hypertension, and who have documented blood pressures that place them in the low risk sub-category of Stage 1 hypertension (systolic BP 130-139 mmHg, and/or diastolic BP 80-89 mmHg). This, in the absence of known clinical cardiovascular disease, risk for cardiovascular disease of ≥ 10%, or other medical conditions associated with likelihood for development of hypertension, and who have not yet been started on pharmacological treatment. Participants will be randomly assigned to receive 8-16 sessions of either acoustic stimulation linked to brain activity (HIRREM and continued current care, HCC), over a maximum of 4 weeks, or to continued current clinical care (CCC). Both groups will continue their other current care throughout, including nonpharmacological, and lifestyle modification therapies. 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), a quality of life measure (Quality of Life Scale, QOLS), and a brief questionnaire about physical activity (International Physical Activity Questionnaire – Short Form, IPAQ-SF), along with drop stick reaction testing, and dynamometry for grip strength.

Measures will be collected at an enrollment visit (V1), for both groups. Intervention will begin 0-14 days thereafter for the HCC group. BP and heart rate (HR) recording will be repeated prior to the start of the 7th session for the HCC group. Post-intervention data collections will include an immediate post-intervention visit (V2, 1-14 days after intervention completion for HCC, 4-6 weeks after V1 visit for CCC), an intermediate post-intervention visit (V3, primary outcome, 4-6 weeks after intervention completion for HCC, and 8-10 weeks after V1 for CCC), and a final follow up visit (V4, 12-14 weeks following completion of the intervention for HCC, and 16-18 weeks after V1 for CCC). The primary outcome will be differential change in the systolic and diastolic BP from V1 to V3. Following V4, those in the CCC group will be offered an opportunity to receive a course of HCC. Those who accept will have a brainwave assessment 0-14 days before starting sessions and continue to be followed for data collections at 1-7 days (V5), 4-6 weeks (V6), and 12-14 weeks (V7) after completing their HIRREM sessions. Participants will have up to 3 months to crossover. We will utilize linear mixed models (LMMs) to contrast longitudinal changes in systolic and diastolic blood pressure between the HCC and CCC 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 the newly defined lower risk sub-category of Stage 1 primary hypertension, a condition now lacking evidence-based therapies in a randomized, clinical trial. The primary outcome, change in blood pressure, is a practical, objective physiological parameter. The objective secondary outcomes evaluating autonomic cardiovascular regulation, may also provide important insights about the importance of the autonomic nervous system, as well as the impact of stress, in this setting. The study will confirm feasibility of a randomized clinical trial using a closed-loop acoustic stimulation intervention in this population, identify any unique challenges for working with this cohort, and provide estimates of effect size, which might justify larger controlled trials. A positive result would suggest that HIRREM may have benefit as a noninvasive, non-drug alternative for initial management of Stage 1 hypertension. The study will also help to identify characteristics of subgroups that might experience differential effects/benefits from HIRREM, and will allow evaluation of any impact on autonomic cardiovascular regulation.

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 D, 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.

Hypertension and impaired autonomic function increases the risk of many cardiovascular disorders. Classification of severity, and specific clinical management recommendations are based on blood pressure levels (Whelton PK, et al., 2017). 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 OA & Oparil S, 2000). Autonomic imbalance, dysregulation, or hyperarousal, often associated with chronic stress has been implicated as a potential causal factor (Mancia G, & Grassi G, 2014). Numerous lifestyle management strategies are recommended, but for many evidence is lacking, or they prove difficult to maintain (Oza R, & Garcellano M, 2015, Heydayati SS, Elsayed EF, Reilly RF, 2011). Noninvasive, nondrug strategies related to high blood pressure, specifically targeting autonomic dysregulation/hyperarousal 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). The brain appears to play a role with the initiation of hypertension (Jennings JR, & Zanstra Y, 2009). Evidence suggests a bihemispheric model of autonomic responses to traumatic stress; right side sympathetic, left side parasympathetic (Lee SW, et al., 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 the flexibility and dynamic range 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 GK, et al., 2011; Wu JS, et al., 2008), and may be a predictor for development of prehypertension/hypertension (Chinagudi S, et al., 2013). Vagal tone is lower in those with hypertension, and may precede development of the disorder (Thayer JF, & Lane RD, 2009). 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 DA, 2008; Pal GK, et al., 2011), or both increased sympathetic and decreased vagal tone (Pal GK, et al., 2013). Impaired autonomic cardiovascular regulation may be a viable therapeutic target for those with high blood pressure. 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 S, et al., 2016; Lin G, et al., 2012; Wang S, et al., 2010; Xu XY, et al. 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 KU, 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 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 L, et al., 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. Although exact mechanisms await confirmation, it appears that with rapid updating regarding its own electrical activity, intended to support frequency-matching or resonance between the acoustic stimulation and oscillating brain networks, the brain is supported towards auto-calibration, and self-optimization. As a closed-loop process, no conscious or cognitive activity is required, yet the brain pattern is observed to shift on its own terms towards improved balance, and often reduced hyperarousal.

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 JM, et al., 2013). Better sleep is foundational for overall 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 480 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 (Tegeler CL, et al., 2017; Tegeler CH, et al., 2017; Tegeler CH, et al., 2012; Tegeler CH, et al., 2016; Tegeler CH, et al, 2015). Improved autonomic cardiovascular regulation has also been observed in those receiving HIRREM, including a cohort of adolescents with Postural Orthostatic Tachycardia Syndrome (Fortunato JE, et al., 2013. In addition, correlation has been reported between high frequency electrical brain pattern asymmetry scores at baseline, and measures of autonomic cardiovascular regulation (Tegeler CH, et al., 2015) .

<u>Specific Relevant Pilot Data:</u>

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 co-morbid hypertension (Shaltout HA, Tegeler CL, Tegeler CH, 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:

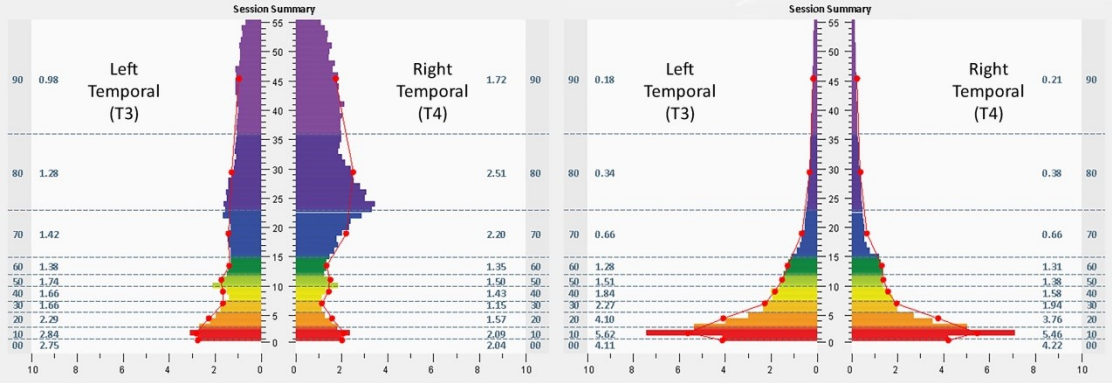


Figure Legend: FFT spectral displays from a 63 years old female participant, as an example of changes observed in electroencephalic data, with frequency (Hz, central Y axis) plotted against transformed amplitude (μv, X axis). Data represents one minute of data recorded from the T3/T4 montage with eyes 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 on 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.

Besides reduction in self-reported symptoms, and improved network connectivity on whole brain, resting MRI studies, all measures HRV and BRS measures increased in this cohort, 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; Tegeler CH, 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.

Newly published guidelines have reclassified categories of blood pressure elevations, and provide clear recommendations for management (Whelton PK, et al., 2017). Overall, goals and targets have been shifted lower, emphasizing the importance of blood pressure levels for future health risks and outcomes, and have eliminated the category of "pre-hypertension." Those with systolic blood pressure of 120-129 mmHg, and diastolic of < 80 mmHg, are classified as having elevated blood pressure. Stage 1 hypertension now includes those with systolic blood pressure of 130-139 mmHg, or diastolic of 80-89 mmHg., while those with blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic, are classified as Stage 2 hypertension. There is further sub-classification of Stage 1 hypertension into lower and higher risk subcategories. Those with known clinical atherosclerotic cardiovascular disease, or a risk for cardiovascular disease of ≥ 10%, are considered in a higher risk sub-group, and pharmacological treatment is recommended. Those lacking the above fall in a lower risk sub-group, and the use of nonpharmacological therapy, with monitoring of the blood pressure in 3-6 months, is recommended.

Hypothesis:

The use of acoustic stimulation linked to brain activity (in-office HIRREM plus continued current care, HCC) will be associated with greater reduction in systolic and diastolic blood pressure than that seen

with continued current clinical care alone (CCC), among patients classified in the lower risk subgroup of Stage 1 primary 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 (HCC), to continued current clinical care will reduce systolic and diastolic blood pressure, as compared with continued current clinical care alone (CCC), in patients with documented blood pressure values that place them in the lower risk subgroup of Stage 1 primary hypertension.

Secondary Objectives:

Evaluate whether the use of HCC will result in greater differential changes for a variety of physiological, behavioral, and function outcome measures outlined below, as compared to CCC.

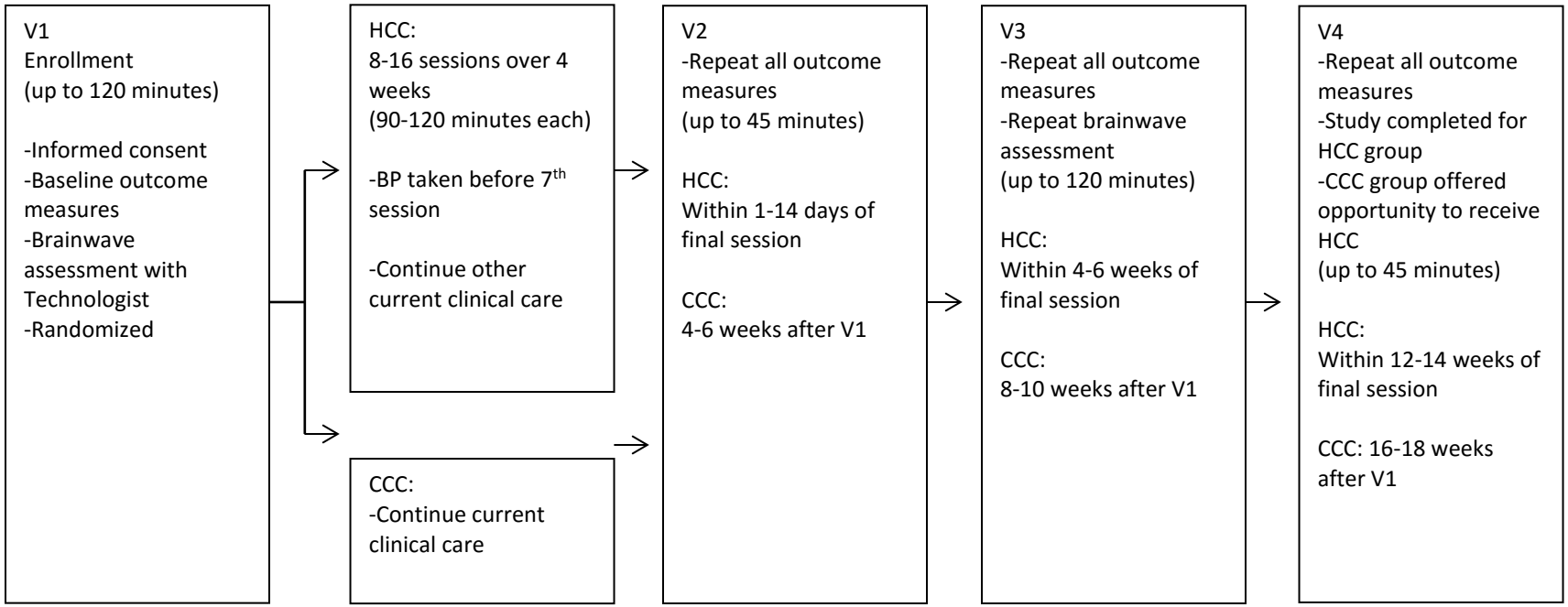
1. Autonomic nervous system functions, as manifested by heart rate, HRV, and BRS. We expect to see greater changes in autonomic activity and an improvement of sympatho-vagal balance in the HCC group. This would be reflected as changes in heart rate, and an increase of HRV and BRS parameters such as the standard deviation of the R-R interval (SDNN), 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. Physical activity recall questionnaire and a short form about satisfaction with current level of physical activity. This will evaluate for any large swings in physical activity level between groups that could influence blood pressure.
4. Overall quality of life as evaluated using the QOLS measure. We expect to see greater improvement in overall quality of life scores in the HCC group.
5. Functional performance evaluated using drop stick reaction testing. We expect to see more improvement in the HCC group.
6. Functional performance evaluated by grip strength, using a hand dynamometer. We expect to see greater improvement of grip strength in the HCC group.
7. 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:

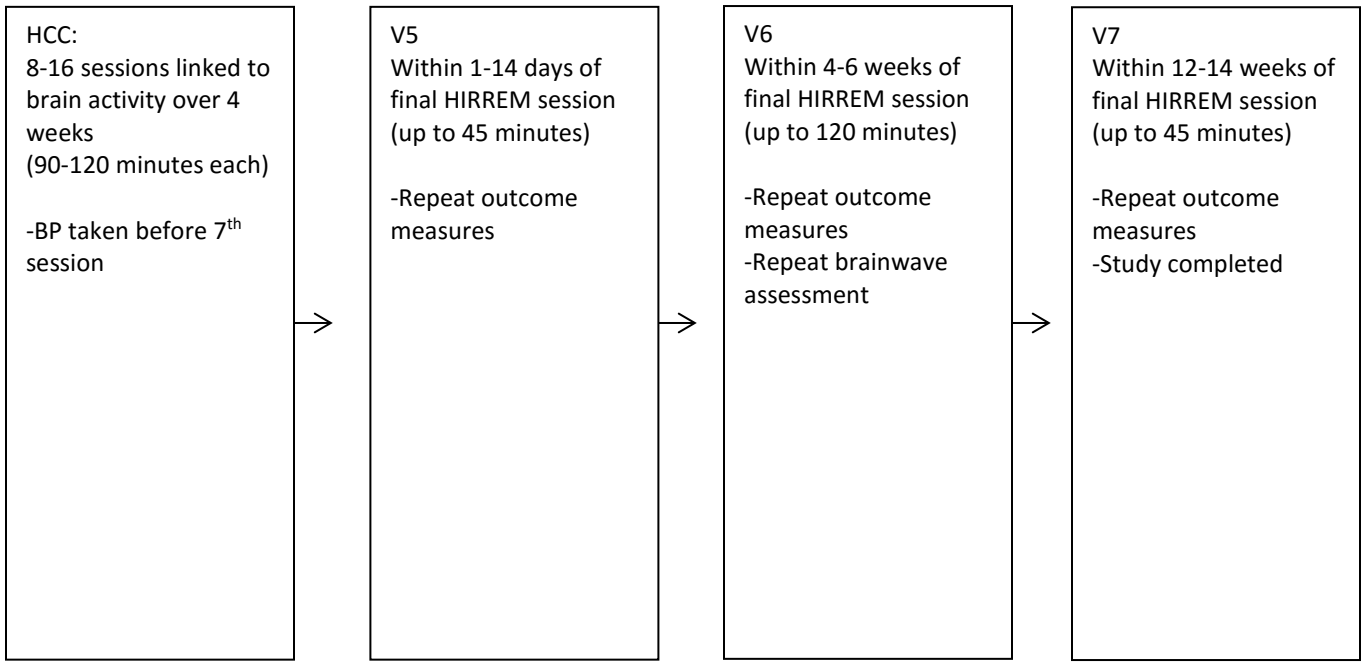
This will be a randomized, single site, pilot clinical trial. Assuming a potential drop-out rate of 20%, up to 24 subjects will be enrolled to achieve a goal of having at least 20 subjects (10 per group) complete the study, per protocol. Participants will be recruited from among patients who have been diagnosed with Stage 1 primary hypertension, based on blood pressures between 130-139 mmHg systolic, and/or 80-89 mmHg diastolic, as documented by their health care providers on two separate occasions during the prior 18 months. This, in the absence of known clinical cardiovascular disease, risk for cardiovascular disease of ≥ 10%, or other medical conditions associated with likelihood for development of hypertension, and who have not yet been started on pharmacological treatment.

Those who have no other exclusions, are interested to participate, and provide informed consent will be randomly assigned to receive 8-16 sessions of in-office acoustic stimulation linked to brainwave activity (HCC), over a maximum of 4 weeks, while continuing their other current clinical care, or to continue their current clinical care alone (CCC). 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 (Quality of Life Scale, QOLS), short physical activity recall (International Physical Activity Questionnaire, IPAQ-SF), and function performance measures (drop stick reaction testing, and grip strength). All measures will be collected at an enrollment visit (V1), for both groups. Intervention will begin 0-14 days thereafter for the HCC group. BP and heart rate (HR) recording will be repeated prior to the start of the 7th session for the HCC group. Post-intervention data collections will include an immediate post-intervention visit (V2, 1-14 days after intervention completion for HCC, 4-6 weeks after V1 visit for CCC), an intermediate post-intervention visit (V3, primary outcome, 4-6 weeks after intervention completion for HCC, and 8-10 weeks after V1 for CCC), and a final follow up visit (V4, 12-14 weeks following completion of the intervention for HCC, and 16-18 weeks after V1 for CCC). The primary outcome will be differential change in the systolic and diastolic BP from V1 to V3. Following V4, those in the CCC group will be offered the opportunity to receive a course of HCC, and those who accept will have up to 3 months to schedule a brainwave assessment 0-14 days before starting sessions and continue to be followed for data collections at 1-14 days (V5), 4-6 weeks (V6), and 12-14 weeks (V7) after completing their HIRREM sessions.

Stage 1 Hypertension Study Flow Chart



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



Participants/Subjects:

Participants will be recruited by physician referral and advertisement, from among adults ages 18 and older with a diagnosis of Stage 1 primary hypertension, and absence of clinical atherosclerotic cardiovascular disease, or a cardiovascular risk score of ≥ 10, placing them in the lower risk sub-group for Stage 1 hypertension. Stage 1 Hypertension will be defined by blood pressure readings between 130-139 mmHg systolic, and/or 80-89 mmHg diastolic, documented by their health care provider on two occasions, at two separate office visits, during the prior 18 months. A prior diagnosis of Stage 2 hypertension, the presence of known cardiovascular disease, or other conditions associated with development of hypertension such as renovascular disease, renal failure, pheochromocytoma, aldosteronism, are not present. Those who have been recently diagnosed, and who at their health care provider's recommendation, are attempting nonpharmacological or lifestyle modifications, will also be eligible. Cardiovascular risk will be calculated using the tool provided online by the American College of Cardiology (Cardiology, 2017). Those who also meet other inclusion/exclusion criteria, and are interested to participate in the study, will be offered participation. Each subject must be able to provide an informed consent. As part of the screening process, potential participants will need to provide documentation of having BP in the target range, and results from their most recent cholesterol testing (total cholesterol, HDL, and LDL).

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 and cholesterol testing documentation as noted above, the cardiovascular risk will be calculated. If confirmed that they have < 10 % risk for cardiovascular disease, 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, a blood pressure will be obtained to confirm eligibility. Those with BP less than 130 mmHg systolic or 80 mmHg diastolic, or systolic BP ≥ 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, or continuation of current care. 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. Prior to randomization, women of childbearing potential will also have a urine pregnancy test performed at the WFBH Outpatient Laboratory, 2nd floor, Piedmont Plaza 1 Building. If positive, they will be excluded from the study.

Inclusion Criteria:

Adults, ≥ 18 years of age, diagnosed with Stage 1 primary hypertension, who have systolic BP ranging from 130-139 mmHg, or diastolic BP ranging from 80-89 mmHg, who under their medical provider's management are not on medical therapy, and who do not have known clinical cardiovascular disease or a cardiovascular risk score of ≥ 10%.

Exclusion Criteria:

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
Weight is over the chair limit (285 pounds)
Known atherosclerotic cardiovascular disease
Cardiovascular risk score of ≥ 10% (per http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/)
Prior diagnosis of stage 2 hypertension
Ongoing need for treatment of hypertension with medications
Known seizure disorder
Known or anticipated pregnancy
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
Are enrolled in another research study that includes an active intervention
Have previously received brainwave optimization (BWO), used a B2 or B2v2 wearable device, or previously participated in a HIRREM research study

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, in a new cohort of participants, using a wait-list control, we are not able to calculate an accurate 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/CCC 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 0-14 days later. Participants will receive 8-16 in-office intervention sessions over a maximum of 4 weeks. HCC 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 received 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.

In the HCC group, one to fourteen days after the final intervention session there will be a post-intervention data collection visit (V2). V2 will be 4-6 weeks after V1 for the CCC group. All measures will be repeated at V2, but no brainwave assessment will be obtained. An intermediate post-intervention data collection visit, will occur at four to six weeks after completion of the intervention for the HCC group, and 8-10 weeks after V1 for the CCC group, 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 for the HCC group, and 16-18 weeks after V1 for the CCC group, with repeat of the outcome measures and a brainwave assessment. At V4, official study involvement is complete for those in the HCC group, while those randomized to the CCC group will be offered an opportunity to be scheduled to receive a course of HCC. Those who accept will receive a course of in-office acoustic stimulation linked to brainwaves (brainwave assessment 0-14 days before starting sessions), as described for the HCC group, and will continue to be followed for data collections at 1-14 days (V5), 4-6 weeks (V6), and 12-14 weeks (V7), as done during the initial intervention period, after completing their HCC sessions. Participants will have up to 3 months to crossover.

Enrollment Visit:

Informed consent is obtained, and blood pressure is then obtained. All participants will have been previously documented to have prior blood pressure values that meet the parameters for the lower risk sub-group of Stage 1 primary hypertension. 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 130 mmHg systolic pressure, and diastolic pressure less than 80 mmHg, and thus do not meet criteria for Stage 1 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). Prior to randomization, women of childbearing potential will also have a urine pregnancy

test performed at the WFBH Outpatient Laboratory, 2nd floor, Piedmont Plaza 1 Building. If positive, they will be excluded from the study. The V1 visit will require about 2 hours of time.

Intervention Period:

During the intervention period, subjects will receive in-office sessions of acoustic stimulation linked to brainwave activity (HIRREM, HCC), 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 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. Those assigned to the CCC group will continue with their current clinical care, including any life-style, non-pharmacological therapies that they may be employing.

Post-Intervention Data Collection Visits:

For participants in the HCC group, between 1-14 days after completion of the intervention, participants will return for a post-intervention data collection visit (V2). Those in the CCC group will return at 4-6 weeks after V1. All measures will be repeated, but no brainwave assessment done. This visit will take about 45 minutes.

Between 4-6 weeks after completion of the intervention, participants in the HCC group will return for the primary outcome data collection visit (V3). This will occur at 8-10 weeks after V1 for those in the CCC group. 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 in the HCC group will return for a final data collection visit (V4). The V4 visit will be between 16-18 weeks after V1 for those in the CCC group. All measures including a brainwave assessment will be repeated for a final time. This will complete the official study involvement for participants in the HCC group, while those in the CCC group will be offered an opportunity to be scheduled to 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 support relaxation and auto-calibration of neural oscillations through reflecting back audible 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 Sessions:

Participants assigned to both study groups will continue their current clinical care. The HIRREM intervention group (HCC), will also receive a course of 8-16 in-office 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. During 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 protocols will occur with eyes closed, for which the subject will be instructed to relax. Some protocols will occur with eyes open, during which the subject can read, or do other activities such as a word search, or just relax.

Although there are similarities to methods such as neurofeedback, or traditional biofeedback, HIRREM uses an algorithm-based observation for the brain to view itself, which provides an opportunity for subject-unique auto-calibration, self-adjustment, 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. In addition, no active, conscious, 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 choose 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 8 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.

Safety:

Evidence to date indicates that the HIRREM intervention has 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 results from IRB-approved studies at WFSM (now over 480 participants to receive HIRREM), we are not aware of any serious adverse events resulting from HIRREM sessions.

Non-serious, temporary, and somewhat paradoxical effects have been reported by study participants. This includes things such as the participant reporting being more aware of, or more affected by their feelings, or by those around them, changes in sleep, including dreams, emotions, or energy levels, or a feeling of fullness in the head or mild headache. In the course of provision of HIRREM as part of five IRB-approved studies at WFSM, such non-serious, temporary effects have been estimated to occur in ten percent or less of participants. Based on recent analysis of a placebo controlled trial of HIRREM for moderate to severe insomnia (n = 107), such non-serious, temporary adverse effects, that were judged to go beyond the intensity, expression, or nature of pre-existing health conditions, were reported during study participation by 10.7% in the HIRREM group, and 13.7% in the placebo group. All episodes were brief, typically resolving in hours to 1-2 days, but at the most lasted less than one week. Skin irritation at the site from the paste used to affix the sensors to the scalp was reported by a single participant (<1%) (Personal communication).

All HIRREM sessions are administered by Technologists who have been certified in the procedure, including guidelines for addressing any adverse effects that may occur. In the event that any adverse effect is prolonged or intense, participants will be advised to see their primary care physician, or if needed, to see a mental health professional for additional evaluation or treatment. It acute, and severe, participants will be referred to the Emergency Department. There are no anticipated additional risks associated with continuation of current clinical care.

If the study team learns that the participant, or someone else is in danger of harm, the study team will report that information to the proper authorities.

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 period visits for all participants. Those in the CCC group, who later receive HCC, will also have an additional three post-interventions data collection visits.

Demographics:

Demographic information will include embedded elements to allow calculation of the Charlson Comorbidity Index Score (Charlson ME, 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. 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, & Rose BD, 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 CH, Vallieres A, & Morin CM, 2001; Morin CM, et al., 2011). The PSQI is a 19 item inventory that assesses sleep quality over a 1-month time interval (Buysse DJ, et al., 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 MW, 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 LS, 1977). Scores range from 0-60, with a score of 16 commonly used as a clinically relevant cut-off (Smarr K.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 RL, et al., 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 EB, et al., 1996; Weathers FW, et al., 1993).

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 S, Kamarck T, & Mermelstein R, 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) (Burckhardt CS, & Anderson KL, 2003; Burckhardt CS, et al., 1989; Offenbächer M, et al., 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 KA, et al., 2003; Bradley KA, et al., 2007; Bush K, et al., 1998).

Physical Activity:

Participants will be given the International Physical Activity Questionnaire (IPAQ-SF). This is a 4 question questionnaire asking about physical activity in the last 7 days (Lee PH, et al., 2011). Participants will also answer some subjective questions about their exercise and physical activity, including a Likert scale about current satisfaction regarding physical activity.

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. Only one set of trials will be used for comparison at follow up data collections. This simple clinical measure has been evaluated by Eckner et al., and demonstrated utility in testing comparable to computerized testing methods (Eckner JT, Kutcher JS, & Richardson JK, 2010). Our pilot data demonstrate improved reaction testing associated with use of HIRREM for athletes with persisting post-concussion symptoms (Tegeler CH, 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 HC, 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 J, et al., 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, or too high to meet criteria Stage 1 hypertension, and are thus considered screen failures, and do not complete the rest of the at the enrollment visit, will 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 number, and first name will appear on the data collection form. Any other 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 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)
International Physical Activity Questionnaire – Short Form (IPAQ-SF)
Physical Activity Satisfaction Form

B:
Handout for Study Participants

C:
Medical History/Screening Form

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