

AWARD NUMBER: W81XWH-15-1-0516

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

PRINCIPAL INVESTIGATOR: Theresa Pape, DrPH

CONTRACTING ORGANIZATION:

Chicago Association for Research and Education in Science
Hines, IL 60141

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
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14. ABSTRACT This study is a double blind randomized placebo-controlled clinical trial using repeated measures . The objective is to improve recovery of functional skills for persons living in states of seriously impaired consciousness 3 to 12 months after severe TBI. This will be achieved by determining the neurobehavioral and neural effects of repetitive transcranial magnetic stimulation (rTMS), which is a non-invasive technique to stimulate the brain. The evidence of therapeutic efficacy from the literature in non-TBI related neurologic populations combined with our preliminary findings with severe TBI, indicate that rTMS merits investigation as a neurotherapeutic for severe TBI and that the proposed repetitive TMS protocol should be examined to determine effectiveness in inducing structural and functional neural plasticity and improving neurobehavioral recovery after severe TBI. Specific Aims: Aim I will determine presence, direction and sustainability of rTMS-induced neurobehavioral effects measured with the Disability Rating Scale. Aim II will determine the presence, direction and sustainability of rTMS-induced changes in functional neural activation and whether or not these changes correlate with improving neurobehavioral function. Aim III will examine the effect of rTMS on white fiber tracts and whether or not the rTMS-related effects correlate with improving neurobehavioral function. Aim IV addresses the need to confirm rTMS safety for severe TBI.					
15. SUBJECT TERMS Neurobehavioral, intermittent Theta Burst Stimulation(iTBS), Traumatic Brain Injury (TBI), Vegetative (VS), Minimally Conscious (MCS)					
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Table of Contents

	<u>Page</u>
1. Introduction.....	4
2. Keywords.....	4
3. Accomplishments.....	4
4. Impact.....	5
5. Changes/Problems.....	5
6. Products.....	5
7. Participants & Other Collaborating Organizations.....	5-9
8. Special Reporting Requirements.....	9
9. Appendices.....	9

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)¹ 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; 50% complete

Milestones Achieved: 2nd level IRB approval by HRPO/ORP; 0% complete

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; 50% complete

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

Milestones Achieved: All study materials and procedures finalized at both study sites; 100% complete

Major Goal 3: Participant Recruitment, iTBS/APT Intervention and Follow-up (Months 6-45); 5% complete

Major Goal 4: Data Analysis (Months 4-48); 0% complete

What was accomplished under these goals?

Major Goal 1: The protocol and supporting documentation have been submitted to Hines VA and scheduled for review on November 21st. Northwestern reviewed it on 10/14 and requested changes on the 19th, due on 11/17.

Major Goal 2: All study staff have been hired at Hines VA and Northwestern.

Major Goal 3: A data repository containing names of past participants with mild traumatic brain injuries from other studies was created by Co-Investigator, Dr. Amy Herrold. Dr. Herrold continually adds to this repository through a study of her own. This repository will be used for subject recruitment for the current study.

What opportunities for training and professional development has the project provided? Nothing to report.

How were the results disseminated to communities of interest? Nothing to Report.

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

For the next reporting period, the goals are to obtain Hines, SCVMC, and Northwestern IRB approvals and HRPO/ORP approval. We will begin subject recruitment and screening procedures and have 2-3 subjects enrolled at Hines VA or Northwestern University. The MagVenture device for Hines VA will be purchased once IRB/HRPO approval is received; thus when the MagVenture device is ordered and delivered, Hines VA staff will be trained on using this device. The Performance Assessment of Self-Care Skills (PASS) test has been chosen as the functional performance outcome measure of attention for this study (i.e., it replaces the AMPS). The Placebo APT training will be computer-based.

4. IMPACT: Nothing to report.

5. CHANGES/PROBLEMS:

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

Problems:

- Brett Blabas, Biomedical Engineer at Hines VA is expected to terminate her employment on November 11th. She has agreed to act as a consultant to ensure a smooth transition while we look to hire a replacement.
- The Hines IRB has been transitioning to an electronic system that has delayed the review of protocols. It is scheduled to be reviewed on November 21st.

6. PRODUCTS: Nothing to Report

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project?

Name: Brett Blabas, MS No Change

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

Name: Theresa Pape, DrPH, MA, CCC-SLP
Project Role: PI
Nearest person month worked: 1
Contribution to Project: Dr. Pape has overseen protocol development, staffing at each study site and overall project flow.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

The following changes have occurred in the active other support of the PI and key personnel:

Pape, Theresa Louise-Bender

New Support

JW150040 (PI-Pape)	08/16 – 07/20	2.4 Calendar Months
	\$3,014,625	

“Advancing Clinical Outcomes, Biomarkers and Treatments for Severe TBI”
Congressionally Directed Joint Warfighter Medical Research Program

This proposal was submitted to support three projects complementing Dr. Pape’s currently funded DoD CDMRP project # W81XWH-14-1-0568. The purpose of Project 1 is to address a series of critical measurement issues that will advance endpoint development for the TBI research community. This will be achieved by leveraging the unique data collection procedures already being implemented as part of currently funded research. The purpose of Project 2 is to identify specific miRNA in peripheral blood and within microparticles altered by the rTMS intervention and that are correlated with the neurobehavioral outcomes as well as neurophysiological outcomes. The purpose of Project 3 is to optimize subject recruitment and support 8 additional bed days per subject for currently funded CDMRP Phase II clinical trial.

No Grant No. (PI-Pape)	04/16-04/17
	\$10,000

Disabled National Veterans Fondation (DVNF)

Financial Assistance Grant

Deborah Onaderu

Junior Program Officer

Email: donadeu@dvnf.org; Phone #202-737-0522

This funding will support the participation of Veterans and Military personnel in two funded clinical trials. The clinical trials are funded by federal research grants, but there are fiscal barriers that will prohibit severely disabled and vulnerable Veterans and Military personnel from taking advantage of an opportunity to participate in a clinical trial. One of the clinical trials enrolls patients remaining in states of seriously impaired consciousness after severe TBI and the other trial enrolls patients with mild TBI and PTSD who are experiencing persisting impairments in attention.

Parrish, Todd

New Support

B6500002/B6500003 (Parrish)

01/01/15-09/30/18

0.24 CY

Advocate Health and Hospitals Corporation

\$23,425

The Parkinson's Progression Markers Initiative (PPMI) – T1 Standardization Sub-study

The goal of this project is to oversee implementation of T1 standardization and ongoing quality control and to work with sites to implement protocol and adjust parameters related to the PPMI T1 standardization sub-study.

Herrold, Amy

New Support

JW150040 (PI-Pape)

08/16 – 07/20

2.4 Calendar Months

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Kletzel, Sandra

New Support

JW150040 (PI-Pape)

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2.4 Calendar Months

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Bhaumik, Dulal

New Support

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Issac, Linda

New Support

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Duong, Thao

New Support

JW150040 (PI-Pape)

08/16 – 07/20
\$3,014,625

2.4 Calendar Months

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Trudy Mallinson

New Support

JW150040 (PI-Pape)

08/16 – 07/20
\$3,014,625

2.4 Calendar Months

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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: None