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TITLE: Efficacy of Repetitive Transcranial Magnetic Stimulation for Improvement of Memory in Older Adults with TBI

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CONTRACTING ORGANIZATION: Palo Alto Veterans Institute for Research, Palo Alto, CA

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Background: Recent advances in both AD and TBI have tested non-pharmaceutical interventions that target chronic symptom improvement (e.g., non-invasive brain stimulation, exercise and cognitive training). In order to provide targeted therapies to patients who suffer from chronic sequela of TBI it is necessary to understand mechanisms of repair within the context of an aging brain. Repetitive TMS (rTMS) delivers therapeutic, non-invasive brain stimulation, is FDA-approved for treatment for major depression (George et al., 2010) and currently used for treatment of pain (PI: Ashford; Co-I: Adamson), PTSD, anxiety, improvement of executive function in mild and moderate TBI (PI: Adamson), severe TBI (PI: Pape; Co-I: Adamson), memory enhancement (Wang et al, 2014) and dementia (PI: Cheng; Co-I: Adamson). This treatment can induce neuronal long-term potentiation (Wang et al 2011; 2014) resulting in synaptic repair (Cheeran et al., 2008; Lu et al., 2013) leading to improvements in memory function through hippocampal-cortical circuits (Venkatesan et al., 2014) and brain connectivity measured by resting state-fMRI (rs fMRI) particularly in default mode and central executive network (DMN & CEN; Liston et al., 2014). We primarily propose to assess the efficacy of rTMS to improve memory performance and to test rs-fMRI (i.e. DMN) as a potential biomarker to capture response to treatment in older patients suffering with chronic symptoms related to previous brain injuries (depression, PTSD etc). In addition, we assess other established biomarkers longitudinally (e.g., hypometabolism via PET FDG, cortical oscillation via electroencephalography (EEG), Brain Derived Nerve Growth Factor (BDNF) and hippocampal volume from structural MRI) to capture patient response to treatment that may signal early dementia.

Hypotheses: Primary: Subjects with TBI who receive active rTMS treatment (rTMS_A) will: a) show significantly greater improvement from baseline in memory performance post rTMS intervention compared to subjects who received sham rTMS treatment (rTMS_S), and b) show stronger functional connectivity within and between DMN and CEN post rTMS intervention compared to patients who received sham (rTMS_S).

Secondary: 1. Quality of Life (QOL): scores on QOL scale will improve with rTMS treatment in patients who receive rTMS treatment. 2. Sustained Improvement: At 6-month follow-up, patients with TBI in rTMS_A group would be more likely to have sustained greater brain connectivity compared to patients in the rTMS_S group predicting better memory performance. 3. Moderators of Response: The following variables may moderate memory function improvement in patients with TBI post intervention and at 6- follow-up: Age, health condition variables (severity of symptoms at baseline, time to injury, baseline cognitive performance, TBI type, comorbidities (PTSD, sleep, depression), substance abuse, medication use, fatigue); physiological and biological variables

(baseline hippocampal volume and/or microstructure, baseline connectivity in DMN & CEN, EEG resting and task-related cortical oscillations, and Brain Derived Neurotrophic Factor (BDNF) genotype. 4. Mediators of Response: To assess the mechanism of rTMS in synaptic repair/regeneration, pre and post changes will be assessed in depression and PTSD measures, Plasma BDNF, FDG PET hypometabolism in precuneus/posterior cingulate area, EEG resting and task-related cortical oscillations, and connectivity of DLPFC (stimulation site & part of CEN) with other DMN.

Specific Aims: Primary Aim: a) To assess the efficacy of rTMS to predict improvement in memory performance pre and post rTMS intervention in older patients with TBI, and b) To assess rs-fMRI as a biomarker to detect these changes in memory performance. Secondary Aims: To assess the mechanism of rTMS in synaptic repair/regeneration by assessment of structure & functional brain activity (PET/MRI, EEG & fMRI), genetic, cognitive and behavioral function factors (including QOL, depression and PTSD).

Research Strategy: We propose to collect baseline, post treatment, and 6 month follow-up data in 50 older subjects (age 50-75 yrs)with mild and moderate TBI with chronic symptoms including memory complaints. Recruitment will be at DVBIC at VAPAHCS and surrounding community. Following screening, patients will be randomized into 1 of 2 treatment groups: rTMS or sham (treatments for 20 sessions (Location: Left DLPFC; Power: 120% of motor threshold; Pulse frequency: 10 Hz); trial duration: 28 weeks (1-2 weeks screening, 2 weeks treatment and 24 week follow-up). Simultaneous collection of FDG PET MRI, rs-fMRI and resting and task-related EEG at baseline, post rTMS treatment and 6-month follow-up at Stanford. Neuropsychological, self-report of memory performance, every-day function and chronic health complaints will also be collected.

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1. INTRODUCTION:

We primarily propose to assess the efficacy of rTMS to improve memory performance and to test rs-fMRI (i.e. DMN) as a potential biomarker to capture response to treatment in older patients suffering with chronic symptoms related to previous brain injuries (depression, PTSD etc.). In addition, we will assess other established biomarkers longitudinally (e.g., hypometabolism via PET FDG, cortical oscillation via electroencephalography (EEG), Brain Derived Nerve Growth Factor (BDNF) and hippocampal volume from structural MRI) to capture patient response to treatment that may signal early dementia.

2. KEYWORDS:

TBI, AD, fMRI, PET MRI, BDNF, memory, cognition, PTSD

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1: Prepare protocol for the study (Q1) - 100% complete
Major Task 2: Study Preparation (Q1) - 100% complete
Subtask 1: Obtain Regulatory Approval (FDA, HRPO, R&D & IRB) - 100% complete
Subtask 2: Identify all VA and Stanford Imaging Centers and Clinics needed for study - 100% complete
Subtask 3: Recruit and Train Study Staff - 100% complete
Subtask 4: Initiate patient recruitment plan 100% complete
Subtask 5: Facilitate training, supervision and fidelity checks with new staff - 100% complete
Subtask 6: Set up Access Database - 100% complete
Major Task 3: Conduct the rTMS trial (Specific Aim 1 & 2)
Subtask 1: Conduct Study, Report Findings - Initiated
Screen potential participants using telephone screening and consent (*n*= 50)
Milestone Achieved: 1st participant consented, screened and enrolled (100% complete)
Milestone Achieved: Study begins (100% complete)
Evaluate and randomly assign participants to one of the two rTMS treatment groups (initiated – see progress below)
Assess all participants' pre-post rTMS for all variables (Specific Aims 1 &2) (initiated – see progress below)
Milestone Achieved: Collect data pre-post rTMS (Specific Aim 1) (initiated)

What was accomplished under these goals?

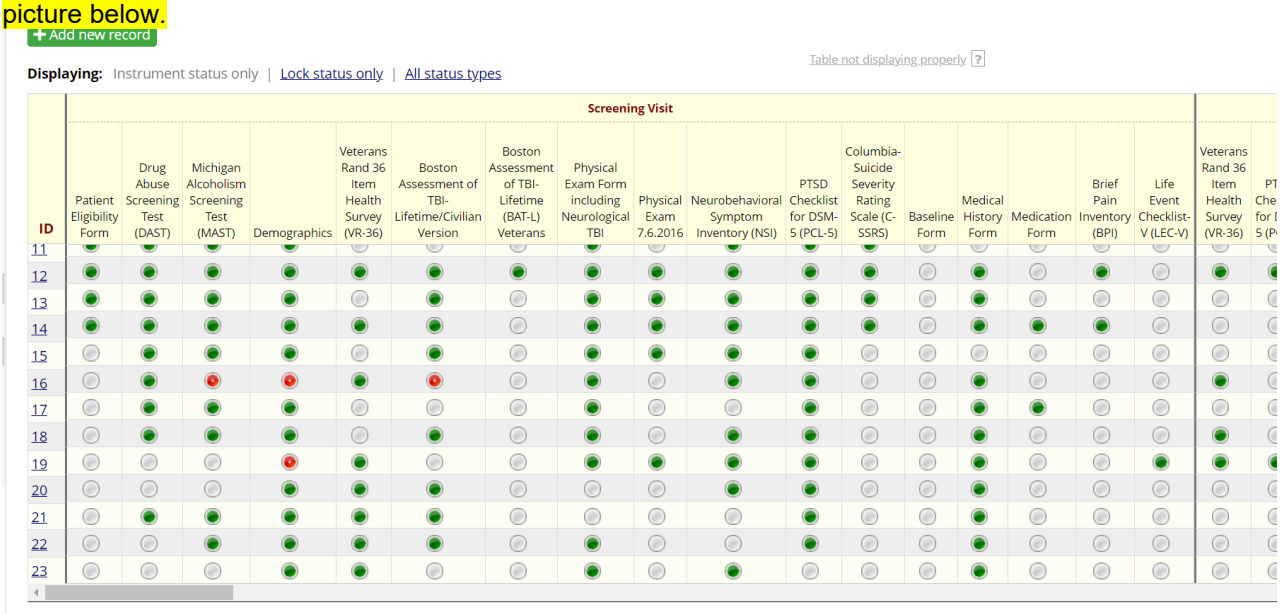
We are continuing to recruit, screen, and enroll. Nine participants have undergone complete treatment and completed the 6 month follow-up. Four participants were in active treatment, but due to COVID-19 we will restart them from the beginning of treatment. Two more participants have been screened and are anticipating enrollment in Oct 2021.

Total Phone Screened: estimate of 115
Total Screened (in person): 28
Total Current Enrollment: 28
Total Withdrew: 5
Ineligible: 2

As all research activities were halted due to COVID19 shutdown in March 2020, recruitment and enrollment goals were not met during the year of 2020. After VA research operations and Stanford lifted restrictions for patient facing research in Feb 2021, recruitment efforts have increased. However, due to continued worries about COVID-19 and the Delta variant, potential participants still show concern about traveling to the VA for research.

In addition to continuing our clinical trial with additional recruitment and enrollment, we have also achieved some major goals. Please note, we have not broken the blind of the study so we cannot report on the pre and post rTMS results.

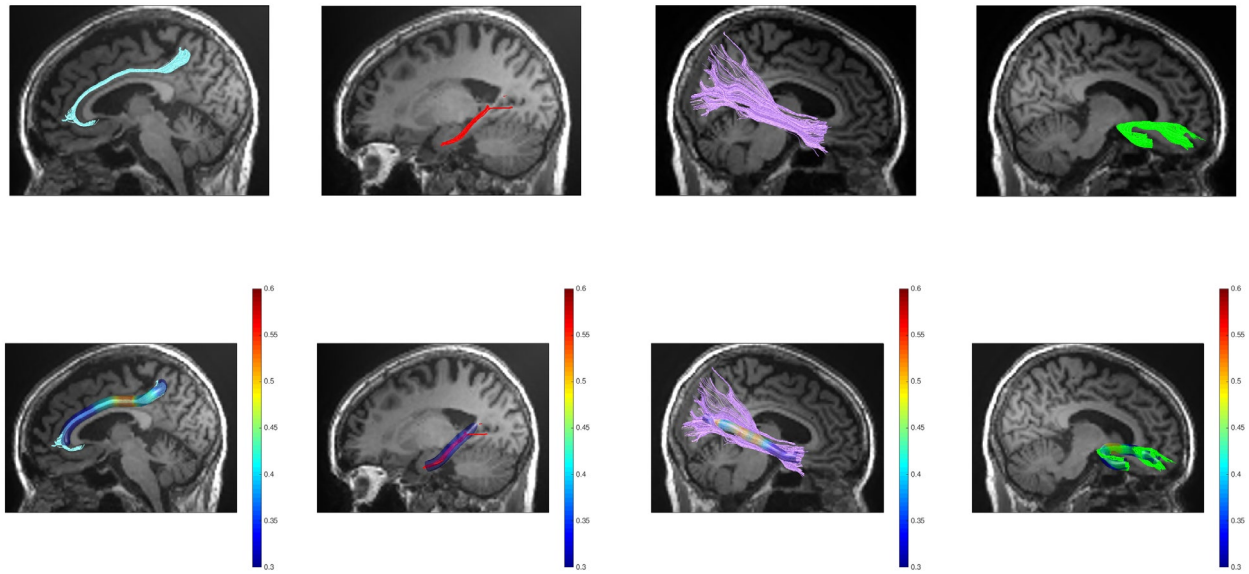
1. We have created our RedCap® database and continue to add our data in this database. Please see the picture below.



2. We have also analyzed our baseline CTI MRI data with respect to TBI and comparing it to controls we have from other studies. We are using state-of-the art tractography techniques to display the results. None of it is published yet.

See figure below.

3. We will also be breaking our blind in Summer.



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Fiber Tracts and FA Profiles

What opportunities for training and professional development has the project provided?
2

There have been many opportunities for training and professional development under this project. Research coordinator, Kaitlly Zhu, has attended VA Clinical rTMS In-Person Training which was held at the VA Palo Alto. She has also attended the In-Person TMS Cobot Training that was held in VA Livermore and has attended multiple online webinars hosted by the Clinical TMS Society.
Kaitlly also had the opportunity to train volunteer research assistants within the lab which included recruitment, Veteran interactions, screening calls and shadowing.

We also have a large summer student volunteer program where high school and undergraduate students shadow the TMS work we do and have an opportunity to learn about research. We have collaborated with Stanford Neurosurgery and Psychiatry departments for this.

How were the results disseminated to communities of interest?

Although we have not published yet we have been speaking about our study and submitted an abstract for a talk at American Psychological Association (APA) Division 20&3 Joint Symposia titled: "Harnessing neural-based metrics to enhance innovative treatment strategies for improving cognitive decline in TBI" and we were accepted for a 17 minute talk at the in-person 2022 meeting to be held in August 2022 in Minneapolis. We are very excited about this.

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

After completing the remaining 6 month follow-ups, we will begin our analysis of all the participant data and lift study-blind. We will let participants know whether they were in the active or sham group, and allow those who were in the sham group receive active treatment.

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:

New clinical research coordinator, Kaitlly Zhu; Kaitlly is leaving Feb 25th 2022. We are hiring a part-time RA who will continue the follow-up. Based on the money left, we may not reach the stated number of participants but we will break the blind in summer and report our results. We hope the APA talk will be the first dissemination stage for this study.

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

VA Research Operations and Stanford are slowly lifting restrictions of patient facing research due to COVID-19. We plan to up recruitment efforts to get ourselves back on track with enrollment goals.
Kaitlly Zhu is leaving on Feb 25th 2022, we are training a new part-time person who will continue and do follow-ups.

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

Significant changes in use or care of human subjects

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.

Abstract for 17 min talk accepted for APA 2022 in Minneapolis. Harnessing neural-based metrics to enhance innovative treatment strategies for improving cognitive decline in TBI"

- **Website(s) or other Internet site(s)**

We have this study listed here on our website for recruitment: https://med.stanford.edu/adamson-lab/researchtopic/tbimemory.html

- **Technologies or techniques**

Nothing to Report

- **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:	**Maheen Adamson**
Project Role:	**Principal Investigator**
Researcher Identifier	N/A
Nearest person month worked:	3.0 CM

Contribution to Project:	Dr. Adamson revised the protocol including the screening and neuropsychological testing batteries. Contacted all co-I and consultants, met with radiology staff at Stanford and set up the data collection process with them. This was also done with the clinical rTMS team at VAPA and the EEG data collection team. Dr. Adamson submitted the IRB/ HRPO/ RDIS/ DVBIC/ FDA paperwork. Dr. Adamson worked with PAVIR to set up the job description and interviewed about 5 candidates to select one. She also received the FDA IDE and worked on the IRB comments. Minor modifications are being made to the protocol at the request of HRPO, which have received FDA and IRB approval. We anticipate final approval from HRPO and HRPP in due course.
Name:	**Kaitlly Zhu**
Project Role:	**Research Assistant**
Research Identifier:	N/A
Nearest Person Month Worked:	9.0 CM
Contribution to Project:	Ms. Zhu has been assisting with study setup, including familiarizing herself with the study protocol, instruments, and neuroimaging techniques; purchasing equipment; training in screening procedures, and rTMS. She has been trained in the protocols and will be conducting recruitment, testing, treatment and data collection.
Name:	**Michael Zeineh**
Project Role:	**Co-Investigator (Stanford)**
Research Identifier:	N/A
Nearest Person Month Worked:	0.12 CM
Contribution to Project:	Dr. Zeineh has been responsible for the overall study design and interpretation of the data in collaboration with the other investigators on the project, including monitoring the analysis conducted by the postdoc.
Name:	**Emily Dennis**
Project Role:	**Research Associate (Stanford)**
Research Identifier:	N/A
Nearest Person Month Worked:	1.8 CM
Contribution to Project:	Ms. Dennis has been working to confirm the fidelity of the acquired datasets, and used advanced imaging software to produce segmentations of hippocampal substructures.

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?

Stanford University
Palo Alto, CA
Stanford University is a subawardee on this project; Dr. Michael Zeineh is the subaward PI. Stanford will perform the PET-MR data acquisition under Dr. Zeineh's supervision. Dr. Zeineh will design and monitor the detailed MR imaging protocol in the first year. Funding has been provided for a postdoctoral fellow in the second year to investigate the fidelity of the data and perform novel segmentation on the high-resolution PETMRI to deliver multi-parametric maps of the hippocampal subfields. This will be analyzed in conjunction with the whole-brain data analysis with our VA collaborators to understand the impact of transcranial magnetic stimulation on patients with a history of traumatic brain injury.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: