Cereset Research to Reduce Stress in Healthcare Workers in the Time of COVID-19

Brief Title: Cereset Research In Healthcare Workers During COVID-19

08/02/2022

NCT04682197

Title:

Cereset Research to Reduce Stress in Healthcare Workers in the Time of COVID-19

Principal Investigator:

Charles H. Tegeler, MD[1]
Department of Neurology
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157-1078
E-mail: ctegeler@wakehealth.edu
Phone: 336-716-7651
Fax: 336-716-5813

Funding: The Susanne Marcus Collins Foundation, Inc.

Key Words: stress, anxiety, COVID-19, Coronavirus, neurotechnology, autonomic dysregulation, acoustic stimulation, neuromodulation, hyperarousal, brain electrical activity, wellbeing, allostasis, HIRREM, Cereset Research

Abstract:

This study will enroll up to 166 healthcare workers, age 18 or older, who have symptoms of stress with a goal of 138 to complete the intervention. Participants will be randomly assigned to either an Early Intervention (EI) group which will receive 4 CR sessions of audible tones echoing current brainwave activity, following enrollment, or a Delayed Intervention (DI) group which will continue current care only and will serve as a control group. Participants in both groups will continue their other current care throughout the study.

The primary outcome will be change in stress as measured by the Perceived Stress Scale (PSS). Secondary outcomes to be collected include symptom inventories for insomnia (Insomnia Severity Index, ISI) and anxiety (Generalized Anxiety Disorder-7, GAD-7). Exploratory measure include depression (Center for Epidemiological Studies- Depression Scale, CES-D), traumatic stress (PTSD Checklist for civilians, PCL-C), overall quality of life (QOLS), social support (ISEL-12), the Multiple Ability Self-Report Questionnaire (MASQ) for cognitive function, Fatigue Severity Scale (FSS) for fatigue, and mental health (Depression, Anxiety, and Stress Scale, DASS-21). Details about COVID-19 status, interaction, workplace engagement, healthcare utilization, and exposure will be collected. Pre- and post-intervention data collection of physiological parameters (Heart rate, HR, and measures of autonomic cardiovascular regulation assessed by heart rate variability) will also be assessed as exploratory outcomes.

Symptom questionnaires will be collected at an enrollment visit (V1), and participants will be randomly assigned to the EI or DI groups. For those in the EI group, the intervention will begin 0-7 days thereafter. Sessions will be administered over 10 business days. Follow-up data collections will be obtained at 2 weeks following enrollment (V2) [0-14 days after completion of the intervention for the early intervention group], and 4-7 weeks after the V2 (V3, primary outcome). Following V3, those in the DI group will be offered the opportunity to cross over to receive 4 CR intervention sessions and will continue to be followed for data collections at 0-14 days (V4) after completing their sessions, and 4-7 weeks (V5) after V4. Mean contrasts will be used to compare the changes in measures of perceived stress (PSS) from V1 to V3, the primary outcome, in the early vs. delayed intervention groups. Similar analysis will occur for secondary outcomes.

Background, Rationale, and Context:

Background:

Abnormal electroencephalographic (EEG) asymmetries have been reported in a variety of neurological, cardiovascular, and psychophysiological conditions including insomnia, attention deficit hyperactivity disorder (ADHD), anxiety, autism spectrum disorders, depression, dyslexia, post-traumatic stress disorder (PTSD), and traumatic brain injury (TBI) (Avram, Baltes, Miclea, & Miu, 2010; T. S. Hale et al., 2010; Hale et al., 2009; T.S. Hale et al., 2010; Kemp et al., 2010; Lazarev, Pontes, Mitrofanov, & deAzevedo, 2010; Marzano, Ferrara, Sforza, & De, 2008; Metzger et al., 2004; Moscovitch et al., 2011; Rabe, Beauducel, Zollner, Maercker, & Karl, 2006; Riemann et al., 2010; Spironelli, Penolazzi, & Angrilli, 2008; Stroganova et al., 2007; Thibodeau, Jorgensen, & Kim, 2006; Wolynczyk-Gmaj & Szelenberger, 2011). 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 (Beckham et al., 2003; H. Cohen et al., 2000; Katz-Leurer, Rotem, Keren, & Meyer, 2010; Spiegelhalder et al., 2011; Tobaldini et al., 2013).

Autonomic regulation of the cardiovascular system can be evaluated by measuring heart rate variability (HRV) or baroreflex sensitivity (BRS). HRV can indicate the physiological capacity to produce dynamically varied responses to the changing needs of an environment. Prospective studies show that decreased HRV is a risk factor for incident cardiovascular disease (Tsuji et al., 1996) and all-cause mortality (Dekker et al., 1997). In addition, depressed HRV is often reported across behavioral disorders (Beauchaine & Thayer, 2015), including military personnel and veterans with diagnosed PTSD (E. A. Lee et al., 2013; Minassian et al., 2014; J. Park et al., 2017; J. E. Park et al., 2017; Shah et al., 2013), and as a pre-deployment predictor of new post-deployment PTSD diagnoses or symptom severity (Minassian et al., 2015; Pyne et al., 2016). In adults, low HRV is also a risk factor for adverse cardiovascular outcomes (Kleiger, Miller, Bigger, & Moss, 1987; Tsuji et al., 1996), new onset of diabetes (Carnethon, Golden, Folsom, Haskell, & Liao, 2003), progression of chronic kidney disease (Chandra et al., 2012), and all-cause mortality (Dekker et al., 1997). Due to the pervasiveness of diminished HRV in behavioral health disorders, it has also been suggested as a trans-diagnostic biomarker for psychopathology (Beauchaine & Thayer, 2015). As a measure that can be obtained easily and noninvasively, HRV warrants consideration as a target for observation and intervention on a public health basis (Marsac, 2013). HRV may also inform and support the development and dissemination of advanced practices which are beneficial for physical and mental health, or adaptive neurovisceral integration (Thayer, Hansen, Saus-Rose, & Johnsen, 2009).

A wide variety of behavioral, physical exercise, and pharmacological therapies have been shown to increase HRV (Nolan, Jong, Barry-Bianchi, Tanaka, & Floras, 2008). Especially for interventions that entail relatively non-specific features, the effects likely depend on the capacity to influence both central and peripheral nervous system pathways. An important question is whether focused engagement of critical central structures, especially those known to have specific roles for autonomic management, may be a way to produce more efficient or impactful effects on HRV.

The bihemispheric model for autonomic management of traumatic stress (Lee SW., 2014) begins with recognition that the right and left hemispheres are primarily responsible for cortical management of the sympathetic and parasympathetic divisions, respectively. The BHAM suggests that temporal lobe electrical asymmetry may be an indication of traumatic stress exposure, associated with health effects including reduced HRV. It also suggests that interventions to reduce asymmetrical activity may be a way to de-rigidify what have become stuck stress response patterns to facilitate a state of enhanced autonomic flexibility and dynamic range, including increased HRV. Closed-loop therapies with real time monitoring for modulation of biological function offer a precision-guided, patient-centric strategy for brain-based therapies (Bellesi, Riedner, Garcia-Molina, Cirelli, & Tononi, 2014). Healthcare workers experience constant stress, exacerbated during the COVID-19 pandemic, work long hours, and are more vulnerable to developing rigidified stress responses. This study is important because it offers a nondrug, noninvasive alternative to medications to help healthcare workers mitigate, and manage stress and develop resilience.

HIRREM:

High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM®), developed by Brain State Technologies (BST), LLC, Scottsdale, AZ, is a commercially available, noninvasive, closed-loop, allostatic, acoustic stimulation neurotechnology to facilitate client-unique relaxation and auto-calibration of cortical neural oscillations by echoing auditory tones in near real time (Gerdes, Gerdes, Lee, & Tegeler, 2013). HIRREM is intended to support more adaptive forms of symmetry at the temporal lobes and other cortical regions. HIRREM is aligned with the BHAM as well as the broader physiological paradigm of allostasis (stability through change), which recognizes the brain as the organ of the central command (Sterling, 2012). As a closed-loop neurotechnology (i.e., an intervention whose inputs are objectively measured real-time neurological data), HIRREM does not depend on conscious, cognitive activity, volitional self-regulation, or behavioral monitoring.

Relevant Pilot Data:

Since 2011, the HIRREM Research Program at WFSM has enrolled over 600 participants in eight IRB-approved clinical studies to evaluate the effects and potential benefits of HIRREM. Participants in these studies have received a total of over 6,000 HIRREM sessions. Use of HIRREM has been associated with reduced sleep symptomatology and reduced high frequency amplitudes in adults with insomnia (C. H. Tegeler et al., 2012), reduced menopausal symptoms in women (C. H. Tegeler, Tegeler, Cook, Lee, & Pajewski, 2015), improved sleep in athletes with persisting post-concussion symptoms (C. H. Tegeler et al., 2016), and reduced temporal lobe high frequency asymmetry and symptoms in self-reported post-traumatic stress (C. H. Tegeler et al., 2017), and reduced symptoms of military-related traumatic stress (Catherine L. Tegeler et al., 2017). For the latter military cohort, maximal reduction in symptom scores was observed at one month following completion of the intervention. Improved autonomic cardiovascular regulation has also been observed in those receiving HIRREM, including a cohort of adolescents with Postural Orthostatic Tachycardia Syndrome (Fortunato et al., 2016). 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). There was improved network connectivity on whole brain rest MRI was observed in participants with military-related traumatic stress (S. W. Lee et al., 2018).

Notably, a placebo controlled efficacy trial of in-office HIRREM for moderate to severe insomnia demonstrated a clinically meaningful reduction of insomnia symptoms (≥ 6 point reduction on the ISI), and statistically significant additional benefit associated with use of HIRREM at two months post-intervention, as compared to a sham placebo of random audible tones not linked to brainwaves (C. L. Tegeler et al., 2017). HIRREM was well tolerated, and the benefit was durable through the final post-intervention data collection (4 months). The symptom-related primary outcomes from this large, controlled trial are highlighted in Figure 1 below.

Continuous recording (10 minutes) of blood pressure and heart rate also allowed for analysis of autonomic cardiovascular regulation, including multiple measures of HRV and BRS. This physiological data was obtained at all study visits. Analysis also demonstrated significant improvement in multiple

objective measures of autonomic cardiovascular regulation including increased BRS (HFα, and Sequence ALL) and HRV (SDNN, and rMSSD), associated with this short term use of in-office HIRREM, compared to the placebo intervention of random audible tones not linked to brainwaves (Figure 2). The benefit was seen at all follow up data collections, and was durable through the final follow up visit at 4 months post-intervention (Shaltout, Tegeler, Lee, & Tegeler, 2017). There was no significant improvement in autonomic function observed in the placebo group at any time point. It is not clear whether these results reflect a cause, an effect, or both, relative to the observed improvement of insomnia symptoms.

Figure 1:

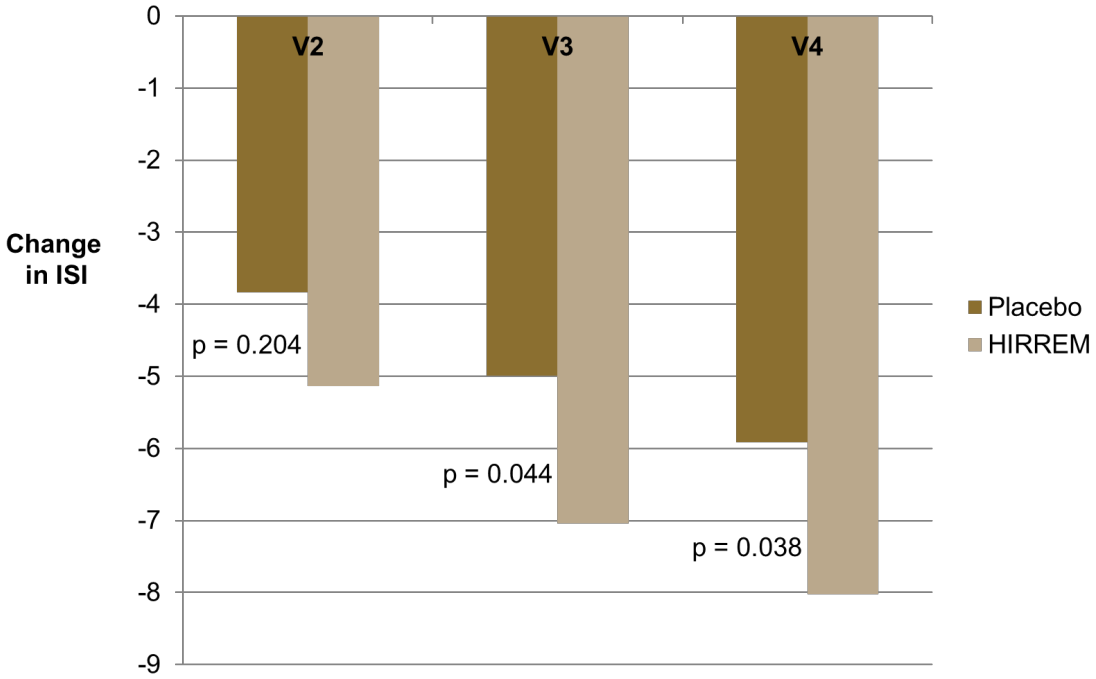
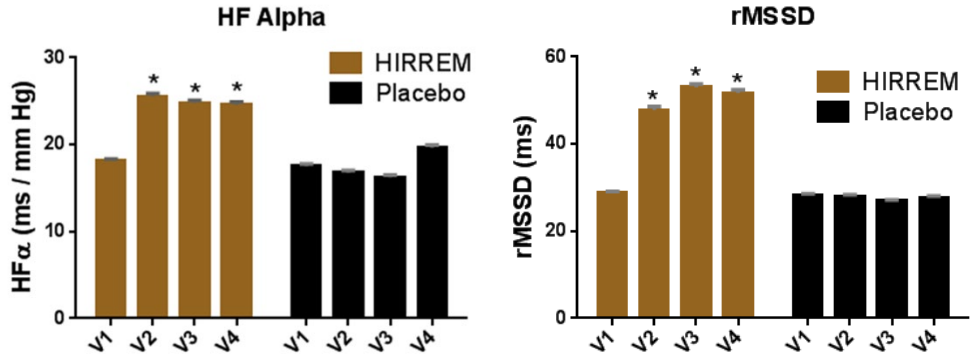


Figure 2:



New Developments:

In spite of the many benefits demonstrated in the above-mentioned studies, and highlighted by the placebo-controlled trial for insomnia, the in-office HIRREM approach used for research since 2011 remains very operator dependent. This, and the time required for sessions (typically 10-20 sessions of 90-120 minutes each), limit the scalability of the intervention. To reduce the length of sessions, and reduce operator dependence, while increasing scalability, an updated version of hardware, and software, with fewer sessions has been developed by BST, to be used with more standardized protocols and fewer sessions. The upgraded platform for medical research using this technology has been rebranded as Cereset Research™ (CR). Cereset is short for "cerebral reset." Cereset is currently offered commercially as a technique for relaxation, well-being, and stress management. As a low risk general wellness device, Cereset is exempt from FDA regulation (personal communication, Brain State Technologies/Cereset)

CR is based on the same core technology and algorithms for noninvasively identifying, and rapidly echoing brainwaves back as audible tones in a closed-loop paradigm, embodied in HIRREM. The CR system includes the use of 64-bit processing architecture for faster feedback, the use of 4 sensors, and the use of standard protocols (while retaining flexibility with length and sequencing of the standard protocols), all done with eyes closed. Four sensors are placed on the scalp at a time. However, only one pair of sensors are actively echoing feedback. The software automatically switches from one pair to the other between protocols. This reduces the number of sensor placement changes needed during a session by half, resulting in shorter session time and fewer interruptions. Although benefit was seen with in-office HIRREM, and CR uses the same core technology, the benefits of this new approach using fewer sessions and more standardized protocols requires confirmation. This version of the technology is now limited to 4 paired sensor placement locations: F3/F4 and P3/P4, FP1/FP2 and T3/T4, C3/C4 and O1/O2, and AFZ/POZ and CB1/CB2.

As of May 2021, 103 participants have enrolled in an exploratory study using CR for stress, anxiety, or insomnia, and preliminary results show significant improvement in symptom inventories including perceived stress, as with legacy HIRREM. This study will evaluate the effects of a greatly reduced dose of CR in healthcare workers with symptoms of stress during the time of COVID-19. The primary goal is to explore for change in the Perceived Stress Scale (PSS). The secondary focus is to evaluate the effect of CR on anxiety and insomnia and to explore its potential effect on other self-reported symptoms and autonomic cardiovascular regulation.

Based on the electrical pattern being observed in real time and being informed by prior research and clinical experience, the CR Smart Protocol computer software also chooses what design is needed – balance, coherence, or harmony – to best support the location being observed to relax itself at that moment. This includes use of one-sided or two-sided relaxation depending on what is needed in each 30 second to 1-minute time interval, and reduces variability and operator dependence of application. Within these placement options, the Technologist may still adjust the sequencing of protocols and the number of minutes at each location after reviewing session data. CR incorporates the use of fewer sessions, compared to prior studies with HIRREM. The new protocols for CR are expected to provide a robust majority of the benefits that have been reported to date with HIRREM, but this requires confirmation in research studies. The increased standardization of the process, with reduced variability

of application and operator dependence, along with fewer sessions, will strengthen the scalability of the refined intervention.

Participants in our Cereset exploratory study had an average of 8.6 (SD 1.4) CR intervention sessions over 13.7 (SD5.2) calendar days. They were on site for 7.9 (SD 1.8) seat days. There was a range of 4 to 7 protocols run during session and session lasted from 40 to 64 minutes.

Table 1. Preliminary Data: Cereset Outcomes from Exploratory Open-label Study

Insomnia Severity Index (ISI)

	V1	V2	V3	V4
Count	103	98	89	79
Mean (SD)	12.9 (5.5)	8.8 (5.2) ***	7.1 (5.7) ***	7.0 (5.1) ***

Center for Epidemiological Studies- Depression Scale (CES-D)

	V1	V2	V3	V4
Count	103	99	89	80
Mean (SD)	19.6 (11.1)	12.9 (8.4) ***	11.4 (8.6) ***	11.5 (9.1) ***

Generalized Anxiety Disorder-7 (GAD-7)

	V1	V2	V3	V4
Count	103	99	89	80
Mean (SD)	9.1 (5.3)	5.2 (4.4) ***	4.4 (4.0) ***	4.1 (3.7) ***

Perceived Stress Scale (PSS)

	V1	V2	V3	V4
Count	103	99	89	79
Mean (SD)	19.8 (6.3)	16.8 (5.9) ***	14.7 (6.6) ***	15.1 (6.2)***

Quality of Life Scale (QOLS)

	V1	V2	V3	V4
Count	103	99	89	78
Mean (SD)	80.3 (12.9)	84.0 (11.9) ***	85.9 (13.1) ***	85.6 (13.6) ***

PTSD Checklist for Civilians (PCL-C)

	V1	V2	V3	V4
Count	103	99	88	77
Mean (SD)	39.3 (11.5)	31.7 (8.7) ***	28.5 (9.1) ***	27.8 (8.7) ***

* = P < 0.05
** = P < 0.01
*** = P < 0.001

Note: The mean (SD) duration from last session to V2 was 3.9 (6.0) days, from last session to V3 was 42.7 (8.6) days, last session to V4 was 83.4 (12.4) days for the table above.

Cohorts within this exploratory study are published for pain and caregivers. (C. Tegeler et al., 2021a, 2021b)

This pilot study will evaluate the effects of using this more standardized, approach, and fewer sessions with CR, in participants with self-reported symptoms of stress.

Importance:

This randomized, waitlist-controlled study will evaluate the effects of the use of CR intervention in healthcare workers with symptoms of stress during the period of COVID-19. Healthcare workers of all types have been impacted personally, professionally, and financially by the pandemic, resulting in higher levels of stress and anxiety. Additional, brief, noninvasive, non-drug strategies are needed to help mitigate the effects of the acute trauma associated with the pandemic. The primary outcome will be change in Perceived Stress Scale (PSS) a measurement of how different situations affect feelings and perceived stress, in the early intervention group compared to delayed intervention control. Data will also be collected on a variety of additional relevant symptoms including insomnia, anxiety and autonomic cardiovascular regulation, for which benefits have been shown in prior studies using HIRREM. Data collected will assess the effects of a low dose CR approach (only 4 sessions) to help participants begin to mitigate stress. A successful outcome of reduced stress would suggest benefit for this more scalable, generalizable approach to the use of the CR technology. The effect of this minimalist approach on autonomic function and other self-reported symptoms will also be explored. This information will be useful for planning larger randomized trials in more homogeneous cohorts and evaluating the appropriateness of direct clinical implementation of the intervention. The proposed study might also help to identify characteristics of individuals who may experience differential effects/benefits from this low dose application of CR.

Healthcare Worker Burden:

Data from the Wake Forest Baptist Health's 2020 Personal Health Survey shows that WFBH has a great need for cost-effective therapies to help address emotional health including sleep trouble, stress, and depression. Despite a smaller sample size due to COVID-19, the projected cost in medical claims and lost productivity for key emotional health outcomes are seen in Table 2. This small cross-sectional analysis of WFBH shows over $6 Million dollars of healthcare costs. If these results are generalizable across the enterprise, costs will be even greater (Source: Aggregate Health Analysis, WFBH Employees, BestHealth For Us 2020, 6/25/2020).

Table 2. Key Emotional Health Outcomes from 2020 Personal Health Survey

Outcome Measure	Typical US %	WFBH %	# Within Guidelines	# At Risk	Projected Costs in Claims and Productivity
Depression Distribution	5.4%	11%	1271	162	$3,342,682

Sleep Distribution	10%	41%	852	581	$2,277,520
Stress Distribution	40%	19%	1154	279	$414,315

COVID-19:

COVID-19 quickly became a world pandemic. Researchers are trying to quantify downstream health effects of the associated acute trauma and chronic stress. Studies demonstrate that the circumstances surrounding COVID-19 have increased symptoms of stress, anxiety, depression, and insomnia in the general public (Qiu et al., 2020; Rajkumar, 2020; Wang et al., 2020; Y. Zhang & Ma, 2020). Other literature notes that people across the world have more fear, anger, and feelings of loneliness (Shuja, Aqeel, Jaffar, & Ahmed, 2020). Some studies suggest that women are more vulnerable to developing psychological distress and higher levels of posttraumatic stress symptoms (PTSS) in general (N. Liu et al., 2020; Qiu et al., 2020).

Quarantine periods over 10 days are associated with increased risk for PTSS (Brooks et al., 2020). Across the world, many cities have faced multi-week lockdowns for public safety. In addition to being stuck at home, constant bombardment of news and social media have also shown to increase the odds of self-reporting anxiety (Gao et al., 2020). Many healthcare workers and the general public are facing new challenges each day.

Within the healthcare field, studies have shown that healthcare workers have a higher prevalence of anxiety, depression, somatization, and insomnia to nonmedical health workers (Liang, Chen, Zheng, & Liu, 2020; McAlonan et al., 2007; K. Zhang, Zhou, Liu, & Hashimoto, 2020; Y. Zhang & Ma, 2020). Without new interventions or solutions to mitigate increased arousal, healthcare workers are at a higher risk of developing long-lasting health impacts of stress related to COVID-19. One study highlighted that more than half of healthcare professionals reported depressive symptoms, 44.7% reported anxiety, and 36.1% sleep disturbance (S. Liu et al., 2020). Frontline workers also show more severe degrees of mental health symptoms than other healthcare workers (Lai et al., 2020).

Sleep and social support are hypothesized to help mitigate the effects of stress on the body and decrease PTSS symptoms, specifically levels of anxiety, stress, and self-efficacy (N. Liu et al., 2020; Xiao, Zhang, Kong, Li, & Yang, 2020)).

This study will focus on a heterogeneous group of healthcare workers including physicians, nurses, support staff (PA, NP, respiratory therapists, diagnostic personnel, etc.), mental health professionals, administration, and medical center staff.

Objectives:

The primary objective of this study is to evaluate the effect of CR to improve the Perceived Stress Scale (PSS) in healthcare workers with symptoms of stress, compared to waitlist control, at 4-6 weeks post intervention.

The secondary objective is to evaluate the effect of CR on self-reported symptom inventories of insomnia and anxiety. We will also evaluate exploratory measures for mood, post-traumatic stress, quality of life, social support, cognitive function, and autonomic cardiovascular regulation (heart rate variability, HRV).

Methods and Measures:

Design:

This will be a single site, open label, randomized, wait-list controlled, pilot clinical trial.

Setting:

Study visits and sessions will be conducted in Suite 504, Department of Neurology, Piedmont Plaza II.

Subjects Selection Criteria

Participants/Subjects:

Healthcare workers aged 18 and older with symptoms of stress, who also meet the inclusion criteria outlined below, and are interested in receiving CR, will be offered enrollment. The participant must be able to provide informed consent.

Interested individuals, for whom no exclusions are identified, based on initial phone or email communications, will receive an email with details of the study, a link to a short video outlining the study, and a link to complete an online eligibility screening form. Once the screening form is completed, it is reviewed by the study team. If potential participants have no clear exclusions, the Study Coordinator will contact them to answer any questions.

Those who respond positively to the question about risk for suicide within the last 3 months will be ineligible for enrollment and provided with a behavioral health resources list. For individuals who are eligible, they will be sent a welcome email, which includes information about the study, a schedule of study visits, a "Process and Study Details" document and a copy of the current informed consent document for their review. This study will not actively seek to enroll pregnant women. However, because no adverse effects have been observed in the small number of pregnant women that have enrolled in prior studies, if they are otherwise deemed eligible based on the presence of an appropriate condition or symptom; they will not be excluded due to the pregnancy.

Inclusion Criteria:

- Employed healthcare workers aged 18 years and older.
- Ability to comply with basic instructions and be able to sit still, comfortably during sessions.
- Experiencing symptoms of stress meeting threshold score on the Perceived Stress Scale (PSS ≥ 14).

Exclusion Criteria:

- Unable, unwilling, or incompetent to provide informed consent/assent.
- Physically unable to come to the study visits, or to sit still, comfortably in a chair for up to 1 hour.
- Severe hearing impairment (because the subject will be using ear buds during CR).
- Weight is over the chair limit (400 pounds).
- Currently enrolled in another active intervention research study.
- Prior use of: HIRREM, HIRREM-SOP, Brainwave Optimization (BWO), Cereset, Cereset Home, or a wearable configuration of the same (B2, or B2v2).
- Prior use of the following modalities within one month before enrollment: electroconvulsive therapy (ECT), prior use of transcranial magnetic stimulation (TMS), transcranial direct current stimulation (TDCS), alpha stimulation, eye movement desensitization and reprocessing (EMDR), brain spotting, neurofeedback, biofeedback, or deep brain stimulation (DBS).
- Known seizure disorder.
- Thoughts of active suicide within the last 3 months.
- Current, significant symptoms of long-COVID.
- Current medical student.

Participants will be asked to report use of alcohol, recreational drugs, CBD products, chiropractic, cranial-sacral therapy, and bio-energy work during the intervention, and until V3 and then for the crossover group at V4 and V5.

Sample Size:

Up to 166 participants might be enrolled to get the target sample of 138 to complete intervention. With this target sample size, the study will have 80% power with alpha of 0.05 to detect a clinically meaningful change in the perceived stress scale of 3 points, assuming PSS standard deviation similar to our Cereset Research exploratory study preliminary data (SD 5.62 for difference in PSS from V1 to V3). The clinically meaningful change of 3 points on the PSS was selected based on literature regarding clinically meaningful change in this scale, clinical experience of the investigators, and because this magnitude of change, if detected, would be clinically significant enough to warrant clinical implementation as the immediate next step. The selected target difference in the primary outcome is slightly higher than a minimally important difference of 2.19 to 2.66 points(Drachev et al., 2020), but it is greater than an established clinically relevant difference of 4 points demonstrated in a clinical sample(Plantinga, Lim, Bowling, & Drenkard, 2017). In addition to evaluating the primary question about whether the intervention results in a 3 point improvement in PSS scores at 4-7 weeks post intervention compared to waitlist controls, the study will also explore for potential targets for future research, including those taking selected medications, and those with comorbid conditions or symptoms of interest.

Intervention and Interactions:

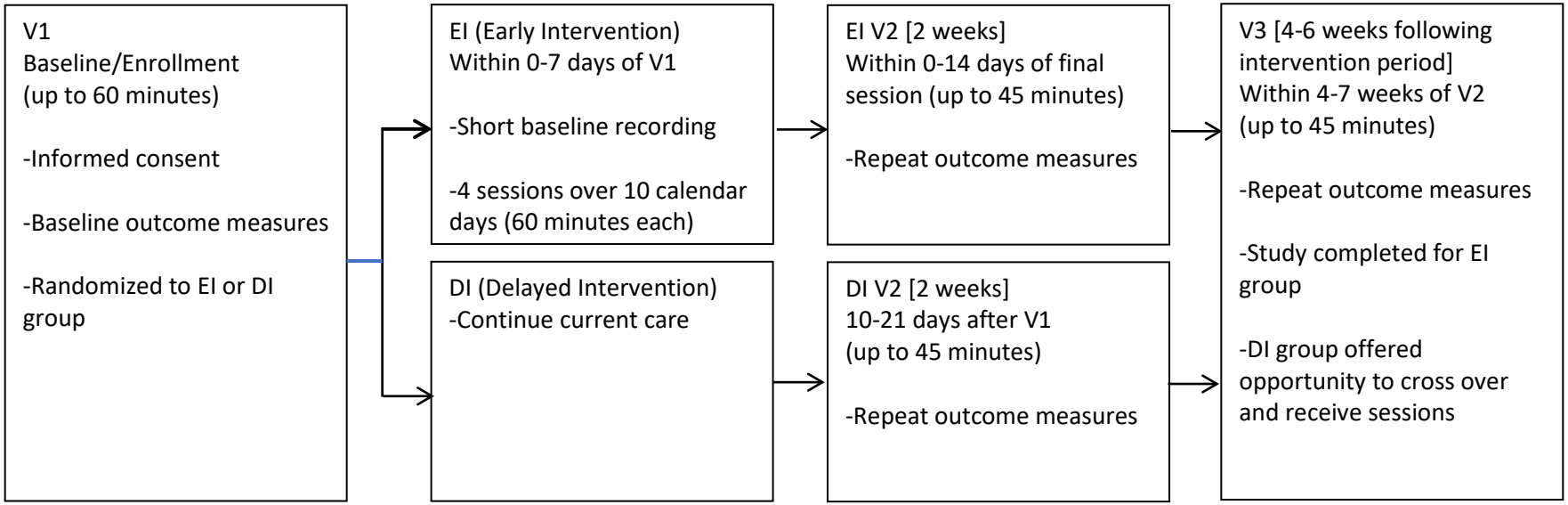
Participants will be randomly assigned to either an Early Intervention (EI) group which will receive 4 CR sessions of audible tones echoing current brainwave activity following enrollment, or a Delayed

Intervention (DI) group which will continue current care only and will serve as a control group through the V3 follow-up visit. Participants in both groups will continue their other current care throughout the study.

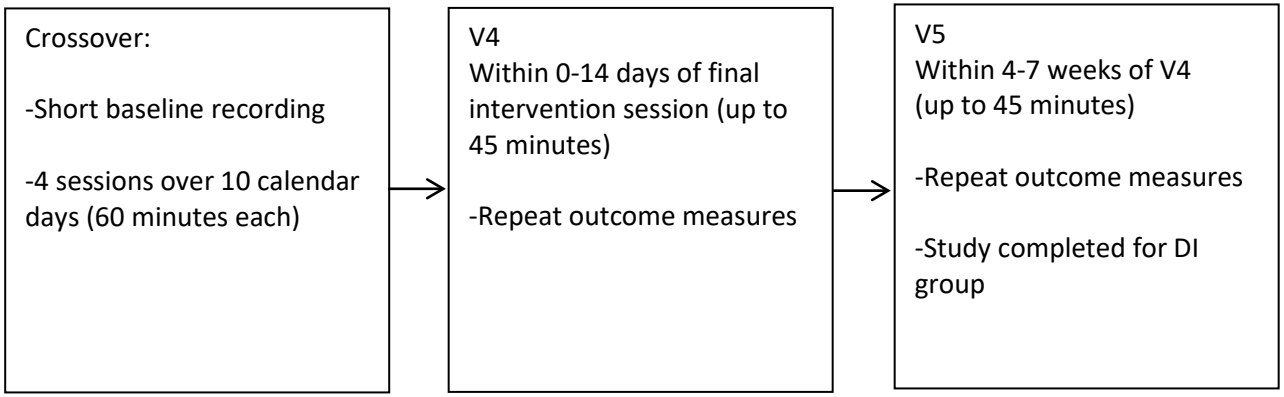
Schedule of Activities

		Intervention (4 Sessions over 10 calendar days)				Post Intervention Data Collection		Crossover Intervention (4 sessions over 10 calendar days)				Crossover Post Intervention Data Collection (DI group oly)	
Event	Enrollment (V1) Baseline Data Collection	Baseline Recording and Session 1 (E1) *{Within 0-7 days of V1}*	Session 2 (E2)	Session 3 (E3)	Session 4 (E4)	Post Intevention (V2) Data Collection *{Within 0-14 days of E4/10-21 days post enrollment}*	Post Intervention (V3) Data Collection *{Within 4-7 weeks of V2}*	Crossover Baseline Recording and Session 1 (D1) {Within 3 months of V3}	Crossover Session 2 (D2)	Crossover Session 3 (D3)	Crossover Session 4 (D4)	Post Intervention (V4) Data Collection *{Within 0-14 days of final D4 Intervention}*	Post Intervention (V5) Data Collection *{Within 4-7 weeks of (V4) data collection}*
Informed consent	X												
Demographics	X												
Perceived Stress Scale (PSS) - Standard	X						X						X
Perceived Stress Scale (PSS) - Since last data collection						X						X	
Insomnia Severity Index (ISI) - Standard	X						X						X
Insomnia Severity Index (ISI) - Since Since last data collection						X						X	
Center for Epidemiological Studies Depression Scale (CES-D)	X					X	X					X	X
Generalized Anxiety Disorder 7-Item (GAD-7) - Standard	X						X						X
Generalized Anxiety Disorder 7-Item (GAD-7) - Since last data collection						X						X	
PTSD Checklist for Civilians (PCL-C) - Standard	X						X						X
PTSD Checklist for Civilians (PCL-C) - Since Since last data collection						X						X	
Fatigue Severity Scale (FSS)	X					X	X					X	X
Quality of Life Scale (QOLS)	X					X	X					X	X
Interpersonal Support Evaluation List (ISEL-12)	X					X	X					X	X
Multiple Ability Self-Report Questionnaire (MASQ)	X					X	X					X	X
Depression, Anxiety, and Stress Scale (DASS-21)	X					X	X					X	X
EQ-5D Self-Report Health State Question	X					X	X					X	X
WHO's Heath and Work Performance Questionnaire (HPQ)	X						X						X
Healthcare Utilization	X						X						X
COVID Questions	X					X	X					X	x
COVID Healthcare Worker Study Barriers to Participation Survey							X						X
FAROS HRV Recording	X					X	X					X	X
Randomized *{EI=Early Intervention DI=Delayed Intervention}*	X												
Cereset Research Intervention		X		X	X	X			X		X	X	X	
Study Coordinator Data Entry	X					X	X					X	X
Technologist Data Entry		X		X	X	X			X		X	X	X	

Cereset Research – COVID-19 Study Flow Chart:



Crossover DI Group



Enrollment Visit:

Informed consent is obtained, medical history and medication list are reviewed from the screening form (Appendix C), and collection of baseline measures is completed. This will occur prior to the start of CR and will require about 45-60 minutes of time. To promote good mental health and well-being, all participants will receive a listing of behavioral health resources at the V1 study visit.

Number of CR Sessions and Length of Study:

All baseline measures will have been collected during the enrollment visit. Participants in the IE group will begin CR sessions 0-7 days following V1 data collection, and will receive 4 CR sessions, along with continued care. CR sessions will occur while relaxing in a zero gravity chair, and are approximately 1 hour in length. The first two sessions must be received over 5 calendar days and all four should be completed within 10 business days.

Participants in the IE group who begin sessions immediately after V1, receive sessions, have V2 immediately, V3 four weeks after, may be in the study about 5 weeks. At the other end of the spectrum, a participant who delays the start of sessions until 7 days after V1, and receives sessions, then does not get V2, or V3 until the end of the allowable visit windows, might be in the study for about 8-9 weeks. The DI group may be in the study for 10 to 18 weeks.

Post-Intervention Data Collection Visits:

Within 7 days after completion of the intervention, participants in the IE group will return for a post-intervention data collection visit (V2). Measures will be repeated. This visit will take about 30-45 minutes. Those in the DI group will return for V2 10-21 days after V1, with target of 14 days.

Between 4-7 weeks after completion of the V2, participants will return for the primary outcome data collection visit (V3). This visit will require about 30-45 minutes, and will be considered the time point for assessing primary outcomes. At the V3 visit, those in the EI group will be done with the study. Those in the DI group will be offered the opportunity to crossover and receive sessions within the next month. After receiving sessions, there will be V4 and V5 data collections.

Brainwave Assessment:

The short baseline brainwave recording occurs as part of the first session. The assessment creates a map of frequencies and amplitudes. Our pilot data also suggest that this information is also useful for correlating with autonomic function (HRV), and that changes can be observed in frequencies and amplitudes from pre- to post-intervention. For the assessment, with the participant in a sitting position, sensors are sequentially placed over up to two areas of the scalp to record two-minute epochs of data while the brain is at rest with eyes closed. For the assessment, measurements are taken at homologous regions of the bilateral hemispheres according to the 10-20 International System at FP1/FP2 and T3/T4, and F3/F4 and P3/P4. The data are processed to identify patterns and imbalances of frequencies and amplitudes. The baseline brainwave assessment takes about 5 minutes to complete.

CR Sessions:

Each session requires about 1 hour, and will include 2 paired protocols, working with different locations on the scalp. Each protocol will typically last between 8-12 minutes. For the sessions, with the subject comfortably at rest, sitting or reclining in a zero gravity chair, the sensors are placed over the specific target areas on the scalp corresponding with brain regions/lobes to be observed. 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 an auditory tone, which is played back to the subject via earbuds with as little as a 4-8 millisecond second delay. Thus, the brain pattern is echoed back to the participant from moment to moment, providing the brain with rapid updating about its frequencies, amplitudes, and patterns. All protocols will occur with eyes closed, and participants will be instructed to relax. Participants can fall asleep if they wish, without loss of effect since no conscious, cognitive activity is required with this closed-loop approach.

Although similar in appearance to other methods such as neurofeedback, CR is distinctly different. CR uses an algorithm-based approach to allow the brain to observe, and resonate with itself. This non-judgmental, closed-loop paradigm supports the brain to auto-calibrate, self-adjust, or relax, typically resulting in shifts toward improved balance and reduced hyperarousal. There is no learner in the loop, no operant conditioning, no need to try to train one's brain to do anything. There is also no attempt to force the brain towards a standardized or ideal pattern of frequencies and amplitudes.

As with HIRREM, the exact mechanism of the effect with CR remains to be fully understood, but may involve resonance between the echoed tones and oscillating brain networks, which can be thought of as being much like a musical instrument tuning itself. A key aspect of observed beneficial effects may also be related to the observed improvement in downstream autonomic function, as evidenced by increased (improved) HRV and BRS, apparently associated with increased dynamic range and flexibility of autonomic responses managed by the brain.

Outcome Measures:

A series of measures will be collected at data collection visits (Appendix A; schedule of activities).

Primary Outcome Measure:

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 (S. Cohen, Kamarck, & Mermelstein, 1983).

Secondary Outcome Measures:

Insomnia:

The severity of insomnia symptoms is measured using two self-report symptom inventories with each data collection visit. This includes the Insomnia Severity Index (ISI). The ISI is a 7-question measure, with responses from 0-4 for each question, yielding scores ranging from 0-28(Bastien, Vallieres, & Morin, 2001; Morin, Belleville, Belanger, & Ivers, 2011).

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).

Exploratory Measures:

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). If the CES-D score is > 35 on the V1 baseline survey the study coordinator will obtain more information about the depression (onset, duration, evaluation, hospitalization, treatment, other therapy), and again ask the initial screening questions for risk of suicide.

Traumatic Stress:

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

Fatigue:

Fatigue Severity Scale (FSS) is a nine-item instrument to assess how fatigue interferes with daily activities. Items are scored on a 7-point scale ranging from 1=strongly disagree to 7=strongly agree. Total scores range from 9 to 63 and the higher the rating demonstrates greater fatigue severity (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989).

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).

The self-rating health question from the EQ-5D on a scale of 0-100 (0 = worst imaginable health state, 100 = best imaginable health state) will also be administered (Balestroni & Bertolotti, 2012; Rabin & de, 2001).

Social Support:

The Interpersonal Support Evaluation List – Shortened Version (ISEL-12) is a 12-item scale that was modified from a 40-item scale used to assess perceptions of social support. Three dimensions are evaluated: appraisal support, belonging support, and tangible support. Each item is scaled from 1 to 4 for "Definitely True" to "Definitely False." (S. Cohen et al., 1983; S. Cohen & Wills, 1985). Scores are summed and higher scores correlate with more perceived social support.

Cognitive Function:

The Multiple Ability Self-Report Questionnaire (Seidenberg, Haltiner, Taylor, Hermann, & Wyler, 1994) is a self-report questionnaire commonly used to assess perceived cognitive dysfunction. The MASQ has 38 items and assesses five cognitive domains, including language, visual/perceptual ability, verbal memory, visual memory, and attention (Williams & Arnold, 2011).

Mental Health Status:

The Depression, Anxiety, and Stress Scale (DASS-21) is a self-report scale with 21 items (Le et al., 2019; D. Lee, 2019). These questions are divided into three subscales to depression, anxiety, and stress, respectively. The depression subscale scoring ranges from normal (0-9), mild depression (10-12), moderate depression (13-20), severe depression (21-27, and extremely severe depression (28-42). The anxiety subscale scoring ranges from normal (0-6), mild anxiety (7-9), moderate anxiety (10-14), severe anxiety (15-19), and extremely severe anxiety (20-42). The stress subscale ranges from normal (0-10), mild stress (11-18), moderate stress (19-26), sever stress (27-34), and extremely severe stress (35-42). This scale is routinely used in COVID-19 (Wang et al., 2020) and SARS literature (McAlonan et al., 2007).

Work Engagement:

The absenteeism and presenteeism questions of the World Health Organization's Heath and Work Performance Questionnaire (HPQ) will be administered to gauge work engagement. This abbreviated subset of questions includes 11 questions for worked time (Kessler et al., 2004; Kessler et al., 2003)

Healthcare Utilization:

Hospitalizations, emergency department, urgent care and clinic visit counts will be collected for the prior 3 months at enrollment, and then throughout follow-up.

COVID-19:

Questions about COVID-19 experience, exposure, and demographics will be collected. These details will allow us to characterize the population and decide if there is any correlation between exposure status (i.e. working in a particular high risk area) and symptom scores.

Heart Rate (HR), and Heart Rate Variability (HRV):

Continuous heart rate will be recorded while the participant is breathing normally in seated position for 10 minutes using Faros 180 heart rate monitor (Bittium Corporation, Oulu, Finland). Beat to beat intervals (RRI) files will be generated at 1000 Hz via the data acquisition software. The files will be analyzed with Nevrokard HRV software (by Nevrokard Kiauta, d.o.o., Izola, Slovenia). The recordings will be visually inspected to ensure data quality (dropped beats or gross motion artifacts are excluded) and the first 5 minutes of usable tracings will be analyzed. Measures of heart rate variability (HRV) in the frequency domain will be derived and these measures will be integrated over specified frequency ranges (LF: 0.04-0.15 Hz; HF: 0.15-0.4 Hz). Power of RRI spectra in LF, HF range (LF_{RRI} and HF_{RRI}) and total power (TP) will be calculated in normalized units and the ratio of LF/HF will be used as a measure of sympatho-vagal balance. ("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). Data are saved to Excel spreadsheets for further statistical analysis by study team members.

Exploration for Unexpected Barriers, Challenges, or Detrimental Factors:

A REDCap element will be added to data collection at V3 and V5, the final official data collection visit, seeking input regarding any challenges or barriers faced during the study related to factors such as availability of session dates or times, restrictive guidelines for when sessions need to occur, tasks performed during data collections, comfort of the session chair/equipment, difficulty sitting still, office location and accessibility trouble, competing other therapeutic modalities, length of the research study, or any other issues.

Analytical Plan:

Data will be analyzed using the most recent versions of SAS (SAS Institute, Inc., Cary, NC) or the R Statistical Computing Environment. Histograms and descriptive statistics will be examined to evaluate the distribution of study outcomes. Mean contrasts will be used to compare the changes in symptom scores for the primary outcome of Perceived Stress Scale from V1 to V3 in the early intervention vs. delayed intervention groups, as well as secondary and exploratory outcomes/symptom scores. Linear mixed models, which can accommodate within-subject correlations due to repeated assessments over time, may also be used to generate point estimates for effect size along with 95% confidence intervals to support a future larger study if the results in this study do not support immediate clinical application, and potentially for other studies examining other outcomes or potentially more select samples. The association of outcome measures with baseline participant characteristics will also be explored.

Human Subjects Protection:

Subject Recruitment Methods:

Subjects will be recruited by physician referral, word of mouth, and through advertisement (elevator ads, posters, flyers, table outside cafeteria, video overview of study, etc.).

Informed Consent:

The research staff will obtain written informed consent or assent from each competent subject.

Subject Communication Methods:

Participants will be contacted by phone, email, and texting during the study. The study team is going to explore texting for appointment reminders and rescheduling.

Videoconference Data Collection Visit Alternative:

During this time of COVID-19, institutionally approved videoconferencing platforms might be used to interact with study subjects. In person visits are preferred, but in case of office closures or safety reasons the study team might collect data collections through REDCap and videoconferencing.

Confidentiality and Privacy:

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

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

Safety:

Based on experience reported by Brain State Technologies/Cereset, garnered from provision of case management support, feedback from their clients (now reported to be about 130,000), and feedback

from the HIRREM provider community, as well as results from IRB-approved studies at WFSM (now over 600 participants to receive HIRREM), we are not aware of any serious adverse events resulting from HIRREM sessions.

Non-serious, temporary, and somewhat paradoxical effects have been reported by study participants. This includes things such as the participant reporting being more aware of, or more affected by their feelings, or by those around them, changes in sleep, including dreams, emotions, energy levels, or a feeling of fullness in the head or mild headache. In the course of provision of HIRREM as part of nine IRB-approved studies at WFSM, such non-serious, temporary effects have been estimated to occur in ten percent or less of participants. Based on recent analysis of a placebo controlled trial of HIRREM for moderate to severe insomnia (n = 107), such non-serious, temporary adverse effects, that were judged to go beyond the intensity, expression, or nature of pre-existing health conditions, were reported during study participation by 10.7% in the HIRREM group, and 13.7% in the placebo group. All episodes were brief, typically resolving in hours to 1-2 days, but at the most lasted less than one week. Skin irritation at the site from the paste used to affix the sensors to the scalp was reported by a single participant (<1%) (Personal communication). Since CR uses the same core technology and approach as HIRREM, the risk profile is expected to be similar. A participant in the Explooratory research study, who completed the Cereset Research intervention 3 weeks prior, committed suicide. There have now been over 14,000 people who have used this generation of the technology in clinical practice, and over 80 in similar research studies, with no other reports of serious adverse events. It is not believed that the Cereset Research intervention played a causative role in this tragic event.

All CR sessions are administered by Technologists who have been trained 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.

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

If someone has a 10 point or greater increase in depression (as measured by the CES-D) at a follow up visit, they will be given a community resources handout for mental health. The increase is one standard deviation from the typical drop from baseline in the Exploratory Study.

The manufacturer of Cereset Research recently provided the following update regarding safety and regulatory status:

“This technological approach has been used across several branded versions in what are now about 130,000 individuals, with no serious adverse events reported. The device now branded as Cereset, which will be used in research studies as Cereset Research, uses the same core technology and approach as HIRREM, echoing brainwaves in real time as audible tones. Cereset is commercially available as a wellness technology to help manage stress, restore hope, and achieve restful sleep. Cereset software was tested hundreds of times in our office before going to production beginning in October of 2017.

Since then, thousands of sessions using Cereset software have been provided clinically in 25 other offices across the country without any issues. Results thus far have exceeded our expectations.

We previously shared that the HIRREM equipment used at WFSM since 2011, was registered with the FDA as a Class 2 device under regulation number 21 CFR 882.5050 (biofeedback device), and was thus exempt from FDA 510(k) pre-market notification procedures. Based on the same core technology, with a well-documented, extremely favorable risk profile for this approach, the same applies for Cereset. Importantly, Cereset now falls under more recent FDA guidance provided in a document issued on July 29, 2016, regarding General Wellness: Policy for Low Risk Devices. As a low-risk, general wellness device, Cereset is exempt from FDA regulation. Versions of Cereset Research are currently being used as part of IRB-approved research studies at the Uniformed Services University for Health Sciences, and Womack Army Medical Center, as well as at WFSM (as HIRREM-SOP)." (Lee Gerdes, CEO, Brainstate Technologies/Cereset, February 10, 2019, personal communication).

Participant Compensation:

Participants in this research project will not receive any monetary compensation.

Data and Safety Monitoring:

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

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

Reporting of Unanticipated Problems, Adverse Events, or Deviations:

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

Appendices

A:
Perceived Stress Scale (PSS)
Insomnia Severity Index (ISI)
Generalized Anxiety Disorder 7-Item (GAD-7)
Center for Epidemiological Studies Depression Scale (CES-D)
PTSD Checklist for Civilians (PCL-C)
Fatigue Severity Scale (FSS)
Quality of Life Scale (QOLS)
Interpersonal Support Evaluation List (ISEL-12)
Multiple Ability Self-Report Questionnaire (MASQ)
Depression, Anxiety, and Stress Scale (DASS-21)
EQ-5D Self-Report Health State Question
World Health Organization's Heath and Work Performance Questionnaire (HPQ)
*Workplace healthcare utilization, missed/medical appointments, etc.

B:
COVID-19 Healthcare Worker Study - Screening Video

C:
Handout for Study Participants – "Process and Study Details"

D:
Eligibility Screening Form

E:
Study Coordinator Email Script
Study Coordinator Data Collection Forms
Behavioral Health Resource List

References:

Avram, J., Baltes, F. R., Miclea, M., & Miu, A. C. (2010). Frontal EEG activation asymmetry reflects cognitive biases in anxiety: evidence from an emotional face Stroop task. *Appl Psychophysiol Biofeedback, 35*(4), 285-292. doi:10.1007/s10484-010-9138-6

Balestroni, G., & Bertolotti, G. (2012). [EuroQol-5D (EQ-5D): an instrument for measuring quality of life]. *Monaldi Arch Chest Dis, 78*(3), 155-159. doi:10.4081/monaldi.2012.121

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]

Beauchaine, T. P., & Thayer, J. F. (2015). Heart rate variability as a transdiagnostic biomarker of psychopathology. *Int J Psychophysiol, 98*(2 Pt 2), 338-350. doi:10.1016/j.ijpsycho.2015.08.004

Beckham, J. C., Taft, C. T., Vrana, S. R., Feldman, M. E., Barefoot, J. C., Moore, S. D., . . . Calhoun, P. S. (2003). Ambulatory monitoring and physical health report in Vietnam veterans with and without chronic posttraumatic stress disorder. *J Trauma Stress, 16*(4), 329-335. doi:10.1023/a:1024457700599

Bellesi, M., Riedner, B. A., Garcia-Molina, G. N., Cirelli, C., & Tononi, G. (2014). Enhancement of sleep slow waves: underlying mechanisms and practical consequences. *Front Syst Neurosci, 8*, 208. doi:10.3389/fnsys.2014.00208

Blanchard, E. B., Jones-Alexander, J., Buckley, T. C., & Forneris, C. A. (1996). Psychometric properties of the PTSD Checklist (PCL). *Behav. Res. Ther, 34*(8), 669-673. doi:10.1016/0005-7967(96)00033-2

Brooks, S. K., Webster, R. K., Smith, L. E., Woodland, L., Wessely, S., Greenberg, N., & Rubin, G. J. (2020). The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet, 395*(10227), 912-920. doi:10.1016/s0140-6736(20)30460-8

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. Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/nur.4770120604/abstract

https://onlinelibrary.wiley.com/doi/abs/10.1002/nur.4770120604?sid=nlm%3Apubmed

Carnethon, M. R., Golden, S. H., Folsom, A. R., Haskell, W., & Liao, D. (2003). Prospective investigation of autonomic nervous system function and the development of type 2 diabetes: the Atherosclerosis Risk In Communities study, 1987-1998. *Circulation, 107*(17), 2190-2195. doi:10.1161/01.cir.0000066324.74807.95

Chandra, P., Sands, R. L., Gillespie, B. W., Levin, N. W., Kotanko, P., Kiser, M., . . . Saran, R. (2012). Predictors of heart rate variability and its prognostic significance in chronic kidney disease. *Nephrol Dial Transplant, 27*(2), 700-709. doi:10.1093/ndt/gfr340

Cohen, H., Benjamin, J., Geva, A. B., Matar, M. A., Kaplan, Z., & Kotler, M. (2000). Autonomic dysregulation in panic disorder and in post-traumatic stress disorder: application of power spectrum analysis of heart rate variability at rest and in response to recollection of trauma or panic attacks. *Psychiatry Res, 96*(1), 1-13.

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

Cohen, S., & Wills, T. A. (1985). Stress, social support, and the buffering hypothesis. *Psychol Bull, 98*(2), 310-357.

Dekker, J. M., Schouten, E. G., Klootwijk, P., Pool, J., Swenne, C. A., & Kromhout, D. (1997). Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in

middle-aged and elderly men. The Zutphen Study. *Am J Epidemiol, 145*(10), 899-908. Retrieved from https://watermark.silverchair.com/145-10-899.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAApUwggKRBgkqhkiG9w0BBwagggKCMIICfgIBADCCAncGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMLBXawd53ymzzXWmzAgEQgIICSN9cNi4Qrs71SGei8_9r8WC0la825dCJY6n691N2cr_ClEhLIeEM-qOlULIIgkhK-sOiur-DK7peUopciFICYS86uHx65JeST6TdSLn57ttN8O6_sQqnbf5r5m03GzyGMLN3j8bKhgflAp1DJcIL2r957xRBBBnnwofWpdQznj8Ck65LTn3nwPRV-JNKHbuRsS3AiAtmTP3Aoo2BbModgdxgyXhb2Ry3kWaHwqsrY-3uWNQYJQOJZeF8TjdqKTSFBlcyjvM-9VXt6kHgcy16unrepZA0_x7LMH-Uo569l5tPZdpotcw02z0CljgOJKMLFMVFl6pEcDbeM_5J-Ai2rCucjg3Z6Fs94C-mfvzzB91KYTVj_yz49tlLudEQzbaPIhncLehuZQD76eKNm0sl4mg6u6UrSH_QDvj6fV3ET-YwGZy1wVRqsNjYItI8NflJbs_tNw7rWdZu_JGgN1PGKWLymLK33FO9UQjb0LmoU_0gsEaEJ1GM5d17LG1e4GBDWM49-NhF_NiShggfJBrvzEEuw2MUqpavMkGjPeSqyJ_plr9TyQRNGRxs5PFS02VCMY9T540HNkBJbeo9A6Et3HD9OwgqJwnybfQ_czKYUn__4EdUqmRXXsMy3NjgJz1bay32FXzhoHCf2Kkv22qax1NyzcOVo5UeH88qdmP2OmbLFlrGpWFnJNjyTAcILOUfrIO3m68__G9Lk-mDiMIEXCFxgY22_JmQkTq-9rKWvqPNGBRAv1cpA-rZf5aKhLY3oEXY3aEVwtkP

Drachev, S. N., Stangvaltaite-Mouhat, L., Bolstad, N. L., Johnsen, J. K., Yushmanova, T. N., & Trovik, T. A. (2020). Perceived Stress and Associated Factors in Russian Medical and Dental Students: A Cross-Sectional Study in North-West Russia. *Int J Environ Res Public Health, 17*(15). doi:10.3390/ijerph17155390

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

Gao, J., Zheng, P., Jia, Y., Chen, H., Mao, Y., Chen, S., . . . Dai, J. (2020). Mental health problems and social media exposure during COVID-19 outbreak. *PLoS One, 15*(4), e0231924. doi:10.1371/journal.pone.0231924

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]

Hale, T. S., Smalley, S. L., Dang, J., Hanada, G., Macion, J., McCracken, J. T., . . . Loo, S. K. (2010). ADHD familial loading and abnormal EEG alpha asymmetry in children with ADHD. *J Psychiatr Res, 44*(9), 605-615. doi:10.1016/j.jpsychires.2009.11.012

Hale, T. S., Smalley, S. L., Hanada, G., Macion, J., McCracken, J. T., McGough, J. J., & Loo, S. K. (2009). Atypical alpha asymmetry in adults with ADHD. *Neuropsychologia, 47*(10), 2082-2088. doi:10.1016/j.neuropsychologia.2009.03.021

Hale, T. S., Smalley, S. L., Walshaw, P. D., Hanada, G., Macion, J., McCracken, J. T., . . . Loo, S. K. (2010). Atypical EEG beta asymmetry in adults with ADHD. *Neuropsychologia, 48*(12), 3532-3539. doi:S0028-3932(10)00346-5 [pii];10.1016/j.neuropsychologia.2010.08.002 [doi]

Katz-Leurer, M., Rotem, H., Keren, O., & Meyer, S. (2010). Heart rate and heart rate variability at rest and during exercise in boys who suffered a severe traumatic brain injury and typically-developed controls. *Brain Inj, 24*(2), 110-114. doi:10.3109/02699050903508234

Kemp, A. H., Griffiths, K., Felmingham, K. L., Shankman, S. A., Drinkenburg, W., Arns, M., . . . Bryant, R. A. (2010). Disorder specificity despite comorbidity: resting EEG alpha asymmetry in major

depressive disorder and post-traumatic stress disorder. *Biol. Psychol, 85*(2), 350-354. doi:S0301-0511(10)00218-8 [pii];10.1016/j.biopsycho.2010.08.001 [doi]

Kessler, R. C., Ames, M., Hymel, P. A., Loeppke, R., McKenas, D. K., Richling, D. E., . . . Ustun, T. B. (2004). Using the World Health Organization Health and Work Performance Questionnaire (HPQ) to evaluate the indirect workplace costs of illness. *J Occup Environ Med, 46*(6 Suppl), S23-37. Retrieved from http://ovidsp.tx.ovid.com/ovftpdfs/FPDDNCIBMEDGCH00/fs043/ovft/live/gv021/00043764/00043764-200406001-00004.pdf

Kessler, R. C., Barber, C., Beck, A., Berglund, P., Cleary, P. D., McKenas, D., . . . Wang, P. (2003). The World Health Organization Health and Work Performance Questionnaire (HPQ). *J Occup Environ Med, 45*(2), 156-174. Retrieved from http://ovidsp.tx.ovid.com/ovftpdfs/FPDDNCIBMEDGCH00/fs047/ovft/live/gv024/00043764/00043764-200302000-00007.pdf

Kleiger, R. E., Miller, J. P., Bigger, J. T., Jr., & Moss, A. J. (1987). Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol, 59*(4), 256-262.

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol, 46*(10), 1121-1123. doi:10.1001/archneur.1989.00520460115022

Lai, J., Ma, S., Wang, Y., Cai, Z., Hu, J., Wei, N., . . . Hu, S. (2020). Factors Associated With Mental Health Outcomes Among Health Care Workers Exposed to Coronavirus Disease 2019. *JAMA Netw Open, 3*(3), e203976. doi:10.1001/jamanetworkopen.2020.3976

Lazarev, V. V., Pontes, A., Mitrofanov, A. A., & deAzevedo, L. C. (2010). Interhemispheric asymmetry in EEG photic driving coherence in childhood autism. *Clin. Neurophysiol, 121*(2), 145-152. doi:S1388-2457(09)00612-9 [pii];10.1016/j.clinph.2009.10.010 [doi]

Le, T. A., Le, M. Q. T., Dang, A. D., Dang, A. K., Nguyen, C. T., Pham, H. Q., . . . Ho, R. C. M. (2019). Multi-level predictors of psychological problems among methadone maintenance treatment patients in difference types of settings in Vietnam. *Subst Abuse Treat Prev Policy, 14*(1), 39. doi:10.1186/s13011-019-0223-4

Lee, D. (2019). The convergent, discriminant, and nomological validity of the Depression Anxiety Stress Scales-21 (DASS-21). *J Affect Disord, 259*, 136-142. doi:10.1016/j.jad.2019.06.036

Lee, E. A., Bissett, J. K., Carter, M. A., Cowan, P. A., Pyne, J. M., Speck, P. M., . . . Tolley, E. A. (2013). Preliminary findings of the relationship of lower heart rate variability with military sexual trauma and presumed posttraumatic stress disorder. *J Trauma Stress, 26*(2), 249-256. doi:10.1002/jts.21797

Lee, S. W., Laurienti, P. J., Burdette, J. H., Tegeler, C. L., Morgan, A. R., Simpson, S. L., . . . Tegeler, C. H. (2018). Functional Brain Network Changes Following Use of an Allostatic, Closed-Loop, Acoustic Stimulation Neurotechnology for Military-Related Traumatic Stress. *Journal of Neuroimaging, 1*, 70-78. doi:10.1111/jon.12571

Lee SW., G. L., Tegeler CL., Shaltout HA., Tegeler CH. (2014). A bihemispheric autonomic model for traumatic stress effects on health and behavior. *Frontiers Psychology, 5*, Article 843. doi:10.3389/fpsyg.2014.00843

Liang, Y., Chen, M., Zheng, X., & Liu, J. (2020). Screening for Chinese medical staff mental health by SDS and SAS during the outbreak of COVID-19. *J Psychosom Res, 133*, 110102. doi:10.1016/j.jpsychores.2020.110102

Liu, N., Zhang, F., Wei, C., Jia, Y., Shang, Z., Sun, L., . . . Liu, W. (2020). Prevalence and predictors of PTSS during COVID-19 outbreak in China hardest-hit areas: Gender differences matter. *Psychiatry Res, 287*, 112921. doi:10.1016/j.psychres.2020.112921

Liu, S., Yang, L., Zhang, C., Xiang, Y.-T., Liu, Z., Hu, S., & Zhang, B. (2020). Online mental health services in China during the COVID-19 outbreak. *The Lancet Psychiatry, 7*(4), e17-e18. doi:10.1016/S2215-0366(20)30077-8

Marsac, J. (2013). [Heart rate variability: a cardiometabolic risk marker with public health implications]. *Bull Acad Natl Med, 197*(1), 175-186.

Marzano, C., Ferrara, M., Sforza, E., & De, G. L. (2008). Quantitative electroencephalogram (EEG) in insomnia: a new window on pathophysiological mechanisms. *Curr. Pharm. Des, 14*(32), 3446-3455. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19075720

http://www.eurekaselect.com/68051/article

McAlonan, G. M., Lee, A. M., Cheung, V., Cheung, C., Tsang, K. W., Sham, P. C., . . . Wong, J. G. (2007). Immediate and sustained psychological impact of an emerging infectious disease outbreak on health care workers. *Can J Psychiatry, 52*(4), 241-247. doi:10.1177/070674370705200406

Metzger, L. J., Paige, S. R., Carson, M. A., Lasko, N. B., Paulus, L. A., Pitman, R. K., & Orr, S. P. (2004). PTSD arousal and depression symptoms associated with increased right-sided parietal EEG asymmetry. *J Abnorm Psychol, 113*(2), 324-329. doi:10.1037/0021-843x.113.2.324

Minassian, A., Geyer, M. A., Baker, D. G., Nievergelt, C. M., O'Connor, D. T., & Risbrough, V. B. (2014). Heart rate variability characteristics in a large group of active-duty marines and relationship to posttraumatic stress. *Psychosom Med, 76*(4), 292-301. doi:10.1097/psy.0000000000000056

Minassian, A., Maihofer, A. X., Baker, D. G., Nievergelt, C. M., Geyer, M. A., & Risbrough, V. B. (2015). Association of Predeployment Heart Rate Variability With Risk of Postdeployment Posttraumatic Stress Disorder in Active-Duty Marines. *JAMA Psychiatry, 72*(10), 979-986. doi:10.1001/jamapsychiatry.2015.0922

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. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21532953

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079939/pdf/aasm.34.5.601.pdf

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079939/pdf/aasm.34.5.601.pdf

Moscovitch, D. A., Santesso, D. L., Miskovic, V., McCabe, R. E., Antony, M. M., & Schmidt, L. A. (2011). Frontal EEG asymmetry and symptom response to cognitive behavioral therapy in patients with social anxiety disorder. *Biol Psychol, 87*(3), 379-385. doi:10.1016/j.biopsycho.2011.04.009

Nolan, R. P., Jong, P., Barry-Bianchi, S. M., Tanaka, T. H., & Floras, J. S. (2008). Effects of drug, biobehavioral and exercise therapies on heart rate variability in coronary artery disease: a systematic review. *Eur J Cardiovasc Prev Rehabil, 15*(4), 386-396. doi:10.1097/HJR.0b013e3283030a97

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

Park, J., Marvar, P. J., Liao, P., Kankam, M. L., Norrholm, S. D., Downey, R. M., . . . Rothbaum, B. O. (2017). Baroreflex dysfunction and augmented sympathetic nerve responses during mental stress in veterans with post-traumatic stress disorder. *J Physiol, 595*(14), 4893-4908. doi:10.1113/jp274269

Park, J. E., Lee, J. Y., Kang, S. H., Choi, J. H., Kim, T. Y., So, H. S., & Yoon, I. Y. (2017). Heart rate variability of chronic posttraumatic stress disorder in the Korean veterans. *Psychiatry Res, 255*, 72-77. doi:10.1016/j.psychres.2017.05.011

Plantinga, L., Lim, S. S., Bowling, C. B., & Drenkard, C. (2017). Perceived stress and reported cognitive symptoms among Georgia patients with systemic lupus erythematosus. *Lupus, 26*(10), 1064-1071. doi:10.1177/0961203317693095

Pyne, J. M., Constans, J. I., Wiederhold, M. D., Gibson, D. P., Kimbrell, T., Kramer, T. L., . . . McCune, T. R. (2016). Heart rate variability: Pre-deployment predictor of post-deployment PTSD symptoms. *Biol Psychol, 121*(Pt A), 91-98. doi:10.1016/j.biopsycho.2016.10.008

Qiu, J., Shen, B., Zhao, M., Wang, Z., Xie, B., & Xu, Y. (2020). A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. *Gen Psychiatr, 33*(2), e100213. doi:10.1136/gpsych-2020-100213

Rabe, S., Beauducel, A., Zollner, T., Maercker, A., & Karl, A. (2006). Regional brain electrical activity in posttraumatic stress disorder after motor vehicle accident. *J. Abnorm. Psychol, 115*(4), 687-698. doi:2006-20696-004 [pii];10.1037/0021-843X.115.4.687 [doi]

Rabin, R., & de, C. F. (2001). EQ-5D: a measure of health status from the EuroQol Group. *Ann. Med, 33*(5), 337-343. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11491192

https://www.tandfonline.com/doi/abs/10.3109/07853890109002087

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

Rajkumar, R. P. (2020). COVID-19 and mental health: A review of the existing literature. *Asian J Psychiatr, 52*, 102066. doi:10.1016/j.ajp.2020.102066

Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., & Nissen, C. (2010). The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med. Rev, 14*(1), 19-31. doi:S1087-0792(09)00041-0 [pii];10.1016/j.smrv.2009.04.002 [doi]

Seidenberg, M., Haltiner, A., Taylor, M. A., Hermann, B. B., & Wyler, A. (1994). Development and validation of a Multiple Ability Self-Report Questionnaire. *J Clin Exp Neuropsychol, 16*(1), 93-104. doi:10.1080/01688639408402620

Shah, A. J., Lampert, R., Goldberg, J., Veledar, E., Bremner, J. D., & Vaccarino, V. (2013). Posttraumatic stress disorder and impaired autonomic modulation in male twins. *Biol Psychiatry, 73*(11), 1103-1110. doi:10.1016/j.biopsych.2013.01.019

Shaltout, H. A., Tegeler, C. L., Lee, S. W., & Tegeler, C. H. (2017). 0363 IN SUBJECTS WITH INSOMNIA, USE OF A CLOSED-LOOP ACOUSTIC STIMULATION NEUROTECHNOLOGY IMPROVES HEART RATE VARIABILITY AND BAROREFLEX SENSITIVITY: RESULTS OF A PLACEBO-CONTROLLED CLINICAL TRIAL. *Sleep, 40*(suppl_1), A135-A135. doi:10.1093/sleepj/zsx050.362

Shuja, K. H., Aqeel, M., Jaffar, A., & Ahmed, A. (2020). COVID-19 Pandemic and Impending Global Mental Health Implications. *Psychiatr Danub, 32*(1), 32-35. doi:10.24869/psyd.2020.32

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

Spiegelhalder, K., Fuchs, L., Ladwig, J., Kyle, S. D., Nissen, C., Voderholzer, U., . . . Riemann, D. (2011). Heart rate and heart rate variability in subjectively reported insomnia. *J Sleep Res, 20*(1 Pt 2), 137-145. doi:10.1111/j.1365-2869.2010.00863.x

Spironelli, C., Penolazzi, B., & Angrilli, A. (2008). Dysfunctional hemispheric asymmetry of theta and beta EEG activity during linguistic tasks in developmental dyslexia. *Biol. Psychol, 77*(2), 123-131. doi:S0301-0511(07)00158-5 [pii];10.1016/j.biopsycho.2007.09.009 [doi]

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]

Sterling, P. (2012). Allostasis: a model of predictive regulation. *Physiol Behav, 106*(1), 5-15. doi:S0031-9384(11)00307-6 [pii];10.1016/j.physbeh.2011.06.004 [doi]

Stroganova, T. A., Nygren, G., Tsetlin, M. M., Posikera, I. N., Gillberg, C., Elam, M., & Orekhova, E. V. (2007). Abnormal EEG lateralization in boys with autism. *Clin. Neurophysiol, 118*(8), 1842-1854. doi:S1388-2457(07)00202-7 [pii];10.1016/j.clinph.2007.05.005 [doi]

Tegeler, C., Howard, L., Brown, K., Kellar, D., Asif-Fraz, F., Gerdes, L., . . . Shaltout, H. (2021a). Exploratory Study of Acoustic Neuromodulation Improves Caregiver Burden, Insomnia, Stress, Anxiety, and Autonomic Function (4166). *Neurology, 96*(15 Supplement), 4166.

Tegeler, C., Howard, L., Brown, K., Kellar, D., Asif-Fraz, F., Gerdes, L., . . . Shaltout, H. (2021b). Exploratory Study of Acoustic Neuromodulation Improves Pain, Autonomic Function, and Symptoms of Insomnia, Stress, and Anxiety in Individuals with Chronic Pain (4291). *Neurology, 96*(15 Supplement), 4291.

Tegeler, C. H., Cook, J. F., Tegeler, C. L., Hirsch, J. R., Shaltout, H. A., Simpson, S. L., . . . Lee, S. W. (2017). Clinical, hemispheric, and autonomic changes associated with use of closed-loop, allostatic neurotechnology by a case series of individuals with self-reported symptoms of post-traumatic stress. *BMC Psychiatry, 17*(1), 141. doi:10.1186/s12888-017-1299-x

Tegeler, C. H., Kumar, S. R., Conklin, D., Lee, S. W., Gerdes, L., Turner, D. P., . . . Houle, T. T. (2012). Open label, randomized, crossover pilot trial of high-resolution, relational, resonance-based, electroencephalic mirroring to relieve insomnia. *Brain Behav, 2*(6), 814-824. doi:10.1002/brb3.101 [doi]

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 and Behavior, 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, 22*(6), 650-655. doi:10.1097/GME.0000000000000422 [doi]

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

Tegeler, C. L., Howard, L. J., Schmidt, K. D., Cook, J. F., Kumar, S., Simpson, S. L., . . . Tegeler, C. H. (2017). 0389 USE OF A CLOSED-LOOP ACOUSTIC STIMULATION NEUROTECHNOLOGY IMPROVES SYMPTOMS OF MODERATE TO SEVERE INSOMNIA: RESULTS OF A PLACEBO-CONTROLLED TRIAL. *Sleep, 40*(suppl_1), A145-A145. doi:10.1093/sleepj/zsx050.388

Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H. (2009). Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Ann Behav Med, 37*(2), 141-153. doi:10.1007/s12160-009-9101-z

Thibodeau, R., Jorgensen, R. S., & Kim, S. (2006). Depression, anxiety, and resting frontal EEG asymmetry: a meta-analytic review. *J Abnorm Psychol, 115*(4), 715-729. doi:10.1037/0021-843x.115.4.715

Tobaldini, E., Nobili, L., Strada, S., Casali, K. R., Braghiroli, A., & Montano, N. (2013). Heart rate variability in normal and pathological sleep. *Front Physiol, 4*, 294. doi:10.3389/fphys.2013.00294

Tsuji, H., Larson, M. G., Venditti, F. J., Jr., Manders, E. S., Evans, J. C., Feldman, C. L., & Levy, D. (1996). Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation, 94*(11), 2850-2855.

Wang, C., Pan, R., Wan, X., Tan, Y., Xu, L., Ho, C. S., & Ho, R. C. (2020). Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. *Int J Environ Res Public Health, 17*(5). doi:10.3390/ijerph17051729

Williams, D. A., & Arnold, L. M. (2011). Measures of fibromyalgia: Fibromyalgia Impact Questionnaire (FIQ), Brief Pain Inventory (BPI), Multidimensional Fatigue Inventory (MFI-20), Medical Outcomes Study (MOS) Sleep Scale, and Multiple Ability Self-Report Questionnaire (MASQ). *Arthritis Care Res (Hoboken), 63 Suppl 11*, S86-97. doi:10.1002/acr.20531

Wolynczyk-Gmaj, D., & Szelenberger, W. (2011). Waking EEG in primary insomnia. *Acta Neurobiol. Exp. (Wars.), 71*(3), 387-392. doi:7144 [pii]

Xiao, H., Zhang, Y., Kong, D., Li, S., & Yang, N. (2020). The Effects of Social Support on Sleep Quality of Medical Staff Treating Patients with Coronavirus Disease 2019 (COVID-19) in January and February 2020 in China. *Med Sci Monit, 26*, e923549. doi:10.12659/msm.923549

Zhang, K., Zhou, X., Liu, H., & Hashimoto, K. (2020). Treatment concerns for psychiatric symptoms in patients with COVID-19 with or without psychiatric disorders. *Br J Psychiatry*, 1. doi:10.1192/bjp.2020.84

Zhang, Y., & Ma, Z. F. (2020). Impact of the COVID-19 Pandemic on Mental Health and Quality of Life among Local Residents in Liaoning Province, China: A Cross-Sectional Study. *Int J Environ Res Public Health, 17*(7). doi:10.3390/ijerph17072381