

AWARD NUMBER: W81XWH-15-1-0516

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

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CONTRACTING ORGANIZATION: Chicago Association for Research and Education in Science  
Hines, IL

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<b>14. ABSTRACT</b> 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.					
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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: 2<sup>nd</sup> level IRB approval by HRPO/ORP;*

Initial IRB approvals were obtained from both Northwestern University and Hines VA IRB. HRPO 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. Core staff have completed training on iTBS and cognitive intervention, and finalizing procedures are in progress. Additional staff are 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 was bolstered by initiating services of Patient Wing, a web-based recruitment platform. Patient Wing contract expired on 8/30/22 and was not renewed at this time as the study team has obtained access to a new database of potential research participants through Northwestern Medicine. The study team continues to screen 14 applicants from Patient Wing, and will continue to attempt contact with all Patient Wing applicants and complete the screening process to enroll any eligible applicants from this recruitment source. The Northwestern Medicine Enterprise Data Warehouse (EDW) required IRB approval for access which was obtained on 7/19/22. Recruitment of the initial list of 246 civilians with history of mild TBI and PTSD documented in their medical record has been initiated and will be the focus on civilian recruitment for the next interim.

Over the past year, 614 new screenings have been completed with a total of 1,715 potential subjects screened to date. At the time of this report, 1,086 of those potential subjects were excluded and we were unable to achieve contact with 215 potential subjects to screen for participation. Five hundred eighty-eight letters have been sent to potentially eligible participants, with 242 individuals declining participation or opting out of being contacted. After screening of the electronic medical record, 237 individuals are currently being contacted for telephone screening. One hundred thirty-five telephone screenings have been completed to date, with 19 Diagnostic Confirmation Screenings completed to date. Six participants have completed full study participation.

Recruitment and Enrollment Activities	Current Reporting Period	Total to Date
Participants Screened	614	1715
Excluded	438	1086
Telephone Screenings Completed	55	135
Diagnostic Confirmations Completed	14	19
Excluded Following Diagnostic Confirmation Screening	5	9
Self-Withdrawn	4	4
Completed Study Participation	3	6

**Major Goal 4: Data Analysis (Months 4-48):** The study team has completed data analysis for the first 6 participants to inspect data quality and integrity. Initial findings indicate consistency between our study outcomes that span the WHO ICF levels of functioning (body structure, function, activities and community). Across all of these study outcomes, we see very promising patterns of improved performance in both treatment conditions during treatment provision, frequent trends of superior improvement in the iTBS + APT condition relative to iTBS alone, generally strong retention of gains in follow-up analysis. We also see strong pattern of continued gains, after treatment cessation, for iTBS+APT participants. This pattern suggests that we are restoring skills for at least three weeks and that the combined iTBS+APT neuromodulation treatment may enable continued gains in skills targeted for remediation. It will be important to advance understanding, when the study is completed, who needs the combined treatment to enable continued skill restoration after treatment cessation. Our limited placebo data, at this time, indicates a pattern across the outcomes of marginal or absent performance change in our placebo

control participant, increasing our confidence that improvements in our treatment group participants were not attributable to test practice effects or placebo alone. In aggregate we perceive these data to provide very encouraging signs of meaningful treatment group improvements in neural function, as indicated by rsFC and eye tracking metrics, supporting gains in skills targeted for remediation (attention) and that these gains translate to symptom reduction, improved task performance efficiency, and enhanced engagement in activities and involvement in life situations/societal engagement.

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

A new polytrauma candidate has completed interviews and is currently applying for the VA Polytrauma Post-Doctoral Research Fellowship offered through the Office of Academic Affiliations. Dr. Alexandra Aaronson is a Psychiatrist and recipient of a VA RR&D Level I Career Development Award (CDA) and Dr. Pape is her CDA I Primary Mentor. As such, Dr. Aaronson has been actively engaged in this study as one component of her advanced research training supported with her CDA I award. Based, in part on these training opportunities, Dr. Aaronson recently received notification of funding for a Level II CDA via VA RR&D to continue examining the use of iTBS to address suicidality in TBI.

### **How were the results disseminated to communities of interest?**

The past year has been productive in disseminating information through publications and conference presentations. See Section 4 Products for publications.

#### Publications:

Lindsey A Ellison R Herrold A Aaronson A Kletzel S Stika M Guernon A Bender Pape T (in press, 2022) 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. (PMID: 35872613)

#### Invited Talks:

2022: **Bender Pape T** Featured Speaker, National VA Research Week, Repurposing Research – Sponsor Feature: Cures Within Reach, “Mild TBI + PTSD: Brain Modulation for Cognitive Rehabilitation”, Chicago Association for Research and Education in Science, Hines, IL.

2022: **Bender Pape T** Featured Speaker, VA VISN 12 Quarterly Polytrauma Grand Rounds, Neuromodulation & Neurorehabilitation for Mild TBI + PTSD, Virtual to VISN 12 and invited guests.

2020: **Bender Pape T** Symposia, “Neuromodulation in Neurorehabilitation of TBI with and without Co-Occurring Mental Health Conditions,” VA VISN 12 Polytrauma/TBI Conference, COVID19 Virtual Platform.

#### Oral Presentations: Abstracts:

Guernon A Larson E Brady S **Bender Pape T** (2022) Attention Training Paired with Neuromodulation to Enhance Benefit after TBI, 62nd Annual Convention, Illinois Speech and Hearing Association, Oral Presentation, Oral Presentation, Rosemont IL.

**Bender Pape T** (2022) Neuromodulation for Neurologic Recovery, Transcranial Magnetic Stimulation for TBI. North American Neuromodulation Society's Annual Conference, Symposia, Orlando FL.

VanLandingham H Gonzalez C Ellison R Lindsey A Aaronson A Kletzel S Guernon A Stika M Herrold **A Bender Pape T** (2021, February). Pairing Neurostimulation and Cognitive Intervention: A Theoretical Framework for Treatment of Co-Occurring TBI and PTSD. Poster presented at International Neuropsychological Society Annual Conference, Online.

#### Abstracts:

Herrold A Livengood S Siddiqi S **Bender Pape T** (2021) Customizing rTMS treatment targeting for co-occurring alcohol use disorder and mild traumatic brain injury using multi-modal neuroimaging data as neurobiological markers. , 4<sup>th</sup> International Brain Stimulation Conference, Symposia, Charleston, SC, Brain Stimulation: 14 (2021) e1721 (FS4F.06)

#### Poster Presentations: Published Abstracts:

Wisinger A Stika M Gonzalez C Cladek A Ellison R Riordan P Herrold A Kletzel S Aaronson A Lindsey A **Pape T Smith B** (2021). Predictors of Cognitive Functioning Among Veteran with Mild Traumatic Brain Injury (mTBI); Abstract #1024410 at ACRM Annual Conference Progress in Rehabilitation Research: Translation to Clinical Practice; 2021 Sept 28; Virtual; # Brain Injury ISIG David Strauss, Ph.D. Memorial Award

#### **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 subjects passing the Telephone Screening will progress to Diagnostic Confirmation Screening. As mentioned above, we also plan to utilize a new database resource through Northwestern Medicine (EDW) which is able to sort individuals who have already consented to being contacted for research opportunities and have documented histories of mild TBI and PTSD. We are also bolstering our recruitment efforts through new regulatory guidance and our recent approvals which allow us to contact Veterans or civilians via email or text, in addition to our existing processes of letters and telephone calls. This new communication strategy will allow us to contact potential participants through multiple avenues and be responsive via their preferred communication method. We have also recruited new volunteer staff, who can assist in increasing volume of mailings and email recruitment to increase our rates of first contact to potential participants. 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. In response, we revised the study protocol in year 5 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.

Incidence of COVID diagnosis and exposure impacted recruitment during the winter surge (December 2021-February 2022), as facility specific screening requirements at Hines and NU both limited in person attendance for research appointments if the individual had a close contact with someone with COVID within the past 14 days or that had themselves tested positive within the past 40 days. Although CDC guidelines had reduced the length of time for quarantine following infection, local hospital facilities did not update their guidelines until January 20, 2022 and high transmission rates continued to limit ability to bring participants in for in-person testing.

In response to recruitment barriers, we have considered what regulatory changes we can make to the protocol, updated recruitment strategies, and shifted staffing to address problems with recruitment. During the past reporting period, the number of study arms was reduced to maximize the strength of findings with a smaller pool of participants. Study exclusion criteria that didn't impact safety were eliminated to improve recruitment (i.e., removing 10 years max time since TBI). We have increased reimbursement by \$75 to address surging gas prices which may be a barrier for participants ability to drive to study sites.

Participant no show rate and time commitment required to complete study procedures continues to be a barrier to enrollment. Over the past year, 26% of Diagnostic Screening appointments resulted in no shows; this is lower than the past quarter though at 55% no show rate. Over the past year, 30% of participants have declined participation due to the time commitment required that is not feasible with other life commitments. We will

continue to provide memory supports in the form of reminders, and provide flexible scheduling options, to try to minimize these barriers to recruitment. Additionally stringent inclusion/exclusion criteria necessary for safety of participants and the ability to achieve meaningful conclusions has resulted in a high rate of screened participants being excluded (71%).

## 6. PRODUCTS:

Lindsey A Guernon A Stika M Bender Pape T (in press, 2022) The Diagnostic Intersection of Cognitive-Communication Disorders and Aphasia Secondary to TBI Among Veterans, *International Journal of Language & Communication Disorders* (Manuscript ID TLCD-2022-0008.R1)

Cogan AM Bender Pape T Yeaw J DeKoven M Anupindi R, Jordan N (2022) Health care resource utilization and costs for adults with mild traumatic brain injury with chronic vestibular impairment. *Archives of Physical Medicine and Rehabilitation*, 103(1):90-97 (PMID: 34634230).

Stika M Riordan P Aaronson A Herrold A Ellison R Kletzel S Drzewiecki M Evans C Mallinson T High W Babcock-Parziale J **Bender Pape T** Smith B (2021) Cognition and other Predictors of Functional Disability Among Veterans with Mild Traumatic Brain Injury and Post-Traumatic Stress Disorder. *Journal of Head Trauma Rehabilitation*, 36(1): 44-55 (PMID: 32898030)

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 (in press, 2022) 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*. (PMID: 35872613)

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 Raij 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).

Book Chapter:

**Bender Pape T** Barrington N Webber E Stutzmann G (in press, 2023) Exogenous Induction of Neuroplasticity: Non-Invasive Neurostimulation, IN *Encyclopedia of Human Brain*, 2nd edition, Jordan Grafman (Editor), Section: Neuroplasticity, A.M. Barrett and Keith McGregor (Section Editors),

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.