AWARD NUMBER: W81XWH-17-2-0057

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 LLC
Scottsdale, AZ 85260

REPORT DATE: October 2018

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2018	Annual	30 Sep 2017 –29 Sept 2018

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

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-17-2-0057

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Lee Gerdes, PI; Dr. Charles H. Tegeler Co-Investigator, Wake Forest Medical; Dr. Roy, UHUHS PI; and Dr. Wesley Cole, WAMC PI

E-Mail:lee.gerdes@brainstatetech.com

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Brain State Technologies LLC
Scottsdale, AZ 85260

8. PERFORMING ORGANIZATION REPORT

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
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, closedloop, 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 USUHS/Walter Reed with one subject completing the ten sessions successfully without incident. WAMC is engaged in completing the IRB/HRPO approval process for WAMC and expects enrollment to begin in November, 2018.

Posting completed at Clinical Trials dot Gov - https://www.clinicaltrials.gov NCT03649958

15. SUBJECT TERMS
mTBI, concussion, insomnia, PTS, headache, anxiety, pain, depression, sleep, Post-Concussion Syndrome, Chronic pain, sleep disorders, behavioral symptoms, head

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified		19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

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 at USUHS/Walter Reed with one subject completing the ten sessions which was well tolerate. WAMC is engaged in completing the IRB/HRPO approval process for WAMC and expects enrollment to begin in November, 2018. A total of 106 participants will be enrolled at the two sites and 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: Assemble and Train Research Team, Lay Study Foundation	Months	Month Completed
Draft CRADA for approval at USU, WAMC, & Brain State Tech	5-7	9
Finalize study protocol, including consent form, recruitment fliers, and all other pertinent documents, and submit for IRB approval	1-3	3
Develop SOPs for all study procedures	1-3	4
Train study staff on all study procedures	7-9	11
Submit amendments, adverse events and protocol deviations as needed	As Needed	Yes
Milestone Achieved: CRADA approval at USU, WAMC & BST	5-7	yes
Milestone Achieved: IRB approval at USU, WAMC	7	USU-6; WAMC submitted
Milestone Achieved: HRPO second level IRB approval	8	USU-7; WAMC submitted

Task - Draft CRADA for approval at USU, WAMC, & Brain State Tech.

The necessary agreements and CRADA have been completed and approved between Brain State Technologies (BST), Uniformed Services University, Walter-Reed Hospital, Henry-Jackson Foundation, WAMC, and Geneva Foundation. The expected completion was in months 5-7 but was completed in month 9 due to the need for a 4-way CRADA to include Henry-Jackson Foundation, Walter Reed Hospital, Uniform Services University, and BST.

Task - Finalize study protocol, including consent form, recruitment fliers, and all other pertinent documents, and submit for IRB approval to be accomplished in months 1-3.
This task was completed on time. Study protocol has been finalized. Initial IRB completed and approved at USUHS. IRB amendments are now awaiting approval at USUHS. HRPO approval received at USU. The amended IRB and HRPO submission are now awaiting approval at WAMC and anticipated by 15 November 2018.

Task – Develop SOPs for all study procedures. This task completed on time in months 1-3.
HIRREM-SOP software was completed and used to provide on-line education modules for staff training at WAMC and USU.

Task - Train study staff on all study procedures.
Staff at WAMC and USU was mentored thru on-line education and successfully used the on-line education program to train as technologists approved to use HIRREM-SOP. This task was completed and has been utilized successfully as an on-line training course to train staff at both USUHS and WAMC. Additionally hands-on training by Catherine Tegeler from Wake Forest Medical and Lee Gerdes BST has been completed on-site for staff at both USUHS and WAMC. The staff at both sites has completed successful work with HIRREM-SOP on test subjects. Additionally data collection procedure training was also completed at both sites.

Methods of recruitment, randomization, and study participant data collection are in place at both sites, and are actively being utilized at USUHS.

Major Task 1-B: Establish Technical Infrastructure for Study One	Months	Month Completed
Acquire and configure hardware needed for both study sites	7-8	8
Generate a clinical trial database for brain activity patterns, on cloud-based server	1-3	3
Milestone Achieved: All equipment delivered and tested at both study sites	7-9	9

Task - Acquire and configure hardware needed for both study sites.
This task was completed successfully with all hardware and electronics acquired, shipped, and fully installed at each test site – USU & WAMC.

Task - Generate a clinical trial database for brain activity patterns, on cloud-based server.
This task has been done differently to allow for completely de-identified data to be backed up locally at each site. Plans are underway to create a means to upload that data to the cloud as participants are completed.

Major Task 2: Recruit Participants & Conduct Study One Procedures	Months	Month Completed
Initiate recruitment of study participants through multiple avenues	7-22	In process
Obtain informed consent from each eligible, interested participant	7-22	In process
Randomize each participant to one of 3 study arms	7-22	In process
Collect data on study participants throughout conduct of study and follow up periods	7-25	In process
Milestone Achieved: Enrollment of 106 participants (53 at each site) into Study 1 at an average rate of 2-4 per site per month	24	
Milestone Achieved: Collection of outcome measures from all 106 participants	25	

Tasks associated with Major Task 2 above.
The process is in place at USU and has been successfully used for their first participant. WAMC has been trained in the process and are awaiting secondary IRP and secondary HRPO approval from WAMC since this process changed after the initiation of the project and WAMC no longer accepted the USU IRB and HRPO approval without review of these applications. WAMC anticipates approvals by mid-November 2018.

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

Nothing to Report.

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 25 Cereset offices by 2019) as a Cereset Tech Coach.

How were the results disseminated to communities of interest?

Nothing to Report. Results have not been compiled.

Presentations have been made at Walter Reed, NICoE, and USU to inform staff of the study and the technology. Additionally the study has been posted in Clinical Trials dot Gov - https://www.clinicaltrials.gov NCT03649958.

An information table has been staffed periodically with posters announcing the study at Walter Reed and will also be done at WAMC when they are eligible to receive participants.

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

Both testing sites will participate in seeking and enrolling study participants, as well as collecting participant data and furnishing the test or placebo application.

When both sites are enrolling participants, BST will issue a press release regarding the on-going trial in order to increase awareness of the study to potential participants and their families.

4. Impact

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

Though the project is only begun, the concept that the brain can be supported to heal itself with a novel technological "echo" of the brain rhythm has caused many people to consider the possibilities. As a child who yells in a cave, valley, or tunnel to hear his/her echo enjoys the experience, the brain enjoys hearing itself and presents itself differently because of the experience.

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

The PI was changed during the last reporting period due to the original PI leaving the company. The change was approved during the first year.

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

One of the problems not anticipated was the amount of time required for the 4-way CRADA. The second problem encountered involved the amount of discussion required to IRB committee due to HIRREM-SOP being a novel intervention for mTBI. Both of these problems have been resolved and the project is moving forward.

The third problem discovered involved the changes in the eIRB which prompted much confusion and back-and-forth discussion. The issues were many but we now hope that the eIRB is stable and we can move forward together.

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:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	
Months worked:	1.7
Contribution to Project:	Mr. Gerdes oversaw of all aspects of project execution including leading team conference calls, overseeing CRADA and sub-award negotiations, supporting IRB approval process and HRPO submissions, coordinating hardware and software configuration and testing, and site setup plans.

Name:	Paul Hastings
Project Role:	Lead Software Engineer
Researcher Identifier (e.g. ORCID ID):	
Months worked:	3.1
Contribution to Project:	Mr. Hastings orchestrated the adaptation of HIRREM-SOP platform for CDMRP utilization.

Name:	Russell Loucks
Project Role:	Lead Software Engineer
Researcher Identifier (e.g. ORCID ID):	
Months worked:	4.8
Contribution to Project:	Mr. Loucks adapted HIRREM-SOP software for CDMRP placebo

	utilization.

Name:	Sung Lee
Project Role:	Principal Investigator Sep 30, 2017 to Dec 20, 2017
Researcher Identifier (e.g. ORCID ID):	
Months worked:	1
Contribution to Project:	Sung Lee organized conference calls and efforts to ascertain study protocol until Dec 20, 2017.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Yes, the Principal Investigator was approved for a change from Sung Lee to Lee Gerdes.

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

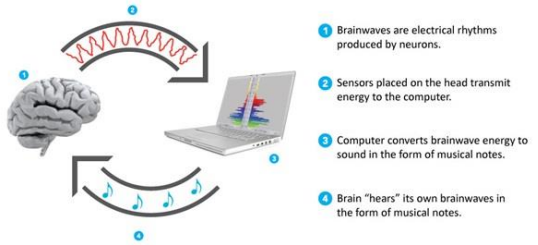
PI's: L. Gerdes (BST); M. Roy (USU); W. Cole (WAMC) **Orgs**: Brain State Tech.; Uniformed Services Univ.; Womack Army Medical Center **Award Amount:** $2,833.185

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 shortened office (2 sessions) plus wearable, vs office office (10 sessions), to assess scalability. Both studies, primary outcome is 3-month change in Neurobehavioral Symptom Inventory. Study 2 only to be funded if Study 1 shows efficacy of technology beyond sham.



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	17	18	19	20	21
Obtain IRB approvals					
Conduct Study One					
Analyze data; determine if Study Two is indicated					
Conduct Study Two (if indicated)					
Complete Study Two; analyze data					
Estimated Budget ($K)	**$550**	**$600**	**$800**	**$600**	**$365**

Updated: 27 Oct 2018

Goals/Milestones

CY17 Goal – Obtain Approvals and Begin Study One
Complete Obtain IRB approvals
CY18 Goals – Conduct Study One
☐ Train technologists to deliver intervention
☐ Begin recruitment for Study One
☐ Initiate study for 106 participants across both sites
CY19 Goal – Transition between Study One and Two
☐ Complete follow-ups for Study One participants
☐ Analyze data and determine whether Study Two is indicated
☐ Submit application to FDA, if indicated
☐ Begin Study Two, if indicated
CY20 Goal – Conduct Study Two
☐ Complete study for 86 participants across both sites
CY21 Goal – Complete Study Two and begin Data Presentations
☐ Analyze data and submit for presentations

9. Appendices

None