

AWARD NUMBER: W81XWH-15-1-0516

TITLE: Neuromodulation and Neurorehabilitation for Treatment of Functional Deficits after mTBI plus PTSD

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REPORT DATE: October 2021

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;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE October 2021		2. REPORT TYPE Annual		3. DATES COVERED 30Sep2020 - 29Sep2021	
4. TITLE AND SUBTITLE Neuromodulation and Neurorehabilitation for Treatment of Functional Deficits after mTBI plus PTSD				5a. CONTRACT NUMBER W81XWH-15-1-0516	
				5b. GRANT NUMBER N/A	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Dr. Theresa Pape E-Mail: Theresa.BenderPape@va.gov				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Chicago Association for Research and Education 5000 South 5 th Avenue Bldg. One C347 Hines, IL 60141				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 This study will determine (i) the magnitude of immediate and sustained effects of a current clinical standard interactive computer attention processing training (APT) when combined with intermittent theta burst stimulation (iTBS), a type of repetitive transcranial magnetic stimulation (TMS) and (ii) determine how APT + iTBS changes the neurocognitive system of attention in individuals with persistent attention deficits related to mTBI and PTSD. Previous studies have shown that iTBS can produce alterations in cerebral function that facilitate learning and recovery from neurologic injury.					
15. SUBJECT TERMS Neurobehavioral, intermittent Theta Burst Stimulation(iTBS), Attention Processing Training (APT), Mild Traumatic Brain Injury (mTBI), Post-traumatic Stress Disorder (PTSD)					
16. SECURITY CLASSIFICATION OF: Unclassified			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 8	19a. NAME OF RESPONSIBLE PERSON USAMRDC
a. REPORT	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

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1. INTRODUCTION: The purpose of this study is to determine the magnitude of immediate, sustained and long term effects of the current clinical standard interactive computer attention processing training (APT) combined with intermittent theta burst transcranial magnetic stimulation (iTBS) in Veterans, Active Duty Military Personnel and Civilians with persisting attention deficits related to Mild Traumatic Brain Injury (mTBI) and Post Traumatic Stress Disorder (PTSD) and to determine how APT + iTBS changes the neurocognitive system of attention in these individuals. This study is a randomized clinical trial (RCT) that directly addresses the intent of the Neurosensory and Rehabilitation Research Award program announcement (W81XWH-14-CRMRP-NSRRA), specifically the Clinical Trial Research Focus Area of Neuromusculoskeletal Rehabilitation. The proposed work will impact the health care needs of Active Duty Military Personnel and Veterans with mTBI and PTSD (mTBI + PTSD) because the anticipated findings will advance our understanding of long-term remediation of attentional deficits and how this translates to improved functioning in everyday life. This research is also likely to provide new avenues for treatment research for all TBI, fundamentally advancing the field of TBI neurorehabilitation.

2. KEYWORDS:

Attention Processing Training (APT), Intermittent Theta Burst Stimulation (iTBS), Mild Traumatic Brain Injury (mTBI), Post-Traumatic Stress Disorder (PTSD), Randomized Clinical Trial (RCT)

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Goal 1: Regulatory Requirements (Months 1-6)

Milestones Achieved: Local IRB approval for VA and NMH;

Milestones Achieved: 2nd level IRB approval by HRPO/ORP;

Initial IRB approvals have been obtained from both Northwestern University and Hines VA IRB. HRPO has reviewed and approved the study at Northwestern University as of December 21, 2017. HRPO reviewed and approved the study at Hines VA as of 11-23-2018. Local IRB approved requested changes with an effective date of 11-26-2018.

Major Goal 2: Coordinate Study Staff and Logistics for Study (Months 1-6)

Subtask 2a: Hiring and Training of Study Staff

Milestones Achieved: Study staff hired and trained at both study sites;

Subtask 2b: Development of study related materials and finalize logistics

Milestones Achieved: All study materials and procedures finalized at both study sites; All study staff have been hired at Hines VA and Northwestern. Training of staff to administer neuropsychological evaluations, iTBS, and cognitive intervention is complete. Training procedures were previously on hold due to the COVID-Administrative Hold and remote working environments. Core staff have completed training on iTBS and cognitive intervention, and finalizing procedures are in progress. Additional staff will be trained as needed to support changes in volume of subjects and paid time off for core staff.

Major Goal 3: Participant Recruitment, iTBS/APT Intervention and Follow-up (Months 6-45):

Study Cohort data has been acquired through the use of the VA Data Access Request Tracker (DART). Vetting of cohort data for recruitment is ongoing (approximately 30,000 records remained after initial vetting process). Screening of civilians has been bolstered by initiating services of Patient Wing, a web-based recruitment platform. During the current reporting period, 431 new screenings have been completed with a total of 1101 potential subjects screened to date. At the time of this report, 668 of those potential subjects were excluded and we were unable to achieve contact with 150 potential subjects to screen for participation. 429 letters have been sent to potentially eligible participants, with 152 individuals declining participation or opting out of being contacted. An additional 127 individuals are in the process of being contacted for telephone screening after screening of the electronic medical record. 80 telephone screenings have been completed to date, with 9 individuals having been scheduled for a Diagnostic Confirmation Screening. 5 participants have been enrolled to date, 3 have completed their participation.

Recruitment Activities	Current Reporting Period	Total to Date
Participants Screened	431	1101
Telephone Screenings Completed	28	80
Diagnostic Confirmations Screenings Scheduled	9 (3 no shows, 1 excluded due to EtOH relapse prior to DCS)	9
Diagnostic Confirmations Completed	5	5
Enrolled and Consented	5	5
Excluded or Lost to Follow Up Following Diagnostic Confirmation Screening	2	2
Completed Study Participation	3	3
DCS = Diagnostic Confirmation Screening		

Major Goal 4: Data Analysis (Months 4-48): Nothing to report.

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

Two VA polytrauma research fellows have completed training for treatment provision and testing procedures. They have been and/or are currently actively engaged in conducting research procedures for the trial.

How were the results disseminated to communities of interest?

One article in revision/provisional acceptance (Lead Author Lindsey, A)

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

During the next reporting period, we will continue recruitment efforts and plan to progress subjects who have passed Telephone Screening to Diagnostic Confirmation Screening. We will contract with Patient Wings, an online recruitment platform. We plan to increase recruitment efforts by utilizing additional staff, including Project Manager and new volunteers to bolster

recruitment efforts. For all subjects who qualify for participation based on Diagnostic Confirmation Screening, we will schedule all research procedures minimizing any delays. We will continue training of staff to use TMS equipment, deliver iTBS protocol and administer active and sham APT to maximize staffing available for enrollments.

4. **IMPACT:** Nothing to report.

5. **CHANGES/PROBLEMS:**

Changes in approach are **not** anticipated at this time.

Problems: Prior recruitment problems were indicated by several possible participants that the time commitment required for participation in this study was too burdensome. Over the past year we revised the study protocol to reduce that burden on participants and increase the rate of recruitment. Additionally, recruitment, enrollment and progress toward research goals was significantly impacted by the COVID-19 pandemic. A mandatory 13 month pause on in person research activities limited our ability to initiate enrollment. The prolonged delay of potential participants who, prior to COVID mandated hold, qualified to move forward from Telephone Screening to Diagnostic Confirmation Screening resulted in multiple participants being lost. The extended delay also significantly impacted funding available to meet all study goals and support staffing necessary to maximize opportunities for concurrent enrollments of participants. The PI considered if aspects of the study could be completed remotely to advance to enrollment sooner, but the nature of the intervention and lack of validation of study outcomes to be completed remotely eliminated this option. The PI is employing post-doctoral fellows to support staffing and possibly allow increased opportunities for concurrent enrollment of participants, staggering subject enrollments to maximize number of procedures that can be completed weekly. Over the next quarter, we plan to seek additional staffing support through posting an opening for an additional post-doctoral fellow and seeking additional volunteers to support completing research procedures. Lastly, we have completed a protocol amendment to allow civilian participants to complete their study participation in the more affordable VA setting to achieve maximal recruitment within the available remaining funds

6. **PRODUCTS:**

Herrold A Pennington D Li X Ge L Bender Pape T Jordan N Chambers A Mallinson T Cobia D Sander A Batki S (under review) Co-occurring mild Traumatic Brain Injury and Posttraumatic Stress Disorder elevates alcohol

Lindsey A Ellison R Herrold A Aaronson A Kletzel S Stika M Guernon A **Bender Pape T** (provisional acceptance, 2021) rTMS/iTBS and Cognitive Rehabilitation: A Theoretical Framework and Review Examining Paired Treatment to Remediate Deficits Associated with TBI and PTSD. The Journal of Neuropsychiatry and Clinical Neurosciences (Manuscript # APPI-JN-21-09-0227)

Cogan AM Weaver J Scholten J **Bender Pape T** Mallinson T (2021) Psychometric properties and sex differences on the Mayo-Portland Adaptability Inventory Participation subscale (M2PI) in Veterans with TBI. Archives of Physical Medicine and Rehabilitation, 102(11): 2193-2200 (PMID 34175272).

Herrold A Siddiqi S Livengood S **Bender Pape T** Higgins J Adamson M Leung A Rajj T (2020) Customizing TMS applications in traumatic brain injury using neuroimaging. Journal of Head Trauma Rehabilitation, 35(6): 401-411 (PMID: 33165153).

Cogan AM Scholten J Smith B Eapen B **Bender Pape T** Mallinson T (2020) Self-reported participation restrictions among male and female veterans with traumatic brain injury in Veterans Health Administration outpatient polytrauma programs. Archives of Physical Medicine and Rehabilitation, 101(12): 2071-2079 (PMID: 32795563).

Herrold A Kletzel S Mallinson T* **Bender Pape T*** Weaver J Guernon A Smith B Babcock-Parziale J High W Sesso-Osburn F Vis L (2019) Psychometric measurement properties of the World Health Organization Disability Assessment Schedule 2.0 (WHODAS) evaluated among Veterans with mild traumatic brain injury and behavioral health conditions. Disability and Rehabilitation, 24: 1-10 (PMID: 31549869).

Herrold A Smith B Aaronson A Coleman J **Pape T L-B** (2019) Relationships and evidence-based theoretical perspectives on persisting symptoms and functional impairment among mild traumatic brain injury and behavioral health conditions. Military Medicine, 184(1): 138-147 (PMID 30901443).

The lab continues development of manuscripts for APT standardization and a manual for APT administration.

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project?

Name: Ann Guernon, MS, CCC-SLP, CCRC No Change

Name: Theresa Pape, DrPH, MA, CCC-SLP No Change

Katie Kestner, DPT
Clinical Research Manager
1 person month

Kelly Krese, DPT
Research Therapist
1 person months
No change

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?

Organization Name: Northwestern University

Location of Organization: Chicago, IL, USA

Partner's Contribution to the Project: Collaboration

8. SPECIAL REPORTING REQUIREMENTS: None.

9. APPENDICES: Quad chart attached.