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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
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6. AUTHOR(S)

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13. SUPPLEMENTARY NOTES

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; **100% complete**
Milestones Achieved: 2nd level IRB approval by HRPO/ORP; **90% 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; **85% complete**
Subtask 2b: Development of study related materials and finalize logistics
Milestones Achieved: All study materials and procedures finalized at both study sites; ***85% complete***
Major Goal 3: Participant Recruitment, iTBS/APT Intervention and Follow-up (Months 6-45); **0% 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. HRPO has reviewed and approved the study at Northwestern University as of December 21, 2017. HRPO requested changes were approved by the Hines IRB on March 5, 2018 and forwarded to HRPO for review on

March 12, 2018. Additional requests were made by HRPO on April 9, 2018 and have been submitted to the local IRB for review. We anticipate that these changes will be approved by local IRB and submitted to HRPO for review in November, 2018.

Major Goal 2: All study staff have been hired at Hines VA and Northwestern. Training, development of study materials, and finalizing procedures are in progress.

Major Goal 3: Nothing to report.

Major Goal 4: Nothing to report.

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 April 2018.

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

During the next reporting period, we anticipate beginning recruitment and enrollment of participants at Northwestern. We also anticipate full HRPO approval for Hines VA by the end of next reporting period with planned recruitment and enrollment to be initiated as soon as approvals are in place. We will continue training of staff to use TMS equipment, deliver iTBS protocol and administer active and sham APT protocols in anticipation of enrolling participants in November of 2018.

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

5. **CHANGES/PROBLEMS:**

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

Problems: Staff turnover in the Hines IRB has delayed approval/completion of the IRB paperwork needed to obtain full HRPO approval.

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:

Parrish, Todd

New Support

Grant No: R01MH100177
Period of Performance: 02/01/2018 – 01/31/2019
Time Commitment: 1.15 calendar months
Grantor:NIMH via UCLA (subcontract)
Grant Award: $182,093
Grant title: Symtom Dimensions of Threat and Reward-Related Neurocircuitry
Objective:

Grant No: P30AG013854
Period of Performance: 07/01/2018-06/30/2019
Time Commitment: 1.20 calendar months
Grantor: NIH/ NIA
Grant Award: $633,338
Grant title: Alzheimer's Disease Core Center
Objective: The ultimate goal of an Alzheimer's Disease Core Center (ADC) is to promote innovative research on dementia and its treatments while ensuring that patients and caregivers become the beneficiaries of resultant advances.

Grant No: P50DA044121
Period of Performance: 09/01/2018- 08/31/2023
Grantor: NIH
Grant Award: $1,386,389
Grant title: Center for chronic pain and drug abuse

Completed

Grant No: R01NS085002
Period of Performance: 06/01/16-04/30/18
Time Commitment: 0.6 calendar months
Grantor: NIH/NINDS
Grant Award: $260,411
Grant title: Cerebral Small Vessels in Motor and Cognitive Decline
Objective: The overall goal of this study is to identify vascular measures of cerebral small vessels which precede the onset of cognitive and motor decline and are predictive of clinical and radiographic outcomes in small vessel disease.

Rosenow, Joshua

New Support

Grant No.: R01DC017426 (PI: Zelano)
Period of Performance: 05/01/18-04/30/23
Time Commitment: 0.36 calendar months
Grantor: NIH/NIDCD
Grant Award: $324,709
Grant Title: "The function of respiratory-linked local field potential oscillations in human olfactory and limbic brain regions"
Objective: The proposed project focuses on respiratory-aligned human local field potential oscillations in olfactory cortex, their role in olfactory coding mechanisms and their propagation to adjacent non-olfactory limbic areas.

Mallinson, Trudy

New

Grant No.: N/A
Performance Period: 06/01/2018-12/31/2019
Time Commitment: .12 FTE
Grantor: GWU
Grant Award: $197,000
Project Title: No One Listens To Me
Objective: The purpose of this study is to create a measurement tool for individuals in disordered states of consciousness from the perspective of family caregivers. The project will involve interviewing family caregivers, creating data-drive vignettes, and pilot testing a new observer-reported outcome measure.

Completed

Grant No.: N/A
Performance Period: 10/01/2017-09/30/2018
Time Commitment: 3 calendar months
Grantor: Truven Health Analytics
Grant Award: $200,976
Project Title: Testing Experience and Functional Assessment Tools (TEFT) in Community-Based Long Term Services and Supports Demonstration
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.

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 REORTING REQUIREMENTS:** Quad Chart

9. **APPENDICES:** None

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

MR141205
W81XWH-15-1-0516

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

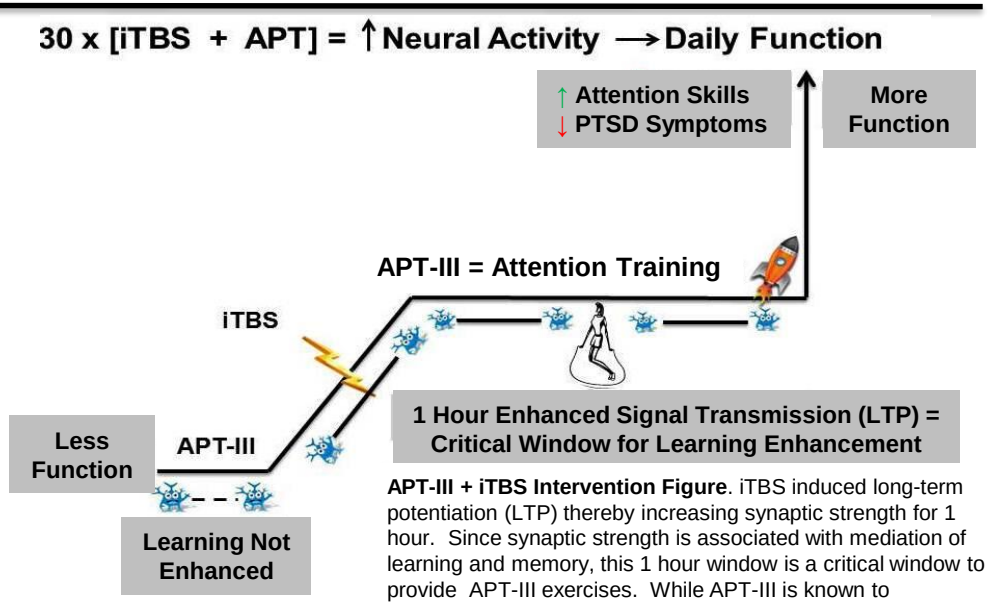
Study Objectives:

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.

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 October 2018



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: $82,900 To-date Expenditure: $823,580