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

PRINCIPAL INVESTIGATOR: Theresa Pape, DrPH

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

It is estimated that 12-16% of veterans suffer a mild traumatic brain injury (mTBI) during deployment. This can result in persistent symptoms causing persistent disability. Moreover, incidence of post-traumatic stress disorder (PTSD) is increased among veterans with mTBI. Unfortunately there are few to no treatments that induce or accelerate functional recovery after mTBI.

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. Specific Aim I will determine immediate effects of Active APT-III + Active iTBS on neuropsychological measures of attention, measures of function and symptoms between baseline and endpoint. Aim II will determine sustainability and long-term of effects of Active APT III+ Active iTBS for neuropsychological, symptom and functional outcome measures, by comparing endpoint and 10-week post-treatment follow up. Aim III will determine how effects identified for Aims 1 & 2 relate to the underlying neurocognitive system of attention by examining the relationship between the functional and structural connectivity of the attention networks with the neuropsychological, functional and symptoms outcomes. Aim IV addresses the need to confirm safety of iTBS in this population.

15. SUBJECT TERMS

Neurobehavioral, intermittent Theta Burst Stimulation(iTBS), Mild Traumatic Brain Injury (mTBI), Attention Processing Training (APT), Post-Traumatic Stress Disorder (PTSD)

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a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
	Unclassified	Unclassified	Unclassified	8	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

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; **100% 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; **95% complete**
Subtask 2b: Development of study related materials and finalize logistics
Milestones Achieved: All study materials and procedures finalized at both study sites; ***95% 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 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: 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: 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. 109 records have been screened in CPRS during this period, none of those records were eligible for study participation. An additional 178 letters and telephone screenings have been completed with potential participants, of those 178, we are still attempting to make contact with 130, 12 have indicated the study time commitment is too burdensome, 6 opted out of being contacted, 18 were not able to be contacted (i.e incorrect contact information in the medical record or no way to leave a message) and 12 did not meet inclusion/exclusion criteria. Civilian participants are currently being screened for study participation as well. Approximately 5 have met study inclusion criteria, 4 have opted out of the study due to the time commitment and 1 is moving onto the next level of screening. No participants have been enrolled to date.
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? Nothing to report.

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 enrollment of participants at Northwestern and Hines VA. 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. We also plan to submit substantive revisions to the study protocol to reduce the burden to participants. Planned changed including reduction of treatment sessions from 30 to 20 and providing 3 treatments per day to reduce the number of days required for participants to travel to study sites. Reimbursement will also be increased to $575. Reduction in the assessment battery is also planned to decrease the burden to participants.

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

5. **CHANGES/PROBLEMS:**

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

Problems: The only problem encountered during this period has been with recruitment and enrollment. We have heard from several possible participants that the time commitment required for participation in this study is too burdensome. As mentioned

previously, we have plans to revise the study in order to reduce that burden on participants.

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

R01AR074274 (Apkarian)
02/01/2019-12/31/2023
NIH/NIAMSD
Brain Pathophysiology of Osteoarthritis Pain
We propose testable hypotheses regarding mechanisms underlying chronic OA pain and those that control TKR outcomes. The primary goals of this proposal are (1) to characterize the neurologic mechanisms for chronic OA knee pain, and (2) to define neurologic mechanisms that differentiate success and failure of TKR.

IIS-1837999 (Huang, Shen, Parrish)
01/01/2019-12/31/2022
NSF BIGDATA: IA
Collaborative Research: Asynchronous Distributed Machine Learning Framework for Multi-Site Collaborative Big Brain Data Mining This project focuses on designing principled multisite collaborative big data mining algorithms for analyzing multimodal brain imaging genomics and human connectomics data to yield mechanistic understanding from gene to brain structure and circuitry to function and to phenotypic outcomes with the potential of leading to the next major brain science discoveries.

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.

Mallinson, Trudy

Completed

2017/10/01-2018/09/30
HHSM-500-2010-000251, Centers for Medicare and Medicaid Services
Stokes, Teja (PI)
Medicaid and CHIP Policy Implementation and Evaluation (MACPIE) Task Order
HHSM-500-T0006, TEFT – Technical Assistance
This project sought to develop quality performance measures related to functional status for beneficiaries in Home and Community-based Services waiver programs. The project involved reviewing literature, defining performance measures, and developing the business case for these measures, preparing for NQF submission.
Role: Co-Principal Investigator on GW Subcontract

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:** None.

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

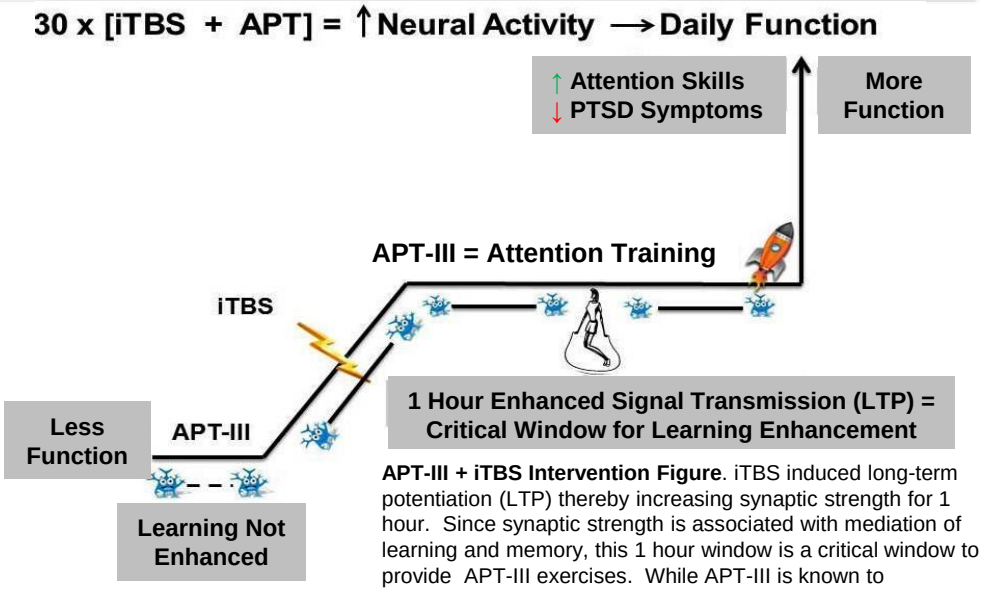
Study Objectives:

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 2019



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: $52,535 To-date Expenditure: $1,080,778