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TITLE: Neuromodulatory Treatments for Pain Management in Complex TBI Using Mobile Technology

PRINCIPAL INVESTIGATOR: Eric Elbogen, PhD

CONTRACTING ORGANIZATION: Duke University
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14. ABSTRACT - We aim to test whether mobile neurofeedback and mindfulness training lowers pain symptoms in Veterans with complex TBI. We are randomly assigning 300 Veterans with TBI and chronic pain into three groups (100 Veterans per group). Veterans in all groups receive an iPod Touch with a mobile application (app) installed. Veterans in group 1 receive a Muse headset, used to measure brain activity, and the "Mobile Neurofeedback" app; Veterans in group 2 receive the "Mindfulness Coach" app, which provides mindfulness training; Veterans in group 3 (control), receive the "Relaxing Nature" app, which provides ambient sounds for unstructured relaxation. Veterans are instructed to use their respective mobile apps independently 10 minutes a day, 4 times a week, for 12 weeks. Over the 12 weeks, research staff visit Veterans' homes twice to reinforce training, troubleshoot technical problems, and collect usage data. Staff also contact participants by phone twice to provide technical support and collect usage data. We interview Veterans, measure clinical outcomes, and measure brain activity with an electroencephalograph (EEG) at 0, 3, and 6 months. We expect that Veterans in the neurofeedback and mindfulness groups will have significantly reduced pain symptoms at the end of 3 months, with long-term improvement persisting at 6 months. We hypothesize reductions in pain symptoms will correlate with changes in brainwave activity. Given links between pain and negative outcomes, we will also examine outcomes related to drug abuse, violence, and suicidality. Finally, given these interventions may affect other biological systems, we will explore whether neurofeedback and mindfulness improve cardiovascular health by measuring heart rate variability.					
15. SUBJECT TERMS Neurofeedback, Neuromodulatory Treatments, Traumatic Brain Injury, Chronic Pain, Mobile applications, Alpha amplitude, Alpha frequency, Heart Rate Variability					
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1. INTRODUCTION:

The purpose of this study is to conduct a randomized controlled trial to test the efficacy of using mobile technology to deliver neuromodulatory interventions for reducing pain among Veterans with complex TBI.

Aim 1: Examine the effectiveness of mobile interventions for reducing pain symptoms in Veterans with complex TBI. Hypothesis 1: Given preliminary data and empirical support for neurofeedback and mindfulness, we hypothesize that Veterans in the two intervention groups will report less pain at 3 months compared to Veterans in the control group.

Aim 2: Investigate the impact of neurofeedback and mindfulness on brainwave activity in Veterans with complex TBI and chronic pain. Hypothesis 2: Given research on electroencephalogram (EEG) and pain, we hypothesize that Veterans in the two intervention groups will show increased (8–12 Hz) alpha power at 3 months compared to Veterans in the control group.

Given connections to adverse outcomes, we will explore whether neuromodulatory interventions impact: (i) risk behaviors, with a hypothesis of lower levels of suicidality, aggressiveness/ violence toward others, and use of alcohol and drugs for the neurofeedback and mindfulness groups compared to the control group; and (ii) heart rate variability (HRV), with a hypothesis of significantly greater improvements in HRV compared Veterans to the control group.

2. KEYWORDS:

- Neurofeedback
- Neuromodulatory Treatments
- Traumatic Brain Injury
- Chronic Pain
- Mobile applications
- Alpha amplitude
- Alpha frequency
- Heart Rate Variability

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**
 - Prepare for Clinical Trial (months 0-6): 100% complete
 - Baseline Interview/Data Collection (months 6-30): Ongoing
 - Implementation of Mobile Neurofeedback Intervention (months 4-30): Ongoing
 - Follow-up Interview/Data Collection (months 10-36): N/A for this reporting period
 - Data Analysis and Dissemination (months 12-36): N/A for this reporting period
- **What was accomplished under these goals?**
 - Prepare for Clinical Trial (months 0-6)

- During this reporting period, the study received IRB approval from Duke University and the Durham VA. The study team developed all data collection systems, and research assistants were trained for data collection and mobile intervention implementation.
- Baseline Interview/Data Collection (months 6-30)
 - Recruitment efforts during this reporting period include social media boosted posts and advertisements, contacting previous research participants who consented to a research repository, posting flyers and tri-fold handouts at various VA clinics and medical facilities, and contacting local college and university military associations.
 - The informed consent, initial screening, and interview processes began during this reporting period and are ongoing. As of 9/30/18 (report period end date), 5 participants had completed the informed consent and initial screening/interview process and an additional 11 potential participants were pre-screened over the phone and scheduled for baseline interviews. At the time this report was submitted (10/29/18), 11 participants had completed the informed consent and initial screening/interview process and an additional 7 were pre-screened over the phone and scheduled for baseline interviews.
 - The “Study Intervention/Implementation Team” met weekly during this reporting period. The “Data Management/Biostatistician,” “Veterans, TBI, and Pain Expertise,” and “EEG/HRV” Core Teams met frequently during this reporting period.
- Implementation of Mobile Neurofeedback Intervention (months 4-30)
 - Initiation of the intervention began during this reporting period and is ongoing. Participants were randomized into one of the three intervention groups and given an iPod Touch and instructions to practice the intervention for 12 weeks at home.
 - Individualized support calls and visits began during this reporting period and are ongoing. Per the study protocol, research staff visit the participant at their home (or similar location) to reinforce training related to their app, troubleshoot any difficulties, observe participants utilizing the intervention. They have also conduct support calls, per the protocol, to collect data on intervention utilization and tolerability and troubleshoot any technical difficulties.
- Follow-up Interview/Data Collection (months 10-36)
 - Follow-up interviews and data collection did not begin during this reporting period. The currently enrolled participants are actively engaged in the 12-week intervention, and follow-up interviews are expected to begin in December 2018.
- Data Analysis and Dissemination (months 12-36)
 - Not applicable. Data analysis, conference presentations, and manuscript preparation were not conducted during this reporting period, and were not expected during this reporting period.

- **What opportunities for training and professional development has the project provided?**
 - Nothing to Report.
- **How were the results disseminated to communities of interest?**
 - Nothing to Report.
- **What do you plan to do during the next reporting period to accomplish the goals?**
 - During the next reporting period, the study team will continue and expand upon recruitment efforts to continue to enroll participants in this study. Baseline interviews/data collection and implementation of the mobile neurofeedback intervention will be ongoing.
 - Follow-up interviews/data collection will begin during the next reporting period.

4. IMPACT:

- **What was the impact on the development of the principal discipline(s) of the project?**
 - Nothing to report.
- **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:

- **Changes in approach and reasons for change**
 - Changes were made to the EEG and HRV equipment and procedures for baseline and follow-up data collection sessions. These changes were approved by the DOD along with the accompanying budget justification.
- **Actual or anticipated problems or delays and actions or plans to resolve them**
 - There was a slight delay in beginning recruitment for the study as the team awaited DOD approval of an equipment/budget change and institutional IRB approvals. The team has since concentrated on recruitment and enrollment for the study. At the time this report was submitted (10/30/18) there were 11 participants enrolled and 7 scheduled for baseline interviews.
- **Changes that had a significant impact on expenditures**
 - An updated budget justification was submitted and approved by the DOD during the study initiation phase. Expenditure changes included a different EEG/HRV data collection system and the software needed to analyze the data, change in brand of neurofeedback headsets, and updated research supply expenses for these new procedures and systems.

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

- **Publications, conference papers, and presentations**
 - **Journal publications.** Nothing to Report.
 - **Books or other non-periodical, one-time publications.** Nothing to Report.
 - **Other publications, conference papers, and presentations.** Nothing to Report.
 - **Website(s) or other Internet site(s)**
<https://psychiatry.duke.edu/BehavioralTechLab>
 The lab website is used for recruitment purposes and will be used for disseminating results once the study is complete and results have been submitted for publication.
- **Technologies or techniques**
 As part of this study, our IT manager has created three original mobile applications (relaxing nature sounds, mindfulness exercises, and neurofeedback). All mobile applications are used for study data collection with pre- and post-session ratings for pain, anger, and stress.
- **Inventions, patent applications, and/or licenses**
 Nothing to Report.
- **Other Products**
 Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	<i>Eric Elbogen, Ph.D.</i>
Project Role:	<i>Principal Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0002-8341-8028</i>
Nearest person month worked:	<i>4</i>
Contribution to Project:	<i>Dr. Elbogen has led the strategic planning and implementation of the study design, monitored the study's progress in collaboration with co-investigators, supervised the research staff, and directed instrument adaptation and development.</i>

Name:	<i>Lana Watkins, Ph.D.</i>
Project Role:	<i>Co-Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0003-1889-5730</i>
Nearest person month worked:	<i>3</i>
Contribution to Project:	<i>Dr. Watkins has helped implement the ECG protocol to obtain HRV data. She has begun analyzing the data and supervising the data technicians</i>

Name:	<i>Aatif Husain, M.D.</i>
Project Role:	<i>Co-Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>N/A</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Dr. Husain has worked closely with the Clinical Research Coordinators and EEG Technician to ensure proper operation, reporting, and interpretation of the EEG machine</i>

Name:	<i>Tung Tran, MS, M.D.</i>
Project Role:	<i>Co-Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>N/A</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Dr. Tran has worked closely with Dr. Elbogen and the Clinical Research Coordinators to implement, monitor, report, and interpret the neurofeedback portion of the study</i>

Name:	<i>Amber Alsobrooks, MS, MA, LPA.</i>
Project Role:	<i>Clinical Research Coordinator</i>
Researcher Identifier (e.g. ORCID ID):	<i>N/A</i>
Nearest person month worked:	<i>6</i>
Contribution to Project:	<i>Ms. Alsobrooks has conducted research interviews, interventions, data collection, documentation, and recruitment of study participants.</i>

Name:	<i>Sara Battles, MA</i>
Project Role:	<i>Clinical Research Coordinator</i>
Researcher Identifier (e.g. ORCID ID):	<i>N/A</i>
Nearest person month worked:	<i>6</i>
Contribution to Project:	<i>Ms. Battles has conducted research interviews, interventions, data collection, documentation, and recruitment of study participants.</i>

Name:	<i>Kiera Molloy</i>
Project Role:	<i>Clinical Research Specialist, Sr</i>
Researcher Identifier (e.g. ORCID ID):	<i>N/A</i>
Nearest person month worked:	<i>6</i>
Contribution to Project:	<i>Ms. Molloy has conducted research interviews, interventions, data collection, documentation, and recruitment of study participants.</i>

Name:	<i>Jamie Wylie, MA</i>
Project Role:	<i>Operations Coordinator</i>
Researcher Identifier (e.g. ORCID ID):	<i>N/A</i>
Nearest person month worked:	<i>4</i>
Contribution to Project:	<i>Ms. Wylie has been responsible for equipment procurement and distribution, expense reporting, and subject reimbursement.</i>

Name:	<i>Jeffrey Hertzberg</i>
Project Role:	<i>IT Manager</i>
Researcher Identifier (e.g. ORCID ID):	<i>N/A</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Mr. Hertzberg programmed the mobile applications and neurofeedback equipment, and ensured the data are secure and encrypted for all mobile applications.</i>

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
 - Nothing to Report

- **What other organizations were involved as partners?**
 - Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** N/A

- **QUAD CHARTS:** see page 11

- **APPENDICES:** N/A



Neuromodulatory Treatments for Pain Management in Complex TBI using Mobile Technology (W81XWH-17-1-0591)

PI: Elbogen

Org: Duke University

Award Amount: \$2,598,606

Study Aim. TBI and chronic pain commonly occur together and are associated with poor outcomes for military Service members and Veterans. But pharmacological treatments can be associated with prescription drug abuse, and non-pharmacological treatments with low adherence. Two treatments that target changing how the brain modulates pain are *neurofeedback* and *mindfulness*, which have been shown to reduce chronic pain and can be administered feasibly via mobile technology. This study aims to evaluate the efficacy of these mobile interventions for reducing pain symptoms in Veterans with TBI.

Approach. N=300 Veterans with complex TBI will be randomly assigned to three groups. Each will receive an iPod Touch with a different mobile application (app) installed. Group 1 will receive a EEG headset, used to measure EEG brain activity and a “Neurofeedback” app. Group 2 will receive the “Mindfulness” app, developed by the DoD and VA, which provides mindfulness training. Group 3, the control group, will receive the “Relaxation” app, which provides unstructured relaxation. Veterans will be instructed to use mobile apps independently 10 minutes a day, 4 times a week, for 12 weeks. Data will be collected at 0, 3, and 6 months. We hypothesize participants in the intervention groups will report reduction in pain symptoms and show enhanced alpha brain activity on EEGs. We will explore if treatments also improve cardiovascular health and reduce drug abuse, violence, and suicidality in Veterans.



Veterans with complex TBI will use scientifically-supported, cost-effective, and self-directed treatment-- neurofeedback and mindfulness-- on mobile devices to reduce pain symptoms and improve mental and physical health.

Timeline and Cost

Activities	FY	17	18	19	20
Prepare for Clinical Trial					
Conduct Baseline/Follow-up Data Collection					
Implementation of Intervention					
Data analysis and manuscript preparation					
Estimated Budget (\$K)		\$690	\$610	\$700	\$600

Goals/Milestones

- FY17 Goal** – Prepare for clinical trial
 - ✓ Obtain study approval from Duke IRB and USAMRMC
- FY18 Goals** – Implement clinical trial
 - ✓ Develop data collection system
 - ✓ Train research personnel
 - ✓ Begin recruitment, baseline data collection, implement intervention
- FY19 Goal** – Communicate study progress/findings
 - Begin follow-up data collection
 - Present study progress at national conferences
- FY20 Goals** – Data analysis and production of deliverables
 - Conduct statistical analysis
 - Prepare manuscripts for publication

Updated: (October 2018)