Title:

Randomized Controlled Pilot Trial of HIRREM-SOP for Insomnia

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Abstract:

Background: 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. Prior research demonstrates that the use of HIRREM is associated with reduced symptoms of insomnia, and traumatic stress and anxiety, and improved autonomic cardiovascular regulation across heterogeneous cohorts. HIRREM has been safe and well tolerated in about 500 people across six IRB-approved studies. However, the current in-office HIRREM approach remains very operator dependent (extensive Technologist education and experience) and takes a sizeable time commitment from the participant (typically ten to twenty sessions of 90-120 minutes each). To reduce participant time required, and operator dependence, while increasing scalability, a new generation of hardware and software has been developed. Based on the same core technology and algorithms to mirror brainwaves with audible tones, this now includes the use of faster, 64-bit processing architecture for faster feedback, the use of 4 sensors, and the use of a standard series of protocols, all done with eyes closed (HIRREM Standard Operating Procedure, HIRREM-SOP). Although only 2 sensors are active at a time, applying 4 sensors, for which the software can switch from one pair to the other automatically, cuts in half the number of sensor placement changes needed, with reduced session time and interruptions. The placebo condition has also been modified so there is randomness to both the pitch and the timing of the tones, using tones that have not been acoustically engineered. This pilot study will evaluate feasibility and effects of this standardized, fixed dose, enhanced approach, and the effectiveness of blinding for the placebo condition in participants with symptoms of insomnia.

Objectives:

The primary objective of this randomized pilot study is to evaluate the effect of 10 sessions of standardized acoustic stimulation linked to brain activity (HIRREM-SOP), compared to 10 sessions of nonspecific acoustic stimulation not linked to brain activity (randomly generated tones), on symptoms of insomnia, based on change in ISI score from V1 to V3. The secondary objective is to evaluate the effectiveness of blinding for the placebo condition based on the expectation measure regarding group assignment prior to the 5th session. Tertiary, exploratory objectives include evaluation of the effects on other symptom and physiological measures.

Methods:

This will be a randomized, single site, double-blinded, placebo-controlled, pilot clinical trial, enrolling adults aged 18 or older, who have self-reported symptoms of at least mild insomnia. Up to 24 will be enrolled, seeking 20 to complete the protocol. Participants will be randomly assigned to receive 10 sessions of either acoustic stimulation linked to brainwave activity (HIRREM-SOP, BCC), or nonspecific acoustic stimulation with randomly generated tones not linked to brain activity (nonspecific acoustic stimulation, NCC), using otherwise identical study procedures, 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), and stress (Perceived Stress Scale, PSS). Measures will be collected at an enrollment visit (V1), and the intervention will begin 0-14 days thereafter. Post-intervention data collections will be obtained at 0-14 days (V2) after completion of the intervention, and 4-6 weeks (V3, primary outcome) after the V2. An expectation measure for group assignment will be obtained at V1, prior to the 5th intervention session, and at V3 data collections. The primary outcome is differential change in ISI from V1 to V3. The secondary outcome is the effectiveness of blinding for the placebo condition based on the expectation measure regarding group assignment prior to the 5th session. All other measures are tertiary and exploratory. Following V3, those in the NCC group will be offered the opportunity to cross over to receive a course of acoustic stimulation linked to brainwaves, and will continue to be followed for data collections at 0-14 days (V4) after completing their crossover sessions, and 4-6 weeks (V5) after V4. Linear mixed models (LMMs) will be used to contrast longitudinal changes in systolic and diastolic blood pressure between the BCC and NCC groups. Mean contrasts will be used to compare the changes in ISI between groups from V1 to V3, our primary test of efficacy. Comparisons of changes in all other outcomes will be assessed in a similar fashion.

Importance:

This study will explore the use of HIRREM-SOP for insomnia, in a randomized, controlled pilot clinical trial. Results will provide important insights regarding the effect of a new generation of this novel closed-loop, acoustic stimulation, applied using a standardized protocol and a fixed number of sessions. This, in a population shown to benefit from use of the legacy technology. It will confirm feasibility of use for the upgraded technology in this population, provide estimates of effect size, and assess effectiveness of blinding for a modified placebo control condition. All will be useful for planning future controlled trials. Although not anticipated with this small pilot trial, a positive result would suggest that HIRREM-SOP might have benefit as a noninvasive, non-drug alternative for initial management of sleep trouble. The study may also help to identify characteristics of subgroups that may experience differential effects/benefits from HIRREM-SOP.

Background:

Insomnia is the most prevalent sleep disorder and is associated with significant psychosocial and somatic pathology. Up to 50% of the US adult population reports symptoms of insomnia on a weekly basis and approximately 12% meets criteria for insomnia disorder [1]. Cross-sectional studies demonstrate that 40 to 60 percent of individuals with insomnia exhibit depressive symptoms [2, 3], 10 to 25 percent may have clinical depression, and 20 to 30 percent have an anxiety disorder [4, 5]. Chronic insomnia is associated with reduced quality of life, higher absenteeism, impaired job performance, and higher healthcare utilization [6, 7]. In a large population-based study, a linear relationship was demonstrated between insomnia prevalence and number of self-reported co-morbid medical disorders [8]. Insomnia severity has been correlated with suicidal thinking in a clinical trial population [9].

Although these cross-sectional associations are often interpreted to suggest that a variety of pathologies can result in secondary insomnia, prospective studies have found insomnia to be a risk factor for acute myocardial infarction [10] and depression [11]. In long-term follow-up of 1,741 individuals who had undergone polysomnography, insomnia was found to confer an independent and significantly increased risk for mortality [12]. More recently, chronic sleep disturbance has been suggested as a possible risk factor for Alzheimer's Disease [13].

Disturbed synchronization of neural oscillations and suboptimal proportionation, or hyperarousal of electroencephalographic (EEG) signatures, are reported in insomnia [14-16]. Autonomic dysregulation, identified by measures of heart rate variability (HRV), is reported with insomnia [17, 18]. Allostasis views the brain as the organ of central command to facilitate flexible orchestration of system functions to meet changing conditions and demands, and views disease as rigidification, or loss of dynamic range of response [19]. Closed-loop therapies with real time monitoring for modulation of biological function offer a precision-guided, patient-centric strategy for brain-based therapies [20].

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 [21]. 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 of varying pitch and timing 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 at that moment. This rapid updating regarding its pattern allows the brain a chance to auto-calibrate, self-adjust, "relax," and reset/get unstuck from what has been stuck stress/trauma response patterns. The brain electrical patterns are typically 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. As later described, HIRREM-SOP uses the same core technology and approach.

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 [22]. 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.

Relevant Pilot Data:

Since 2011, the HIRREM Research Program at WFSM has enrolled almost 500 participants in six IRB-approved clinical studies to evaluate the effects and potential benefits of HIRREM. Use of HIRREM has been associated with reduced sleep symptomatology and reduced high frequency amplitudes in adults with insomnia [23], reduced menopausal symptoms in women [24], improved sleep in athletes with persisting post-concussion symptoms [25], reduced symptoms, and temporal lobe high frequency asymmetry in self-reported post-traumatic stress [26], and reduced symptoms of military-related traumatic stress [26]. Improved autonomic cardiovascular regulation has also been observed in those receiving HIRREM, including a cohort of adolescents with Postural Orthostatic Tachycardia Syndrome [27]. In addition, correlation has been reported between high frequency electrical brain pattern asymmetry scores at baseline, and measures of autonomic cardiovascular regulation [28].

In addition, a placebo controlled efficacy trial of in-office HIRREM for moderate to severe insomnia demonstrated a clinically meaningful reduction of insomnia symptoms (≥ 7 point reduction on the ISI), and statistically significant additional benefit associated with use of HIRREM, as compared to a sham placebo of random audible tones not linked to brainwaves [29]. HIRREM was well tolerated, and the benefit was durable through the final follow up visit, 4 months after completion of the intervention (Figure 1).

Continuous recording (10 minutes) of blood pressure and heart rate also allowed for analysis of autonomic cardiovascular regulation, including multiple measures of heart rate variability and baroreflex sensitivity. Data were obtained at all study visits. Analysis demonstrated significant improvement in multiple objective measures of autonomic cardiovascular regulation including increased baroreflex sensitivity (HFα, and Sequence ALL) and heart rate variability (SDNN, and rMSSD), associated with this short term use of in-office HIRREM, compared to a placebo intervention of random audible tones not linked to brainwaves (Figure 2). The benefit was seen at all follow up data collections, and was durable through the final follow up at 4 months post-intervention [30]. There was no significant improvement seen in the placebo group at any time point. It is not clear whether these results reflect a cause, an effect, or both relative to the observed improvement of insomnia symptoms.

Figure 1:

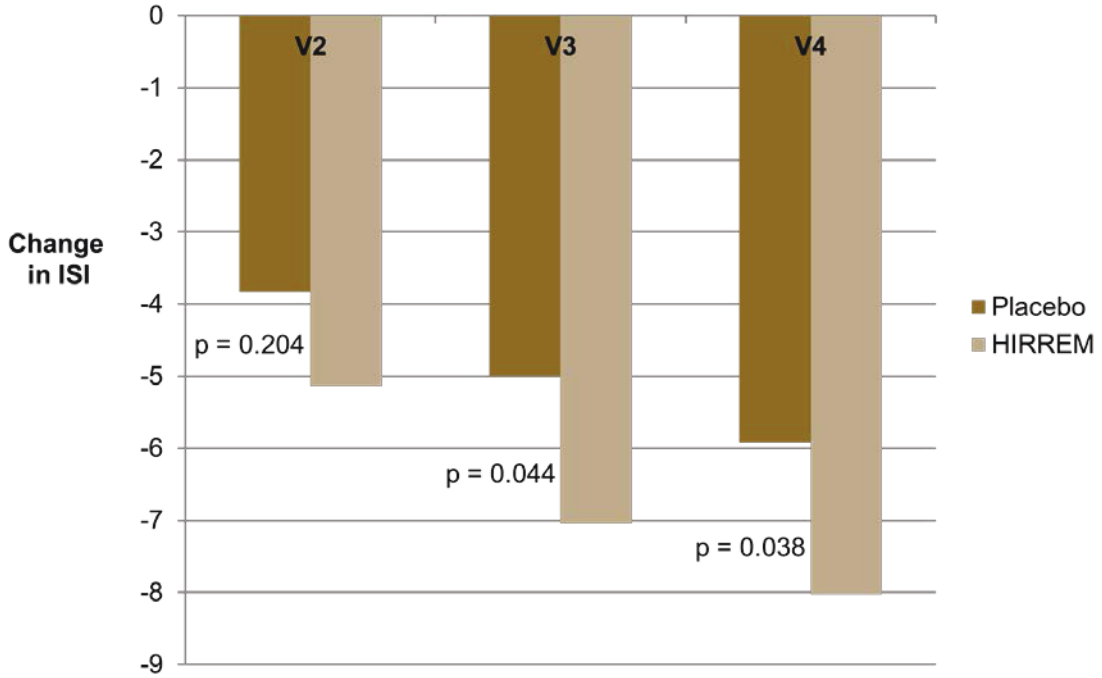
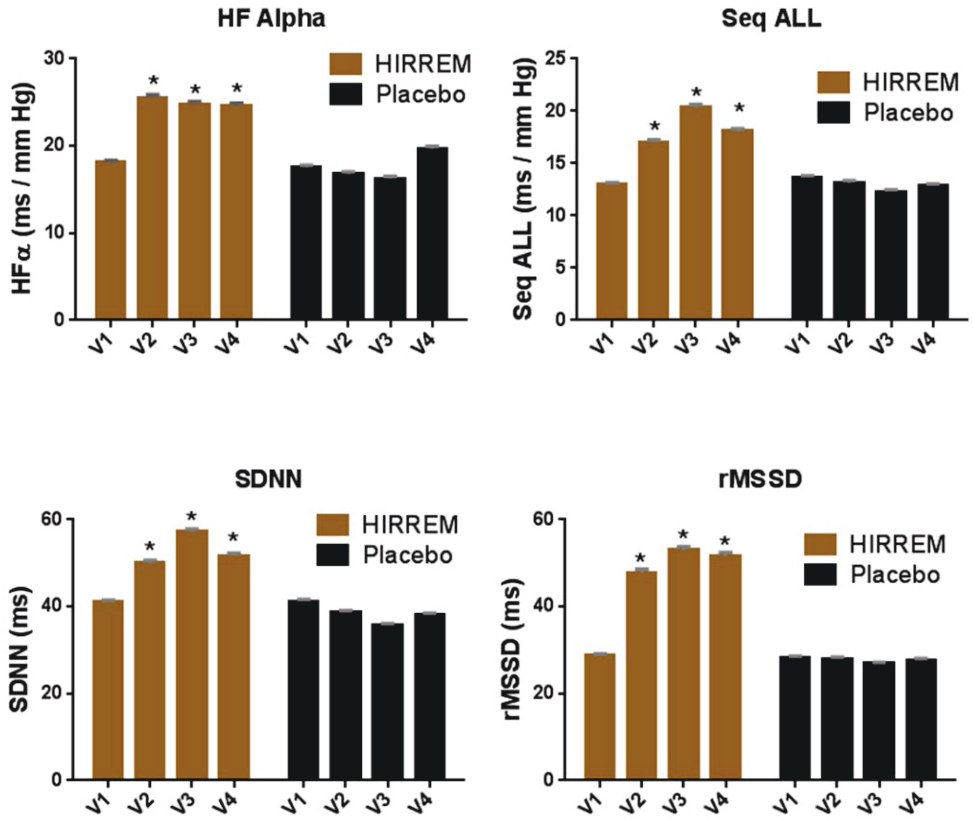

0
-1
-2
-3
-4
-5
-6
-7
-8
-9
Change in ISI
V2
V3
V4
p = 0.204
p = 0.044
p = 0.038
Placebo
HIRREM

Figure 2:


HF Alpha
HFα (ms / mm Hg)
HIRREM
Placebo
Seq ALL
Seq ALL (ms / mm Hg)
SDNN
SDNN (ms)
rMSSD
rMSSD (ms)
V1
V2
V3
V4

New Developments:

The in-office HIRREM approach used for research since 2011 remains very operator dependent (extensive Technologist education and experience required), and requires a lot of time for sessions (typically 10-20 sessions of 90-120 minutes each). To reduce the length of sessions, and reduce operator dependence, while increasing scalability, a new generation of hardware and software has been developed. Although based on the same core technology and algorithms for rapidly mirroring brainwaves back as audible tones in a closed-loop paradigm, the improved device includes the use of faster, 64-bit processing architecture for faster feedback, the use of 4 sensors, and the use of a standard series of protocols, all done with eyes closed (HIRREM-SOP). Although only 2 sensors are active at one time, the Technologist can apply 4 sensors at the same time. The software can switch from one pair to the other automatically, which effectively cuts in half the number of sensor placement changes needed during a session, yielding a shorter session time with fewer interruptions.

Informed by experience with prior controlled trials, the placebo condition has also been modified. The modified approach includes intentional randomness to both the pitch of the tones, as well as the timing and occurrence of the tones. In addition, characteristics of the tones themselves are not acoustically engineered. This appears to hold great promise as an improved placebo condition for use as a control in research evaluating this intervention.

This pilot study will evaluate feasibility of using this standardized, enhanced approach with HIRREM-SOP, and the effectiveness of the blinding for the placebo condition, in participants with symptoms of insomnia.

Research Design and Method:

Objectives:

Primary Objective:

The primary objective of this randomized pilot study is to evaluate the effect of 10 sessions of standardized acoustic stimulation linked to brain activity (HIRREM-SOP, BCC), compared to 10 sessions of nonspecific acoustic stimulation not linked to brain activity (randomly generated, nonspecific tones, NCC), in addition to continued current care, on symptoms of insomnia, based on change in ISI score from V1 to V3.

Secondary Objectives:

The secondary objective is to evaluate the effectiveness of blinding for the placebo condition based on the expectation measure regarding group assignment prior to the 5th session.

Tertiary/Exploratory Objectives:

Evaluate whether the addition of acoustic stimulation linked to brainwaves (BCC group), as compared to the addition of nonspecific acoustic stimulation not linked to brainwaves (NCC group), to continued current care, will result in greater differential changes in a variety of physiological, and behavioral 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 BCC 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. Additional behavioral outcomes such as insomnia (assessed by the 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), and stress (as assessed by the Perceived Stress Scale, PSS). We expect to see greater improvement in these symptom inventory scores in the BCC group.

Overview:

This will be a single site, single blind, placebo controlled, pilot clinical trial, enrolling adults who have insomnia. Assuming a potential dropout rate of 20%, up to 24 subjects will be enrolled to achieve a target of 20 subjects (10 per group) that complete the study. Subjects aged 18 or older, with symptoms of at least mild insomnia as defined by either subthreshold, moderate, or severe clinical insomnia by the Insomnia Severity Index (ISI ≥ 8), not attributable to another known cause (e.g. obstructive sleep apnea, restless legs syndrome, benign prostatic hypertrophy), will be randomly assigned to receive 10 sessions of acoustic stimulation linked to brain activity over 4 weeks (BCC), or 10 sessions of acoustic stimulation not linked to brain activity over 4 weeks (NCC). Sessions will be 1-1.5 hours in length. Both groups will continue their other usual 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), and stress (Perceived Stress Scale, PSS).

Measures will be collected at an enrollment visit (V1), and the intervention will begin 0-14 days thereafter. Post-intervention data collections will be obtained at 0-14 days (V2) following completion of the intervention, and 4-6 weeks (V3, primary outcome) following V2. Analyses for primary outcomes will include differential change in ISI from V1 to V3, and the expectation measure for group assignment prior to the 5th session. The blind will be broken at the V3 visit, and those in the NCC group will be offered the opportunity to cross over to receive acoustic stimulation linked to brainwaves. All study personnel except for the Technologists will remain blinded to group assignment, so that data collection will be carried out by individuals without knowledge of group assignment.

Sample Size and Statistical Analysis:

As a pilot study evaluating upgraded technology, and a standardized protocol, there are no data on which to base formal sample size estimates. The protocol is thus written with the goal of having 20 subjects (10 per group) to be enrolled and complete the study. For analysis, we will utilize linear mixed models (LMMs) to contrast longitudinal changes in ISI scores between the BCC and NCC groups. Mean contrasts will be used to compare the changes in ISI 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.

Participants/Subjects:

Adults ages 18 and older who have self-reported insomnia, who also meet inclusion criteria outlined below, and who are interested in receiving acoustic stimulation linked to brainwaves or acoustic stimulation not linked to brainwaves, will be considered for possible enrollment. Subjects will be recruited by physician referral, word of mouth, and through advertisement. The participant must be able to provide informed consent.

Interested subjects will be informed with a more detailed description of the study, and the extent of the time commitment will be explained 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.

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. For those confirmed to have an eligible baseline ISI score, baseline study measures obtained, and randomization will be completed 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 a welcome email with details.

Inclusion Criteria:

- Adults aged 18 years and older.
- Clinical Insomnia (Insomnia Severity Index $\geq$ 8) persisting by self-report for at least a month.
- Subjects must have the ability to comply with basic instructions and be able to comfortably sit still with the sensor leads attached.

Exclusion Criteria:

- Unable, unwilling, or incompetent to provide informed consent.
- Physically unable to come to the study visits, or to sit in a chair for several hours.
- Known seizure disorder.
- Known obstructive sleep apnea.
- Diagnosed periodic limb movement disorder or known restless legs syndrome.
- Known urinary problem (i.e. benign prostatic hypertrophy) which is the likely cause of the sleep disturbance.
- Severe hearing impairment (because the subject will be using ear buds during HIRREM-SOP).

- Ongoing need for treatment with opiate, benzodiazepine, or anti-psychotic medications, anti-depressant medications (SSRI, or SNRI's), sleep medications such as zolpidem or eszopiclone, stimulants such as Adderall, Provigil, or Ritalin, or thyroid hormone.
- Anticipated and ongoing use of recreational drugs, alcohol, or energy drinks.
- Weight is over the chair limit (285 pounds).
- Currently in another active intervention research study.
- Previous history of receiving or using HIRREM, Brainwave Optimization, HIRREM-SOP, or the wearable B2.

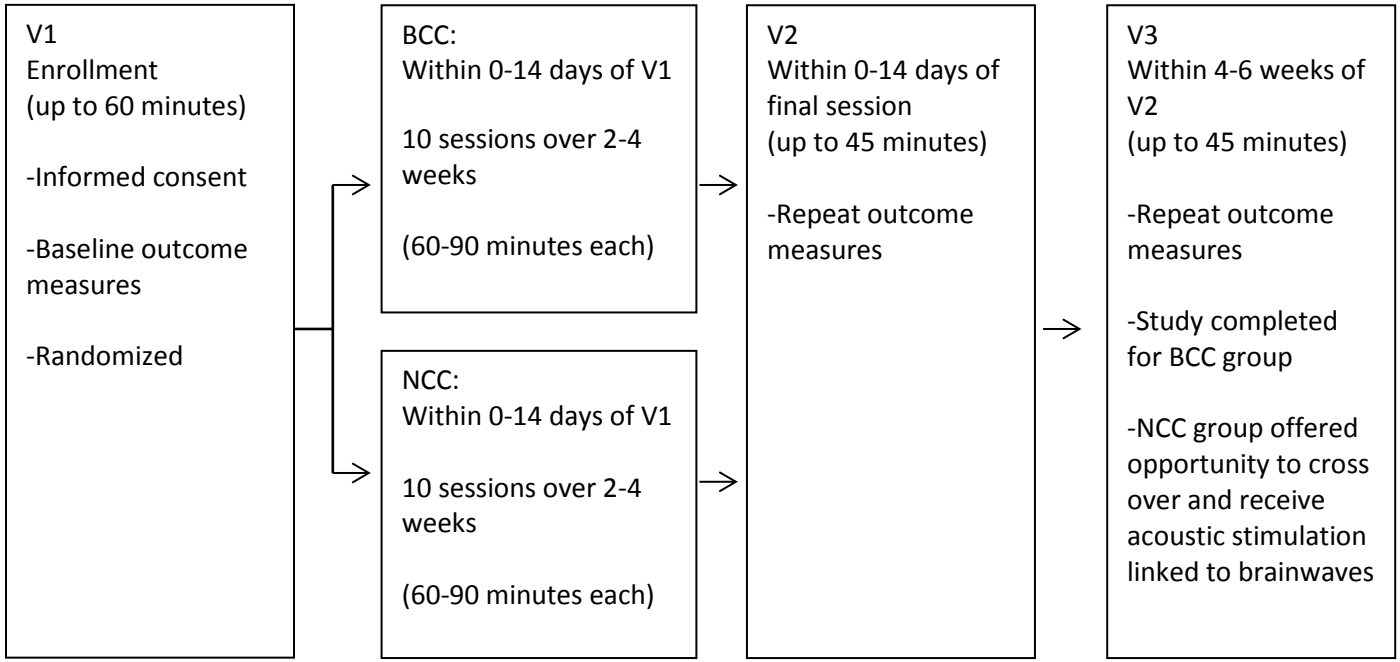
Participants are encouraged to discuss their participation with their health care provider following completion of the study because the intervention may alleviate some of the need for medications they were on previously. Participants are requested to abstain from using any alcohol or recreational drugs during the intervention, and until the final data collection visit for their group (V3 for BCC and V5 for those in the NCC group who decide to cross over) since use of these substances may cause reversal or cessation of any benefits. In addition, the participants are also advised to suspend chiropractic, cranial-sacral therapy, bio-energy work, and are asked to refrain from caffeine use after 1:00 pm during the intervention and until the one-month follow-up data collection.

Number of Sessions and Length of Study:

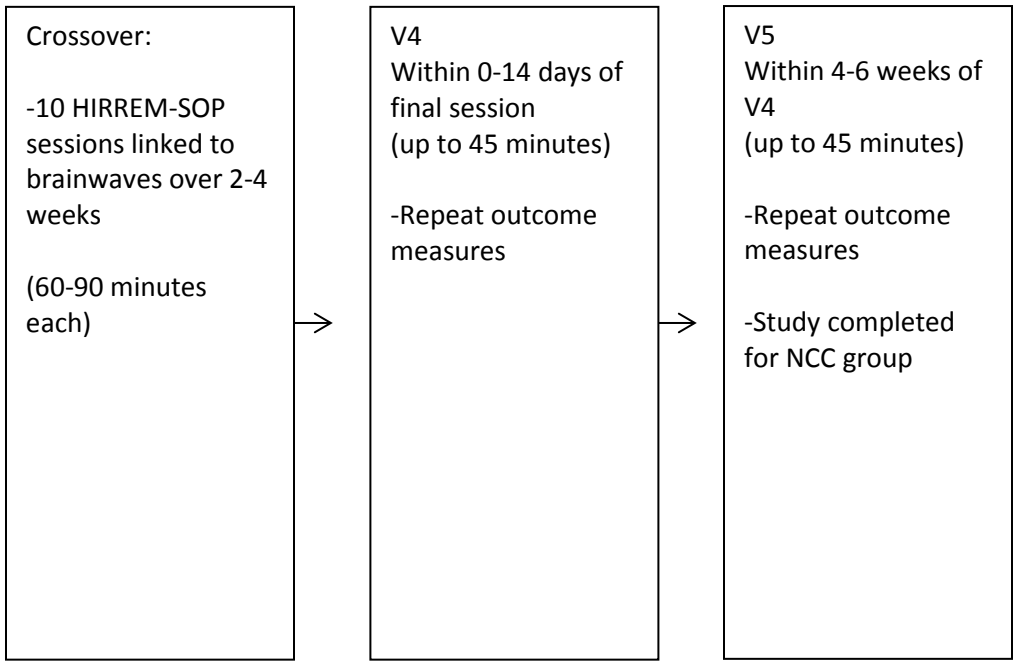
All baseline measures will be collected during the enrollment visit (V1), which will require 45-60 minutes. Zero to fourteen days after V1, participants will commence 10 sessions of acoustic stimulation linked to brain activity or not linked to brain activity, to be received over a one-month period. Since this is a fixed-dose intervention, every attempt will be made to complete all sessions within a two-week period. Sessions will be 1-1.5 hours in length. Participants will receive the first two sessions on consecutive days when beginning the intervention, and the first 3 sessions within the first five calendar days. To minimize participant time, following the first two sessions received as single sessions on consecutive days, up to two sessions might then be received per day, with a break of at least one hour between sessions.

Zero to fourteen days after the final intervention session there will be a post-intervention data collection visit (V2). All measures will be repeated. Four to six weeks after completion of the V2, 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. The V2 and V3 visits are expected to require about 30 minutes. At V3, official study involvement is complete for those in the BCC group, while those randomized to the NCC group will be offered an opportunity to receive acoustic stimulation sessions linked to brainwave activity, to begin within one month of the V3 visit. Those who opt to do so will receive a course of acoustic stimulation linked to brainwaves, will continue to be followed for data collections at 0-14 days (V4) after crossover sessions, and 4-6 weeks (V5) after V4.

HIRREM-SOP Insomnia Study Flow Chart



Crossover NCC Group



Version 1.3
09.12.2019

High-resolution, relational, resonance-based, electroencephalic mirroring standard operating procedure (HIRREM-SOP):

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. HIRREM-SOP is a new release from Brain State Technologies that utilizes updated computer processing and algorithms. The core technology for HIRREM-SOP is the same as, and upgraded from, the HIRREM technology that has been used successfully at Wake Forest School of Medicine for the last seven years.

Previous clinical studies of HIRREM have included an initial assessment intended to identify patterns of brain activity with respect to hemispheric symmetry and proportionation of amplitudes across the frequency spectrum [21]. Recordings were 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), eyes partially open (one minute), and eyes open (EO; one minute) conditions. Identification of patterns on this assessment was intended to permit strategic, Technologist-driven selection of the protocols (scalp montages and software designs) for the first session, especially with respect to those brain regions showing activity patterns that might be most likely to benefit from closed-loop monitoring and resonance-based mirroring. Protocols and timing for subsequent sessions were selected based on brain activity patterns observed in the previous session, and dependent on judgment of the Technologist.

In contrast, and toward the goal of evolving the paradigm for clinical trial methodology with respect to HIRREM-SOP, the present study is based on a maximally reductionistic hypothesis-testing and analysis strategy. In order to specifically identify the role of software algorithms – and to reduce not only provider-subject interactions but also limit the Technologist evaluation of brain activity patterns – as the basis for potential improvements, HIRREM-SOP sessions will be delivered based on a fixed set, and number of protocols (standard operating procedure) that will be identical for every client. The HIRREM-SOP protocols are designed based on cumulative experience of key personnel from the Wake Forest School of Medicine – Brain State Technologies academic-industry collaboration. These standardized protocols are projected to permit a robust majority of the benefits that have been reported to date, without introducing new or additional risk. Standardization of the HIRREM-SOP process will also reduce variability in the intervention delivery and thereby strengthen the generalizability of the study findings.

HIRREM-SOP sessions consist of only four potential paired placement options that are all run with eyes closed (F3/F4 and P3/P4, C3/C4 and O1/O2, FP1/FP2, and T3/T4, and AFZ/POZ and CB1/CB2). Each paired protocol will run two pairs of montages so that the participant is able to relax and have fewer disruptions during a session. In the past, the Technologists would change the placements between each protocol, so this will effectively cut in half the number of times the participant is interrupted while relaxing. While four sensors are placed on the participant's head at once, only two sensors are actively

mirroring. The other two sensors are simply observing how the brain is responding and recording that data. Each pair of protocol is set to play one at a time. For example, in the pair F3/F4 and P3/P4, F3/F4 will be mirrored back while P3/P4 are only observed. When the F3/F4 exercise concludes, the program will automatically start the P3/P4 mirroring protocol, while F3/F4 will be observed. At each location, based on the electrical pattern at the time, HIRREM-SOP software chooses what protocol will best support that area to relax itself. This process also provides information on how the brain is responding globally to shifts occurring locally.

Non-specific acoustic stimulation:

Individuals assigned to the nonspecific acoustic stimulation group (NCC) will undergo sessions that mimic HIRREM-SOP in all appearances and procedures, including behaviors and subjective intentionality of the Technologist, and the number and scalp locations of protocols delivered during each session. However, in place of acoustic stimulation consisting of tones that vary in pitch and timing based on algorithmic analysis of real time brain activity, participants assigned to the NCC group will receive tones generated by a random signal generator. This includes randomness for both the timing, and the pitch of the tones, which are also not acoustically engineered. Technologists will be specifically instructed and trained to maintain comparable mental and behavioral interactional styles with all participants, both to minimize or eliminate confounding effects of Technologist subjectivity on differential outcomes associated with BCC and NCC groups, and to maintain subject blinding.

Safety:

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 about 500 participants who have received HIRREM), the study team is 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 sleep amount, quality, or dreams, changes in 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). Since it uses the same core technology and approach, with what is actually less actual time of intervention, it is anticipated that the safety profile for HIRREM-SOP will be similar. No serious adverse effects are anticipated with use of either HIRREM-SOP, or nonspecific acoustic stimulation.

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 two post-intervention visits for all participants. If a participant in the NCC group wishes to cross over following their initial study commitment, they will also be followed for two additional data collections post-active HIRREM-SOP sessions.

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 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 [31]. 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.

Self-Report Symptom Scales:

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 [32, 33]. The PSQI is a 19 item inventory that assesses sleep quality over a 1-month time interval [34]. 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 [35].

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 [36]. Scores range from 0-60, with a score of 16 commonly used as a clinically relevant cut-off [37].

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 [38]. The GAD-7 score (the sum of 7 items scores, 0-3) can range from 0 to 21.

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 [39].

Expectation Measure:

At V1, prior to the 5th intervention session, and at V3, participants will be asked which group they believe they are assigned to, acoustic stimulation linked to brainwaves, or non-specific acoustic stimulation. The sample of primary interest will be the follow up prior to the 5th session. These expectation measures will allow evaluation of the effectiveness of blinding between the two interventions.

Participant Compensation:

Participants in this research project will receive $100 in monetary compensation for time, trouble, and inconvenience related to study visits. Participants who do not complete the entire study will receive a prorated portion of this amount ($25 each for completion of V1, interventions, V2, and V3). There is no additional compensation available for those who choose to cross over to receive HIRREM-SOP (visits V4-V5).

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)
Perceived Stress Scale (PSS)
Pittsburgh Sleep Quality Index (PSQI)

B:
Handout for Study Participants

C:
Medical History/Screening Form
Expectation Measure

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