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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

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<b>14. ABSTRACT</b> This study is a <b>double blind randomized placebo-controlled clinical trial using repeated measures</b> . The <b>objective</b> 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 48 study participants recruited and completion of research participation; 18.75 % completed*

Major Goal 4: Data Analysis (Months 5-36); 20% 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. At the end of last quarter, an updated referral list from PRC emerging consciousness programs was received. 5 unique individuals were identified from that list, 3 active duty military and 2 veterans. None of these individuals were eligible, 3 had regained consciousness and 2 had experienced non traumatic injuries. A total of 70 applications have been received on the PatientWing site from July-September 2020. 22 remained eligible after answering initial inclusion/exclusion questions, 48 were excluded. 5 applicants proceeded to phone screening with the research coordinator. 4 of those applicants were excluded. The remaining 17 LARs/applicants have not been responsive to the study coordinator.

For Major Goal 4, preliminary RCT and JWF project findings, collectively, suggest that rTMS safely improves neurobehavioral function beyond measurement error with some patients demonstrating optimal behavioral gains and some demonstrating partial behavioral gains. In terms of safety, we are in the process of using the RCT data and data from past rTMS studies with DoC patients to compute a preliminary seizure risk ratio for persons receiving 30 rTMS sessions while remaining in a state of DoC after TBI (two manuscripts in 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. If the administrative hold due to Covid-19 is lifted, our goal is sequential enrollment. 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:** Administrative hold on study due to Covid-19.

**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:* 3  
*Contribution to Project:* No change

*Name:* Ann Guernon, MS, CCC-SLP, CCRC  
*Project Role:* Clinical Research Coordinator at Hines VA  
*Nearest person month worked:* 3  
*Contribution to Project:* No change

*Name:* Elyse Walsh, DPT  
*Project Role:* Research Clinical Therapist  
*Nearest person month worked:* 3  
*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?**

Nothing to report

### **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

**QUAD CHARTS:** See attached Quad Chart.