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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  
Hines, IL 60141

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> This study is a <i>double blind randomized placebo-controlled clinical trial using repeated measures</i> . The <i>objective</i> 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. <b>Specific Aims:</b> 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.					
<b>15. SUBJECT TERMS</b> Disability Rating Scale (DRS), Neurobehavioral, Repetitive Transcranial Magnetic Stimulation (rTMS), Traumatic Brain Injury (TBI), Vegetative (VS), Minimally Conscious (MCS)					
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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 fMRI, 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; 14% 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 Goals 3 and 4, 5 civilian participants were enrolled at Northwestern and 1 civilian participant was enrolled at SCVMC. The following is a comprehensive list of enrollment time frames: N04 2/13/18-5/1/18 then re-enrolled for active treatment as N17 5/2/18-6/7/18, N06 6/18/18-8/22/18, N07 8/22/18-10/31/18 and S01 3/23/18-5/17/18. Participant N05 was enrolled on 4/4/18 however withdrawn from study participation on 5/9/18 due to medical instability. Study physicians felt this participant could not safely continue with study procedures. Participants N05, N06, and N07 were direct referrals from Shirley Ryan AbilityLab physician and participant N04/N17's LAR contacted the study team through [clinicaltrials.gov](http://clinicaltrials.gov). During this reporting period we have screened 15 active duty/veterans, and 34 civilians, 9 of which were eligible.

**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 all three sites. Our goal is sequential enrollment at Northwestern with a plan to enroll 3 participants in the Chicago area and 2 participants at SCVMC.

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

**5. CHANGES/PROBLEMS:**

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

**Problems:** We recognize that we have deviated from the proposed patient enrollment timeline and have solutions in place to promote progress. The problems that we have experienced in the last year and the respective solutions are described below:

- During the prescreening phase, we continue to experience communication barriers with external staff at long-term care facilities who have reported inconsistent information regarding the patient's medical status.
  - While reviewing records is routine, we will continue to practice of cross referencing verbal reports with medical order from the preceding 24 hours.
- We are at the mercy of the provider to send acute care records which can take up to a few months to obtain.
  - Families/ LARs have been assisting with record acquisition and decreased the amount of time to 2-3 months.
- In order to realign our enrollment progress with what was projected, we were approved for dual enrollment at the Clinical Research Unit at Northwestern Memorial Hospital.
- Veteran and military referrals have been sparse.
  - Dr. Pape has spoken with the VA Central Office PM&R and Polytrauma Medical Director, Dr. Joel Scholten. He will discuss the importance of referrals with the PRC Chiefs during leadership meeting.

- Dr. Pape is also working with Dr. Ian Craig to target mining of the VA EMR. Dr. Craig is validating search terms to target eligible subjects near Hines VA and SCVMC.
- Research subjects residing at long term care facilities are at risk of losing their placement if the facility will not hold their bed.
  - SCVMC researchers are working to identify facilities with potential participants who are willing to work with researchers to set up a readmission plan.
- Civilian air ambulance transportation has been difficult to arrange for subjects outside the Wings of Hope radius.
  - We are actively seeking philanthropic grants to support flights outside the Wings of Hope radius
  - We are limiting civilian recruitment within the Wings of Hope flying radius of Midwest, East Coast, and portions of the South.

**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.

**Santa Clara Valley Medical Center**

*Name:* Thao Duong, MD  
*Project Role:* Site PI  
*Nearest person month worked:* 1  
*Contribution to Project:* Oversaw implementation, recruitment efforts, and training for neurobehavioral battery. Performed rTMS and physical and neurobehavioral batteries.

*Name:* Ben Dirlikov  
*Project Role:* Co-Investigator/EEG Technician  
*Nearest person month worked:* 3

*Contribution to Project: Oversaw finance, implementation, administration, and team management at SCVMC. Prepared for and performed EEGs.*

*Name: Michael Prutton  
Project Role: Biomedical Engineer  
Nearest person month worked: 2*

*Contribution to Project: Assisted EEG training, preparation, and performance. Coordinated recruiting plans and planned/organized study tasks. Oversaw implementation, recruitment efforts, and training for neurobehavioral battery.*

*Name: Arshad Ali  
Project Role: Research Associate  
Nearest person month worked: 1*

*Contribution to Project: Assisted EEG performance. Coordinated recruiting plans and planned/organized study tasks. Oversaw implementation, recruitment efforts, and training for neurobehavioral battery.*

**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: 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: Symptom 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**

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

Organization Name: Santa Clara Valley Medical Center

Location of Organization: San Jose, CA, USA

Partner’s Contribution to the Project: Collaboration

**8. SPECIAL REPORTING 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)

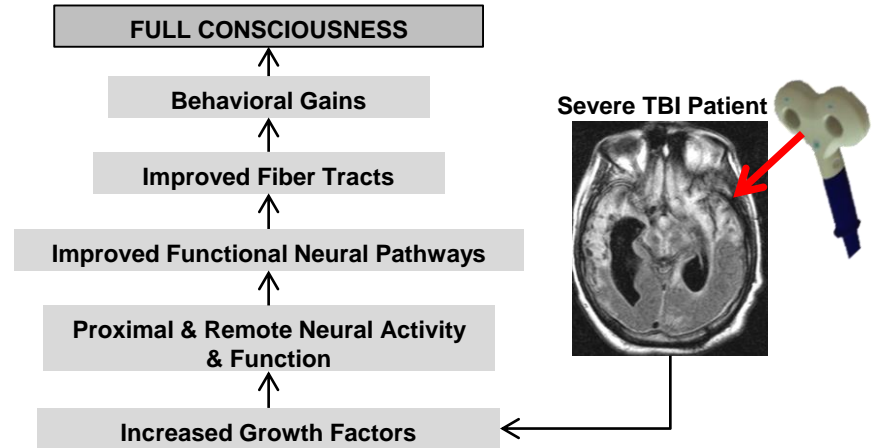
Award Amount: \$2,993,848

## 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 become more organized.

## Timeline and Cost

Activities CY	14	15	16	17	18
FDA & IRB Revisions, Contracts		[Green bar]			
Subject Enrollment & Data Collection			[Green bar]		
Data Entry, Processing & Analyses			[Green bar]		
<b>Estimated Budget (\$3,000,000)</b>					

## 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:

### Budget Expenditure to Date

Quarter Expenditure: \$272,765

Grant-to-date Expenditure: \$2,058,098

Updated: October 2018