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TITLE: rTMS: A Treatment to Restore Function after Severe TBI

PRINCIPAL INVESTIGATOR: Theresa Pape, DrPH

CONTRACTING ORGANIZATION:
Chicago Association for Research and Education in Science
Edward Hines, Jr. VA Hospital
5000 S. 5th Ave, MC151H
Hines, IL 60141

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6. AUTHOR(S)

Dr. Theresa Pape

E-Mail: Theresa.Pape@va.gov

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Chicago Association for Research and Education
5000 South 5th Avenue
Bldg. One C347
Hines, IL 60141

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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

Disability Rating Scale (DRS), Neurobehavioral, Repetitive Transcranial Magnetic Stimulation (rTMS), Traumatic Brain Injury (TBI), Vegetative (VS), Minimally Conscious (MCS)

16. SECURITY CLASSIFICATION OF: Unclassified			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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1. **INTRODUCTION:** The rationale, based on published evidence and pilot data from three subjects, indicate that repetitive Transcranial Magnetic Stimulation (rTMS) holds promise as a treatment for severe Traumatic Brain Injury (TBI). TBI alters the lives of the patient, their family and society. Severe TBI is particularly devastating with some survivors recovering full consciousness swiftly while others remain in states of seriously impaired consciousness (SIC). Both recovery trajectories involve complex and potentially chronic cognitive and physical impairments. Evidence that cortical processing can occur even while unconscious and evidence of late recoveries continues to accumulate suggesting that SIC is a modifiable condition. Advanced medical care saves and sustains the lives of persons incurring severe TBI and there is a growing body of evidence indicating that this devastating injury is modifiable but there are few to no treatments that induce or accelerate functional and adaptive recovery for survivors of severe TBI. Optimal functional recovery after severe TBI, without targeted treatments, is unlikely. To address the need for targeted treatments that induce functional and structural changes in the brain, ultimately improving neurobehavioral functioning, we propose examining the therapeutic effectiveness of rTMS. The objective is to improve functional recovery for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 12 months after severe TBI. The approach is to determine the neurobehavioral effect of rTMS, the relationship between neurobehavioral changes and net neural effects, and to identify and define the neural mechanisms related to neurobehavioral improvements by providing 30 active or placebo rTMS sessions. The Disability Rating Scale (DRS) will be used at four time points to measure neurobehavioral recovery slopes. Net neural effects will be measured at three time points using fcMRI, resting state EEG (EEG-Rest), a language fMRI task and changes in EEG power spectrum when listening to a semantic processing task (EEG-Task). We will examine changes in structural integrity of fiber tracts using DTI. Measures are collected prior to, during, after and at follow up from active and placebo rTMS treatments.

2. **KEYWORDS:**

Disability Rating Scale (DRS)
Neurobehavioral
Repetitive Transcranial Magnetic Stimulation (rTMS)
Traumatic Brain Injury (TBI)
Vegetative (VS)
Minimally Conscious (MCS)

3. **ACCOMPLISHMENTS:**

What were the major goals of the project?

Major Goal 1: Regulatory Requirements (Months 1-4)
Milestones: Local IRB approval and HRPO/ORP approval; **100% completed**
Major Goal 2: Coordinate Study Staff and Logistics for Study (Months 1-4)
Subtask 2a: Hiring and Training of Study Staff
Milestones: Study staff hired and trained at all 3 study sites; **100% completed**
Subtask 2b: Development of study related materials and finalize logistics
Milestones: All study materials and procedures finalized at all 3 study sites; **100% completed**
Major Goal 3: Participant Recruitment, rTMS Intervention and Follow-up (Months 4-32)
Milestones: All 58 study participants recruited and completion of research participation; **16% completed**
Major Goal 4: Data Analysis (Months 5-36); **0% completed**

What was accomplished under these goals?

For Major Goal 1, All 3 subject recruitment sites have full IRB and HRPO approvals necessary to recruit and enroll participants into the study.

For Major Goal 2, all study staff have been hired at all three sites.

For Major Goal 3, we have been actively recruiting through Hines VA and Northwestern. Between 10/1/18 and 9/30/19 we have screened 40 potential participants, both civilian and veteran/active duty military. We have enrolled 1 civilian who was randomized to the placebo group and re-enrolled to the active treatment group and 1 civilian completed the follow up phase of the study. Study participation for the civilian randomized to placebo group commenced on 5/6/19 and active group participation was complete as of 9/6/19. In addition, we have received IRB approval through NU to use Patient Wing online recruitment tool for civilian referrals. Since the site went live on 6/27/19 we have had 33 applicants, 8 of whom have been eligible based on answers to initial inclusion/exclusion pre-screening questions asked at the time of application submission. 1 of these civilians has a signed Pre-screen consent form and is in the medical record review process.

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 we will continue subject recruitment at Hines VA and Northwestern. Our goal is sequential enrollment at Northwestern. We will continue using Patient Wing as a recruitment tool to increase our number of referrals and potential participants. We anticipate this will have a positive impact on our enrollment numbers through Northwestern.

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

5. **CHANGES/PROBLEMS:**

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

Problems: We have experienced low enrollment to date.

RE-EVALUATION OF RECRUTIMENT STRATEGIES AND REFERRAL SYSTEMS

Direct Patient Referrals from Specialty Hospitals/Units:

- Direct referrals of civilians from physicians at emerging consciousness programs at the Shirley Ryan Ability Lab and the Texas Institute for Rehabilitation Research have been the most successful strategy to date with the majority of our enrolled patients coming from these referrals
    - While direct referrals continue to be made by study physicians for screening prior to acute rehabilitation admission, families continue largely to choose admission to standard rehabilitation prior to enrolling in an experimental trial.
- The paucity of VA PRC referrals was discussed between the PI, Dr. Pape, and Dr. Joel Scholten, the VA Central Office PM&R and Polytrauma Medical Director. During his monthly leadership meetings with the PRC Chiefs (medical directors of the emerging consciousness programs at each PRC), he emphasizes importance of referrals to the study. To date, however, there have been no PRC referrals. Thus, we continue to receive lists from the VA CO emerging consciousness program database as the method for identifying study candidates from PRC admissions.

DART/VINCI**:**

- Veterans diagnosed with severe TBI and admitted to a VA hospital or medical center with the primary reason for admission being severe TBI, were identified using the national inpatient files available at VA Informatics and Computing Infrastructure (VINCI). We accessed these data files on VINCI using the Data Access Request Tracker (DART) system and then searched the database according to the ICD9CM and ICD10CM codes that allowed us to search by three eligibility criteria. Records from 9/30/2016 to date, were searched (i.e., approximately past 3 years).
    - This national search yielded a list of 33,398 unique Veterans,
    - After filtering outpatient files, the sample was reduced to 4,546 unique Veterans
    - After filtering for only station 578 (Hines VA), the sample was further reduced to 98 unique Veterans
    - After filtering for deaths and bad addresses, the final group of Veterans to be screened was 80
    - We have screened 10 of the 80 to date and these 10 were not eligible (i.e., they are accounted for in Table 1 above). We are actively screening the remaining 70 Veterans on the list.
    - After screening the Hines VA Veterans records, we will then identify duty stations within the radius of the donated air ambulance service and screen these records from the filtered list.

Study Flyer Distributions and Inservice's:

- Since October of 2017 study flyers at Landstuhl Regional Medical Center (LRMC) have been distributed by Dr. Kendra Jorgensen, Defense and Veterans Brain Injury Centers (DVBIC) Director for Landstuhl. To date, no families have contacted the study team.
- Dr. Saafan Z. Malik, Director, Research Division, DVBIC distributed via email the study information to the 16 DVBIC military treatment facilities.
- Dr. Maheen Adamson, Disordered Consciousness point of contact for DVBIC, presented this research opportunity during their routine meetings
- My study team continues to send email reminders to specialty providers and continues to provide in-services at Level I trauma centers throughout the Chicago-land area as well as extended care facilities
- Study flyers have also been posted on salient web sites locally and nationally

New Recruitment Strategy Implemented 6.25.19

- **We recently hired the services of PatientWing,** which provides an online interface for potential participant families searching for clinical trials and provides contact information for the study team (https://www.patientwing.com). All trials from clinicaltrials.gov are uploaded and synchronized daily with the PatientWing site. Participants and families can search for clinical trials based on conditions and geography. Each trial has a "landing page" which provides trial specific information, such as inclusion criteria, as well as a contact form. The page will also hold "pre-screener" questions to collect further information about participant eligibility. These questions will not require families to provide any PHI. When a potential participant's family enters contact information and answers the pre-screener questions, an email notification is sent to the study contact listed on the site. PatientWing fully complies with patient privacy (HIPAA and GDPR) and FDA (21 CFR Part 11) regulations to ensure patient information is secure and handled properly. In addition, all patient communication on the portal and any associated marketing follows the appropriate Institutional Review Board approved materials. **This recruitment tool has been approved by the Northwestern IRB and is awaiting approval from Hines VA IRB.**

6. **PRODUCTS:** Nothing to Report

7. **PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:**

What individuals have worked on the project?

Hines VA and Northwestern Memorial Hospital

Name: *Theresa Pape, DrPH, MA, CCC-SLP*
Project Role: *PI*
Nearest person month worked: *1*
Contribution to Project: *No change*

Name: *Ann Guernon, MS, CCC-SLP, CCRC*
Project Role: *Clinical Research Coordinator at Hines VA*
Nearest person month worked: *1*
Contribution to Project: *No change*

Name: *Elyse Walsh, DPT*
Project Role: *Research Clinical Therapist*
Nearest person month worked: *1*
Contribution to Project: *Dr. Walsh is actively involved in subject recruitment and screening and data collection procedures for the enrolled participant. She is responsible for facilitating the patient's enrollment from admission to discharge.*

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

Parrish, Todd

New Support

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: 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

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

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.

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

QUAD CHARTS: See attached Quad Chart.

rTMS: A Treatment to Restore Function after Severe TBI

PT130274
W81XWH-14-1-0568

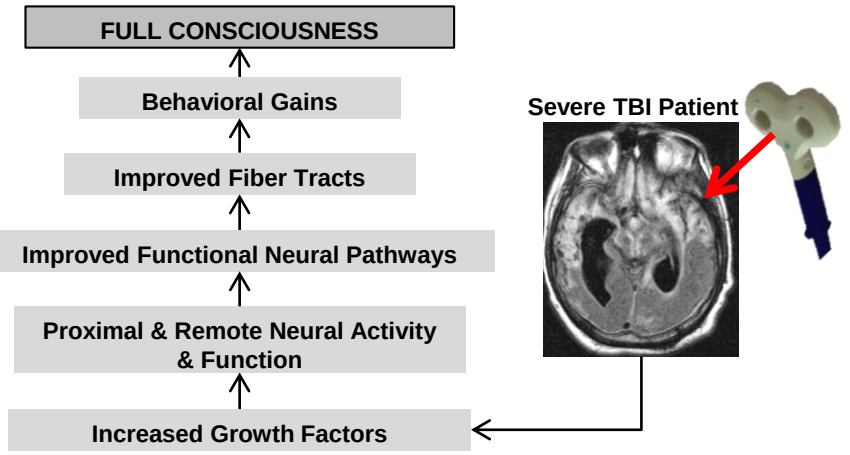
PI: Theresa Pape, DrPH **Org:** Chicago Association for Research and Education in Science (CARES) **Award Amount:** $2,993,848

Study Aims

1. Determine safety of repetitive Transcranial Magnetic Stimulation (rTMS) for severe TBI.
2. Determine if rTMS is related to improved neurobehavioral functioning during rTMS and during the 3 week follow up after stopping rTMS.
3. Determine whether rTMS associated changes in functional neural activation to auditory stimuli correspond with activation in higher order brain regions.
4. Determine whether rTMS is related to changes in white fiber tracts directly under and remote from site of stimulation.

Approach

To address the need for robust treatments that safely induce and modulate neural activity and result in improved functional recovery for severe TBI, we propose a double blind randomized sham controlled clinical trial.



rTMS changes behavior, thought to be due to rTMS up-regulation of BDNF. BDNF improves neural health and activity. As rTMS-associated neural activity increases, activation within functional neural pathways will becomes more organized.

Timeline and Cost

Activities CY	14	15	16	17	18
FDA & IRB Revisions, Contracts					
Subject Enrollment & Data Collection					
Data Entry, Processing & Analyses					
Estimated Budget ($3,000,000)					

Updated: October 2019

Goals/Milestones

CY14 & CY15 Goals – Study Start-Up
☑ Obtain local IRB and HRPO approval
☑ Obtain FDA IDE approval
CY16 Goals – Enrollment of 6 subjects
☑ Enroll 2 subjects at SCVMC & 4 at NU/Hines VA
☐ Database Entry for all 6 subjects
CY17 Goals – Enrollment of 30 subjects
☐ Enroll 15 subjects at SCVMC & 15 at NU/Hines VA
☐ Database Entry for all 30 subjects
CY18 Goals – Enrollment of 22 subjects
☐ Enroll 12 subjects at SCVMC & 10 at NU/Hines VA
☐ Complete Database Entry and Analyses
Comments/Challenges/Issues/Concerns: Recruitment barriers as addressed in EWOF
Budget Expenditure to Date
Quarter Expenditure: $43,686
Grant-to-date Expenditure: $2,320,486