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, Scottsdale, AZ

REPORT DATE: October 2021

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Development 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 2021	Annual Report	30Sep2020-29Sep2021

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
W81XWH-17-2-0057

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER
PT160186

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development 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, 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 until late 2020. Phase 1 intervention of this study with 106 participants was completed in the last 12 months. Phase 2 of this study has commenced.

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

15. SUBJECT TERMS
None listed.

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)*

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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 Phase (Study) One participant enrollment was completed by September 30, 2021 following COVID shut down in March, 2020. Those qualified were randomized into test and control in a single blind study. Follow-up data is being gathered.

2. Keywords

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

3. Accomplishments

Study 1: Task/Milestone	**Target Completion Date/Quarter**	**Status**
Major Task 1-A: Assemble and Train Research Team, Lay Study Foundation		
- Draft CRADA for USU, WAMC, & BST	Oct 2017 or Y1Q1	Completed
- Develop SOPs for all study procedures	Mar 2018 or Y1Q2	Completed
- HRPO second level IRB approval for WAMC	May 2018 or Y1Q3	Completed
- Train study staff on all study procedures	June 2018 or Y1Q3	Completed
Major Task 1-B: Establish Technical Infrastructure for Phase One		
- Acquire and configure hardware	May 2018 or Y1Q3	Completed
- Generate brain pattern clinical trial database	Dec 2017 or Y1Q1	Completed
- Milestone: Equip. delivered and tested	June 2018 or Y1Q3	Completed
Major Task 2: Recruit Participants & Conduct Phase One Procedures		
- Initiate recruitment of participants	Sep 2019 or Y2Q4	Completed
- Obtain informed consent forms from participants	Jul 2021 or Y4Q4	Completed
- Randomize participants to one of 2 study arms	Jul 2021 or Y4Q4	Completed
- Collect data on study participants	Nov 2021 or Y5Q1	In Process
-Plan Phase 2 using tACS rather than wearable	Jul 2021 or Y4Q4	Completed
Major Task 3: Analyze Data and Report Results		
- Review all data for accuracy	Jan 2022 or Y5Q2	In Process
- Prepare results for presentation	Mar 2022 or Y5Q2	In Process

Study 2: Task/Milestone	Target Completion Date/Quarter	Status
Major Task 1-A: Assemble and Train Research Team, Lay Study Foundation		
- Review CRADA, finalize protocol, Submit to IRB	Jul 2021	Completed
Major Task 1-B: Establish Technical Infrastructure		
- Deliver equipment and train staff	Sep 2021	Completed
Major Task 2: Recruit Participants & Conduct Study	Sep 2022	In Process
Major Task 3: Analyze Data, Report Results, Continue Transitions	Sep 2022	In Process

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

Abstracts – See Appendix B.

1. Roy MJ, Cole W, Choi YS, Rachels N, O'Malley HS, Bellini PG, Brewer M, Gerdes L, Tegeler CA, Tegeler C. Allostatic Neurotechnology, a Novel Approach for Re-setting the Brain to Relieve Symptoms after Mild Traumatic Brain Injury. International Society for Traumatic Stress Studies Annual Meeting (meeting held virtually due to COVID-19), November, 2020.
2. Hannah O'Malley; Wesley Cole; Y. Sammy Choi; Nora Rachels, Paula Bellini; Makayla Brewer; Lee Gerdes; Catherine Tegeler; Charles Tegeler,; Michael J. Roy. Randomized Controlled Trial of Allostatic Neurotechnology to Treat Mild Traumatic Brain Injury. 15th Annual Amygdala, Stress and PTSD Conference: Stress and the Mind. Uniformed Services University, Bethesda, MD, April, 2021.
3. Roy MJ, Cole W, Choi YS, Rachels N, O'Malley HS, Bellini PG, Brewer M, Gerdes L, Tegeler CA, Tegeler C. Allostatic Neurotechnology, a Novel Approach for Re-setting the Brain to Relieve Symptoms after Mild Traumatic Brain Injury. Society for Brain Mapping and Therapeutics Annual Meeting, Los Angeles, CA, July, 2021.
4. Hannah O'Malley; Wesley Cole; Y. Sammy Choi; Nora Rachels, Paula Bellini; Makayla Brewer; Lee Gerdes; Catherine Tegeler; Charles Tegeler,; Michael J. Roy. Allostatic Neurotechnology, a Novel Approach for Re-setting the Brain to Relieve Symptoms after Mild Traumatic Brain Injury. Accepted for oral presentation at Military Health Services Research Symposium, Orlando, FL, August, 2021, meeting canceled due to pandemic, but presented at Center for Neuroscience and Regenerative Medicine/San Antonio Military Medical Center Joint Research Symposium (virtual), August, 2021, and USU Military Health Research Forum, November, 2021.

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 44 Cereset offices by 2022) as a Cereset Tech Coach.

How were the results disseminated to communities of interest?

Abstracts and virtual presentations presented and published on line for Military Health System Research Symposium (MHSRS); ISTSS; Annual Amygdala Stress and PTSD Conference; Society for Brain Mapping and Therapeutics; Center for Neuroscience and Regenerative Medicine/San Antonio Military Medical Center Joint Research Symposium.

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

Both testing sites are seeking and enrolling study participants for Study 2, as well as collecting remaining participant data for Study 1.

To Date for Study 1:
Screened: 80 at Bragg, 85 at USU/WR
Consented: 78 at Bragg, 47 at USU
Enrolled: 74 at Bragg, 38 at USU
Refused: 2 at each site, none in past year
Withdrawals: 9 at Bragg, 7 at USU

To Date for Study 2:
To date, 6/86 (7%) have been consented and enrolled for the Study 2.

4. Impact

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

Blinded analysis combining all study participants together demonstrates a clinically and statistically significant reduction on Neurobehavioral Symptom Inventory (NSI) scores, from an average of 41.0 at Baseline to 27.2 after the intervention; and the improvement is largely maintained with the score of 28.4 at 6 months.

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 for Study 2 is completed.

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:	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

Name:	Carissa Remillard
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

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

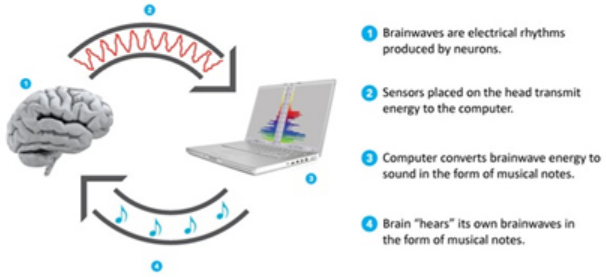
PI's: L. Gerdes (BST); M. Roy (USU); W. Cole (WAMC) **Orgs**: Brain State Tech.; Uniformed Services Univ.; Womack Army Medical Center **Award Amount:** $2,833,185

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
Obtain IRB approvals					
Conduct Study One					
Analyze data, report results, Study Two design and approval					
Conduct Study Two					
Complete Study Two; analyze data					
Estimated Budget ($K)	**$300**	**$450**	**$550**	**$750**	**$783**

Updated: 29 Oct 2021

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 Goals – Complete Study Two and begin Data Presentations
☐ Conduct Study Two intervention sessions and follow ups
☐ Analyze data and submit for presentations
Comments/Challenges/Issues/Concerns
☐ Planned schedule disrupted by COVID-19
☐ Compressed schedule for completion of Study Two
Budget Expenditures to Date
☐ Projected Expenditures: $1,675,000
☐ Actual Expenditures: $1,583,161

9. Appendices

Appendix A. IRB Phase 2 Oct. 2021

OCT 2021 CR for Neurotech.pdf

Appendix B.

Neurotech Abstract 12MAR2021.docx

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