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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
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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.

Table of Contents

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

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:** *Provide a brief list of keywords (limit to 20 words).*

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

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

All these goals have been accomplished:
Goals/Milestones
CY17 Goal – Regulatory setup
 Obtain FDA, IRB, HRPP (DHA/DVBIC), HRPO (Army) approval
CY18 Goals – rTMS trial, Year 1
 Finalize FDA IDE, HRPO approval & IRB modification
 Initiate staff training and study set up (PET MRI, EEG, rTMS)
 Database design and development
 Participant recruitment
CY19 Goal – rTMS trial, Year 2
Ongoing participant recruitment and enrollment, begin follow ups

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results

achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

After approval from the FDA on October 3rd, 2019, we then submitted to HRPO and after all the approvals we started recruitment in Dec-Jan of this year.

Despite our delays, we have screened 95 patients on phone and in person. 23 are enrolled. We have collected all measures with success, except for EEG and are entering data on RedCap as well. COVID-19 has halted research plans as of early March 2020 and we are in the works of recontinuing enrollment. The IRB, RDIS is approved and Lucas PET MRI at Stanford just gave us the green light so we are now screening patients to start the study. Ms. Srija Seenivasan is helping us. She is hired as an RA on another TMS study. Harlene has left the position but we are interviewing for another RA and Srija Seenivasan is the POC on the study. We are approved by the VA to bring research subjects in now during Phase II Research.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Dr. Angela Phillips, a polytrauma Fellow, is being mentored by Dr. Adamson and has been supervising Srija Seenivasan, the RA for all the stimulation needs. There are several graduate students who are helping with the neuropsych testing and data entry. There is also patient interaction for them that is very good for training.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Dr. Adamson was invited to present at DOD annual CDMRP review meeting at Fort Dietrich in August as well. Data flow and current processing was shared with the committee.

However, this is a double blind Randomized Clinical Trial so we cannot share results until data collection is complete and blind is broken.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

I would like to be able to report at least 50% of recruitment done. So we can move closer to analyzing data and breaking the blind.

4. IMPACT: D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to Report Yet.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are*

significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to report

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use of biohazards and/or select agents

NA

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to Report

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

https://stan.md/NeurorehabLab

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

FDA IDE – G180005

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

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:	**Harlene Grewal (she has left, and we are interviewing a new person for hire)**
Project Role:	**Research Assistant**
Research Identifier:	N/A
Nearest Person Month Worked:	9.0 CM
Contribution to Project:	Ms. Grewal has been assisting with study setup, including familiarizing herself with the study protocol, instruments, and neuroimaging techniques; purchasing

	equipment; training in screening procedures, EEG, and rTMS; and has begun identifying potential participants.
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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

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: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.