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

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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. 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, Mindfulness

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Table of Contents

1. INTRODUCTION:

The purpose of this study is to conduct a randomized controlled comparative effectiveness trial to test the efficacy of using mobile technology to deliver neuromodulatory interventions (mindfulness, neurofeedback, relaxation) 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. Primary hypothesis: Given preliminary data and empirical support for neurofeedback and mindfulness, we hypothesize Veterans in the mindfulness and neurofeedback groups will report less pain intensity at 3 months compared to Veterans in the relaxation group, persisting at 6 months.

Aim 2: Investigate the impact of neurofeedback and mindfulness on pain interference and brainwave activity in Veterans with complex TBI and chronic pain. Secondary hypothesis: We hypothesize that Veterans in mindfulness and neurofeedback groups will show greater reduction in pain interference and greater increase in alpha (8–12 Hz) power at 3 months compared to Veterans in the relaxation group, persisting at 6 months.

Aim 3: 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 relaxation group; and (ii) heart rate variability (HRV).

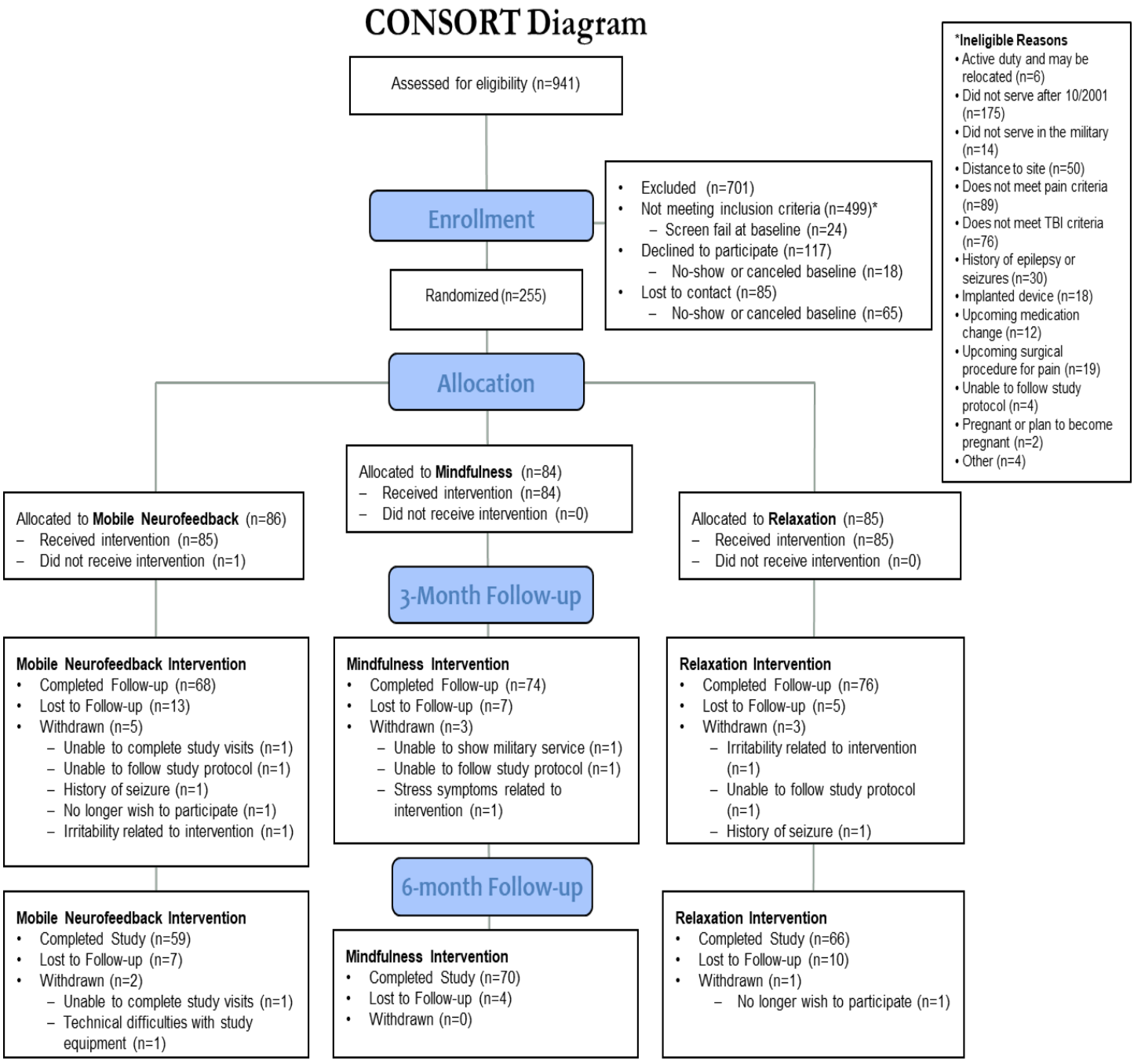
2. KEYWORDS:

- Neurofeedback
- Neuromodulatory Treatments
- Traumatic Brain Injury
- Chronic Pain
- Mobile applications
- Alpha Power

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**
  - Prepare for Clinical Trial
  - Baseline Interview/Data Collection
  - Implementation of Mobile Neurofeedback Intervention
  - Follow-up Interview/Data Collection
  - Data Analysis and Dissemination
- **What was accomplished under these goals?**
  - Prepare for Clinical Trial: complete
  - Baseline Interview/Data Collection: complete
  - Implementation of Mobile Neurofeedback Intervention: complete
  - Follow-up Interview/Data Collection: complete
  - Data Analysis and Dissemination: current
- **What opportunities for training and professional development has the project provided?**
  - Not applicable.
- **How were the results disseminated to communities of interest?**
  - Currently conducting analyses. Dissemination will begin once data analysis of primary and secondary hypotheses is completed. Additionally, we are currently preparing data files to submit to Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System to share with other Investigators.

Study Participant Enrollment: In total, we screened n=941 potential participants and ultimately enrolled n=255 post 9/11 Veterans meeting criteria for TBI and chronic pain. Final sample demographics were: 80% male (n=204) and 20% female (n=51); 78% non-Hispanic (n=198), 10% Hispanic (n=26), and remainder unknown; 73% White (n=186), 16% Black (n=40), 4% American Indian or Alaska Native (n=11), 2% Asian (n=4), 2% Native Hawaiian or Pacific Islander (n=5), and the remainder unknown. At six months, we retained n=195 Veterans with TBI and Chronic Pain (76% retention) which to our knowledge is comparable to, or better than, clinical studies for this population.



Study Analysis Results: Data collection ended September 2022 and we have conducted initial statistical analysis of the randomized controlled comparative effectiveness trial of neuromodulatory treatments on the primary outcome of pain intensity and secondary outcome of pain interference. Below we summarize preliminary study results that are currently under analysis and preparation.

- **Mobile Application Utilization:**
  - Participants were randomized into 3 groups: neurofeedback, mindfulness, and relaxation. All were asked to use a mobile app associated with each group for 10-minute sessions 4 times a week on their own for 12 weeks for a total of 48 sessions.
    - Veterans with TBI and chronic pain showed they were able to use neuromodulatory treatments on their own at home across all conditions (mean=44 sessions).
    - Participants showed highest usage of Relaxation (mean=49 sessions), then Mindfulness (mean=47 sessions), and Neurofeedback (mean=37 sessions).
    - Of note, Neurofeedback involved use of both an EEG headset and mobile app, whereas Relaxation and Mindfulness only involved use of a mobile app, which could account for this difference.
    - Regardless, Veterans across all conditions including Neurofeedback showed good compliance with the neuromodulatory treatment protocol calling for 48 sessions to be done independently at home.
    - This is the first study we are aware of that demonstrated feasibility for this mobile technology implementing neuromodulatory treatments for this population.
- **Effectiveness of Interventions:**
  - *For the primary outcome, analyses revealed that Veterans with TBI and chronic pain showed significantly reduced pain intensity at 3-months which persisted at 6 months across neuromodulatory treatment conditions.*
    - To examine treatment effects between data collection periods, paired t-tests were used to compare within-subjects differences between baseline to 3-month follow-up pain intensity, baseline to 6-month follow-up pain intensity, and 3-month to 6-month follow-up pain intensity.
    - In the mindfulness condition, Veterans showed significantly reduced pain intensity from baseline to 3-months ($t=6.78$, $p<.001$) and from baseline to 6-months ($t=5.90$, $p<.001$) but not from 3-months to 6-months ($t=0.86$, $p=.39$). This indicates that decreased pain intensity at 3 months stayed lower for Veterans at 6 months.
    - In the neurofeedback condition, Veterans showed significantly reduced pain intensity from baseline to 3-months ($t=5.06$, $p<.001$) and from baseline to 6-months ($t=5.59$, $p<.001$) but not from 3-months to 6-months ($t=1.36$, $p=.18$). This indicates that decreased pain intensity at 3 months stayed lower for Veterans at 6 months.
    - In the mindfulness condition, Veterans showed significantly reduced pain intensity from baseline to 3-months ($t=7.04$, $p<.001$) and from baseline to 6-months ($t=4.22$, $p<.001$) but not from 3-months to 6-months ($t= -1.68$, $p=.09$). This indicates that decreased pain intensity at 3 months stayed lower for Veterans at 6 months.
  - *For the secondary outcome, we found that Veterans with TBI and chronic pain showed significantly reduced pain interference at 3-months which persisted at 6 months across neuromodulatory treatment conditions.*
    - To examine treatment effects between data collection periods, paired t-tests were used to compare within-subjects differences between baseline to 3-month follow-up pain interference, baseline to 6-month follow-up pain interference, and 3-month to 6-month follow-up pain interference.

        - In the mindfulness condition, Veterans showed significantly reduced pain interference from baseline to 3-months (t=4.82, p<.001) and from baseline to 6-months (t=4.27, p<.001) but not from 3-months to 6-months (t=0.59, p=.55). This indicates that decreased pain interference at 3 months stayed lower for Veterans at 6 months.
        - In the neurofeedback condition, Veterans showed significantly reduced pain interference from baseline to 3-months (t=3.03, p<.001) and from baseline to 6-months (t=4.70, p<.001) but not from 3-months to 6-months (t=0.90, p=.37). This indicates that decreased pain interference at 3 months stayed lower for Veterans at 6 months.
        - In the mindfulness condition, Veterans showed significantly reduced pain interference from baseline to 3-months (t=3.19, p<.001) and from baseline to 6-months (t=3.07, p=.003) but not from 3-months to 6-months (t= -0.53, p=.60). This indicates that decreased pain interference at 3 months stayed lower for Veterans at 6 months.
    - *For the primary hypothesis, we found <u>no differences between study conditions</u> in 0-to-3-month changes or in 0-to-6-month changes on the primary outcome of pain intensity.*
        - Given multiple sessions per person, multilevel modeling (MLM) was used to account for shared variance among observations nested within individuals and to model the change scores in pain intensity to determine if they differed significantly from zero.
        - There was a significant effect of time on pain intensity, consistent with findings above across study conditions (F (2, 404)=68.09, p<.0001).
        - There was not a significant effect of time X treatment on pain intensity (F (4, 404)=1.09, p=.3609), meaning there was not a difference between study conditions and change in pain intensity over the course of the study.
    - *For the secondary hypothesis, analyses revealed <u>no differences between study conditions</u> in 0-to-3-month changes or in 0-to-6-month changes on the secondary outcome of pain interference.*
        - Given multiple sessions per person, multilevel modeling (MLM) was used to account for shared variance among observations nested within individuals and to model the change scores in pain interference to determine if they differed significantly from zero.
        - There was a significant effect of time on pain interference, consistent with findings above across study conditions (F (2, 393) =36.28, p<.0001).
        - There was not a significant effect of time X treatment on pain interference (F (4, 393) =0.57, p=.6813), meaning there was not a difference between study conditions and change in pain interference over the course of the study.

We are currently coding and analyzing the EEG data we collected, though this was limited due to discontinuing data collection during the COVID-19 pandemic. After, we will finish preparing a manuscript to submit to a peer-reviewed scientific journal and also enter main findings on clinicaltrials.gov. Once this main paper is accepted, we will analyze the exploratory hypotheses regarding other outcomes (e.g., suicidal ideation, violence) and submit that exploratory paper to a peer-reviewed scientific journal. Concurrently, we will submit both analyses to national conferences on pain management and neuromodulatory treatments to present results.

4. IMPACT:

- **What was the impact on the development of the principal discipline(s) of the project?**
  - To our knowledge, this is the first study to demonstrate that neuromodulatory treatments delivered via mobile technology were associated with reduced pain intensity and reduced pain interference in Veterans with TBI and chronic pain.
- **What was the impact on other disciplines?**
  - The study may have impact on other disciplines that address pain management in Veterans and non-Veterans; specifically, the findings point to a feasible approach that led to lower pain outcomes long-term that persisted and could therefore be used as an adjunct to clinic-based pain management treatment.
- **What was the impact on technology transfer?**
  - To our knowledge, this is the first study showing that Veterans with TBI and chronic pain had little difficulty independently using this technology to manage chronic pain outside medical facilities and clinics. This provides strong support for the feasibility of technology transfer to Veterans with TBI and chronic pain to use neuromodulatory treatments for pain management on their own at home.
- **What was the impact on society beyond science and technology?**
  - This study has implications for pain management for society. Specifically, it shows that neuromodulatory treatments delivered via mobile technology were associated with reduced pain intensity and reduced pain interference in adults with chronic pain and TBI, who showed they were readily able to use the interventions to treatment chronic pain on their own. As a result, neuromodulatory treatments may serve as a useful adjunct to clinic-based pain management treatment.

5. CHANGES/PROBLEMS:

- Due to COVID-19 pandemic and stay-at-home orders, we began conducting study visits remotely March 2020. As such, the Duke IRB and HRPO has approved the following changes to our protocol:
  - All study visits occurred remotely via telephone, Zoom, and/or Webex.
  - Participants completed the informed consent process via eConsent. Study coordinators still offer ample time for reviewing the informed consent document, verbally explain the elements of informed consent, and participants are required to respond to questions to check for understanding before signing the document.
  - For remote 3-month follow-up visits, in lieu of travel reimbursement, we reimbursed participants $35 for returning their study equipment, to compensate for the time and travel required to ship materials back to us. Participants will still receive $100 reimbursement for completing the study visit.
  - Procedures done in-person, including EEG & HRV readings, were discontinued.
- Despite this, throughout the entire study period, we were able to continue the <u>vast majority</u> study procedures and received Duke IRB and HRPO approval for these changes. Specifically, we could implement the following procedures for the *complete clinical trial study period*:
  - Recruitment
  - Screening
  - Informed consent
  - Baseline interview and survey data collection
  - Implementation of 3-month neuromodulatory interventions with mobile applications
  - Follow-up interviews and survey data collection at 3 months
  - Follow-up interviews and survey data collection at 6 months
  - Data Collection of primary outcome measure (pain intensity)
  - Data Collection of secondary outcome measure (pain interference)

- Due to the COVID-19 pandemic, we also reevaluated our exclusion of pregnant women. This exclusion criterion was originally incorporated into our research because of lack of knowledge about safety; however, we are unaware of studies that report adverse effects of neurofeedback on pregnancy. Additionally, by reducing pain, mobile neurofeedback may at the same time reduce opioid consumption, which is more definitively linked to known risks during pregnancy (https://www.cdc.gov/pregnancy/opioids/basics.html).It could be reasonably argued that neurofeedback may in fact reduce the level of risk for pregnant women by helping lower opioid use. For these reasons, and to ensure consistency with NIH's inclusion policies for pregnant women in clinical research, we no longer excluded pregnant women.

6. PRODUCTS:

- **Publications, conference papers, and presentations**
  - **Journal publications.** We published preliminary data on use of mobile neurofeedback for Veterans with PTSD, TBI, and Chronic Pain. Elbogen EB, Alsobrooks A, Battles S, Molloy K, Dennis PA, Beckham JC, McLean SA, Keith JR, Russoniello C. Mobile Neurofeedback for Pain Management in Veterans with TBI and PTSD. Pain Med. 2021 Feb 23;22(2):329-337. doi: 10.1093/pm/pnz269. PMID: 31697371; PMCID: PMC7901853.
  - **Books or other non-periodical, one-time publications.** Nothing to Report.
  - **Other publications, conference papers, and presentations.** Currently preparing publications, conference papers, and presentations on clinical trial findings.
- **Technologies or techniques**
  - As part of this study, we 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**
  - Duke has filed for a patent on this technology, please see DD-882 and https://patents.google.com/patent/US20210361222A1/en?inventor=eric+elbogen&oq=eric+elbogen
- **Other Products**
  - Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**
  - Primary Investigators: Eric Elbogen
  - Co-Investigators: Jean Beckham, Ph.D. Patrick Calhoun, Ph.D. Aatif Husain, M.D. Tung Tran, MS, M.D. Lana Watkins, Ph.D.
  - Clinical Research Staff: Amber Alsobrooks, Sara Battles, Megan Lanier, Chase Dubois, Alex Thompson, Keira Molloy.
  - IT Programmer: Jeffrey Hertzberg
  - Consultants: Carmen Russoniello, Ph.D., Matthew Mauck, M.D.
- **What other organizations were involved as partners?** Not applicable.

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** not applicable
- **QUAD CHARTS:** attached

APPENDICES: not applicable