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TITLE: Randomized Controlled Trial of Closed-Loop Allostatic Neurotechnology to Improve Sensory Function and Pain Management After Traumatic Brain Injury

PRINCIPAL INVESTIGATOR: Lee Gerdes

CONTRACTING ORGANIZATION: Brain State Technologies, 15150 N Hayden Rd., Suite 106,  
Scottsdale, AZ 85260

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# REPORT DOCUMENTATION PAGE

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<b>14.</b>	<b>14. ABSTRACT</b> Persistent symptoms after mild traumatic brain injury (mTBI), including chronic pain and sensory disturbance, may be related to alterations at the level of neural oscillations. Studies in mTBI patients show disturbed sleep as a core component of symptoms. The purpose of this study is to evaluate a noninvasive, closed-loop, acoustic stimulation neurotechnology (HIRREM-SOP called Cereset Research, using non-invasive BrainEcho technology) as a novel treatment to enable both physiological and clinical recovery from mTBI, through auto-calibration of neural oscillations. The study is conducted as a single blind study at two sites – USUHS/Walter Reed & WAMC. The hypothesis is that usage of Cereset Research neurotechnology (ten sessions, 90 minutes each), will entail greater reduction in persistent symptoms of mTBI, at three months, than exposure to non-specific random tones that are delivered in a comparable way. The participant enrollment has begun at both USUHS/Walter Reed and WAMC. Both sites progressed nicely until March of 2020 when COVID forced a complete shutdown of research interventions. IRB permissions were granted for the sites to do follow-up visits remotely, but no new clients were allowed to be enrolled or begin the intervention process. COVID restrictions have recently been lifted so the sites can again begin to advertise and enroll new participants. COVID caused this study to be delayed at least 4 to 6 months.  Posting completed at Clinical Trials dot Gov : - <a href="https://www.clinicaltrials.gov">https://www.clinicaltrials.gov</a> NCT03649958							
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## 1. Introduction

The purpose of this study is to evaluate a noninvasive, closed-loop, acoustic stimulation neurotechnology (HIRREM-SOP or “Cereset Research” using non-invasive BrainEcho technology) as a novel treatment to enable both physiological and clinical recovery from mTBI, through auto-calibration of neural oscillations. The study is conducted as a randomized controlled single blind study at two sites – USUHS/Walter Reed & WAMC. The hypothesis is that usage of Cereset Research neurotechnology (ten sessions, 90 minutes each), will entail greater reduction in persistent symptoms of mTBI, at three months, than will exposure to non-specific random tones that is delivered in a comparable way. The participant enrollment has begun again following COVID shut down in March, 2020 at both USUHS/Walter Reed and at WAMC. A total of up to a total of 127 participants can now be consented at the two sites since a change for enrollment may have some participants ineligible after they consent on-line to take part. Those qualified are randomized into test and control in a single blind study.

## 2. Keywords

mTBI, concussion, insomnia, PTS, headache, anxiety, pain, depression, sleep, Post-Concussion Syndrome, Chronic pain, sleep disorders, behavioral symptoms, head injuries

## 3. Accomplishments

Major Task 1 A and 1 B completed in year 1.

Year 2

<b>Major Task 2: Recruit Participants &amp; Conduct Study One Procedures</b>	Months	Status
Initiate recruitment of study participants through multiple avenues	7-42	In Process
Obtain informed consent from each eligible, interested participant	7-42	In Process
Randomize each participant to one of 2 study arms	7-42	In Process
Collect data on study participants throughout conduct of study and follow up periods	7-48	In Process
<i>Milestone Achieved: Enrollment of 126 participants (63 at each site) into Study 1 at an average rate of 2-4 per site per month</i>	48	Est. Month 48
<i>Milestone Achieved: Collection of outcome measures from all 126 participants</i>	50	Est. Month 50

### What opportunities for training and professional development has the project provided?

Poster presentations have been prepared for meetings offering Continuing Medical Education over the past 3 years: the 2019 International Society for Traumatic Stress Studies Meeting, as well as the 2018 and 2019 Military Health Services Research Symposia. In addition, oral abstract presentations were provided at the 2019 Society for Brain Mapping and Therapeutics Meeting, and the 2019 Cyberpsychology, Behavior and Social Networking Meeting. In each case, physicians and other medical providers had the opportunity to ask questions and to have them answered by study researchers.

In 2020, Posters were presented for Military Health Services Research Symposia which was canceled (posters attached to this report) and a major presentation was being prepared for the Society for Brain

Mapping and Therapeutics which was canceled as well.

No identified opportunities for training and professional development were part of the project goals, however the staff who completed training may be eligible for other Cereset Research projects, and/or may be eligible later to apply at a Cereset office (there will be 30 Cereset offices by 2020) as a Cereset Tech Coach.

**How were the results disseminated to communities of interest?**

Posters sent to be presented and were published on line for Military Health System Research Symposium (MHSRS) – Appendix A.

**What do you plan to do during the next reporting period to accomplish the goals?**

Both testing sites are seeking and enrolling study participants, as well as collecting participant data and completing the test or placebo application for active participants. The number of people who have completed the invention and post-intervention assessment is  $87/127 = 68.5\%$ . In the coming year, we plan to continue enrollment at both sites to try to achieve the target number of 127 consented, whether found to be fully eligible or not, or 106 consented, eligible, enrolled and randomized (whichever comes first) for study 1 of the protocol, and also submit an amendment to the protocol that will detail modified plans for the conduct of Study 2.

**4. Impact**

**What was the impact on the development of the principal discipline(s) of the project?**

With the completion of the first 71 participants in the study, in order to maintain blinding regarding treatment allocation, we have lumped all study participants together, those receiving the intervention as well as those receiving sham. For the entire study population, the primary outcome measure, the Neurobehavioral Symptom Inventory (NSI) score declined from 40.5 at baseline to 26.8 postintervention, a change that is highly statistically significant. However, we have no way of knowing at this point whether there is a significant difference between the improvement with the intervention vs with the sham, and will not know until the study is completed.

**What was the impact on other disciplines?**

Nothing to Report.

**What was the impact on technology transfer?**

Nothing to Report.

**What was the impact on society beyond science and technology?**

Nothing to Report.

**5. Changes/Problems**

Nothing to Report. Generally there are no new problems or changes outstanding.

**Changes in approach and reasons for change**

Nothing to Report.

**Actual or anticipated problems or delays and actions or plans to resolve them**

An IRB annual review is taking place at both locations and is the only unknown risk currently.

**Changes that had a significant impact on expenditures**

Nothing to Report.

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to Report.

**Significant changes in use or care of human subjects**

Nothing to Report.

**Significant changes in use or care of vertebrate animals.**

Nothing to Report.

**Significant changes in use of biohazards and/or select agents**

Nothing to Report.

**6. Products, Inventions, Patent Applications, and/or Licenses**

Nothing to Report.

**7. Participants & Other Collaborating Organizations**

Individuals that have worked at least one person month on the project during the reporting period are as follows:

Name: Lee Gerdes  
Project Role: PI  
Nearest person month worked: 4  
Contribution to project: Overall study leadership and protocol compliance

Name: Gillan Smith  
Project Role: Senior Hardware Engineer  
Nearest person month worked: 3  
Contribution to project: Adapted HIRREM-SOP software for CDMRP placebo utilization

Name: Makayla Brewer  
Project Role: HIRREM-SOP Technician (Ft Bragg site)  
Nearest person month worked: 12  
Contribution to project: Administer HIRREM-SOP to study participants

Name: Nora Rachels  
Project Role: Research Coordinator (Ft Bragg site)  
Nearest person month worked: 12  
Contribution to project: Coordination of project activities at site

Name: Paula Bellini  
Project Role: Research Coordinator (USU site)  
Nearest person month worked: 12  
Contribution to project: Coordination of project activities at site

Name: Hannah O'Malley  
Project Role: HIRREM-SOP Technician (USU site)  
Nearest person month worked: 12  
Contribution to project: Administer HIRREM-SOP to study participants

Name: Dr. Charles Tegeler

Project Role: Co-Investigator  
Nearest person month worked: 1  
Contribution to project: Protocol compliance

Name: Catherine Tegeler  
Project Role: Senior HIRREM-SOP Technician  
Nearest person month worked: 2  
Contribution to project: Oversight and QC of HIRREM-SOP technicians at each site

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

No, nothing to report.

**What other organizations were involved as partners?**

Name: Womack Army Medical Center  
Location: Fort Bragg, NC 28310  
Contribution to Project: Collaboration: WAMC is providing various project personnel at the Fort Bragg site including Dr. Wesley Cole.

Name: The Geneva Foundation  
Location: Tacoma, WA 98402  
Contribution to Project: Under a funded subaward, the Geneva Foundation is providing various personnel to conduct the study at the Fort Bragg site.

Name: Uniformed Services University of the Health Sciences  
Location: Bethesda, MD 20814  
Contribution to Project: Collaboration: USUHS is providing various project personnel at the USUHS/WRNMMC site including Dr. Michael Roy.

Name: Walter Reed National Military Medical Center  
Location: Bethesda, MD 20889  
Contribution to Project: Facilities: Under a CRADA, WRNMMC is providing facility space needed to conduct the study at the USUHS/WRNMMC site.

Name: The Henry M. Jackson Foundation  
Location: Bethesda, MD 20817  
Contribution to Project: Under a funded CRADA, the Henry Jackson Foundation is providing personnel to conduct the study at the USUHS/WRNMMC site.

Name: Wake Forest University Health Sciences  
Location: Winston-Salem, NC 27157  
Contribution to Project: Under a funded subaward, Wake Forest is providing the services of Charles H. Tegeler, IV, M.D. He serves as the project's Co-Investigator. With a member of his research staff, he assists in various aspects of project management and implementation at both sites.

## 8. Special Reporting Requirements

### Randomized controlled trials of closed-loop allostatic neurotechnology to improve sensory function and pain management after mild traumatic brain injury



PH/TBI RP, Complex Traumatic Brain Injury Rehabilitation Research Award

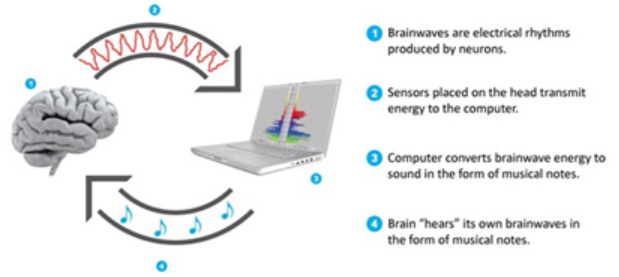
PI's: L. Gerdes (BST); M. Roy (USU); W. Cole (WAMC) Orgs: Brain State Tech.; Uniformed Services Univ.; Womack Army Medical Center  
Award Amount: \$2,833,185

#### Study Aims

- Persisting symptoms after TBI are associated with autonomic nervous system (ANS) dysregulation and sleep disturbance
- Closed-loop, allostatic neurotechnology provides acoustic stimulation based on algorithmic analysis of real time brain activity, supports robust symptom reduction and improvements in ANS regulation, non-drug way
- Promising data in patients with military and sport-related mTBI, PTSD, and in recently completely placebo-controlled study in insomnia (n=97)
- Technology currently office-based, but also recently configured as wearable device through STTR award from US Army Research Office
- Proposed trial data may show that mTBI is treatable condition

#### Approach

Two clinical trials proposed: 1) office-based technology (10 sessions) vs sham (10 sessions) to establish efficacy beyond placebo; 2) non-inferiority trial of micro-stimulation combined with 4 sessions of office-based technology vs 10 sessions of current approach. For both studies primary outcome is 3-month change in Neurobehavioral Symptom Inventory. Study 2 funded if Study 1 shows efficacy of technology.



Technology supports auto-calibration of neural oscillations, toward greater hemispheric symmetry, reduced hyperarousal. No other comparable device with published data showing clinical improvements. Both office and wearable configurations will be tested.

#### Timeline and Cost

Activities	CY	18	19	20	21	22	23
Obtain IRB approvals		█					
Conduct Study One		█	█	█	█		
Analyze data, report results, Study Two design and approval					█	█	
Conduct Study Two						█	
Complete Study Two; analyze data							█
<b>Estimated Budget (\$K)</b>		<b>\$300</b>	<b>\$450</b>	<b>\$400</b>	<b>\$500</b>	<b>\$680</b>	<b>\$500</b>

Updated: 29 Oct 2020

#### Goals/Milestones

**CY18 Goal** – Obtain Approvals and Begin Study One

**CY19 Goals** – Conduct Study One

- Train technologists to deliver intervention
- Begin recruitment for Study One
- Initiate study for 106 participants across both sites

**CY20 Goal** – Continue Performance of Study One

**CY21 Goal** – Complete Study One and Transition to Study Two

- Analyze data and report Study One results
- Design Study Two
- Obtain IRB approvals for Study Two

**CY22-23 Goals** – Complete Study Two and begin Data Presentations

- Conduct Study Two intervention sessions and follow ups
- Analyze data and submit for presentations

## 9. Appendices

Appendix A. Poster presentation at Military Health System Research Symposium (MHSRS)



Neurotech Abstract for 2020 MHSRS mee



Neurotech Abstract for SBMT 2020 meetir