HIRREM Hot Flashes Study

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Title:

High-resolution, Relational, Resonance-based, Electroencephalic Mirroring (HIRREM) for Vasomotor Symptoms in Perimenopausal and Postmenopausal Women: A Randomized Pilot Clinical Trial

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Abstract:

Background:

Up to 80% of women experience menopausal vasomotor symptoms during the perimenopause transition period, such as hot flashes, night sweats, and flushes, although they can vary between individuals. These often last for more than 7 years for over half of women. These symptoms are related to negative outcomes including depressed mood, reduced social quality of life, and decreased quantity/quality of sleep. A common therapy used to address these symptoms is hormone replacement therapy (HRT), although there is concern with long term use and safety is unknown. Noninvasive, non-drug alternative interventions are needed.

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

Methods: This will be a randomized, single site, pilot clinical trial, enrolling up to 40 women, who have at least 5 hot flashes per day (with at least one being categorized as moderate to severe), and who are not taking medications or supplements for management of hot flashes. Participants will be randomly assigned to receive 8-16 sessions over a maximum of 4 weeks of acoustic stimulation linked to brain activity (HIRREM and continued current care, HCC) or will be assigned to a waitlist group (continued current care, CCC). 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 daily hot flash diaries, Hot Flash Related Daily Interference Scale (HFRDIS), the Menopause Rating Scale (MRS), 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), stress (Perceived Stress Scale, PSS), and a quality of life measure (Quality of Life Scale, QOLS), as well as drop stick reaction testing, and dynamometry for grip strength. Measures will be collected at an enrollment visit (V1). Both groups will then maintain a hot flash diary for 7-14 days, after which the intervention will begin for the HCC group. Post-intervention data collections will be obtained at 4-6 weeks (V2, primary outcome) and 12-14 weeks (V3) following completion of the intervention. Follow up data collection for the CCC group will occur at 10-12 weeks (V2), and 18-20 weeks (V3) after the V1 visit. Both groups will maintain a hot flash diary for 1-2 weeks prior to the V2 and V3 visits. The primary outcome will be differential change in hot flash frequency and severity from

V1 to V2 between HCC and CCC, based on data from the hot flash daily diary. Following V3, those in the CCC group will be offered the opportunity to cross over to receive a course of HCC within 3 months, and will continue to be followed for data collections at 4-6 weeks (V4), and 12-14 weeks (V5) after completing their crossover HIRREM sessions. 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 vasomotor symptoms associated with menopause in a randomized, clinical trial. The study will confirm feasibility using a closed-loop, acoustic stimulation intervention for a randomized clinical trial in this population, and will also provide estimates of effect size, which might justify larger controlled trials. A positive result would suggest that HIRREM might have benefit as a noninvasive, non-drug alternative for management of vasomotor symptoms. This, over and above the potential benefit from participating in a clinical trial, and interacting with the study personnel and the study environment. The study will also help to identify the characteristics of subgroups that might experience differential effects/benefits from HIRREM.

Background:

An estimated 22 million women are between the ages of 45 and 54 years, suggesting that they are entering or have begun the perimenopause transition. Of these women, approximately 75% of them will experience vasomotor symptoms (hot flashes) due to the menopause transition, and 25% will seek medical treatment. Around $4 billion is spent annually in the United States on medications to treat women going through menopause.

As individuals go through the menopausal transition, their body begins to reduce the production of estrogen and progesterone. Progesterone is a sleep-promoting hormone, so this can also lead to troubles sleeping or even insomnia.

There is evidence that patients are at an elevated risk of coronary heart disease (CHD) when given standard oral doses of hormone therapy treatments, which are often used to manage symptoms associated with perimenopause (Huang , Sawaya, Vittinghoff, Lin, & Grady, 2009). The risk increases for older postmenopausal individuals when compared to those who more recently went through the menopause transition. Due to safety concerns surrounding the use of hormone therapy, there remains a need for safe, effective, relatively brief, non-pharmacological therapies to help manage symptoms in this population.

Autonomic hyperarousal appears to play an etiological role related to vasomotor symptoms associated with menopause. Use of non-pharmacological strategies such as biofeedback and slow abdominal breathing, EMG-biofeedback, and HRV-biofeedback, targeting downstream autonomic function are reportedly associated with improved autonomic function and reduced blood pressure in those with prehypertension (Chen, Sun, Wang, Lin, & Wang, 2016; Innes, Selfe, & Vishnu, 2010; Lin et al., 2012; Wang et al., 2010; Xu, Gao, Ling, & Wang, 2007). Trials of mind-body, relaxation, behavioral, and complementary interventions have shown promise, possibly related to impact on autonomic hyperarousal (Avis, Legault, Russell, Weaver, & Danhauer, 2014; Befus et al., 2018; Guthrie et al., 2018; Innes et al., 2010; Stefanopoulou & Grunfeld, 2017).

High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM®) was developed by Brain State Technologies, Scottsdale, AZ. It is a commercially available, noninvasive, electroencephalic-based method to facilitate client-unique relaxation and auto-calibration of cortical neural oscillations by reflecting auditory tones in near real time (Gerdes, Gerdes, Lee, & Tegeler, 2013). HIRREM uses scalp sensors to observe brain frequencies and amplitudes in real time, and software-guided algorithmic analysis to identify and translate selected brain frequencies into audible tones to support real-time self-optimization of brain activity. The audible tones are reflected back to the recipient bilaterally, simultaneously, in 4-8 milliseconds, providing an opportunity for the recipient to, figuratively speaking, listen to the song the brain is playing right now. This rapid updating regarding its pattern allows the brain a chance to, self-optimize, 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.

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

Since 2011, the HIRREM Research Program at WFSM has enrolled over 480 participants in five clinical studies to evaluate the effects and potential benefits of HIRREM. Data have shown reduction in symptoms of insomnia, depression, stress/anxiety, military-related traumatic stress, hot flashes, and persisting symptoms after athletic concussion, associated with the use of HIRREM (C. L. Tegeler et al., 2017). Improved autonomic cardiovascular regulation has also been observed in those receiving HIRREM, including a cohort of adolescents with Postural Orthostatic Tachycardia Syndrome (J. E. Fortunato et al., 2016; J.E. Fortunato et al., 2013; C. Tegeler et al., 2014). In addition, correlation has been reported between high frequency electrical brain pattern asymmetry scores at baseline, and measures of autonomic cardiovascular regulation (C.H. Tegeler, Shaltout, Tegeler, Gerdes, & Lee, 2015).

Specific Relevant Pilot Data:

12 women (median age 56 y; range, 46-69 y) were enrolled in an ongoing IRB approved study exploring a variety of neurological, cardiovascular, and psychological conditions, and were identified as also reporting co-morbid perimenopausal symptoms (C. H. Tegeler, Tegeler, Cook, Lee, & Pajewski, 2015). 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 were continuously recorded while supine, with spontaneous breathing. Participants completed a hot flash diary for a median of 3.5 days (range, 1-11 d) before beginning their HIRREM sessions, and maintained through follow up data collection visits. Subjects then received a median of 13 (range, 8-23) HIRREM sessions approximately 90 minutes each (range, 54-102 min). Sessions consisted of 4-9 protocols, from 6-30 minutes each, with up to two sessions per day, and were received over a median of 9.5 days (range, 4-32 d). All measurements were repeated at the follow-up data collection visit at a median of 10 days (range, 0-20 d) after completing their final HIRREM session.

Primary outcomes included hot flash frequency and severity, sleep and depressive symptoms. High frequency (23-36 Hertz) amplitudes from bilateral temporal scalp recordings were measured at baseline and during serial sessions. Median changes (range, p value) for hot flash frequency and severity were -2.32 (-14 to 3, 0.050) and -1 (-3 to 0.8, 0.004), respectively. Sleep and depression scores decreased by -8.5 (-20 to -1, $p = 0.022$), and -5.5 (-32 to 8, $p = 0.015$) points, respectively. Median amplitude in temporal high frequency brain electrical activity was 8.44 microvolts (μv, 6.27-16.66) at baseline and decreased a median of -2.96 μv (-11.05 to -0.65, $p = 0.0005$) by the final session.

Table 1: Hot Flashes: Median (Ranges) Scores at Baseline and Final Day of HIRREM Sessions (*Hot flash score derived by multiplying frequency by worst severity score for each day)

	Baseline	**Final Day**	**Change**	**P value**
Hot Flash Frequency	4.7 (1, 14)	2 (0, 11)	-2.32 (-14, 3)	0.050
Hot Flash Severity	3 (1.2, 4)	2 (0, 3)	-1 (-3, 0.8)	0.004
Hot Flash Score[a]	9.08 (2, 42)	3.5 (0, 17)	-6.42 (-42, 3)	0.011

Table 2: Changes in clinical category for insomnia after HIRREM based on ISI scores

Clinical Category by ISI Score	**Baseline (Percent of Total)**	**Post-HIRREM (Percent of Total)**
No clinically significant insomnia (0-7)	2 (16.67%)	10 (83.33%)
Subthreshold insomnia (8-14)	4 (33.33%)	0
Moderate insomnia (15-21)	3 (25.00%)	2 (16.67%)
Severe insomnia (22-28)	3 (25.00%)	0

Figure 1 (A and B): Figure 1A: Changes in hot flash frequency over time. The Y-axis indicates hot flash frequency. The X-axis indicates the number of days since the start of the HIRREM sessions. Each colored line represents an individual participant in the study. Figure 1B: Changes in hot flash severity over time. The Y-axis indicates hot flash severity (1 = mild, 2 = moderate, 3 = severe, 4 = very severe). The X-axis indicates the number of days since the start of HIRREM sessions. Each colored line represents and individual participant in the study.

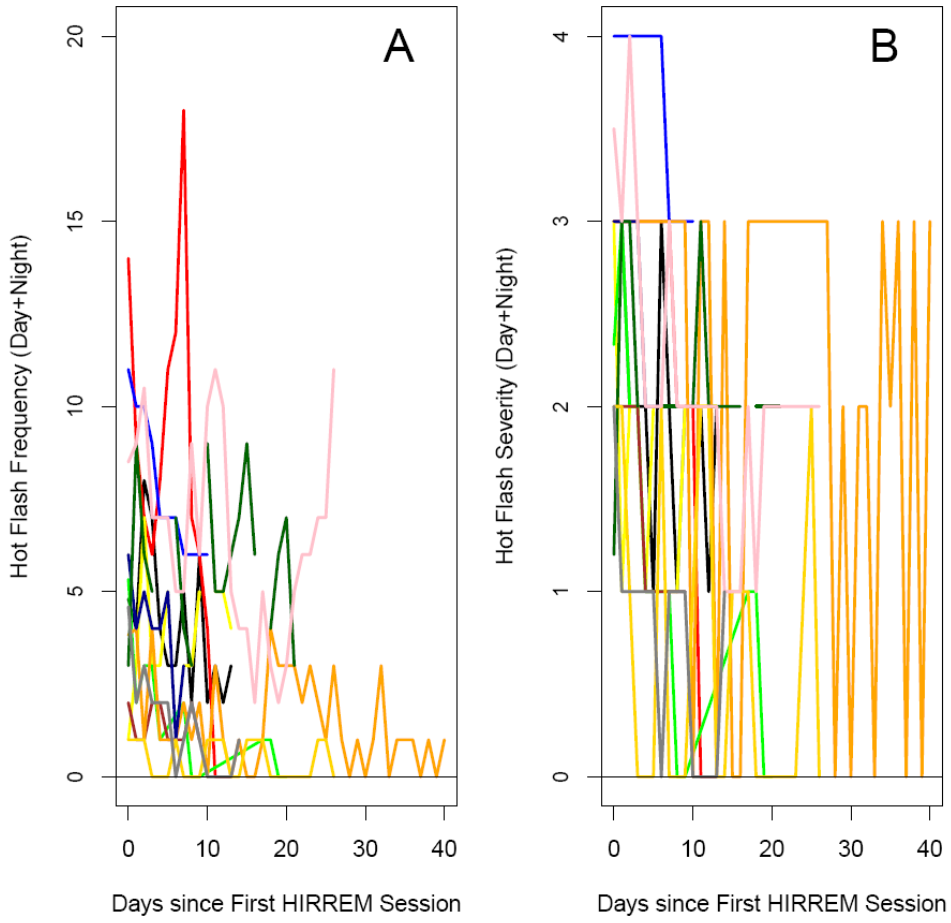
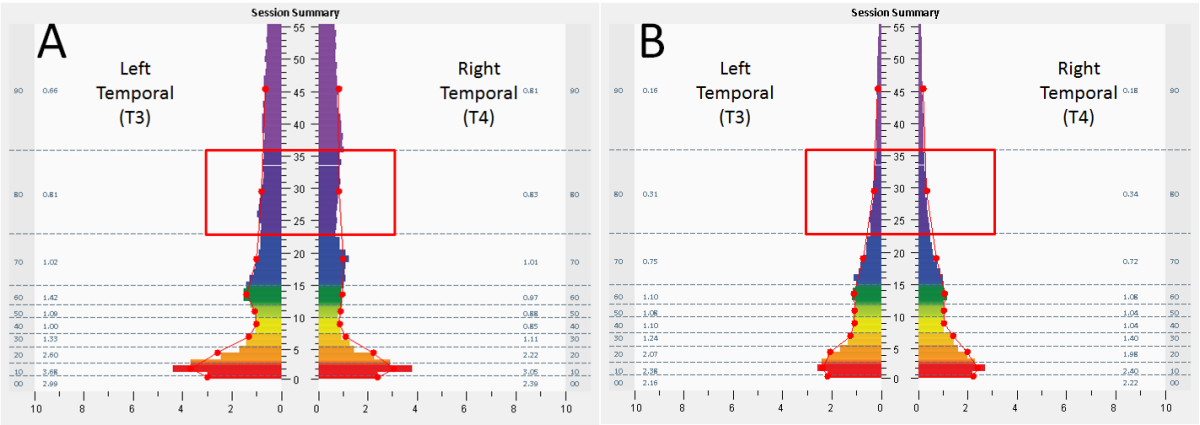


Figure 2 (A and B): Figure 2 (A and B): Example of observed changes in brain electrical pattern. FFT spectral display of electroencephalic data with frequency (Hz, central Y-axis) plotted against transformed amplitude (µv, X-axis). Data represents one minute of data from the T3/T4 montage with EC at the baseline assessment (4-A), and at the penultimate minute of the final session (4-B) for one participant, a 47 year old woman. Note the change of amplitudes in the 23-36 Hz range (dark purple color), outlined by red boxes.



Hypothesis:

The addition of acoustic stimulation linked to brain activity (HIRREM plus continued current care, HCC) will be associated with greater reduction in the frequency and severity of hot flashes experienced than that seen with continued current clinical care alone (CCC), among patients with perimenopausal and postmenopausal vasomotor symptoms.

Research Design and Method:

Objectives:

Primary Objective:

The primary objective of this pilot study is to evaluate whether the addition of acoustic stimulation linked to brain activity (HIRREM, HCC) to continued current clinical care, will reduce the frequency and severity of vasomotor symptoms, as compared with continued current clinical care (CCC) alone in patients with documented perimenopausal and postmenopausal vasomotor symptoms.

Secondary Objectives:

Evaluate whether the addition of HCC to continued current clinical care will result in greater differential changes in a variety of physiological, behavioral, and function outcome measures outlined below, as compared to CCC.

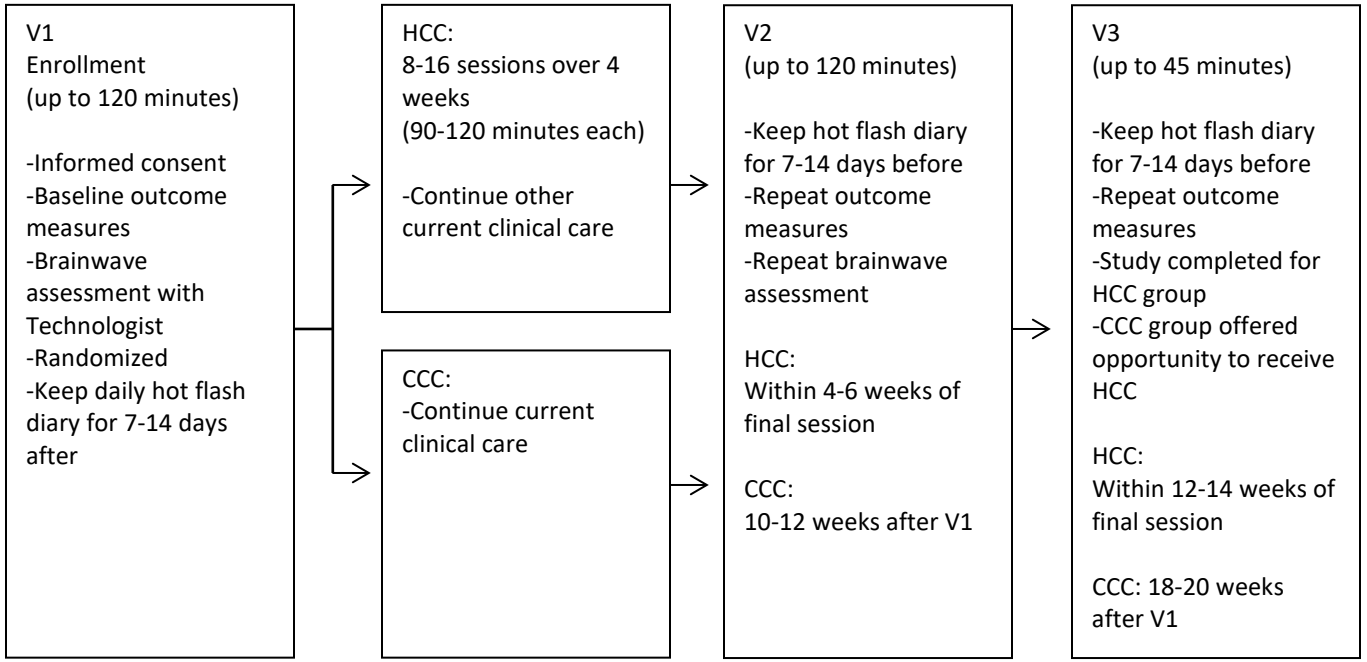
1. Autonomic nervous system functions, as manifested by heart rate, HRV, and BRS. We expect to see greater changes in autonomic activity and an improvement of sympatho-vagal balance in the HCC group. This would be reflected as changes in heart rate, and an increase of HRV and BRS parameters such as the standard deviation of the R-R interval (SDRR), rMSSD, HF alpha, and Sequence Up, Down, or All.
2. Reduction in menopause-related scales: Menopause Rating Scale (MRS) and Hot Flash Related Daily Interference Scale (HFRDIS). We anticipate to see greater improvement in these symptoms in the HCC group.
3. 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), 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.
4. Overall quality of life as evaluated using the QOLS. We hope 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.

Overview:

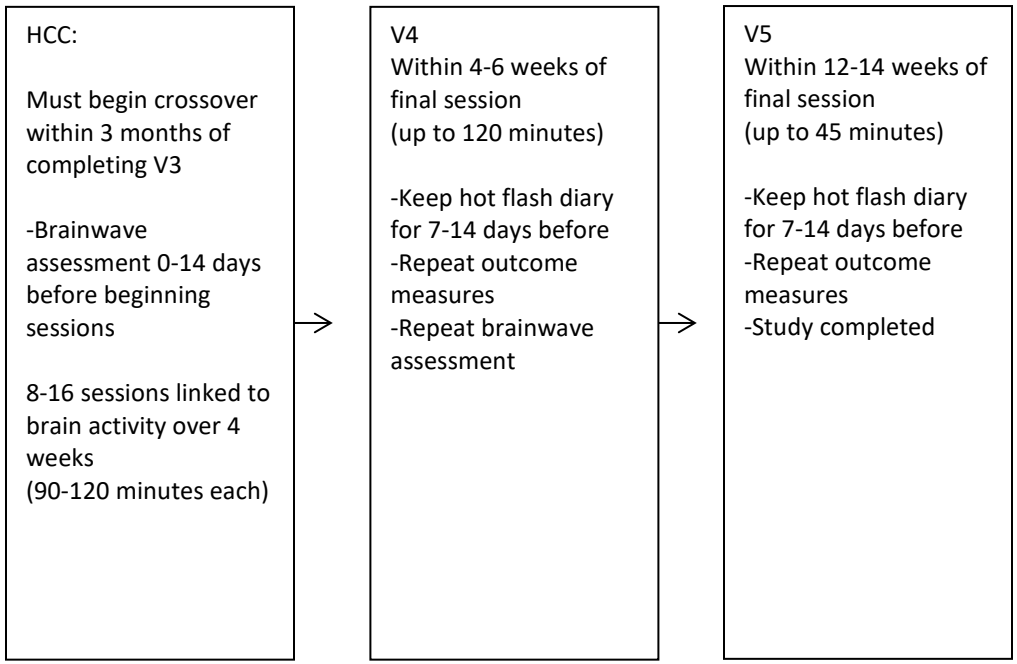
This will be a randomized, single site, pilot clinical trial. Assuming a potential drop-out rate of 20%, up to 48 subjects will be enrolled to achieve a goal of having at least 40 subjects (20 per group) complete the study, per protocol. Patients who have at least 5 hot flashes per day (with at least one being categorized as moderate to severe) will be eligible to participate.

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 a daily hot flash diary (to be completed for 7-14 days by both groups) and many secondary outcome measures including completion of the MRS, HFRDIS, 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, PSS), quality of life measure (QOLS), and function performance measures (drop stick reaction testing, and grip strength). All measures will be collected at an enrollment visit (V1). Both groups will then maintain a hot flash diary for 7-14 days, after which the intervention will begin for the HCC group. Post-intervention data collections will include an intermediate post-intervention visit (V2, primary outcome, 4-6 weeks after intervention completion for HCC, and 10-12 weeks after V1 for CCC), and a final follow up visit (V3, 12-14 weeks following completion of the intervention for HCC, and 18-20 weeks after V1 for CCC). Both groups will maintain a hot flash diary for 1-2 weeks prior to the V2 and V3 visits. The primary outcome will be reduction in frequency and severity of hot flashes score from V1 to V2. Following V3, those in the CCC group will be offered the opportunity to receive a course of HCC within 3 months (will have another brainwave assessment 0-14 days before beginning sessions), and will continue to be followed for data collections at 4-6 weeks (V4), and 12-14 weeks (V5) after completing their HIRREM sessions.

Hot Flash Study Flow Chart



CCC Group Who Complete V1-V3 and Choose to Receive a Course of HCC



Participants/Subjects:

Women ages 40 and older with self-reported perimenopausal and postmenopausal related vasomotor symptoms, who meet the following inclusion criteria and are interested to participate in the study will be recruited from the community by physician referral and advertisement. Each subject must be able to provide an informed consent. The criteria for inclusion will be those experiencing at least five hot flashes per day (with at least one being categorized as moderate to severe).

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, they will be scheduled for an enrollment visit (V1) at which time an informed consent will be completed. 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.

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, randomization will be completed, baseline study measures obtained, and all participants will be instructed how to maintain a hot flash daily diary.

Inclusion Criteria:

Women, age 40 or older, with perimenopausal and postmenopausal related vasomotor symptoms (intact uterus and ovaries), who have at least 5 hot flashes per day (with at least one being categorized as moderate to severe), with what is reported to be a stable pattern for at least one month.

Exclusion Criteria:

Less than 5 hot flashes per day
Does not experience at least 1 moderate to severe hot flash per day
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
Known seizure disorder
Known or potential pregnancy (females with last menstrual period less than one year from enrollment will be tested for pregnancy prior to randomization)
Severe hearing impairment (because the subject will be using headphones during the interventions)
Ongoing need for treatment with opiate, benzodiazepine, or anti-psychotic medications, anti-depressant medications such as SSRI, SNRI, or tricyclic, and sleep medications such as zolpidem or eszopiclone
Use of pharmaceuticals for treatment of vasomotor symptoms or any type of hormone replacement therapy

Use of supplements for improvement of vasomotor symptoms including but not limited to black cohosh, soy isoflavone extract, and red clover leaf extract
Menopausal symptoms resulting from, or associated with surgery, chemotherapy, radiation, or use of other chemicals or medications
Anticipated and ongoing use of recreational drugs, alcohol, or energy drinks
Ongoing need for treatment with thyroid medications
Weight is over the chair limit (285 pounds)
Are enrolled in another research study that includes an active intervention
Have previously received brainwave optimization (BWO), used a B2 or a 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 48 subjects to achieve a goal of having 40 subjects complete the study per protocol (estimated 20 per group).

Number of HCC 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 7-14 days later. Participants will receive 8 to 16 in-office intervention sessions over a maximum of 4 weeks. HCC sessions will be about 1.5-2 hours in length. All will receive a total of 6 sessions during the first three days of the intervention period. Following the initial 6 sessions, some sessions may be arranged as singles (one per day), if needed due to schedule issues. Participants will be encouraged to complete the remainder of the intervention sessions within two-three weeks, with a maximum of four weeks to complete the sessions. If done as two sessions per half day, subject involvement will thus require 4-8 half days during the intervention period.

At the primary post-intervention data collection visit, all measures will be repeated. This visit will occur at 4-6 weeks after completion of the intervention for the HCC group, and 10-12 weeks after V1 for the CCC group. A final data collection visit (V3) will occur 12-14 weeks after completion of the intervention for the HCC group, and 18-20 weeks after V1 for the CCC group, with repeat of the outcome measures, but no brainwave assessment. At V3, 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 within 3 months. Participants who cross over will have a brainwave assessment 0-14 days before starting sessions. Those who opt to do so will receive a course of in-office acoustic stimulation linked to brainwaves, as described for the HCC group, and will continue to be followed for data collections at 4-6 weeks (V4), and 12-14 weeks (V5), as done during the initial intervention period, after completing their HCC sessions.

Enrollment Visit:

Informed consent is obtained, notification of group assignment is made, and all baseline measures are collected, including a brainwave assessment. 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 get the complete all sessions within two to three weeks, and in no longer than 4 weeks, without going longer than 5 days between sessions. 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, participants will return for a post-intervention data collection visit (V2, primary outcome) between 4-6 weeks after completion of the intervention. This will occur at 10-12 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 (V3). The V3 visit will be between 18-20 weeks after V1 for those in the CCC group. All measures other than the 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 45 minutes.

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

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

Brainwave Assessment:

This is the first step in the HIRREM process. It occurs during the V1 enrollment visit, and will be performed on both groups. The assessment creates a map of frequencies and amplitudes, and informs the choice of protocols for the initial HIRREM sessions. Our pilot data also suggest that this information is also useful for correlating with autonomic function (HRV and BRS), and that changes can be observed in frequencies and amplitudes from pre- to post-HIRREM. For the assessment, with the participant in a sitting position, sensors are sequentially placed over six areas of the scalp to record one minute epochs of data while the brain is at rest, or on task, with eyes open and with eyes closed. For the assessment, measurements are taken at homologous regions of the bilateral hemispheres according to the 10-20 International System at F3/F4, C3/C4, P3/P4, T3/T4, FZ/OZ, O1/O2, FP1/FP2, and CB1/CB2 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. A seventh (FP1/FP2, given standardized tasks involving numerical digit recall), and eighth (CB1/CB2, relax with eyes open) location are also measured. 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 V2 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. For the sessions, with the subject comfortably at rest, sitting or reclining, the sensors are placed over the specific target areas on the scalp corresponding with brain regions/lobes to be observed. Brainwaves are monitored in real time, and the dominant frequency within a chosen target frequency band, e.g. delta (0.5-3 Hz) is identified. The dominant frequency is assigned an auditory tone which is played back to the subject via ear phones with as little as 4-8 millisecond second delay. Thus, the subject listens to the energetic "song" being played in the brain from moment to moment, providing the brain with rapid updating about its frequencies, amplitudes, and patterns via an electronic/acoustic mirror of itself.

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

Although 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 in-office 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, effects have been reported by participants in other studies. 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.

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 choose to receive HCC within 3 months, will also have an additional two post-interventions data collection visits.

Demographics:

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

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

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

HRV and BRS Data Processing and Interpretation:

Heart rate is measured as beat-to-beat intervals (RRI) recorded by pulse-wave recording, and will be analyzed using custom software developed by Matlab. Data can be loaded and viewed, and a subset of

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

Menopause -related symptoms:

Hot flash diaries provide a valid and reliable approach to understanding a participant's experience of hot flashes and night sweats (Sloan et al., 2001). An adapted hot flash daily diary that includes daytime and nighttime frequency and severity will be included. Categories are mild (1), moderate (2), severe (3), and very severe (4). Data will be used to calculate a hot flash severity score for each day as the sum number of hot flashes within each severity category multiplied by the severity score of that category, with the resulting sum divided by the total number of hot flashes. Participants will be asked to keep a 7-14 day daily hot flash diary after V1, and then 7-14 days before each subsequent data collection visit.

Hot Flash Related Daily Interference Scale (HFRDIS) is a 10 item measure to capture the daily impact of vasomotor symptoms in a variety of domains within the past week. These domains include work, social activities, leisure activities, sleep, mood, concentration, relation with others, sexuality, enjoyment of life, and overall quality of life. Items are scored from 1 (not at all) to 10 (extremely) (Carpenter, 2001).

The Menopause Rating Scale (MRS) is a survey that generates a score between 0 and 44 based on the individual's symptom severity rankings (Research, 2008). There are 11 symptoms listed related to perimenopause that are each assigned a score of 0 to 4 by the individual. A score of 0 indicates none, 1 is mild, 2 is moderate, 3 is severe, and 4 is very severe. After completion, the individual's score is tallied to create an overall score. Scores from 0-4 are considered zero to little, scores from 5-8 are considered mild, scores from 9-16 are moderate, and scores 17 or greater are considered severe.

Insomnia:

The severity of insomnia symptoms is measured using three self-report symptom inventories with each data collection visit (Appendix A). This includes the Insomnia Severity Index (ISI), the Pittsburgh Sleep Quality Index (PSQI), and the Epworth Sleepiness Score (ESS). The ISI is a 7 question measure, with responses from 0-4 for each question, yielding scores ranging from 0-28 (Bastien, Vallieres, & Morin, 2001; C.M. Morin, Belleville, Belanger, & Ivers, 2011; C. M. Morin et al., 2009). The PSQI is a 19 item inventory that assesses sleep quality over a 1-month time interval (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Items are weighted on a 0-3 interval scale. A global PSQI score is calculated by totaling the seven component scores, providing an overall score ranging from 0 to 21, where lower scores denote a healthier sleep quality. The ESS measures a person's general level of daytime sleepiness, or their average sleep propensity in daily life. The simple questionnaire is based on retrospective reports

of the likelihood of dozing off or falling asleep in a variety of different situations. Rated on a 4-point scale (0-3), it evaluates their usual chances of dozing off or falling asleep while engaged in eight different activities. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24 (Johns, 1991).

Behavioral and Psycho-physiological function:

Depression:

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

Anxiety:

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

Stress:

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

Quality of Life:

Quality of Life:

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

Alcohol Intake Screening:

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

Functional Measures:

Reaction Testing:

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

Grip Strength:

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

Statistical Analysis:

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

Participant Compensation:

Participants will receive up to $100 compensation for time, travel, and inconvenience related to study visits. Subjects who do not complete the entire study will receive a prorated portion of this amount ($25 per visit for completion of each of the three data collection visits, and $25 for completion of the daily hot flash diaries).

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 and first name will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a separate master log. The master log will be kept secure, on a separate, limited access user group on a shared network drive, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Brain State Technologies, LLC (BST) may assist with brain pattern analysis. To accomplish this, BST is to be provided with the first 8 characters from the randomly generated, 36 alpha numeric 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 necessary.

Appendices

A:
Hot Flash Daily Diary
Hot Flash Related Daily Interference Scale (HFRDIS)
Menopause Rating Scale (MRS)
Insomnia Severity Index (ISI)
Pittsburgh Sleep Quality Index (PSQI)
Epworth Sleepiness Score (ESS)
Center for Epidemiological Studies Depression Scale (CES-D)
Generalized Anxiety Disorder 7-Item (GAD-7)
Perceived Stress Scale (PSS)
Quality of Life Scale (QOLS)
AUDIT-C

B:
Handout for Study Participants

C:
Medical History/Screening Form

References:

Avis, N. E., Legault, C., Russell, G., Weaver, K., & Danhauer, S. C. (2014). Pilot study of integral yoga for menopausal hot flashes. *Menopause, 21*(8), 846-854. doi:10.1097/gme.0000000000000191

Bastien, C. H., Vallieres, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med, 2*(4), 297-307. doi:S1389945700000654 [pii]

Befus, D., Coeytaux, R. R., Goldstein, K. M., McDuffie, J. R., Shepherd-Banigan, M., Goode, A. P., . . . Williams, J. W., Jr. (2018). Management of Menopause Symptoms with Acupuncture: An Umbrella Systematic Review and Meta-Analysis. *J Altern Complement Med*. doi:10.1089/acm.2016.0408

Bradley, K. A., Bush, K. R., Epler, A. J., Dobie, D. J., Davis, T. M., Sporleder, J. L., . . . Kivlahan, D. R. (2003). Two brief alcohol-screening tests From the Alcohol Use Disorders Identification Test (AUDIT): validation in a female Veterans Affairs patient population. *Arch Intern Med, 163*(7), 821-829. doi:10.1001/archinte.163.7.821

Bradley, K. A., DeBenedetti, A. F., Volk, R. J., Williams, E. C., Frank, D., & Kivlahan, D. R. (2007). AUDIT-C as a brief screen for alcohol misuse in primary care. *Alcohol Clin Exp Res, 31*(7), 1208-1217. doi:10.1111/j.1530-0277.2007.00403.x

Burckhardt, C. S., & Anderson, K. L. (2003). The Quality of Life Scale (QOLS): Reliability, Validity, and Utilization. *Health and Quality of Life Outcomes, 1*, 60-60. doi:10.1186/1477-7525-1-60

Burckhardt, C. S., Woods, S. L., Schultz, A. A., & Ziebarth, D. M. (1989). Quality of life of adults with chronic illness: a psychometric study. *Res Nurs Health, 12*(6), 347-354.

Bush, K., Kivlahan, D. R., McDonell, M. B., Fihn, S. D., & Bradley, K. A. (1998). The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med, 158*(16), 1789-1795.

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res, 28*(2), 193-213.

Carpenter, J. S. (2001). The Hot Flash Related Daily Interference Scale: a tool for assessing the impact of hot flashes on quality of life following breast cancer. *J. Pain Symptom. Manage, 22*(6), 979-989. doi:S0885392401003530 [pii]

Charlson, M. E., Charlson, R. E., Peterson, J. C., Marinopoulos, S. S., Briggs, W. M., & Hollenberg, J. P. (2008). The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol, 61*(12), 1234-1240. doi:10.1016/j.jclinepi.2008.01.006

Chen, S., Sun, P., Wang, S., Lin, G., & Wang, T. (2016). Effects of heart rate variability biofeedback on cardiovascular responses and autonomic sympathovagal modulation following stressor tasks in prehypertensives. *J Hum Hypertens, 30*(2), 105-111. doi:10.1038/jhh.2015.27

Cheng, J., Edwards, L. J., Maldonado-Molina, M. M., Komro, K. A., & Muller, K. E. (2010). Real longitudinal data analysis for real people: building a good enough mixed model. *Stat Med, 29*(4), 504-520. doi:10.1002/sim.3775

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *J Health Soc Behav, 24*(4), 385-396.

Eckner, J. T., Kutcher, J. S., & Richardson, J. K. (2010). Pilot evaluation of a novel clinical test of reaction time in national collegiate athletic association division I football players. *J. Athl. Train, 45*(4), 327-332. doi:10.4085/1062-6050-45.4.327 [doi]

Fortunato, J. E., Tegeler, C. L., Gerdes, L., Lee, S. W., Pajewski, N. M., Franco, M. E., . . . Tegeler, C. H. (2016). Use of an allostatic neurotechnology by adolescents with postural orthostatic tachycardia syndrome (POTS) is associated with improvements in heart rate variability and changes in temporal lobe electrical activity. *Experimental Brain Research, 234*(3), 791-798. doi:10.1007/s00221-015-4499-y

Fortunato, J. E., Tegeler, C. L., Lee, S. W., N.M., P., Franco, M. F., Cook, J. F., & Tegeler, C. H. (2013). Case series using high-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM) for POTS. *Clinical Autonomic Research, 23*, 225-288. doi:10.1007/s10286-013-0211-0

Gerdes, L., Gerdes, P., Lee, S. W., & Tegeler, C. H. (2013). HIRREM: a noninvasive, allostatic methodology for relaxation and auto-calibration of neural oscillations. *Brain Behav, 3*(2), 193-205. doi:10.1002/brb3.116 [doi]

Guthrie, K. A., Larson, J. C., Ensrud, K. E., Anderson, G. L., Carpenter, J. S., Freeman, E. W., . . . McCurry, S. M. (2018). Effects of Pharmacologic and Nonpharmacologic Interventions on Insomnia Symptoms and Self-reported Sleep Quality in Women With Hot Flashes: A Pooled Analysis of Individual Participant Data From Four MsFLASH Trials. *Sleep, 41*(1). doi:10.1093/sleep/zsx190

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). *Circulation, 93*(5), 1043-1065.

Huang, A. J., Sawaya, G. F., Vittinghoff, E., Lin, F., & Grady, D. (2009). Hot flushes, coronary heart disease, and hormone therapy in postmenopausal women. *Menopause, 16*(4), 639-643. doi:10.1097/gme.0b013e31819c11e4

Innes, K. E., Selfe, T. K., & Vishnu, A. (2010). Mind-body therapies for menopausal symptoms: a systematic review. *Maturitas, 66*(2), 135-149. doi:S0378-5122(10)00043-5 [pii];10.1016/j.maturitas.2010.01.016 [doi]

Johns, M. W. (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep, 14*(6), 540-545.

Krueger, J. M., Huang, Y. H., Rector, D. M., & Buysse, D. J. (2013). Sleep: a synchrony of cell activity-driven small network states. *Eur J Neurosci, 38*(2), 2199-2209. doi:10.1111/ejn.12238

Lin, G., Xiang, Q., Fu, X., Wang, S., Wang, S., Chen, S., . . . Wang, T. (2012). Heart rate variability biofeedback decreases blood pressure in prehypertensive subjects by improving autonomic function and baroreflex. *J Altern Complement Med, 18*(2), 143-152. doi:10.1089/acm.2010.0607

Morin, C. M., Belleville, G., Belanger, L., & Ivers, H. (2011). The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep, 34*(5), 601-608.

Morin, C. M., Vallieres, A., Guay, B., Ivers, H., Savard, J., Merette, C., . . . Baillargeon, L. (2009). Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. *JAMA, 301*(19), 2005-2015. doi:10.1001/jama.2009.682

Offenbächer, M., Sauer, S., Kohls, N., Waltz, M., & Schoeps, P. (2012). Quality of life in patients with fibromyalgia: validation and psychometric properties of the German Quality of Life Scale (QOLS-G). *Rheumatology International, 32*(10), 3243-3252. doi:10.1007/s00296-011-2184-4

Radloff, L. S. (1977). The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement, 1*(3), 385-401. doi: 10.1177/014662167700100306

Report of the committee on methods of clinical examination in electroencephalography: 1957. (1958). *Electroencephalography and Clinical Neurophysiology, 10*(2), 370-375. doi:http://dx.doi.org/10.1016/0013-4694(58)90053-1

Research, B. C. f. E. a. H. (2008, 2008). MRS - the menopause rating scale. Retrieved from http://www.menopause-rating-scale.info/measure.htm

Roberts, H. C., Denison, H. J., Martin, H. J., Patel, H. P., Syddall, H., Cooper, C., & Sayer, A. A. (2011). A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing, 40*(4), 423-429. doi:afr051 [pii];10.1093/ageing/afr051 [doi]

Shaltout HA, T. C., Tegeler CH. (2016). Reduction of Blood Pressure and Improvement of Heart Rate Variability in Hypertensive Cohort Associated With Use of a Closed Loop Neurotechnology. P310.

Sloan, J. A., Loprinzi, C. L., Novotny, P. J., Barton, D. L., Lavasseur, B. I., & Windschitl, H. (2001). Methodologic lessons learned from hot flash studies. *J. Clin. Oncol, 19*(23), 4280-4290.

SmarrK.L. (2003). Measures of depression and depressive symptoms: The Beck Depression Inventory (BDI), Center for Epidemiological Studies-Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Primary Care Evaluation of Mental Disorders-Mood Module (PRIME-MD). *Arthritis Care & Research, 49*(S5), S134-S146. doi:10.1002/art.11410

Spitzer, R. L., Kroenke, K., Williams, J. B., & Lowe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch. Intern. Med, 166*(10), 1092-1097. doi:166/10/1092 [pii];10.1001/archinte.166.10.1092 [doi]

Stefanopoulou, E., & Grunfeld, E. A. (2017). Mind-body interventions for vasomotor symptoms in healthy menopausal women and breast cancer survivors. A systematic review. *J Psychosom Obstet Gynaecol, 38*(3), 210-225. doi:10.1080/0167482x.2016.1235147

Tegeler, C., Fortunato, J., Cook, J., Lee, S., Franco, M., & Tegeler, C. (2014). A Noninvasive neurotechnology, HIRREM, is associated with symptom reduction and improved cardiovascular autonomic measures in adolescents with POTS. *Neurology, 82*(10 supplement), P7.320.

Tegeler, C. H., Shaltout, H. A., Tegeler, C. L., Gerdes, L., & Lee, S. W. (2015). Rightward dominance in temporal high-frequency electrical asymmetry corresponds to higher resting heart rate and lower baroreflex sensitivity in a heterogeneous population. *Brain Behav, 5*(6). doi:10.1002/brb3.343

Tegeler, C. H., Tegeler, C. L., Cook, J. F., Lee, S. W., Gerdes, L., Shaltout, H. A., . . . Simpson, S. L. (2016). A Preliminary Study of the Effectiveness of an Allostatic, Closed-Loop, Acoustic Stimulation Neurotechnology in the Treatment of Athletes with Persisting Post-concussion Symptoms. *Sports Med Open, 2*(1), 39. doi:10.1186/s40798-016-0063-y

Tegeler, C. H., Tegeler, C. L., Cook, J. F., Lee, S. W., & Pajewski, N. M. (2015). Reduction in menopause-related symptoms associated with use of a noninvasive neurotechnology for autocalibration of neural oscillations. *Menopause-the Journal of the North American Menopause Society, 22*(6), 650-655. doi:10.1097/gme.0000000000000422

Tegeler, C. L., Gerdes, L., Shaltout, H. A., Cook, J. F., Simpson, S. L., Lee, S. W., & Tegeler, C. H. (2017). Successful use of closed-loop allostatic neurotechnology for post-traumatic stress symptoms in military personnel: self-reported and autonomic improvements. *Military Medical Research, 4*(1), 38. doi:10.1186/s40779-017-0147-0

Wang, S. Z., Li, S., Xu, X. Y., Lin, G. P., Shao, L., Zhao, Y., & Wang, T. H. (2010). Effect of slow abdominal breathing combined with biofeedback on blood pressure and heart rate variability in prehypertension. *J Altern Complement Med, 16*(10), 1039-1045. doi:10.1089/acm.2009.0577

Xu, X. Y., Gao, J., Ling, D., & Wang, T. H. (2007). Biofeedback treatment of prehypertension: analyses of efficacy, heart rate variability and EEG approximate entropy. *J Hum Hypertens, 21*(12), 973-975. doi:10.1038/sj.jhh.1002237