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 85260

REPORT DATE: *Oct 2019*

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Oct 2019	Annual Report	09/30/2018 - 09/29/2019

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

CONTRACT NUMBER
W81XWH-17-2-0057

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Lee Gerdes, Brain State Technologies PI
Doctor Michael Roy, USUHS PI
Doctor Wes Cole, Fort Bragg PI
Doctor Charles Tegeler, Wake Forest School of Medicine, Co-Investigator
E-Mail: lee.gerdes@brainstatetech.com

5d. PROJECT NUMBER
PT160186

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Brain State Technologies
15150 N Hayden Rd, Suite 106
Scottsdale, AZ 85260

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 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 began in November 2018.

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

14. ABSTRACT

15. SUBJECT TERMS

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 tolerated. USUHS and WAMC have completed the IRB/HRPO approval process.

Enrollment activities have included:
USUHS 24; WAMC 47; Total 71 as of October 2019. 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 and 1 B completed in year 1.

Year 2

	Major Task 2: Recruit Participants & Conduct Study One Procedures	Months	Status
	Initiate recruitment of study participants through multiple avenues	7-33	In Process
	Obtain informed consent from each eligible, interested participant	7-33	In Process
	Randomize each participant to one of 3 study arms	7-33	In Process
	Collect data on study participants throughout conduct of study and follow up periods	7-39	In Process
	Milestone Achieved: Enrollment of 106 participants into Study 1 at an average rate of 2-4 per site per month (will file IRB update change for additional 20 participants due to drop-outs)	7-33	Est. Month 33
	Milestone Achieved: Collection of outcome measures from all 106 participants	7-40	Est. Month 40

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

Poster presentations have been provided at meetings offering Continuing Medical Education over the past 2 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.

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?

No formal data analysis has been performed due to the study being single blind. However, collective data including both test + control has been completed and formulated for a poster presentation at Military Health System Research Symposium (MHSRS) – Appendix A.

Press release made to general press – Appendix B.

TV News Report from WAMC – Appendix C.

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 furnishing the test or placebo application.

BST issued the press release regarding the on-going trial in order to increase awareness of the study to potential participants and their families (See Appendix B).

4. Impact

What was the impact on the development of the principal discipline(s) of the project?
The concept that the brain can be supported to heal itself with a novel technological "echo" of the brain rhythm has caused much discussion both at the MHSRS conference and in general. The collective numbers of test and placebo of Appendix A speak for themselves.

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:	5
Contribution to project:	Overall study leadership and protocol compliance

Name:	Russ Loucks
Project Role:	Lead Software Engineer
Nearest person month worked:	1
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:	LaToya Allen
Project Role:	HIRREM-SOP Technician (Ft Bragg site)
Nearest person month worked:	2
Contribution to project:	Administer HIRREM-SOP to study participants

Name:	Nora Rachels
Project Role:	Research Coordinator (Ft Bragg site)
Nearest person month worked:	10
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:	Gustavo Marino

Project Role:	HIRREM-SOP Technician (USU site)
Nearest person month worked:	8
Contribution to project:	Administer HIRREM-SOP to study participants

Name:	Hannah O'Malley
Project Role:	HIRREM-SOP Technician (USU site)
Nearest person month worked:	4
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:	4
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 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.; WomackArmy Medical Center

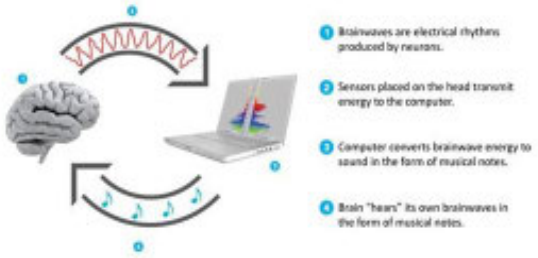
Award Amount: $2,600,000

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
Obtain IRB approvals, Hire & Train Staff				
Conduct Study 1 interventions and followups				
Analyze data, report results, design study 2, get approval				
Conduct Study 2 interventions and followups				
Completed Study 2; analyze data				
Estimated Budget ($K)	$650	$650	$650	$650

Updated: 21 February 2020

Goals/Accomplishments

CY18 Accomplishments
- ☐ Write Protocol, Obtain IRB approvals
- ☐ Write SOPs
- ☐ Train study staff
- ☐ Begin recruitment & enrollment for Study One

CY19 Accomplishments – Continue Study One
- ☐ Enrollment ~75% completed across USU/WR & WAMC, Fort Bragg
- ☐ Conduct intervention sessions and follow-up assessments

CY20 Goal – Finish Study One (S1) and transition to Study Two (S2)
- ☐ Complete enrollment and intervention delivery for 106 S1 participants
- ☐ Analyze data and disseminate results with presentations & publications
- ☐ Design Study 2
- ☐ Obtain IRB approvals for Study 2

CY21-22 Goal – Complete Study Two and Begin Data Presentations
- ☐ Conduct Study Two intervention sessions & follow ups
- ☐ Analyze data and submit for presentations

9. Appendices

Randomized Controlled Trial of Allostatic Neurotechnology to Treat Mild Traumatic Brain Injury

Michael J. Roy, MD, MPH[1], Wesley R. Cole, PhD[2], Y. Sammy Choi, MD[2], Paula Bellini, MA[1], Gustavo Marino[1], Nora Rachels[2], Makayla Brewer[2], Hannah O'Malley[1], Jacques Arrieux[2], Lee Gerdes[3], Catherine Tegeler[4], Charles Tegeler, MD[4].
[1]Center for Neuroscience and Regenerative Medicine, and Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD
[2]Womack Army Medical Center, Fort Bragg, NC; [3]Brain State Tech, Scottsdale, AZ; [4]Wake Forest School of Medicine, Winston-Salem, NC

Abstract

Background: Persistent symptoms after mild traumatic brain injury (mTBI), including chronic pain and sensory disturbance, may be related to alterations in neural oscillations. Studies in mTBI patients show suboptimal proportionation of power across the brain electrical frequency spectrum, including high amplitudes at both low frequency and high frequency ranges, the latter linked with disturbed sleep. Our randomized controlled trial evaluates noninvasive, closed-loop, acoustic echoing neurotechnology as a novel intervention to enable physiological and clinical recovery from mTBI, through auto-calibration of neural oscillations. We hypothesize that acoustic echoing of on one's own brain electrical activity will reduce mTBI symptom severity significantly more than comparably delivered random tones.

Population: Participants are active duty or recently retired service members, or their family members, with mTBI 3 months to 10 years prior, and subsequent persistent symptoms resulting in a Neurobehavioral Symptom Inventory (NSI) Score ≥ 23, enrolled at Uniformed Services University/Walter Reed National Military Medical Center, Bethesda, MD, or Womack Army Medical Center, Fort Bragg, NC.

Design type and procedures: This is a single-blind, controlled clinical trial randomizing 106 individuals, with persisting symptoms after mTBI, to 10 sessions of either closed-loop acoustic echoing neurotechnology, or non-specific acoustic input (random tones). Sessions are completed over 1-5 weeks. Each session includes a series of protocols in which scalp-based sensors monitor brain electrical activity that software algorithms analyze and translate in real time to acoustic patterns (audible tones of variable pitch and timing), echoed back to the user through earbuds. Both groups undergo the same sequence of procedures, and experience comparable levels of social interaction from study investigators and support personnel. Participants and outcomes assessors are blinded to treatment allocation. The primary outcome is differential change in NSI scores at three months, with final follow-up at six months. Secondary outcomes include measures of PTSD, depression, sleep, pain, dizziness, and quality of life, as well as objective measures of reaction time (ANAM simple and procedural reaction times), balance (modified Balance Error Scoring System, mBESS) and heart rate variability (FAROS system).

Preliminary Results: Data is presented for the first 31 participants to complete a baseline assessment, 10 intervention sessions, and a post-intervention assessment. Participants to date are 81% male, with a mean age of 35, 2.4 deployments, and 3.3 TBIs. Mean baseline scores are 41.1 on the NSI, 32.3 on the PTSD Checklist for DSM5 (PCL-5), 8.2 on the PHQ-9 screen for depression severity (≥20 is exclusionary), 15.5 on the Insomnia Severity Index, and 6.1 on the mBESS. The NSI score significantly declined to 26.2 (p<.0001), and the PCL-5 declined to 27.8 (p=.008) for all participants to date, both echoed and random tones, as we remain blinded to participant group assignment.

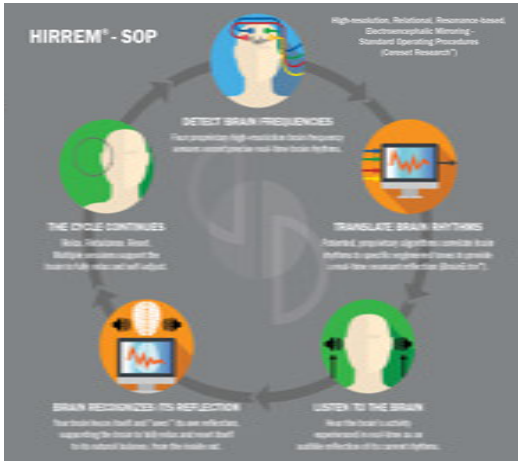
Preliminary Conclusions: Allostatic neurotechnology is an appealing and promising intervention for symptoms after mTBI; completion of the study should provide valuable data regarding efficacy.

Funding and Approvals

This work was funded by the US Army Medical Research and Development Command, with support also provided by the Center for Neuroscience and Regenerative Medicine. It was approved by IRBs at Uniformed Services University, Walter Reed National Military Medical Center, and Womack Army Medical Center.

Intervention

4-lead EEG High resolution (0.01 Hz) Acoustic Neuromodulation



- 10 sessions, ~ 1 hour each, over 1-5 weeks
- Comfortable, zero-gravity chair
- Lights out, eyes closed
- Participant & assessors blinded

Outcome Measures

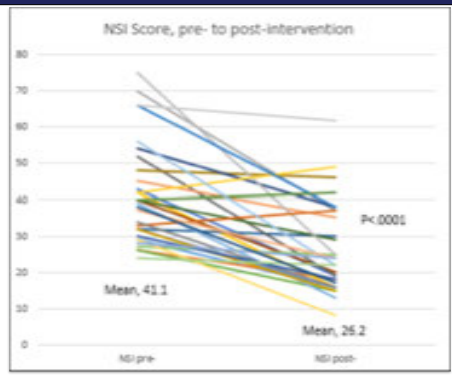
All obtained pre- and post-intervention, and at 3 & 6 months
Primary: NSI Score
Secondary:
PCL5 | ISI | PHQ-9 | PSQI | DVPRS | HIT-6 | mBESS DHI | PGIC | Psychophysiologic (BP, HR, HRV)

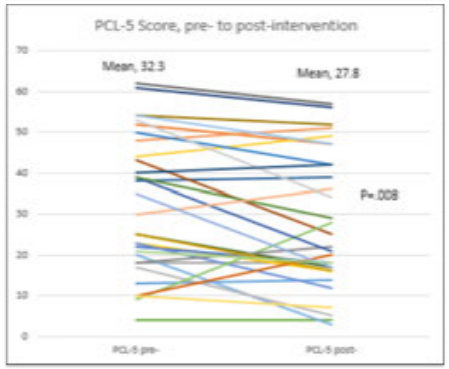
Baseline Data

- N=31 completers of intervention:
- 25 (81%) male
- Mean age 35
- Mean 2.4 deployments
- Mean 3.3 TBIs

* NSI 41.1
* PCL5 32.3
* PHQ-9 9.2
* ISI 16.2

Results





Preliminary Conclusions

- Intervention well-tolerated
- Significant improvement in symptoms evident
- Due to blinding, unclear at this point how much attributable to rest/relaxing environment, vs. echoing of brain patterns

Disclaimer

Any opinions or assertions expressed are solely those of the authors and do not necessarily represent those of Uniformed Services University, the U.S. Army, Department of Defense, or the U.S. Government.

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

Appendix B. Press release.

Cereset® Announces Mild-Traumatic Brain Injury Focused Clinical Trial Progress

Results to date demonstrate that Cereset's technology may help U.S. military personnel suffering from concussion

SCOTTSDALE, Ariz. (PRWEB) October 01, 2019 -- Today Cereset®, the only proven non-invasive technology that helps your brain relax and reset itself, announced the midway point of its randomized research trial for individuals with persisting symptoms following mild-Traumatic Brain Injury (mTBI). The objective of the study is to measure the efficacy of a non-invasive technology which compares tones delivered to a subject's brain guided by the brain's own rhythms, versus random unguided tones. The research trial is being conducted in two locations–Uniformed Services University of the Health Sciences (USUHS) in Bethesda, MD; and Womack Army Medical Center (WAMC) in Fort Bragg, NC.

The impressive interim results to date, which are a combination of test and placebo, indicate a possible breakthrough for an intervention treating mTBI. Once completed, the data can be summarized in separate test and placebo results. The final report for results at the trial's completion will provide definitive measures for the apparent positive changes seen to date.

In the United States, an estimated 190,000 individuals develop persistent symptoms each year following a concussion (mTBI). mTBI has been called the "signature injury" of the wars in Iraq and Afghanistan, with up to 80% of battle injuries attributable to concussive shock waves from an improvised explosive device (IED). Persisting symptoms after mTBI can cause debilitating conditions that may include sleep disturbance, anxiety and/or depression, foggy thinking, headaches, dizziness and behavioral issues. It's generally accepted that Post-Traumatic Stress Disorder (PTSD) often co-occurs with persisting mTBI.

"Once we realized the prevalence of mTBI amongst servicemen, it became our duty to help these soldiers transition back to a functional and healthy brain potential" said Lee Gerdes, Cereset® Founder and CEO. "Cereset® is designed to alleviate the symptoms and negative effects of brain trauma, so individuals no longer feel stuck in a high-stress neurological environment, long after the battlefield. We're pleased that the study is yielding positive results and that our technology is aiding the men and women who take on the selfless responsibilities of defending our country to be fully prepared for the next steps in their lives."

Cereset Research technology has been used in clinical trials at Wake Forest School of Medicine under the direction of Doctor Charles Tegeler, Professor of Neurology. Doctor Tegeler's findings with PTSD and athletes with persisting-post concussion symptoms were instrumental in securing a $2.8M grant from the Office of the Assistant Secretary of Defense for Health/Traumatic Brain Injury Research Program, under Award No. W81XWH-17-2-0057. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense.

Wake Forest School of Medicine is collaborating in this research through Doctor Tegeler's involvement as a Co-Investigator. Lee Gerdes, Cereset®/Brain State is the project's Principal Investigator; Doctor Michael Roy is Principal Investigator at USUHS; and Doctor Wesley Cole is Principal Investigator at WAMC.

For more information on how to participate in the trial please visit cereset.com/research and clinicaltrials.gov/ct2/show/NCT03649958

About Cereset®
Founded in 2003 by Lee Gerdes, Cereset® is the global technology leader in helping your brain relax and reset itself, enabling individuals to achieve higher levels of well-being and balance. The company's patented BrainEcho® technology uses auditory tones to reflect brain frequencies to create new neural pathways that reset the brain. Cereset® legacy technology has been licensed to over 200 affiliate centers in more than 18 countries to successfully empower more than 150,000 clients in North America and Europe. To schedule an appointment at a Cereset® office, or to learn more, visit cereset.com and watch vimeo.com/weareceresetwhat-is-cereset

Disclosure: Please be advised
(1) "The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702 5014 is the awarding and administering acquisition office" and;
(2) "This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs through the Psychological Health/Traumatic Brain Injury Research Program under Award No. W81XWH-17-2 0057. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense."
(3) "In conducting research using animals, the investigator(s) adheres to the laws of the United States and regulations of the Department of Agriculture."
(4) "In the conduct of research utilizing recombinant DNA, the investigator adhered to NIH Guidelines for research involving recombinant DNA molecules."
(5) "In the conduct of research involving hazardous organisms or toxins, the investigator adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories."

Contact Information
Lee Gerdes, CEO
Cereset
http://cereset.com
+1 (480) 265-8800

Online Web 2.0 Version
You can read the online version of this press release here.

Appendix C. TV News report from Fort Bragg.

https://vimeo.com/362851316