HIRREM Developmental Study
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Functional and Physiological Effects of High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM) for Neurological, Cardiovascular and Psychophysiological Disorders

Abnormal electroencephalographic (EEG) asymmetries have been reported in a variety of neurological, cardiovascular, and psychophysiological conditions including Attention Deficit Hyperactivity Disorder ADHD, anxiety, autism spectrum disorders, depression, dyslexia, Post-Traumatic Stress Disorder (PTSD), and traumatic brain injury (TBI).[1,2,3,4,5,6,7,8,9,10,11,12] Many, if not all of these conditions are associated with autonomic imbalance and psychophysiological dysfunction manifested as low heart rate variability or other abnormal measures.[13, 14, 15] It comes as no surprise that EEG asymmetry and autonomic perturbations occur concomitantly as Craig has posited a plausible theory for the anatomic lateralization of autonomic function within the brain.[16] Aiming to balance EEG asymmetries using biofeedback has yielded positive results in the treatment of neurological and psychiatric conditions of interest such as ADHD, depression, anxiety, pain, substance abuse disorders, and TBI.[17,18,19,20,21,22,23] Conventional EEG biofeedback (neurofeedback) employed in these studies utilizes operant conditioning to help individuals consciously learn to alter their brainwave activity, with the goal of ameliorating neurobehavioral symptoms. Specific EEG frequencies and locations are targeted that are believed to influence specific cognitive domains. The goal is to bring the individual's brainwave activity within a range as defined by a control group or normative database.[24] Recent evidence suggests the need to attain idiosyncratic set points for each patient rather than adjust to a single standard.[25] High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM®), can help achieve desired electrical balance in the brain in an individualized manner by functioning as a mirror for the brain to observe its own disequilibrium[26].

HIRREM is an innovative, noninvasive approach to facilitating greater self-regulatory capacity for, by, and through the human brain (Brain State Technologies, LLC, Scottsdale, AZ)(BST). HIRREM may be conceived as a high-resolution electronic mirror that reflects the brain's activity back to itself, in "real time." But rather than use *light* to reflect the brain's changing visual appearance, as would a conventional household mirror, HIRREM instead uses *sound* to reflect the brain's changing pattern of frequency-specific electrical activity. In effect, HIRREM simply creates an opportunity for an individual to "listen to his or her own brain."

The HIRREM system uses unique sensors which are placed on the scalp and held in place using standard EEG conductive paste. The sensors precisely measure and map the surface EEG frequencies and amplitudes of the brain throughout its major lobes. The sensors utilize embedded computer chips that improve filtering of electromagnetic interference/artifact, allow collection of more precise frequency data, and thus demonstrate functional aspects of the brain in greater detail.

The choice of the specific musical tone to be reflected back to the user is made through a mathematical algorithm which identifies the dominant frequency of the individual's EEG spectrum in a floating middle range, in a given instant of time. The dominant EEG frequency is translated to a musical tone whose frequency corresponds to the dominant EEG frequency. The musical tone is played back to the individual through ear buds, with a delay of as little as 12 milliseconds. Since the brain is a dynamic organ, with constantly changing frequencies, the subject hears a series of musical tones. It appears that a phenomenon of resonance occurs between the musical tones being fed back, and the oscillating neural circuits in the subject's brain. The operational theory is that such resonance creates an opportunity for the brain to either dissipate or accrete neural energy in an extremely subtle, noninvasive way. Neural-musical resonance may be a mechanism for auto-calibration of neural networks.

Like any polished mirror, HIRREM is extremely precise, and also "non-judgemental." There is no operant conditioning, and no imparting of normative information by the HIRREM provider, that would aim to explicitly reward, inhibit, entrain, instruct, re-program, or in any other way to over-write the brain's existing pattern of activity. Thus, HIRREM is fundamentally different from other available technologies such as binaural beats, auditory or photic stimulation, "synchronization" and other "brain-enhancement" methodologies.

Based on information received from the licensor, HIRREM has been found to be an extremely safe procedure. The licensors of HIRREM technology are not aware of any serious adverse events that have been associated with undergoing the HIRREM process, among over 50,000 individuals world-wide. On an anecdotal basis, individuals undergoing HIRREM may report an apparent "release of emotions" or paradoxical effects, especially initially, which can manifest as brief periods of increased awareness of emotional states, both positive and negative. These experiences are typically transient, that is, lasting intermittently over the course of one to several days. Based on our own experience with having enrolled over 400 subjects in HIRREM clinical research projects at Wake Forest School of Medicine, reflecting a total of over 4,000 HIRREM sessions, there have been no serious adverse events. Subthreshold changes in emotional symptomatology (not requiring additional clinical intervention or necessitating discontinuation of sessions) have been seen in an estimated 5-10% of subjects.

The purpose of this study is to ascertain the functional and physiological effects of BWO using HIRREM as supplemental care in populations and individuals with a variety of neurological, cardiovascular, and psychophysiological diseases. The scope of the conditions to be investigated is broad since it is the intention of this proposal to allow the recruitment of a wide variety of patients at the discretion of the investigators. One goal is to allow investigators to identify patient cohorts which would be desirable for further study, some of which may not be intuitively obvious, using such data as the basis for pursuit of additional disease-specific projects, or funding opportunities. Anecdotal evidence collected by BST has demonstrated efficacy of treatment for many diseases and disorders of interest including PTSD, TBI, insomnia, ADHD, substance abuse disorders, cardiovascular diseases, gastrointestinal disturbances, and others. It is those conditions along with autism spectrum disorders, depression, dyslexia, anxiety disorders, migraines, hot flashes, and others, for which we seek to formally evaluate the functional and physiologic effects of HIRREM.

As of this submission, two randomized clinical trials utilizing HIRREM have been completed at Wake Forest School of Medicine. This includes a wait-list controlled pilot trial for insomnia (n=20), and a sham placebo controlled trial for migraine (n=30). A manuscript has been published regarding the insomnia study, and one is being prepared related to the migraine work. Results of the insomnia study showed significant reduction in the Insomnia Severity Index (ISI), with the effect persisting for one month following completion of the HIRREM intervention[27]. There was also a significant decrease in symptoms of depression as identified by the CES-D scale. A larger, confirmatory, placebo-controlled trial for insomnia will be launched shortly.

There has also been analysis of several subsets of subjects from this ongoing research project. A case series of subjects with symptoms of Post-Traumatic Stress Disorder (PTSD) was presented as a poster at the annual meeting of the International Society for Traumatic Stress Studies, and a manuscript has been submitted for possible publication. This case series (n=10) showed significant improvements in the symptoms of PTSD (PCL-Civilian scale), sleep (ISI), and depression (CES-D). An abstract based on analysis of outcomes for another case series (n=10) of subjects with physical trauma/TBI was submitted

for possible presentation at the 2013 meeting of the American Academy of Neurology (AAN), showing significant improvements found in the ISI, CESD, and PCL-C scales.

We anticipate that there will be beneficial effects on balance in the autonomic nervous system associated with HIRREM, and thus, believe that heart rate variability (HRV), which reflects balance in the autonomic signal to the heart, is a good objective measure, and represents a relevant outcome for this study, irrespective of the clinical condition. To that end, an additional abstract was submitted for possible presentation at the 2013 AAN meeting. This case series of consecutive subjects enrolled in the project, for a variety of clinical complaints (n=23), showed significant correlation between the brain pattern pre-HIRREM (temporal asymmetry at T3/T4) and a HRV parameter (RMS-SD). This provides support for our understanding regarding lateralization of autonomic function in the HIRREM assessment of surface EEG data.

Evidence of benefit for HIRREM in other conditions, prospectively gathered in a carefully monitored clinical environment through this proposal, can serve as a foundation for the pursuit of future randomized controlled pilot studies, and eventually larger randomized controlled clinical trials. The ultimate goal of this line of study is the development of HIRREM as a noninvasive therapy for a variety of clinical conditions.

Objectives and Hypotheses:

- The primary objective of this proposal is to generate new hypotheses and data for future studies by evaluating the effect of HIRREM as supplemental care for subjects with a number of neurological, cardiovascular, and psychophysiological diseases. The primary analytic outcome to determine the effect and feasibility of HIRREM is HRV as measured by standard outcomes collected using a BIOPAC device for continuous recording of heart rate and blood pressure. This also allows calculation of mean arterial pressure and baroreceptor sensitivity**.** We anticipate a decrease in sympathetic activity and an improvement in sympatho-vagal balance manifested as an increase in HRV parameters.

- Secondary objectives of this proposal include evaluation of the effects of HIRREM on:

    - Autonomic nervous system functions, as manifested by blood pressure and heart rate. Another expected result of a decrease in sympathetic activity and an improvement of sympatho-vagal balance may be a decrease in heart rate and blood pressure.

    - Psycho-physiological functional outcomes as measured using a standardized measure of health status the (EQ-5D) , the Center for Epidemiologic Studies Depression Scale (CES-D), the GAD-7 measure of anxiety, the Insomnia Severity Index (ISI), and the PTSD Check List for civilians or military service members (PCL-C, or PCL-M, respectively. We expect to see an improvement in these measures following HIRREM.

    - Metrics for specific disorders will be measured according to relevant currently accepted assessment tools. Some of the conditions for which treatment is anticipated and the corresponding evaluation tools are in Appendix A. We expect to see improvement in these measures.

- Weight will be measured at the enrollment visit (V1), completion visit (V2) and follow-up visit (V3) to determine the potential impact of HIRREM on weight.

- Reaction time will be measured using the clinical reaction time enrollment visit (V1), completion visit (V2) and follow-up visit (V3).

Research Design and Methods:

This protocol is an assessment of the functional and physiological effects of HIRREM on neurological, cardiovascular, and neurophysiological disorders. It will be a non-randomized, open label, and unblinded before-and-after trial. The intention of this protocol is to evaluate the effect of HIRREM on an objective, physiological common denominator (HRV), across a variety of relevant conditions, as well as changes in clinical symptoms scales, to generate hypotheses and pilot data for investigation in future proposals. HIRREM will be offered as deemed potentially advantageous by the investigator. Patients will be recruited to receive eight to twenty HIRREM sessions in addition to their usual care. HIRREM sessions will be completed over a one month period. Measurements for the primary and secondary outcomes will be obtained at the initial visit and after completion of HIRREM therapy. A follow-up visit (V3) will be performed four to eight weeks after the completion visit (V2). This will consist of several representative questionnaires and surveys and a repeat of recording of blood pressure and heart rate using the BIOPAC device.

1) Subjects Selection Criteria:

Male and Female adults and children over the age of 11 years with a clinical diagnosis consistent with the aims of this proposal, who also meet the inclusion criteria outlined below and are interested in receiving HIRREM, will be enrolled. Subjects will be recruited by physician referral, word of mouth, and through advertisement. Physicians who want to inform prospective subjects about the availability of the research will be provided with copies of the IRB approved consent form and IRB approved ad which they may give to prospective subjects. The physicians do not obtain subjects' consent for the research or act as representatives of the investigators. Physicians provide prospective subjects with information about contacting investigators for information or enrollment; and/or seek or obtain the prospective subjects' permission for investigators to contact them. The participant must be able to provide informed consent.

Inclusion Criteria:

- Male and female adults and children aged 11 years and older.
- Subjects who are over the age of 18 must be able to give informed consent. Children must be able to sign an assent form and have a signed parental permission form.
- Subjects must have the ability to comply with basic instructions and be able to sit still comfortably with the sensor leads attached. Subjects previously diagnosed with a neurologic, cardiovascular, or psychophysiological disease such as ADHD, Asperger Syndrome, chronic pain, dyslexia, depression, insomnia, migraines, PTSD, substance abuse disorder, TBI, and others.
- During the screening process a list of questions, Appendix D, shall be asked to evaluate eligibility, severity and related concerns to be considered for treatment.

Exclusion Criteria:

- Subjects who fail to meet inclusion criteria.
- Subjects who are unable, unwilling, or incompetent to provide informed consent, assent and/or parental permission.
- Subjects physically unable to come to the study visits.
- Subjects with a known seizure disorder.
- Subjects with bilateral hearing impairment (treatment requires the use of headphones).
- Subjects receiving ongoing treatment with opiate, benzodiazepine, anti-psychotic or sleep medications, as well as some anti-depressants or stimulants, except those cases deemed acceptable by the investigator.
- Subjects with anticipated and ongoing use of recreational drugs except when deemed acceptable by the investigator.

Subjects are encouraged to discuss their participation with their healthcare provider following completion of HIRREM since some of their symptoms and conditions may be alleviated and therefore no longer require the same type or dosage of medication. Throughout the course of/ and for three weeks following treatment subjects will be requested to abstain from the consumption of alcohol or use of recreational drugs since the effects of these substances may cause reversal or cessation of the benefits of HIRREM. Additionally, subjects will be asked to discontinue chiropractic practices, cranial-sacral therapy, and bio-energy work during treatment and for the three weeks following treatment. Other instructions and requests may be given to the patient and will be contingent upon the condition(s) being treated and will be at the discretion of the investigator.

2) Number of Subjects:

This protocol is submitted with the intention of uncovering potential for future research and as such the aim is for three hundred subjects to be enrolled and receive HIRREM. This cohort will provide data across a variety of conditions, which can be used to generate estimates of effect size, and serve as pilot data in proposals for future studies.

3) Number of HIRREM Sessions and Length of Study:

All baseline measures will have been collected during the enrollment visit. The period of active HIRREM will begin with an initial assessment to map the patterns of frequencies and amplitudes in the brain. Participants will typically then receive eight to twenty HIRREM sessions over a one month period. Based on objective data regarding brain patterns, evidence of progress with balancing of frequencies and quieting of amplitudes, along with clinical progress, HIRREM may be extended beyond 20 sessions. Participants may be given a brief break of one to two weeks before returning for additional sessions. HIRREM sessions typically are 1.5 hours in length. Participants may receive two HIRREM sessions during a half day period, and thus will spend an average of five half days getting HIRREM during the month. There will then be a post-HIRREM data collection visit (V2) no longer than two weeks after completion of the HIRREM during which outcome measures will be repeated and a follow-up visit (V3) 4-8 weeks after (V2).

a. Enrollment Visit:

Informed consent obtained, brief medical history obtained (Appendix B), and collection of baseline measures. This will occur prior to the start of HIRREM and will require about 45-60 minutes of time. When possible the completed medical history form may be requested and received prior to the enrollment visit.

b. Initial Half Day Session:

On the first day of HIRREM, the participant will have an assessment (about 60 minutes) to determine the pattern of frequencies and amplitudes in his/her brain which may be followed by the first and possibly second HIRREM sessions.

c. Remaining HIRREM Sessions:

Participants may receive two HIRREM sessions in a half day period for an anticipated average total of 10 HIRREM sessions per participant, with five half days spent during the month of HIRREM. Participants may receive up to 20 HIRREM sessions over the course of ten visits. In the event this is deemed appropriate and necessary, and for the benefit of the subject, (see above) the number of HIRREM sessions may be extended.

d. Treatment Completion Visit:

Participants will return for a study completion visit no longer than two weeks following completion of the HIRREM sessions, when post-intervention measures will be obtained. This visit will take 45-60 minutes.

e. Follow-Up Visit:

Follow-up visit will be scheduled for 4 -8 weeks after V2 treatment completion visit. Post intervention measures will be repeated.

4) High Resolution, Relational, Resonance-Based, Electroencephalic Mirroring (HIRREM)

HIRREM is an EEG-based, noninvasive technology to facilitate relaxation and auto-calibration of neural oscillations.

a. Brain Pattern Assessment

This is the first step in the process, occurring prior to the active HIRREM sessions. The assessment is to create a map of the frequencies and amplitudes in the brain. With the participant in a sitting or slightly reclined position, sensors are sequentially placed over seven areas of the scalp, and measurements are taken with eyes closed (1 minute), eyes partially open (1 minute), and eyes open (1 minute). For eyes closed, subjects are asked to rest and relax quietly. For eyes open, subjects are given standardized tasks such as numerical digit recall, reading silently, calculations, or listening comprehension. This allows

evaluation of the brain pattern with the brain at rest, and at task. The data are processed to identify patterns and imbalances, which will then be used to generate specific protocols for the HIRREM sessions that follow. The mapping takes up to 60 minutes to complete.

b. HIRREM Session

Each HIRREM session requires about 90-120 minutes.

For the sessions, with the subject comfortably at rest, sitting or reclining, the sensors are placed over the specific target areas on the scalp corresponding with brain regions/lobes to be addressed. Frequencies and amplitudes 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 a musical note, which is played back to the subject via ear buds within 12-25 milliseconds. Thus, the subject listens to the energetic "song" being played in the brain from moment to moment, providing the brain with a mirror of itself, and its energetic function. Although similar to methods such as neurofeedback, HIRREM uses an algorithm-based observation for the brain to view itself, which results in spontaneous movement toward a more balanced state of function, rather than operant conditioning designed to try to force the brain towards a standardized or ideal pattern of energetics and function. No active involvement by the participant is needed to accomplish this energetic balancing. Correction of brain imbalances associated with persistent autonomic responses may then lead to resolution of symptoms which had been associated with the same.

c. Safety

Based on information received from the sponsor, HIRREM has been found to be an extremely safe procedure. With over 50,000 individuals receiving HIRREM clinically, there have been no serious adverse events reported. Participants may or may not experience improvement. Participants will be closely monitored for any adverse effects of HIRREM. It is common for individuals undergoing HIRREM to report “release of emotions,” which can manifest as brief periods of increased awareness of emotional states, both positive and negative. These experiences are typically transient, that is, lasting intermittently over the course of one to several days. Based on our own experience with having enrolled over 400 subjects in HIRREM clinical research projects at Wake Forest School of Medicine, representing a total of over 4,000 HIRREM sessions, there have been no serious adverse events. Subthreshold changes in emotional symptomatology (not requiring additional clinical intervention or necessitating discontinuation of sessions) have been seen in an estimated 5-10% of subjects. All HIRREM sessions are administered by Technologists who have been certified in this procedure. Their training included protocols for addressing emotional releases that may occur. If emotional releases are more prolonged, or more intense, subjects will be referred to a mental health professional for additional evaluation or treatment.

5) Data Collection and Process

A series of measures will be collected at the enrollment visit and the post-HIRREM data collection visits.

a. Primary Data Sets: Heart Rate Variability (HRV) Measurement

i. HRV Data Acquisition:

Baroreflex sensitivity (BRS) for control of HR, heart rate variability (HRV) and blood pressure variability (BPV): Continuous BP and HR are acquired from noninvasive finger arterial pressure measurements and ECG for a minimum of 8 minutes in subjects lying down quietly. SBP and 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 (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 their squared-coherence modulus is computed if coherence is >0.5 as reported (16). The square-root of the ratio of RRI's and SBP powers is computed to calculate LF, HF alpha indices, which reflect BRS (16). Power of RRI spectra in LF, HF range (LF_{RRI} and HF_{RRI}) are calculated in normalized units and the ratio of LF_{RRI}/HF_{RRI} is used as a measure of sympathovagal balance (17). Power of SBP spectra calculated as LF_{SAP} 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 (18, 19). HRV is determined by computing the standard deviation of beat-to-beat interval (SDRR) 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).

ii. 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, pNN50, VLF, LF, HF, TP, LF/HF, sample asymmetry, sample entropy, and coherence. All of the algorithms for computation of these parameters are derived from information or source code from the Physionet archive (Goldberger). Data are saved to Excel spreadsheets for further statistical analysis by study team members.

b. Blood Pressure (BP)

Blood pressure (BP) measurements will be taken with a finger cuff on two fingers of the left hand while lying down on an examination table.

c. Neuropsychological and Psycho-Physiological Function:

- **i.** The Center for Epidemiologic Studies Depression Scale (CES-D) is a standard paper and pencil depression scale which will help to assess this co-morbidity.
- **ii.** The EQ-5D is a brief, standardized measure of health status developed by the EuroQol Group, and is a paper and pencil survey providing a single index value for health status.
- **iii.** The Generalized Anxiety Disorder-7 (GAD-7) is a seven item screening tool for anxiety that is widely used in primary care.
- **iv.** The Insomnia Severity Index (ISI) is a seven parameter measure of insomnia.
- **v.** Post Traumatic Stress Disorder (PTSD) (Civilian and Military) is a checklist to measure stress severity due to a traumatic experience
- **vi.** Nausea /Dizziness Severity Scale is a screening tool to measure symptoms related to stomach problems

d. Disorder Specific Metrics

- **i.** These may vary across subjects depending on the underlying condition. The table in Appendix A contains some of the conditions to be included and the corresponding assessment tools to measure the effects of HIRREM. This list is not exhaustive and other conditions may be added at the discretion of the investigator. In the event a patient with an unlisted condition is enrolled a currently accepted assessment technique will be employed to collect both initial and final data.

e. Weight

- **i.** This will be measured using a standard scale.

f. Reaction Time

Reaction time testing will be measured by the clinical reaction time apparatus. It is constructed from a meter stick covered in the 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 is converted to reaction. This simple clinical measure has been evaluated by Eckner et al and demonstrated utility in testing comparable to computerized testing methods.[33]

g. T3/T4 Asymmetry

The proprietors of HIRREM have repeatedly observed that EEG asymmetries in the temporal lobes (specifically at T3 and T4 in the 10-20 International System for EEG correspond to autonomic dysfunction. When T4 signals are dominant to T3 signals a sympathetic state is favored which is manifested as symptoms of anxiety, cardiovascular over-drive, and

hyperarousal. When T3 signals are excessively dominant to T4 signals a parasympathetic state is favored which is manifested as symptoms of emotional numbness, cardiovascular underactivity, GI dysfunction, and under-arousal. Lateralization of autonomic activity is not a novel finding, it is in accord with a number of previously published studies which support a hypothesis of autonomic lateralization posited by Craig and previously discussed.[16,28-32] Utilization of HIRREM at T3 and T4 has demonstrated success in ameliorating symptoms associated with autonomic disruption. EEG balance at T3 and T4 is indicative of autonomic balance and benefit according to BST.

Our preliminary data demonstrate correlation between a T3/T4 temporal asymmetry score and objective physiological changes reflective of autonomic signaling to the heart at the baseline assessment. Comparison of such activity at T3 and T4 over time will provide objective physiological outcome data regarding the effect of HIRREM on autonomic balance and function.

6) Statistical Analysis

Data will be analyzed using the most recent versions of SAS (SAS Institute, Inc., Cary, NC). Prior to performing analyses related to the hypotheses, histograms and descriptive statistics will be computed to examine the characteristics and distributions of the data. As detailed below, analytical methods will be conducted through generalized linear models that allow specification of appropriate distribution as well as various covariance types to ensure that inference tests can be interpreted conventionally. If required, nonparametric equivalents to the proposed methods will be used to analyze variables not well characterized by standard distributions. Unless otherwise stated, all relevant analyses will be two-tailed and $p < 0.05$ will be used to determine statistical significance. Because this proposal is designed to estimate effect sizes for future pilot and definitive trials, care will be taken to provide point estimates of effect size for each outcome along with corresponding 95% CI.

This primary objective of this protocol is to evaluate the effect of HIRREM in neurological, cardiovascular, and psychophysiological disorders as measured by standard HRV parameters**.** Also, a variety of secondary outcomes will assess the impact on functional and physiological measures (BP and HR), a number of standard disorder specific clinical measures, and subjective psycho-physiological outcomes. The primary analysis will be examining group differences on the post-HIRREM measure while controlling for baseline levels (i.e., group treated as a fixed effect, with baseline scores entered as a covariate in a generalized model assuming a normal distribution and identity link). Changes in all secondary measures will be indexed using the GLM using the repeated measurements within each individual. The groups will be comprised of a collection of individuals from within the study with a common clinical disorder, although exploratory analysis will also evaluate for common effects in consecutively enrolled subjects.

Human Subjects Protection:

1) Consent and Assent

Written informed consent, or assent and parental permission will be obtained by the research staff from each competent subject.

2) 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. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a separate master log. The master log will be kept secure, 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.

3) 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. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

4) Reporting of Unanticipated Problems, Adverse Events of 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.

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Appendix A: Examples of Disease Specific Assessment Tools

Condition	Assessment Tool
Traumatic Brain Injury	Rivermead Post-Concussion Symptoms Questionnaire
Headache	Daily Headache Diary
Hot Flashes	Daily Diary for Hot Flashes
Mild Cognitive Impairment	Montreal Cognitive Assessment (MoCA)

Appendix B: Medical History Form

Medical History Form

First Name: _____ Date: _____

1. Please check whether you have the following medical problems/health history:

	Yes	No	Year of onset	If yes, please explain
High Blood Pressure				
Stroke				
Seizure/Epilepsy				
Heart Attack				
Heart Arrhythmia				
Lipid Disorder/High Cholesterol				
Diabetes				
Cancer				
Thyroid Disorder				
Fibromyalgia				
Other Chronic Pain				
Chronic Fatigue				
Headaches				
Migraines				
Tinnitus (ringing in the ears)				
Vertigo/Dizziness				
Stress/Anxiety Disorder				
Post-Traumatic Stress Disorder				
Depression				

Insomnia				
Hot Flashes				
ADD/ADHD				
Autism Spectrum Disorder/Asperger's				
Learning Disability/Dyslexia				
Impaired Memory/Mild Cognitive Impairment				
Sports-Related Concussion				
Traumatic Brain Injury/Head Injury				
Difficult Birth (Premature, Induced, C-Section, etc.)				
Other				
Any Surgery				

2. Please list your prescribed medications (those taken regularly and PRN/as-needed/rescue) and duration taking them (for how long, how many times per week/month, or last dose).

Medication	Dose	Time of day taken	Duration taking this

3. Please list any over the counter medication, supplements, vitamins, herbs, etc. that you take (those taken regularly and PRN/as-needed/rescue) and duration taking them (for how long, how many times per week/month, or last dose).

Name	Dose	Time of day taken	Duration taking this

Initial HIRREM Screening

Name: _____ Email address: _____

Address: _____ Telephone number(s): _____

_____ _____

Date of birth: _____ Gender: _____

Referred by: _____ Date screened: _____

Primary complaint:

_____

_____

_____

Secondary complaints:

_____
_____
_____

Other medical problems:

_____
_____
_____

Medications (prescriptions, PRN/as-needed/rescue medicines, over the counter, supplements, vitamins, herbs, etc.) and duration taking them (for how long, how many times per week/month, or last dose):

_____
_____
_____
_____
_____

Comments:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Secondary HIRREM Screening

Name: _____ Date of birth: _____
Date screened: _____ Race: _____

Who is your primary care physician/contact number?

_____

Do you see any other health care providers regularly or use any integrated/complimentary therapies (acupuncture, yoga, massage, healing touch, etc.)?

_____

_____

Please list an emergency contact, the relation, and a phone number.

_____

General questions:

1. Do you consume alcohol? □ Yes □ No
   a. If so, how much? _____
   b. If so, how often? _____
   c. If so, what type? _____
2. Do you consume caffeine (coffee, tea, energy drinks, chocolate, etc.)? □ Yes □ No
   a. If so, how much? _____
   b. If so, how often? _____
   c. If so, what type? _____
3. Are you a: □ Current smoker □ Ex-smoker □ Never smoked
   a. If you have ever smoked, how much? _____
   b. If you have ever smoked, how often? _____
   c. If you have ever smoked, what type? _____
4. Do you have a history of addiction (substance abuse, shopping, etc.)? _____
5. Were you in the military? □ Yes □ No
   a. If so, how many deployments/years did you serve? _____
6. Have you ever had any physical or emotional trauma (accidents, head injuries, childhood events, traumatic events, bad relationships, abuse)? □ Yes □ No
7. What is your marital status? □ Married □ Divorced □ Single □ Widowed □ Other
8. Do you have any children? □ Yes □ No
   a. If so, how many and what age? _____
   b. Have you ever lost a child? □ Yes □ No

Sleep

1. How do you usually sleep? _____

a. Do you have any trouble falling asleep? □ Yes □ No
b. Do you have any trouble staying asleep? □ Yes □ No
c. Do you wake up rested? □ Yes □ No

Headaches/Migraines

1. Do you have headaches? □ Yes □ No
    d. If so, how many per week/month? _____
    e. If so, how long have you had them? _____
    f. If so, do you do anything to alleviate them? _____
2. Did headaches occur from a concussion/TBI? □ Yes □ No
3. Do you have migraines? □ Yes □ No
    a. If so, how many per week/month? _____
    b. If so, how long have you had them? _____
    c. If so, do you do anything to alleviate them? _____

Concussion/Traumatic brain injury (TBI)

1. Have you ever had any concussions or TBIs? □ Yes □ No
    a. Was there more than one concussion or TBI? _____
    b. If so, how many and what kind? _____
    c. If so, when did it occur/what was the cause? _____
    d. If so, did you lose consciousness? _____
    e. If so, did you have to go to the hospital? _____
    f. Were you hospitalized? If so, for how long? _____
    g. Did the injury require brain surgery or drainage of blood or fluid from in or around the brain?
    h. Have you ever had any other head injuries? _____

PTSD

1. Do you have post-traumatic stress disorder? □ Yes □ No
2. How long have you had PTSD symptoms? _____
3. Have you seen a physician for this? □ Yes □ No
4. Do you have a formal diagnosis of PTSD? □ Yes □ No
    a. If so, when was the diagnosis made? _____
5. If you were in the military, in your opinion, did the traumatic event most responsible for your PTSD occur as part of your military service or did it occur as part of civilian life?
    □ Military □ Civilian
    a. If military, was it related to a blast injury? □ Yes □ No

ADHD

1. Do you have difficulty with focus and concentration? □ Yes □ No
2. How long have you had these symptoms? _____
3. Have you seen a physician for this? □ Yes □ No
    a. Did you have a formal evaluation? □ Yes □ No

b. Did a physician give you Adderall? □ Yes □ No

4. Do you have a formal diagnosis of ADD/ADHD? □ Yes □ No
   a. If so, when was the diagnosis made? _____

Hot Flashes

1. Do you have hot flashes? □ Yes □ No
   a. What is the frequency per day/week? _____
2. Do they occur during the day, night, or both? □ Day □ Night □ Both
   a. How severe are they? □ Mild □ Moderate
   □ Severe □ Very Severe

Key: mild - sensation of heat w/o perspiration
moderate - sensation of heat w/perspiration and able to continue activity
severe - sensation of heat w/sweating causing you to stop activity or disrupting your sleep
very severe - sensation of heat w/severe sweating, disrupting activity or requiring a change of sheets or clothes

Comments:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____