

AWARD NUMBER: W81XWH-15-1-0516

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

PRINCIPAL INVESTIGATOR: Theresa Pape, DrPH

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

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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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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; **75% complete***

*Milestones Achieved: 2nd level IRB approval by HRPO/ORP; **25% 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: Initial IRB approvals have been obtained from both Northwestern University and Hines VA IRB. The Northwestern IRB approved package was reviewed by HRPO with all requested changes from HRPO addressed and approved in August of 2017.

These HRPO requested changes have been submitted to the Hines VA IRB and the Northwestern IRB and are awaiting approvals.

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? This study was presented to the Department of Defense In-Progress Review in June 2017.

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

During this next reporting period we anticipate having final regulatory approvals from the local IRBs and HRPO. Training of staff to use TMS equipment, deliver iTBS protocol and administer active and sham APT protocols will be completed in anticipation of enrolling participants in January of 2018.

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

5. **CHANGES/PROBLEMS:**

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

Problems: Staff turnover has delayed the submission of the IRB paperwork following approvals from HRPO.

6. **PRODUCTS:** Nothing to Report

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

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

Completed

Grant No.: None (PI-Pape)

Period of Performance: 04/16-04/17

Award Amount: \$10,000

Grantor: Disabled National Veterans Foundation (DVNF) Financial Assistance Grant

Grant Contact: Deborah Onaderu

Junior Program Officer

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

Objective: 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.

Grant No.: R21HD075192-01A1(PI-Pape)

Period of Performance 08/13-03/17

Time Commitment: 1.2 Calendar Months

Award Amount: \$337,231

Grant Title: "Amantadine + rTMS as a Neurotherapeutic for Disorders Consciousness after TBI"

Grantor: NIH, NICHD

Grant Contact: Mary E Michel (Program Official)

Email: mm108w@nih.gov Phone: 301-496-5289 Fax: 301.402.0832

Objective: Study purpose is to examine the safety and efficacy of Amantadine combined with rTMS for persons living in Vegetative State and Minimally Conscious State at least one year after TBI. Specific aims are to (1) Demonstrate that rTMS parameters are safely tolerated when also receiving Amantadine; (2) Measure Neurobehavioral responses during the Amantadine and rTMS treatment and to distinguish these responses from those manifested with Amantadine Alone and for four independent retrospective control groups; (3) Identify brainstem thalamo-cortical connectivity that changes during provision of Amantadine + rTMS.

Conneely, Mark

Completed

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Herrold, Amy

New Support

Grant Number (PD/PI): SP0046486 (Herrold, Reilly)

Performance period: 9/2017 – 8/2018

Award Amount: \$25,000

Time commitment: 0.24 Calendar Months; Co-Principal Investigator

Source of Funding: Northwestern Memorial Hospital, Women's Board, Eleanor Wood-Prince Grants Initiative

Title: Sensorimotor and cognitive effects of repetitive head trauma among female collegiate athletes.

Objective: To compare changes in brain blood flow, structure and function in mTBI and control athletes. This cross-sectional objective will assess the impact of mTBI on brain blood flow, structure and function during the subacute phase of injury. Comparing CON-C and CON-NC athletes will allow us to determine if there are differences in brain blood flow, structure and function due to subconcussive hits incurred by participating in collision sports.

Kletzel, Sandra

Completed

Grant No.: IK1RX001850 (PI-Kletzel)

Period of Performance: 06/15-06/17

Effort: .24 Calendar Months

Award Amount: \$48,754

Grant Title: "Cognitive Biomarker Targets for Treatment in Veterans with Parkinson's Disease"

Grantor: VA RR&D CDA I

Grant Contact: Susan Andrese, MHA
Acting Administrative Officer, Research & Development
Grants Administrator, Research & Development (151)
Bldg. 1, Room C347
Edward Hines Jr. VA Hospital, Hines, IL 60141
Phone: 708) 202-7447 Fax: 708) 202-2684
Objective: Characterize cognitive function in a cohort of Veterans with Parkinson's Disease using neuropsychological tests and resting state functional connectivity. Identify a neural therapeutic target for Veterans with PD-MCI.

Parrish, Todd

New Support

Grant No.: U01NS102038 (Corcos)
Period of Performance: 09/01/17-06/30/18
Time Commitment: 0.60 CM
Grantor: NIH/NINDS
Grant Award: \$194,258
Grant title: "Neuroimaging Biomarkers in Parkinsonism: Differentiating Subtypes and Tracking Disease Progression"
Objective: This Human Connectome Project (HCP) U01 application focuses on the functional and structural connections between key brain regions in Parkinson's disease (PD), and forms of atypical Parkinsonism including the parkinsonian variant of multiple system atrophy (MSAp) and progressive supranuclear palsy (PSP). Implementing cutting-edge HCP imaging protocols in these cohorts will: 1) advance our understanding of the functional and structural connectivity between key nodes, 2) provide quantitative biomarkers that can improve early diagnosis, and 3) deliver new biological metrics for evaluating target engagement of new brain therapeutics.

Trudy Mallinson

New Support

Period of Performance: 09/30/17-09/29/21
Time Commitment: 0.05 CM
Grantor: Palo Alto Veterans Hospital
Grant Award: \$31,524
Grant title: "Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) as a Personalized Treatment for Sensory and Cognitive Problems in Complex TBI"
Objective: The purpose of this study is to create an algorithm based on patient characteristics that defines the most beneficial response to rTMS treatment for personalized treatment of two major health problems reported in patients with complex TBI, specifically pain and visual disturbances.

Period of Performance: 10/01/17-09/30/18

Time Commitment: 0.25 CM

Grantor: Truven Health Analytics

Grant Award: \$200,976

Grant title: "Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) as a Personalized Treatment for Sensory and Cognitive Problems in Complex TBI"

Objective: The goal of this project is to develop quality performance measures related to functional status for beneficiaries in Home and Community-based Services waiver programs. The project will involve reviewing literature, defining performance measures, and developing the business case for these measures, in preparation for NQF submission.

Completed

Period of Performance: 09/08/15 – 04/30/17

Time Commitment: 0.40 CM

Grantor: Truven Health Analytics

Grant Award: \$555,504

Grant title: "Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) as a Personalized Treatment for Sensory and Cognitive Problems in Complex TBI"

Objective: The goal of this project is to develop, test, and validate standardized functional status items, including self-care and mobility for beneficiaries in Home and Community-based Services waiver programs. The project will involve field-testing items, developing online training materials for the assessors, and reliability and validity analyses of the data.

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



Neuromodulation and Neurorehabilitation for Treatment of Functional Deficits after mTBI + PTSD

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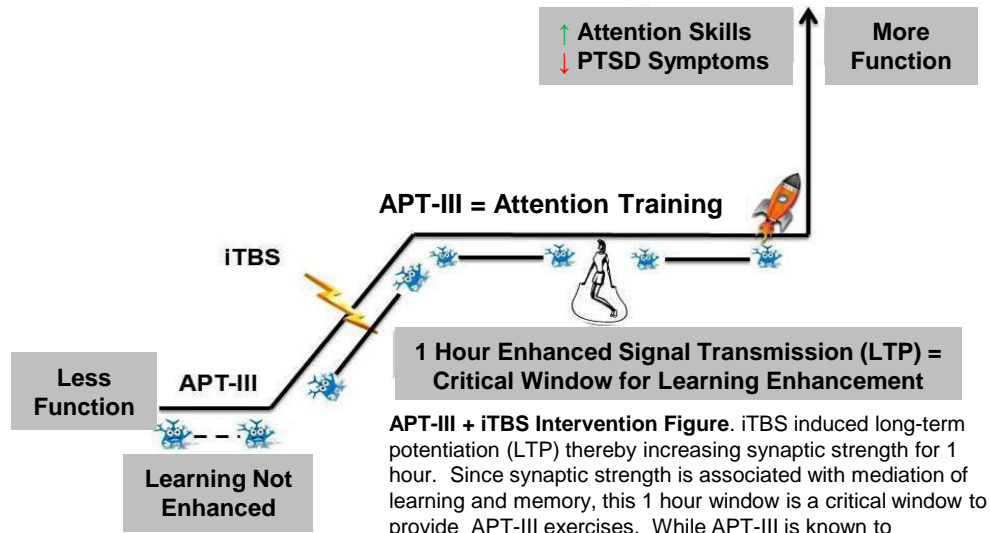
PI: Theresa L.-B. Pape, Dr.PH **Org:** Chicago Association for Research & Education in Science **Award Amount:** \$2,999,030.00

Approach: To address the need for effective long-term remediation of persisting attentional deficits related to mTBI and PTSD, we propose a double blind placebo-controlled randomized clinical trial addressing these

Study Objectives:

1. Determine immediate effects of Active Attention Processing Training (APT-III) + Active intermittent Theta Burst Stimulation (iTBS) on Neuropsychological measures of attention, measures of Function and Symptoms between baseline and endpoint.
2. Determine sustainability and long-term effects of Active APT III+ Active iTBS on neuropsychological, symptom and functional outcome measures, by comparing Endpoint & Follow-up.
3. Determine how effects identified for Objectives 1 & 2 relate to the underlying neurocognitive system of attention.
4. Confirm iTBS safety for mTBI+PTSD.

30 x [iTBS + APT] = ↑ Neural Activity → Daily Function



APT-III + iTBS Intervention Figure. iTBS induced long-term potentiation (LTP) thereby increasing synaptic strength for 1 hour. Since synaptic strength is associated with mediation of learning and memory, this 1 hour window is a critical window to provide APT-III exercises. While APT-III is known to immediately improve attention measures, skill maintenance is unknown. Thus, providing APT-III during the 1 hour window is critical to enhancing attention skills, that when repeated over 30 session will transfer over to improvement in daily function.

Goals/Milestones

CY16 Goal – Study Start-Up

- Obtain FDA IDE approval
- Hire and train study staff
- Finalize study materials and logistics
- Obtain local IRB and HRPO approval
- Enroll 12 subjects at NU and 12 at Hines VA

CY17 Goals – Participant Recruitment & Enrollment

- Enroll 29 subjects at NU and 29 at Hines VA
- Database Entry for all subjects enrolled to date

CY18 Goals – Participant Recruitment & Enrollment

- Enroll 29 subjects at NU and 29 at Hines VA
- Database Entry for all subjects enrolled to date

CY19 Goals – Finish participant enrollment and complete analyses

- Enroll 12 subjects at NU and 12 at Hines VA
- Complete Analyses

Budget Expenditure to Date

Quarter Expenditure: \$59,059 To-date Expenditure: \$587,049

Timeline and Cost

Activities CY	15	16	17	18	19
FDA & IRB Revisions, Contracts					
Subject Enroll & Data Collection					
Data Entry, Processing & Analyses					
Estimated Budget (\$3,000,000)					

Updated September 2017