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TITLE: rTMS: A Treatment To Restore Function After Severe TBI

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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 (DRS). 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 the rTMS-related effects correlate with improving neurobehavioral function. Aim IV will address 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)

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Table of Contents

INTRODUCTION

Advanced medical care saves and sustains the lives of persons incurring severe Traumatic Brain Injury (TBI), but for survivors, there are few to no treatments that induce or accelerate functional and adaptive recovery. Two separate research awards were conferred to address the need for targeted treatments that effectively induce functional and structural changes in the brain that can, ultimately, enable neurobehavioral recovery. The first award supports a clinical trial (Project #1) examining the safety and therapeutic efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) and is funded via the Congressional Directed Medical Research Program (CDMRP) (ID #W81XWH-14-1-0568). This final report relates to Project #1 titled *rTMS: A Treatment to Restore Function After Severe TBI*. Project #2 and Project #3 were funded by the second research award from the Joint Warfighter Medical Research Program (JWMRP) (ID#: W81XWH-16-2-0023). Those projects were addressed in a separate final report which was submitted in February 2022.

To address the need for targeted treatments that induce functional and structural changes in the brain, ultimately improving neurobehavioral functioning, we proposed examining the therapeutic effectiveness of rTMS. The objective was to improve functional recovery for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 24 months after severe TBI. The approach was 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 study was originally powered using the primary outcome, the Disability Rating Scale (DRS) which was collected at four time points (Baseline, Midpoint-after the 15th rTMS treatment session), Endpoint-after final 30th rTMS treatment session, and Follow-up-4 weeks after last rTMS session) to measure neurobehavioral recovery slopes. Given established challenges with detecting treatment effects at the neurobehavioral level, at these same time points a set of three secondary neurobehavioral outcomes were also collected; the Coma Recovery Scale-Revised (CRS-R), Disorders of Consciousness Scale (DOCS25), and the Coma Near Coma Scale (CNC). Net neural effects were measured at three time points (Baseline, Endpoint, and Follow-up) using resting state functional connectivity MRI Data (rsFC), a language fMRI task and, as an experimental outcome, resting state EEG (EEG-Rest) to examine for changes in the power spectrum when listening to a semantic processing task (EEG-Task). We also collected DTI to enable the examination of the structural integrity of fiber tracts.

KEYWORDS

Table 1: Keywords and Acronyms	
Keywords	Acronyms
American Congress of Rehabilitation Medicine	ACRM
Axial Diffusivity	AD
Baseline	BL
Blood Oxygen Level-Dependent	BOLD
Congressional Directed Medical Research Program	CDMRP
Coma Near Coma Scale	CNC
Coma Recovery Scale-Revised	CRS-R
Disorder of Consciousness	DOC
Disorders of Consciousness Scale-25	DOCS-25
Disability Rating Scale	DRS
Data safety monitoring board	DSMB
Diffusion Tensor Imaging	DTI
Electroencephalogram	EEG
Electrooculography	EOG
Endpoint	EP
Follow-up	FU
Fractional Anisotropy	FA
Full Width Half Maximum	FWHM
Functional Magnetic Resonance Imaging	fMRI
Human Research Protection Office	HRPO
Investigational Device Exemption	IDE
Institutional Review Board	IRB
Mean Diffusivity	MD
Minimally Conscious State	MCS
Magnetic Resonance Image	MRI
Motor Threshold	MT
Not Completed	NC
Radial Diffusivity	RD
Relative Volume of Cerebral Spinal Fluid	CSFrv
Relative Volume of Gray Matter	GMrv
Relative Volume of White Matter	WMrv
Resting State Functional Connectivity	rsFC
Repetitive Transcranial Magnetic Stimulation	rTMS
ROI-to-ROI Connectivity Matrices	RRC
Santa Clara Valley Medical Center	SCVMC
Seizure Occurrence	SO
Statement of Work	SOW
Severe Traumatic Brain Injury	sTBI
Seed-Based Connectivity Maps	SBC

Total Intracranial Volume	TIV
Total Volume of Cerebral Spinal fluid	CSFtv
Total Volume of Gray Matter	GMtv
Total Volume of White Matter	WMtv
Traumatic Brain Injury	TBI
Vegetative State	VS

ACCOMPLISHMENTS

What were the major goals of the project?

The major tasks/goals of this clinical trial, according to specific objectives as outlined in the updated and approved Statement of Work (SOW) dated 8/23/21, are reported here by planned and actual completion dates (or percentage completed).

The objective of this project is to improve functional recovery for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 24 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 following specific aims were addressed: (1) determine the presence, direction, and sustainability of rTMS-induced neurobehavioral effects using the DRS and CNC where lower scores indicate more function and the CRS-R and DOCS25 where higher scores indicate more function, (2) determine the presence, direction and sustainability of rTMS-induced changes in functional neural activation to a language task, resting state functional connectivity, resting state EEG power spectrum changes and whether these changes correlate with improving neurobehavioral function, (3) determine the rTMS effect on white fiber tracts and whether rTMS-related effects correlate with neurobehavioral gains, and (4) confirm rTMS safety for severe TBI.

Goal #1: Regulatory Requirements

This goal addresses start-up and ongoing regulatory requirements necessary for study implementation and execution across sites.

Goal #1 Specific Objectives	Completion	
	Planned	Actual
1.1 Submit protocol, informed consent, and other regulatory documents to the site-specific IRB	12/2014	12/2014
1.2 Submit protocol, informed consent, and other regulatory documents for second level IRB approval – ORP and HRPO	01/2015	01/2015
1.3 Submit protocol revisions to the FDA	As needed	As needed
1.4 Submit amendments, adverse events, and protocol deviations	As needed	As needed
1.5 Coordinate with sites for annual IRB reports for continuing review	Annually	Annually
1.6 Submit FDA Reports	Annually	Annually
1.7 Reporting to DSMB	Quarterly	Biannually/As needed

Goal #2: Finalize Staffing, Material Development and Logistics

This goal, divided into two subgoals, addresses the plethora of study start-up training, coordination, source document creation, and logistics necessary for study implementation and execution across sites.

Goal #2 Specific Objectives	Completion	
2a: Hiring and Training Study Staff	Planned	Actual
2a.1 Coordinate with sites for job description and selection of candidates	01/2015	01/2015
2a.2 Development of training materials	01/2015	01/2015
2a.3 Training of research staff in study specific procedures and clinical data collection	01/2015	01/2015
2a.4 Finalize roles and responsibilities for all research procedures	01/2015	01/2015
2a.5 TMS training and brain mapping/motor threshold test training of all research staff administering TMS	12/2014	01/2015
2b: Development of study related materials and finalize logistics	Planned	Actual
2b.1 Develop source documents and templates for data collection	12/2014	01/2015
2b.2 Develop study database	01/2015	01/2015
2b.3 Develop recruitment materials and finalize recruitment plans	01/2015	01/2015
2b.4 Finalize data management plan	12/2014	01/2015
2b.5 Develop randomization protocol for random assignment or treatment groups	12/2014	01/2015
2b.6 Finalize logistics for MRI procedures	12/2014	01/2015
2b.7 Finalize logistics for EEG procedures	12/2014	01/2015
2b.8 Finalize logistics for admission to facilities and transportation between facilities as appropriate	12/2014	01/2015
2b.9 Finalize logistics for medical oversight	12/2015	01/2015

Goal #3: Participant Recruitment, rTMS Intervention and Follow-up

This goal addresses each aspect of the study protocol and study procedures from recruitment through participation completion.

Goal #3 Specific Objectives	Completion	
	Planned	Actual
3.1 Recruit subjects to all recruitment sites	11/2021	03/2022
3.2 Complete clinical data collection as outlined in study procedure flow chart (neurobehavioral, safety, MRI, EEG)	11/2021	12/2021
3.3 Monitor safety data continuously with each subject	03/2022	12/2021
3.4 Provide 30 sessions of active rTMS or placebo rTMS	11/2021	12/2021
3.5 Complete 3-week telephone follow up	03/2022	12/2021

3.6 Complete Endpoint 3 data collection (MRI, EEG, neurobehavioral, safety)	03/2022	12/2021

Goal #4: Data Analysis

This goal addresses coordination, collection, and analysis of data as specified in the approved protocol.

Goal #4 Specific Objectives	Completion	
	Planned	Actual
4.1 Coordinate collection and transmission of data to Hines for data monitoring and entry into database.	03/2022	2/1/22
4.2 Perform analyses according to specific aims/hypothesis and share results with all investigators	03/2022	Aims 1 & 4: 8/30/23 Aims 2 & 3: 90% complete

Goal #5: Dissemination Activities

This goal addresses the dissemination of findings following data collection and analysis. This information also relates to the information reported in the Products Section below which provides a comprehensive list of papers and presentations in different scientific and educational venues.

Goal #5 Specific Objectives	Completion	
	Planned	Actual
5.1 Scoping Review Scoping review of rehabilitation interventions for DoC	12/2016	Published 6/2022 (Appendix 12)
5.2 Manuscript: TMS Safety: All Findings	3/2019	Published 06/2020 Appendix 8
5.3 Manuscript: TMS Safety: Estimate of Seizure Risk	6/2020	To be submitted for peer review 12/2023 Appendix 27
5.4 Manuscript: TMS seizures in Severe TBI, Unexpected origins and time post TMS	6/2021	Not Completed (NC)
5.5 Manuscript: Customizing TMS using rsFC with Severe TBI	10/2019	06/2020 Appendix 6
5.6 Manuscript: TMS Targeting with rsFC in Severe TBI	2/2021	06/2020 Appendix 6
5.7 Manuscript: Developing motion artifact reduction methods (1 of 2) for rsFC in severe TBI using alternate data set	1/2019	10/2020 Appendix 4
5.8 Manuscript: Replicating rsFC motion artifact reduction methods in independent severe TBI sample in an alternate data set	11/2019	10/2020 Appendix 4
5.9 Manuscript: TMS induced change in neural connectivity supporting neurobehavioral recovery (rsFC relative to DTI vs task activation)	1/2020	In process

5.10 Manuscript: TMS induced changes in EEG power spectrum at rest and task based in severe TBI relative to healthy controls	1/2020	In process
5.11 Manuscript: Multi-modal TMS treatment efficacy for Severe TBI	3/2020	In process
5.12 Manuscript: Optimal vs. sub-optimal TMS treatment responders	3/2020	In process
5.13 ACRM Presentations	2016-2021	2018
5.14 Neurotrauma Presentations	2016-2021	2020, 2022
5.15 Other Relevant Conferences	2016-2021	2017, 2018, 2020, 2022, 2023 Appendices 11 - 26
5.16 Final Report	05/2022	12/2023

What was accomplished under these goals?

Accomplishments are described here in terms of significant results including major findings and developments.

Goal #1 Accomplishments: Regulatory Requirements

Project protocol, consent forms, and all IRB-required documents were submitted to all three sites, Hines VA, Northwestern, and Santa Clara Valley Medical Center. Additionally, protocols and consents were submitted to HRPO. Finally, this project was added to the FDA IDE G040195. All necessary approvals were obtained to begin subject recruitment and enrollment at all sites. All IRBs, HRPO, and the FDA were notified of ongoing study amendments, protocol deviations, adverse events, and all other required reporting as necessary.

Goal #2 Accomplishments: Finalize Staffing, Material Development and Logistics

It was necessary to assemble the skilled staff at SCVMC and provide onsite and hands-on training with the Hines VA study team. The training included TMS equipment operation, management and troubleshooting, outcome administration and data collection procedures, data management and setting up MR imaging protocols as well as motor thresholding, behavioral testing, and provision of TMS treatment. Simultaneously, all processes and procedures were being finalized at Hines VA and Northwestern.

Goals #3 Accomplishments: Participant Recruitment, rTMS Intervention, and Follow-up

Recruitment of Veterans, Active-Duty Military, and civilian participants was ongoing throughout the entirety of this project. A total of 15 unique patients (2 veterans, 13 civilians) were enrolled in the double-blinded study. Specifically, 12 participants were initially randomized to and completed the active treatment with three being randomized to placebo. Nine of the participants completed the study as six participants were withdrawn after informed consent was obtained. The three participants randomized to placebo group, after completing the placebo arm of the study, elected to be re-enrolled to the active treatment group during which a partial blind (i.e., nursing, outcome assessors) format was maintained. The final study sample, of participants completing the study, is 12 (9=Active,3= Placebo). See the *Changes/Problems* section below for detailed information regarding recruitment challenges and barriers impeding subject enrollment, equipment limitations, treatment site changes, and the impact the COVID-19 pandemic had on this project.

Goal #4 Accomplishments:

Specific Objective 4.1 Accomplishments: Coordinate collection and transmission of data to Hines for data monitoring and entry into the database.

The treatment efficacy data was collected and then transmitted to Hines VA, for each participant by study timepoints (baseline, midpoint, endpoint, and follow-up). As each study participant completed their participation, their data was examined for quality and then entered into the study database. Regarding safety data, this data was collected and entered into the study database throughout study participation in accordance with a data safety monitoring plan that is approved by the human research protection programs, institutional review boards, the FDA, and the data safety monitoring board assigned to the study.

Specific Objective 4.2 Accomplishments: Perform Data Analyses

The data was organized and cleaned and then used to perform analyses according to the pre-specified specific aims and hypotheses. The results for each hypothesis are reported here. If a manuscript has already been published, then the results are summarized, and the article is cited and appended to this final report.

Specific Aim 1: To determine the presence, direction, and sustainability of repetitive Transcranial Magnetic Stimulation (rTMS) induced neurobehavioral effects.

To address this aim, first, we conducted descriptive analyses to examine comparability between the active and placebo rTMS groups.

Aim 1 Sample Description: The total sample of participants completing the study (Table 2) were largely Caucasian and Hispanic males who were, on average, 31 years of age at injury (range: 19 to 46) and had remained in a state of DoC an average of 1.3 years (range: 1 to 2) at time of study baseline. The total sample had an average motor threshold (MT) of 60% (SD: .09) for the thumb representation (i.e., abductor pollicis brevis, APB) on the primary motor cortex (M1) (range: 46% - 71%). The rTMS treatment groups (Active vs Placebo) did not differ by any of these variables nor by clinical states of VS/MCS or by any of the seven metrics of severity of neuropathological injury.

Table 2: Sample Description by rTMS Groups

		rTMS Groups		
	Totals (N = 12)	**Active (n = 9)**	**Placebo (n= 3)**	**P values**
Mean Age at Injury *	31 (SD: 9.5)	34 (SD: 10.0)	24 (SD: (6.0)	.08
Mean Years post*	1.3 (SD: .44)	1.4 (SD:.41)	.95 (SD: .48)	.18
% Male at Birth	92%	89%	100%	.55
Percent VS*	33%	22%	67%	.16
Percent MCS*	67%	78%	33%	
Race:				
-Caucasian	42%	44%	34%	.67 **
-Asian	16%	12%	33%	
-Hispanic	42%	44%	33%	
CSFrv*	0.36 (SD: .04)	.36 (SD: .04)	.36 (SD: .07)	.88
GMrv*	0.36 (SD: .02)	.37 (SD: .18)	.35 (SD: .26)	.24
WMrv*	0.28 (SD: .03)	.28 (SD: .03)	.29 (SD: .04)	.58
CSFtv*	532.0 (SD: 86.4)	527.4 (SD: 79.1)	545.7 (SD: 139.5)	.85

GMtv*	537.9 (SD: 40.6)	542.4 (SD: 48.7)	524.3 (SD: 5.0)	.30
WMtv*	416.2 (SD: 47.0)	411.1 (SD: 52.3)	431.3 (SD: 42.9)	.56
TIV*	1485.9 (SD: 117.1)	1480.9 (SD: 134.4)	1501.0 (SD: 97.6)	.79
Mean MT	60% (SD: .09)	58% (SD: .09)	58% (SD: .11)	.85

***** Variable also used as a covariate ****** indicates categories compared are Caucasian vs. Other
MT = Motor Threshold of participant's thumb representation (i.e., abductor pollicis brevis, APB) on their primary motor cortex (M1)
MRI T1 3D volume sequences were used to compute these metrics of neural injury severity: Relative Volume of Cerebral Spinal Fluid (**CSFrv**) = normalized by total intracranial volume (Total volume/TIV) (can indicate tissue-type damage); Relative Volume of Gray Matter (**GMrv**) = normalized based upon total intracranial volume (can indicate tissue-type damage); Relative Volume of White Matter (**WMrv**) = normalized based upon total intracranial volume (can indicate tissue-type damage); **rTMS** = Repetitive Transcranial Magnetic Stimulation; Total Volume of Cerebral Spinal Fluid (**CSFtv**) = total cubic voxels, non-normalized (can indicate large volume loss); Total Volume of Gray Matter (**GMtv**) = total cubic voxels, non-normalized (can indicate large volume loss e.g., craniotomy); Total Volume of White Matter (**WMtv**) = total cubic voxels, non-normalized (can indicate large volume loss); Total Intracranial Volume (**TIV)** = cm3

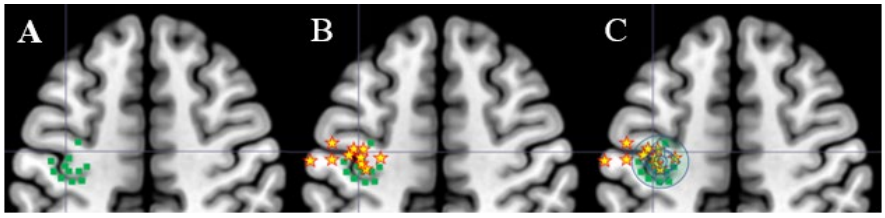


Figure 1: Relative spatial distribution of MT coordinates on MNI brain.
Panel A shows 11 healthy controls (adapted from Yoursy(Yousry, Schmid et al. 1997)) in **green** squares. **Panel B** shows 10 persons with DoC-TBI in **red**/**yellow** stars (all outliers verified by neurosurgeon at time of MT). **Panel C** demonstrates that a 2-4 cm search radius based on anatomical measures of the skull that are sufficient to isolate the MT in healthy controls are not sufficient for persons with DoC. Methods: Yoursy, et.al. (Yousry, Schmid et al. 1997) identified shapes and locations of hand knob in healthy controls using fMRI and a finger movement task. In our clinical trial, neuronavigation is used to identify the hand knob targeting the abductor pollicis brevis (APB) muscle. Single pulse TMS is used to stimulate, and electromyography (EMG) and visual confirmation are used to confirm MT location and strength of motor evoked potentials.

While the treatment groups did not differ by any the metrics of neuropathological injury severity, we found that the neuropathological spatial variability between DoC patients necessitated a different approach to locating the Motor Hotspot (MH), which is critical as this location is used to determine motor threshold as a basis for determining each participant's rTMS treatment intensity and spatial localization of the rTMS treatment site. As illustrated in Figure 1, we found that the standard anatomically based gross measures of skull size used to approximate the most likely location of the hand knob (e.g., circumference, nasion to inion), developed for persons with mild to no neurologic pathology (Awiszus 2003, Mishory, Molnar et al. 2004, Finetto, Glusman et al. 2019) did not precisely locate each participant's MH. As illustrated, the 2-4 cm search radius of the anatomically driven approach would neglect to locate MH and elicit a MT for persons with DoC. While this radius is sufficient to isolate the hand knob anatomy and MH/MT location in brains with mild to no neurologic pathology, for persons with DoC there is a much broader radius of neural targets with proximity to the hand in the homunculus map, including any digit, the hand or wrist, and the mouth, lips, or jaw.

As rTMS treatment intensity is based upon neural sensitivity of the motor cortex, we addressed spatial localization challenges, illustrated in Figure 1, by developing an rsFC based neural navigated approach to locate the hand-knob area using EMG of the Abductor Pollicis Brevis (APB) muscle as well as visual/tactile confirmation of a motor twitch. For persons with DoC, this approach allowed us to locate MH, determine resting or active MT and to identify the lo-cation targeted for rTMS. Future work should develop a training protocol to facilitate clinical adoption of rTMS as the training protocol will provide the basis to establish effective treatment for people with heterogeneous neuropathology exceeding normal variations in neuroanatomy and neural function.

Aim 1 Neurobehavioral Analyses: The intent of the clinical trial was to use, as the primary neurobehavioral outcome, the DRS to measure change as they recovered consciousness and returned to the community. However, as reported in our JWMRP final report (W81XWH-16-2-0023 Revised Final Report) and summarized briefly here, our psychometric findings indicate that the DRS measures neither group well (i.e., disordered consciousness or community living). While results from our sample of 2,291 patients in states of disordered consciousness with DRS item-level data, indicate that there are clearly visible three distinct groups of patients (i.e., comatose, disordered consciousness, and eMCS) measured by 3 distinct sets of DRS items (i.e., those reflecting disordered consciousness; those reflecting consciousness, employment, and overall function), the Rasch Measurement analysis demonstrated that DRS responses are especially Guttman-like. Specifically, once a patient has been scored on one or two DRS items, their scores on the remaining items can be predicted with 100% accuracy. As scores for the DRS test items are predictable, according to scores on preceding DRS items, DRS test items representing the least function appear "clumped" at the low end of the scale, and at the higher end of the scale items are stretched extremely far apart.

As our previously reported JWMRP findings (W81XWH-16-2-0023 Revised Final Report), and as briefly summarized above, indicate that the DRS is limited in use for detecting a change in function over time for persons in states of DoC, we conducted analyses with each of the secondary outcomes collected; the CRS-R, CNC, and the DOCS. For the DOCS, we examined the DOCS total score and each domain measure (DOCS Gustation, Somatosensory, Visual, and Auditory Language) as well as the DOCS Best Response (BR) measure. In addition to descriptive analyses, for each outcome, we compared recovery slopes during the treatment phase, during the follow-up phase, and when these phases were combined. When examining recovery slopes, we used mixed effects regression models and the group variable (Placebo vs Active), and, considering the small sample size, separate models were also run with the group variable and one of each of the covariates specified in Table 2. We also computed and compared mean peak gains between Placebo rTMS (n = 3) and Active rTMS (n = 9) groups during the treatment phase using t-tests and published, or in press, metrics of meaningful change available for each outcome. Specifically, we computed the Effect Size for each mean peak gain by each outcome. We also compared the mean peak gain, by outcome, relative to each outcome's known Distribution-Based Minimally Clinically Important Differences (MCIDs) and Minimal Detectable Change (MDCs). The metrics are established for the DOCS (Mallinson, Pape et al. 2016) and for this project these metrics were computed for the CNC (Appendix 9) (Weaver, Pertsovskaya et al. 2023) and the CRS-R (Appendix 28, manuscript under review). These comparisons are important as the MCID sets a threshold for clinically important change and the MDC determines whether change exceeds measurement error.

Aim 1 Neurobehavioral Results: Examination of the eight recovery slopes (8 outcomes), with and without the covariates listed in Table 2, indicate that these slopes are not significantly different, statistically, between the active and placebo rTMS groups. However, as seen in Table 4, there is a significant difference between groups by mean peak gains. Specifically, during the provision of assigned rTMS treatment, the active rTMS group compared to placebo rTMS made significantly greater average peak gains in the DOCS Somatosensory skills ($p = .02$).

Notably, the computations for the MCIDs and MDC for the DOCS somatosensory domain measure, and the other three DOCS domain measures (Table 4), are in the process of being computed. However, the mean DOCS somatosensory peak gains for the active group, exceed the placebo group's gains by 11.1 units, and the 95% confidence interval for the 3.3 Effect Size indicates that the true effect sizes could fall between .12 and 6.6. The absence of '0' in the confidence interval suggests a clinical benefit, but a comparison wit MCIDs and MDCs, when computed, will further inform us of clinical significance. At this time, the statistical significance, and Effect Size indicates greater peak gains in the active rTMS group's ability to perceive touch, pressure, pain, temperature, position, movement, and vibration. As illustrated in our 2020 publication (Appendix 2) (Bender Pape, Herrold et

al. 2020) conscious perception of these sensations, arising from muscles, joints, skin, and fascia, are dependent on the functioning of the sensory relay nuclei and these skills precede recovery of higher-order cortical skills. This finding is consistent with our previously reported JWMRP findings (W81XWH-16-2-0023 Revised Final Report) indicating that, when all the outcome assessments (DOCS, CRS-R, CNC, DRS) are co-calibrated, the DOCS somatosensory items are the easiest for patients to respond to while CRS-R and DOCS auditory and visual items are the most challenging.

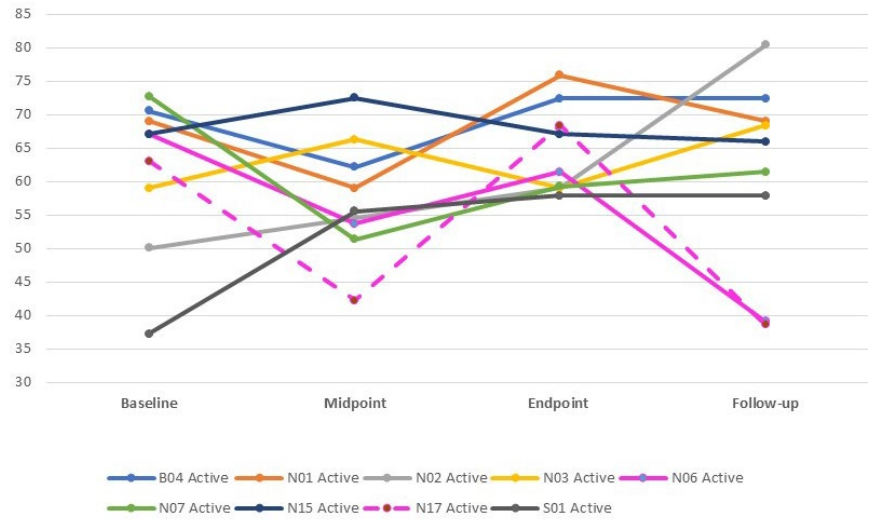
Table 3: Comparison of Mean Peak Neurobehavioral Gains for each Outcome

Outcomes Measures	Interval Scales*	MCIDs				Mean Peak Gains (SD) during rTMS			
		.20	.33	.50	MDC_{95}	Active rTMS	Placebo rTMS	*p*	ES (CI)
DOCS25-Total	0 - 100	2.6	4.4	6.6	5.6	8.9 (7.6)	1.2 (7.5)	.10	.93 (-.5, 2.3)[a]
DOCS Auditory-Lang	0 - 100	NA	NA	NA	NA	12.8 (14.0)	2.9 (10.0)	.16	.69 (-.67, 2.0)[a]
DOCS Somatosensory	***0 - 100***	***NA***	***NA***	***NA***	***NA***	***13.5 (11.5)***	***2.4 (2.7)***	***.02***	***3.3 (.12, 6.6)[b]***
DOCS Visual	0 - 100	NA	NA	NA	NA	10.3 (20.5)	16.5 (15.1)	.33	.29 (-1.0, 1.6) [a]
DOCS Gustation	0 - 100	NA	NA	NA	NA	22.7 (12.9)	15.5 (13.7)	.23	.50 (-.84, 1.8) [a]
CNC- 8 items *	logits	.25	.41	.63	1.25	0.6 (1.1)	0.1 (0.3)	.15	1.3 (-.54, 3.0) [b]
CRS-R	0 - 100	4	6	9	11	4.6 (12.2)	4.2 (2.6)	.47	.13 (-1.2, 1.4) [b]
DRS*	logits	NA	NA	NA	NA	-0.8 (1.1)	-0.33 (1.25)	.31	-.35 (-1.7, .98) [a]

*** Lower scores indicate more function; all other scales are higher scores indicate more function; NA** = Not Currently Available, but there are plans for computations; CNC metrics are in logits and plans are to re-compute using a 0 to 100 interval scale; **ES** = Effect Sizes; [a] Cohens based on pooled SD; [b] Glass's Delta based on Control Groups SD; **CI** = .95 Confidence interval

Seven of the nine participants in the active rTMS group, making DOCS somatosensory gains (7/9), illustrated in Figure 2, experienced their peak gains after 3 and up to 30 active rTMS sessions (average number of sessions preceding peak somatosensory gains = 16, SD = 11, median = 23). Of the two participants who did not make gains, in this domain, one did not demonstrate any gains in any of the neurobehavioral outcome measures. The other participant made gains in Gustation (Swallowing and Smell) and visual skills. The statistically significant difference between the two groups, active and placebo, improves when the mean peak somatosensory gains are compared when the active group means do not include the two participants in the active group who were in the vegetative state at baseline (p = 0.01). Together the wide range in the number of rTMS sessions related to peak somatosensory gains and the improvement in significance when baseline vegetative state is accounted for, suggests a need for a treatment responsiveness analysis that we have added to our plans for future analyses.

Figure 2 DOCS Somatosensory Measures Active Group by Baseline Clinical State (Pink Lines indicates VS)



Comparing mean peak gains with MCID and MDC that are currently available for each outcome (Table 3), provides additional insights into the

clinical significance of receiving additional attention during study participation. Specifically, of the MCID and MDCS currently available, active and placebo rTMS groups made similar peak gains in CRS-R that exceed the .20 MICD distribution-based metric of 4.0. This suggests a neurobehavioral benefit, measured with CRS-R from additional attention due to study participation. However, the 95% confidence interval further suggests that the CRS-R effect size for this clinical trial could also be '0' suggesting that there may be no neurobehavioral benefit, as measured with the CRS-R, from additional attention due to study participation.

Specific Aim 2: Determine the presence, direction, and sustainability of rTMS-induced changes in functional neural activation and whether these changes correlate with improving neurobehavioral function.

To address this aim, we have or are in the process of examining metrics for five functional neural activation study outcomes: (a) Resting-state functional connectivity MRI (fcrMRI); (b) functional Magnetic Resonance Imaging (MRI) –synonym task, (c) functional MRI -familiar voice task; (d) Electroencephalography –Rest (EEG-Rest); (e) EEG-Synonym task (EEG-Task). Once each metric was examined, the relationships (associations) between the DOCS somatosensory peak neurobehavioral gains and each functional neural activation metric were examined.

fcrMRI DMN, Language and SomatoMotor Network Changes (Aim 2a): Results come from fcrMRI analyses performed using CONN (Whitfield-Gabrieli and Nieto-Castanon 2012) (RRID:SCR_009550) release 22.(Nieto-Castanon and Whitfield-Gabrieli 2022) and SPM(Penny, Friston et al. 2011) (RRID:SCR_007037) release 12.6906.

Functional and anatomical data were preprocessed using a flexible preprocessing pipeline(Nieto-Castanon 2020) including realignment with correction of susceptibility distortion interactions, slice timing correction, outlier detection, direct segmentation, and MNI-space normalization, and smoothing. Functional data were realigned using the SPM realign & unwarp procedure(Andersson, Hutton et al. 2001), where all scans were co-registered to a reference image (first scan of the first session) using a least squares approach and a 6-parameter (rigid body) transformation and (Friston, Ashburner et al. 1995) resampled using b-spline interpolation to correct for motion and magnetic susceptibility interactions. Temporal misalignment between different slices of the functional data was corrected following SPM slice-timing correction (STC) procedure (Sladky, Friston et al. 2011)[7,8], using sinc temporal interpolation to resample each slice BOLD time series to a common mid-acquisition time. Potential outlier scans were identified using ART (Whitfield-Gabrieli, Nieto-Castanon et al. 2011) as acquisitions with framewise displacement above 0.9 mm or global BOLD signal changes above 5 standard deviations (Power, Mitra et al. 2014, Nieto-Castanon 2020), and a reference BOLD image was computed for each subject by averaging all scans excluding outliers. Functional and anatomical data were normalized into standard MNI space, segmented into grey matter, white matter, and CSF tissue classes, and resampled to 2 mm isotropic voxels following a direct normalization procedure(Calhoun, Wager et al. 2017, Nieto-Castanon 2020), using SPM unified segmentation and normalization algorithm (Ashburner and Friston 2005) with the default IXI-549 tissue probability map template. Last, functional data were smoothed using spatial convolution with a Gaussian kernel of 8 mm full-width half maximum (FWHM).

In addition, functional data were denoised using a standard denoising pipeline including the regression of potential confounding effects characterized by white matter time series (5 CompCor noise components), CSF time series (5 CompCor noise components), motion parameters and their first order derivatives (12 factors), outlier scans (below 157 factors)[10], session effects and their first order derivatives (2 factors), and linear trends (2 factors) within each functional run, followed by bandpass frequency filtering of the BOLD timeseries between 0.008 Hz and 0.09 Hz. CompCor noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion

parameters, and outlier scans within each subject's eroded segmentation masks. From the number of noise terms included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to range from 40 to 81.7 (average 64.6) across all subjects(Nieto-Castanon 2020).

First-level analyses were conducted. Specifically, seed-based connectivity maps (SBC) and ROI-to-ROI connectivity matrices (RRC) were estimated characterizing the patterns of functional connectivity with 264 ROIs. Functional connectivity strength was represented by Fisher-transformed bivariate correlation coefficients from a weighted general linear model (weighted-GLM), defined separately for each pair of seed and target areas, modeling the association between their BOLD signal time series. To compensate for possible transient magnetization effects at the beginning of each run, individual scans were weighted by a step function convolved with an SPM canonical hemodynamic response function and rectified.

To complete this final report, we analyzed two networks specified in the funded grant (Default Mode Network [DMN] and Language) and added the somatosensory network (i.e., also referred to as SomatoMotor) as the statistically significant between-group neurobehavioral difference was found for the DOCS Somatosensory measure. However, analyses still underway include analyses of change within all other networks (30+) and between network analyses.

Based on the z values, for each ROI, we computed mean z values for each of the three networks. For each participant, we then computed their individual change, within each of these three Networks. The change was computed during the provision of assigned treatment (Endpoint, EP- Baseline, BL), during follow-up (Follow-up, FU – EP), and throughout study participation (FU-BL) (Table 4). The mean individual change, for each group, was compared using t-tests.

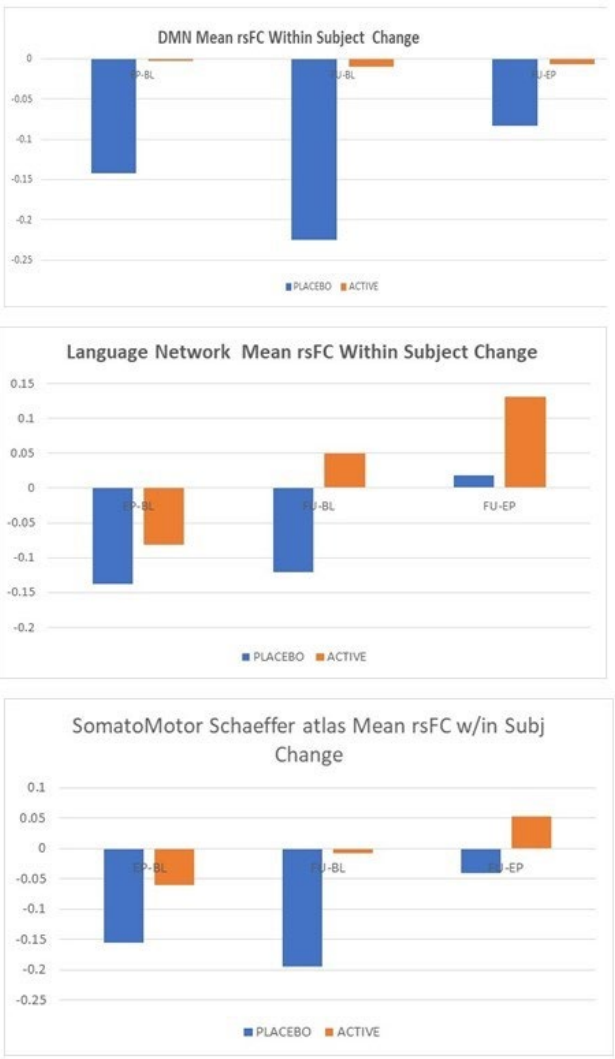
Table 4: Mean Change, Based on Average Individual Change by Groups and Three Networks

	DMN (CONN)	Language (CONN)	Somatosensory (SM2, Schaeffer)
PLACEBO Mean EP-BL	-0.141917878	-0.138147933	-0.15525294
ACTIVE Mean EP-BL	-0.002820953	-0.081818972	-0.061095373
PLACEBO FU-BL	-0.225097313	-0.120111922	-0.195347809
ACTIVE FU-BL	-0.009907909	0.049293339	-0.008479475
PLACEBO FU-EP	-0.083179436	0.018036011	-0.040094868
ACTIVE FU-EP	-0.007086957	0.131112311	0.052615898

As seen in Figure 3, results indicate that fcrMRI change within each of the three networks differed between the Active and Placebo rTMS groups. Findings indicate the presence of a statistically significant difference in change within the DMN between the Active and Placebo rTMS groups (Figure 3, top chart). A significant difference ($p = 0.04$) is observed during the provision of the assigned treatments (EP-BL) and a trend toward significance ($p = 0.06$) is observed throughout study participation (FU-BL). No statistically significant change was made after treatment stopped (FU-EP) ($p = 0.19$) but during this time, when treatment was not provided, the change was largely maintained for the active rTMS group. The changes within the Language Network are noteworthy as the direction of the change is markedly different for each group, but these differences did not approach statistical significance at any of the three timepoints (p-value range: .17 to .46). Within the somatosensory network (i.e., also referred to as the SomatoMotor network), there is a trend toward statistically significant difference between the Active and Placebo rTMS groups ($p = 0.06$) during provision of assigned treatment (Figure 3, bottom chart, EP – BL), with another trend toward statistical significance ($p = 0.09$) throughout study participation (FU – BL). Notably, there was no significant change made after treatment stopped (FU-EP) ($p = 0.41$) but during this time, when treatment was not provided, the change was largely maintained with the flipping from decreasing to increasing.

Functional Magnetic Resonance Imaging (MRI) – synonym task (Aim 2b), functional MRI -familiar voice task (Aim 2c): A preliminary analysis has been completed but is being redone to apply our improved denoising pipeline and frame-by-frame quality check for identifying presence of and examining effects of motion artifact.

Figure 3 - Within Network fcrMRI changes



Relationship between fcrMRI Connectivity Changes and Functional MRI task Activation Changes and Clinically and Statistically Significant Gains in Neurobehavioral Function: To understand how rTMS-induced network changes (i.e., connectivity, task activation) relate to rTMS-induced neurobehavioral gains, we have started examining associations/correlations. For the connectivity data, based on the controversy related to interpreting negative z values (Murphy and Fox 2017), we will continue examining associations by using multiple approaches. Thus, rather than report findings in this final report that are, currently, difficult to interpret, here we report that these additional examinations are in process. Additional examinations are being conducted to clarify the interpretation of the relationships between changes in pathological network function and neurobehavioral recovery.

As noted above, the task activation is being re-run as the improvements made to our pipeline (based on previously published methods, that are available in the online supplemental material)(Bender Pape, Livengood et al. 2020) will allow us to address motion artifact issues, and when completed correlations will also be computed.

The derived associations, for the connectivity and task activation data, will allow us to identify which variables to use in multivariate mixed-effects modeling, which will be used to compare active rTMS and placebo rTMS groups. This analytical modeling will be used to determine the presence, direction, and sustainability of rTMS-related changes on measures of functional neural activation and whether these changes are related to neurobehavioral recovery. This finding will be disseminated when completed in a scientific manuscript.

Electroencephalography Rest (EEG-Rest, aim 2d) and Synonym task (EEG-Task, Aim 2e) Outcomes: As behavioral assessments cannot detect alterations in neurophysiological responses that may occur as a precursor to/or during changes in cognitive state, exploratory EEG outcomes were included to determine usefulness in detecting rTMS-induced changes in neural function. EEG outcomes were added because EEG has been influential in increasing our understanding of cognitive processing in people in states of DoC and may have clinical utility as an assessment tool. Specifically, EEG spectral analysis was used to examine cognitive states captured at rest and during tasks

intended to elicit intentional cognitive processing (i.e., music, comedy, synonym oddballs). Recent work suggests that alpha, theta, and delta frequency bands are particularly important to assessing cognitive functioning in this population with notable differences observed in the extent to which these three bands are present.(Lehembre, Gosseries et al. 2012, Lehembre, Marie-Aurelie et al. 2012, Sitt, King et al. 2014)

Data collection, for both rest and task EEG data, was obtained by continuously recording from 19 AgCl active electrodes using a Nautilus amplifier (Natus). Electrodes were applied according to the international 10–20 system at midline. Online recordings were dc-coupled (with no filters) and, for clinical trial participants, referenced against the tip of the nose. For all participants, impedances were kept below 20 kΩ in accordance with system guidelines. Recordings were sampled at a rate of 1000 Hz. Eye movements (EOG) were monitored with left and right electrodes.

EEG data processing was conducted offline using EEGLAB for preprocessing (Delorme and Makeig 2004). EEG data were notched filtered at 60 Hz and then low pass filtered with a Butterworth filter set to 30 Hz. Data were then downsampled to 250. Bad channels were spline interpolated. Data were epoched at 10,000 ms intervals. Automated and manual artifact detection was performed to keep 10 trials from each stimulus set.

Fieldtrip Toolbox for EEG/MEG analysis was utilized for spectral analysis. (Oostenveld, Fries et al. 2011) Spectral power was estimated across all channels and trials using a Hanning-taper and the Fieldtrip multi-taper frequency transformation method. Smoothing was set for 1 Hz. Frequency was set from 1 -12 Hz with alpha- (8-12), theta- (4-7) and delta-band activity examined (1-4 Hz).

Participants: The exploratory EEG outcomes were collected on seven clinical trial participants and, to date, have been analyzed for five of the seven. We report, here, the results for the five participants and plan to complete all analyses prior to publication of the primary manuscript. All but one of these five participants presented, at baseline, in the vegetative state. Two of the five participants were randomly assigned to Placebo rTMS with three assigned to the active rTMS group. One participant, in the Active group, did not return for follow-up testing.

The EEG exploratory sample (Table 5) is similar to the total sample (Table 2) by age and time post-injury but differs in that the EEG sample included largely persons in the Vegetative State at baseline. The injury severity metrics indicate, accordingly, slightly more severe neuropathological injury. As the two participants, with EEG data currently being analyzed, were both in MCS at baseline the final EEG exploratory sample will be more representative of the total sample for the clinical trial (Table 2).

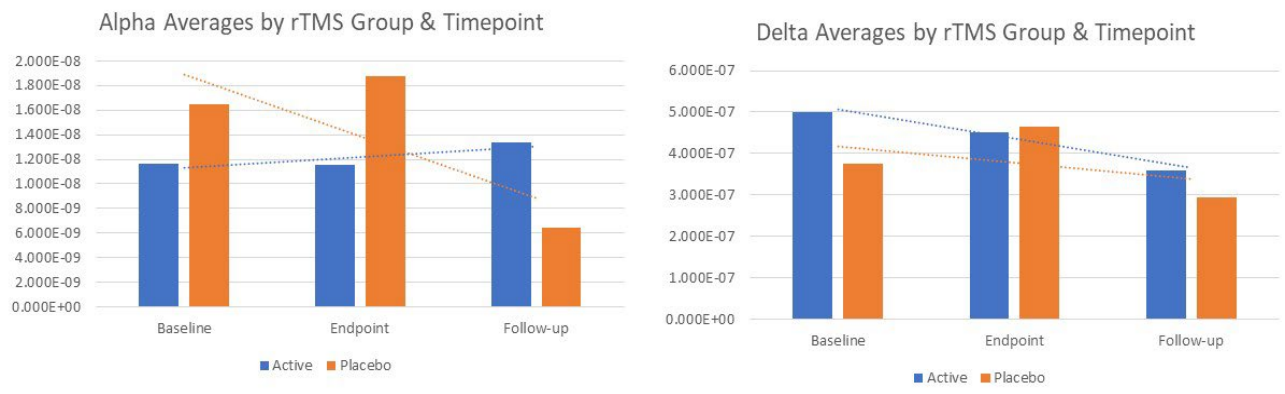
Table 5: Description of Exploratory EEG Sample

	Means (SD) by Groups		
	Total Sample (n = 5)	**Active (n = 3)**	**Placebo (n = 2)**
Mean Age at Injury *	27.6 (10.1)	29.7 (11.7)	24.5 (5.5)
Mean Years post*	1.1 (.4)	1.2 (.4)	1.1 (.5)
% in Vegetative State at Baseline	.80	.67	1.0
CSFrv*	.39 (.03)	.39 (.03)	.39 (.04)
GMrv*	.34 (.02)	.35 (.02)	.35 (.01)
WMrv*	.26 (.02)	.26 (.02)	.27 (.03)
CSFtv*	603.80 (67.17)	596.33 (63.41)	615.00 (71.00)
GMtv*	524.80 (5.23)	526.67 (5.56)	522.00 (3.00)
WMtv*	401.20 (33.39)	390.67 (27.63)	417.00 (35.00)
TIV*	1529.80 (53.38)	1513.67 (58.07)	1554.00 (33.00)

MRI T1 3D volume sequences were used to compute these neural injury severity metrics: Relative Volume of Cerebral Spinal Fluid (**CSFrv**) = normalized by total intracranial volume (Total volume/TIV) (can indicate tissue-type damage); Relative Volume of Gray Matter (**GMrv**) = normalized on total intracranial volume (can indicate tissue-type damage); Relative Volume of White Matter (**WMrv**) = normalized based upon total intracranial volume (can indicate tissue-type damage); **rTMS** = Repetitive Transcranial Magnetic Stimulation; Total Volume of Cerebral Spinal Fluid (**CSFtv**) = total cubic voxels, non-normalized (can indicate large volume loss); Total Volume of Gray Matter (**GMtv**) = total cubic voxels, non-normalized (can indicate large volume loss e.g., craniotomy); Total Volume of White Matter (**WMtv**) = total cubic voxels, non-normalized (can indicate large volume loss); Total Intracranial Volume (**TIV)** = cm3

The preliminary spectral findings for the EEG-rest data, with two participants to still be added to analyses, revealed the presence of alpha wave band activity primarily distributed across the posterior portion of the scalp with increasing polarity observed across each assessment period. Delta band activity was also observed with a primarily anterior distribution and decreased polarity during the final assessment period. The average alpha and delta power, across time by groups (Figure 4), suggest that the averages for each group differ but these are not significantly different ($p > 0.05$). For the Active rTMS group, there is a pattern of Alpha power remaining the same during the time of providing active rTMS treatments (BL to EP) and increasing at follow-up during a time (EP to FU) when no rTMS treatments were provided. For the Placebo rTMS group, no pattern is discernible as variability in alpha power is seen. The trendlines for average delta power are similar but in the opposite direction. They are similar in that the averages suggest the emergence of a pattern of change in delta power for the active group but variability for the placebo group. For the active rTMS group, the average Delta power appears to decrease during the provision of active rTMS (BL to EP) and follow-up (EP to FU).

Figure 4: EEG-Rest Alpha and Delta Waveform averages by Group and Timepoints



Relationship between EEG Spectral Changes and Neurobehavioral Gains: We examined the relationship between changes in alpha and delta power, during the provision of assigned rTMS treatments (active or placebo) and peak neurobehavioral gains in DOCS somatosensory measures, by computing correlations. These correlations indicate that as there is more change in alpha power the greater the gains in somatosensory skills ($r = .80$). Similarly, as there is more change in delta power the greater the gains in somatosensory skills ($r = .87$). Collectively, the patterns of average change by group and these correlations in neurobehavioral skills are consistent with work by Lehembre et al. (2012) (Lehembre, Gosseries et al. 2012, Lehembre, Marie-Aurelie et al. 2012) and Sitt et al. (2014) (Sitt, King et al. 2014) indicate that individuals in a VS in comparison to MCS, display decreased alpha power and increased delta power. Specifically, individuals in MCS are more like healthy neurotypical individuals as they have higher alpha-band activity and lower delta-band activity than those in VS (Chennu, Finoia et al. 2014). Moreover, alpha-band activity is associated with a relaxed attentive state and increases in alpha are an indication of recovery

of attention skills, whereas decreases in delta are associated with reductions in persistent deep sleep. Since the active rTMS group shows a pattern, and because the directionality of the change is correlated with greater neurobehavioral skills, these findings collectively suggest that the active rTMS treatment may be shifting cognitive states to a more alert and attentive state.

For the EEG task data, the spectral analysis to date reveals significant variability in alpha, theta, and delta waves with no consistent discernable pattern in response to treatment. The present analyses did not reveal consistent power over treatment periods for any task EEG outcomes. We will be finalizing these analyses with the two additional participants.

Specific Aim 3: Determine the rTMS effect on white fiber tracts and whether rTMS-related effects correlate with neurobehavioral gains. This will be determined by examining data collected from the Diffusion Tensor Imaging (DTI) sequences as this sequence indirectly measures white fiber tract integrity (i.e., structural connectivity). DTI metrics/measures that are currently being computed for each subject include Fractional Anisotropy (FA), Mean Diffusivity (MD), Radial Diffusivity (RD), and Axial Diffusivity (AD). After computing these metrics, the relationship (associations) between the DTI metrics and the neurobehavioral measures will also be examined. The yielded associations will allow us to identify which variables to use in multivariate mixed-effects modeling, which will be used to compare active rTMS and placebo TMS groups. This analytical modeling will allow us to determine the presence, direction, and sustainability of rTMS-related changes in white fiber tracts and whether these changes are related to neurobehavioral recovery.

Specific Aim 4: To confirm rTMS safety for severe TBI. Considering the paucity of studies comprehensively examining the safety of using rTMS as a treatment for persons in states of disordered consciousness (DoC) after severe Traumatic Brain Injury (sTBI), we examined our safety data to provide a descriptive report of rTMS safety findings and a report of rTMS related seizure risk. Considering the need for rTMS safety data relative to the 18-month pandemic-related mandatory hold on continued enrollment of participants into this placebo-controlled rTMS trial, we based our descriptive report on previously unpublished safety data from a past open-label trial (Pape, Rosenow et al. 2009, Pape, Rosenow et al. 2014) and from a past rTMS and Amantadine trial (Bender Pape, Herrold et al. 2020). We used these descriptive findings to inform our approach to analyzing rTMS seizure risk using the data from this recently completed placebo-controlled rTMS trial.

The descriptive rTMS safety report is based on two previous trials that provided rTMS using the same parameters (Pape, Rosenow et al. 2006) as those of our recently completed placebo-controlled rTMS trial. Specifically, the seven participants in these past trials, each received a total of 30 active rTMS sessions where rTMS was provided within the right or left dorsolateral prefrontal cortex. The participants included persons who were in states of DoC after severe TBI due to widespread neuropathology, but no large lesions in proximity to the site of rTMS. One participant had a ventriculoperitoneal shunt with a programmable valve. In 2020 (Appendix 8) (Kletzel, Aaronson et al. 2020) we reported the cumulative safety findings using summary statistics (e.g., frequency of incidents of hypertension, serious adverse events (AE). This published report indicates that, during and after the 30 active rTMS sessions, average changes for monitored indicators were of mild severity, with 75 non-serious and one serious AE (seizure). The participant incurring a seizure resumed rTMS on anti-epileptics without further seizure activity. Considering elevated risks for this patient population and conservative patient selection, the descriptive findings suggest a relatively safe profile for the specified rTMS protocols. Considering that seizure risk is elevated after TBI, an estimate of rTMS-induced seizure risk by comparing seizure outcomes between an active rTMS and a placebo rTMS group is indicated.

We addressed the need for estimating rTMS-related seizure risk in the second safety report, which will be submitted for peer review in December of 2023 (Appendix 28) and these methods and results are summarized here. To determine that the active rTMS group is as safe as the Placebo rTMS group, we used the EEG safety and clinical safety data derived from three separate rTMS studies that each enrolled unique participants in states of DoC after TBI. All participants received active or placebo rTMS to the dorsolateral prefrontal cortex (DLPFC). In addition to clinical monitoring by researchers and clinicians using an approved safety monitoring protocol, safety EEGs were always obtained on days of rTMS. The relationships between seizure occurrence and rTMS treatment group assignment (Active vs Placebo) were examined by computing prevalence and incidence rates, using logistic regression and computing Pearson correlations. For logistic regression, a model comparing seizure risk, relative to group assignment, was conducted. We also conducted models, each run separately, with the group variable and one of 37 variables/factors known or thought to increase seizure risk after severe TBI (e.g., number of neurosurgeries, presence of shunt, contusions, severity of neuropathology). For associations, we computed correlations between each of these risk factors and the presence/absence of seizures.

Two participants out of 20 were noted to have experienced seizures when their assigned treatment was being provided. The participants who experienced seizures during study participation each recovered their pre-seizure levels of neurobehavioral function and did not exhibit evidence of neurological worsening or destabilization.(Kletzel, Aaronson et al. 2020)

The proportion of rTMS-related seizures was 6% (1/17) as the seizure occurred during the provision of active rTMS. The proportion of seizures during placebo was 33% (1/3) as they occurred during the provision of placebo rTMS. For persons remaining in either VS or MCS an average of 3 years post-TBI who for the three months before study enrollment did not have active seizures and did not require prophylactic seizure management and who, on baseline EEGs, had no evidence of epileptiform discharges, the rTMS-related seizure incidence rate, was 59 per 1,000 persons. The rTMS-related seizure incidence rate is lower than the severe TBI-related seizure incidence rate for the Placebo group of 333 seizures occurring per 1000 persons, which is consistent with incidence rates published by Ritter (2016).(Ritter, Wagner et al. 2016) This report indicated that in persons with moderate to severe TBI, 128 of every 1,000 persons reported late seizure activity. The rTMS-related seizure incidence rate is, however, slightly higher than the incidence rate reported by Annegars (1998) (Annegers, Hauser et al. 1998) where, for every 1,000 persons, incurring a severe TBI, 37 persons had late seizure activity.

The findings from logistic regression analyses indicate that there are no statistical differences between the rTMS treatment groups (Active vs. Placebo), in the occurrence of seizures on the day of rTMS treatment sessions. There was also no difference in any group model that also included one variable/factor known to increase seizure risk for severe TBI. The correlation findings indicate one significant ($p = 0.05$) association ($r = 0.44$) between seizure occurrence and the presence of a VP shunt.

<u>Aims 1 through 4 Conclusions (To Date):</u> As the interpretation of any trial should depend on the totality of the evidence (i.e., the primary, secondary, and safety outcomes) and not just a single endpoint, the completed analyses (to date) indicate that there is a small but important clinical benefit (Effect Size = 3.3, CI: .12 to 6.6) from providing rTMS in isolation, when not paired with a pharmacological or learning based interventions. This Effect Size is similar to effects reported from the Amantadine trial (Giacino, Whyte et al. 2012) where benefits of .40 and .19 points on the DRS were reported for patients who received Amantadine early injury (4 to 16 weeks). While the effect sizes are similar, it is important to note that the participants were in the chronic phases of DoC recovery when receiving the rTMS intervention. These neurobehavioral gains from rTMS in isolation, in this placebo-

controlled trial, are also consistent with our earlier reports (Pape, Rosenow et al. 2009, Pape, Rosenow et al. 2014) from case studies as well as our proof-of-concept study (Bender Pape, Herrold et al. 2020) where participants remaining in states of DoC for up to 15 years after TBI made neurobehavioral gains when receiving rTMS in isolation.

Given COVID-19 and all regulatory barriers discussed in a later section (titled 'Actual or anticipated problems or delays and actions or plans to resolve them), the major limitation of the clinical trial is that the planned sample size was not achieved, meaning that the final study sample is underpowered. Also, our previously reported JWMRP findings (W81XWH-16-2-0023 Revised Final Report) indicate that the planned primary outcome, the DRS, is limited in use for detecting change in neurobehavioral function for the patient population under study. Given these two limitations on detecting treatment effects, we also examined all secondary outcomes and metrics of clinical significance (Minimally Clinically Important Difference, Minimal Detectable Change, and Effect Sizes with confidence intervals).

While the clinical trial findings are based on a small sample size, the findings of clinical benefits in DOCS somatosensory skills are important as they are based on a double-blind randomized placebo-controlled trial. It is also important to note that these neurobehavioral gains were induced with rTMS targeting based on all subjects but two receiving rTMS at the DLPFC as defined using the 5 cm anterior rule. Specifically, the spatial location was standard across patients but our own algorithm (Discussed above and paper provide in Appendix 6) (Herrold, Siddiqi et al. 2020) now provides the capability to personalize the spatial localization of the rTMS target within the DLPFC.

Persons remaining in either VS or MCS an average of 3 years post-TBI who for the three months prior to study enrollment did not have active seizures and did not require prophylactic seizure management and who, on baseline EEGs, had no evidence of epileptiform discharges, the safety findings indicate that 30 rTMS treatment sessions (2 sessions per day, 300 trains of paired pulses per session)(Pape, Rosenow et al. 2006) was well tolerated. These findings are consistent with our previously published descriptive studies regarding the relative safety of rTMS for patients in states of DoC after TBI. (Pape, Rosenow et al. 2009, Pape, Rosenow et al. 2014, Kletzel, Aaronson et al. 2020)Collectively, the findings also indicate that it is safe to widen the scope of future clinical trial participants to include those on anti-epileptics. However, the finding of a significant and moderately strong correlation between seizure occurrence and the presence of VP shunts is a finding the researchers believe is of relevance. Ultimately, the decision to provide rTMS therapeutically should be left to the patient's family (legally authorized representative), researcher, and/or clinician. If patients with VP shunts are included, they should receive anti-epileptics during study participation. If the study population is broadened to include patients previously excluded based on profiles raising safety concerns and/or if patients with VP shunts are included in future studies, then seizure monitoring should continue in the research study. Given the generally poor prognosis of participants with DoC following TBI, the evidence of efficacy reported above (and the evidence anticipated from the additional analyses underway) indicates that the potential benefits appear to outweigh the risks.

To inform the development of future clinical trials, we are in the process of examining treatment responsiveness relative to the rTMS neural target and each participant's unique neuropathology. Thus, future clinical trials should build on this ability to personalize the spatial location of neural targets as this will likely further optimize rTMS-induced neurobehavioral gains. Considering these findings and the 2020 proof of concept study (Appendix 2) (Bender Pape, Herrold et al. 2020) that examined the pairing of rTMS with Amantadine, future trials should focus on pairing rTMS with either pharmacological and/or learning-based interventions.

As stated above, we will complete Aims 2 and 3 analyses that will inform us how changes in pathological connectivity within and between neural networks relate to neurobehavioral recovery. These analyses will also inform the direction of future research, specifically optimal neural targeting when providing rTMS. Also, we are currently examining the relationship between the rTMS-induced gains in somatosensory skills detected in this clinical trial relative to the change in expression of miRNA that was collected in the JWMRP-funded study (W81XWH-16-2-0023 Revised Final Report) (Appendix 10) (Zilliox, Foecking et al. 2023). This will also inform future research on neural targeting and dosing/number of rTMS sessions related to peak neurobehavioral gains and/or needed to sustain those gains.

Goal # 5 Accomplishments: Dissemination Activities

For specific manuscripts, please see the above Goals section that provides a table of manuscripts by planned and actual completion dates for Goal #5. Also, please see the products Section below, which provides a comprehensive list of presentations in different scientific and educational venues, also addressing accomplishments for Goal #5.

What opportunities for training and professional development has the project provided?

Pre-Doctoral and Post-Doctoral Mentorship/Training Experiences

Institution	Trainee	Profession/Title	Mentor/Trainer	Training/Professional Develop. Activities
University of Illinois-Chicago, Dept. of Neurosciences	Noor Chaudhry	BS Candidate Neurosciences, Degree conferred: 12/2021	Theresa Pape	1:1 mentoring in good research practices, clinical testing and treatment procedures and imaging analyses
University of IL at Chicago (UIC) School of Public Health	Yue (Annie) Wang,	PhD Geneticist and PhD Biostatistician	Theresa Pape	Doctoral Dissertation: Bayesian Multimodal Local False Discovery Rate in Neuroimaging
University of IL at Chicago (UIC) School of Public Health	Fei Jie	PhD Biostatistician	Theresa Pape	Doctoral Dissertation: Statistical Methodologies for Neuroconnectivity Analysis using fMRI data
University of IL at Chicago (UIC) School of Public Health	Weihan Zhao	PhD Biostatistician	Theresa Pape	Doctoral Dissertation: Methods for Group Comparisons of Brain Connectivity with Multimodal Neuroimaging

Edward Hines Jr. VA Hospital	Julie Schwertfeger	Doctor of Physical Therapy (DPT) and PhD in Interprofessional Healthcare Studies, Polytrauma Post-Doctoral Fellow	Theresa Pape	1:1 Mentoring in Neural plasticity and Neuromodulation in TBI
Edward Hines Jr. VA Hospital	Andre Lindsey	PhD Speech Language Pathologist, Polytrauma Pos-Doctoral Fellow	Theresa Pape	1:1 Mentoring in Neural plasticity and Neuromodulation in TBI and detecting meaningful treatment effects with EEG/EPs
University of IL at Chicago (UIC) college of Medicine	Paul Thomas	MD/PhD Candidate	Theresa Pape	Doctoral Dissertation: Predicting Treatment responsiveness using Diffusion Tensor Imaging
Edward Hines Jr. VA Hospital	Sherri Livengood	PhD Communication Sciences and Disorders, Polytrauma Post-Doctoral Fellow, Health Research Scientist	Theresa Pape	1:1 Mentoring in Neural plasticity and Neuromodulation in TBI and detecting meaningful treatment effects with multimodal MRI, EEG/EPs
Edward Hines Jr. VA Hospital	Sandra Kletzel	PhD Neuroscience, Polytrauma Post-Doctoral Fellow, Health Research Scientist	Theresa Pape	1:1 mentoring in Clinical Rehabilitation Research, Neural plasticity, and Neuromodulation
Edward Hines Jr. VA Hospital	Alexandra Aaronson	MD Neuropsychiatrist	Theresa Pape	1:1 mentoring in Clinical Rehabilitation Research, Neural plasticity and Neuromodulation
George Washington University	Jennifer Weaver	Occupational Therapist	Trudy Mallinson	Completed a PhD in Translational Health Sciences while working full time as a Project Manager;

				this included taking courses in advanced statistical methods, qualitative inquiry for health professionals, and mixed methods research. Independent studies in Rasch Measurement Theory and the Many Facet Rasch Model were instructed by Dr. Trudy Mallinson.

Capacity Building

Direct Training				
Institution	**Trainee**	**Profession/Title**	**Mentor/Trainer**	**Training/Professional Develop. Activities**
Edward Hines, Jr. VA Hospital	Elyse Walsh Katie Kestner Kelly Krese	Physical Therapists	Ann Guernon and Theresa Pape	Training in regulatory activities and reporting, study coordinator role, data collection (e.g., EEG task and safety, neurobehavioral) and provision of rTMS

Interdisciplinary Collaboration			
Caregiver Collaboration			
Institution or Organization	***Collaborator***	***Role***	***Activity***
No affiliate	Tisha Kot	Caregivers of loved ones (civilian) with disorders of Consciousness	Founded collaborations with caregiver partners
	Paige Ford	Caregiver of loved one (veteran) with disorders of consciousness	
Professional Collaborations			
Institution or Organization	***Collaborator***		***Activity***

Edward Hines, Jr VA Hospital	Theresa Pape, DPH, CCC-SLP Pacheco, MD Monica Steiner, MD	Medical and safety oversight
George Washington University	Trudy Mallinson, PhD	Outcome measurement and co-calibrations
Colorado State University	Jennifer Weaver, PhD, OTR/L CBIS	Outcome measurement and co-calibrations
Lewis University	Ann Guernon, PhD, CCC-SLP	Neurobehavioral test administration and training
Shirley Ryan Ability Lab	Catherine Kestner, PT, DPT, NCS Kelsey Watters, OTR/L, BCPR, CBIS Kelly Krese, PT, DPT, NCS Piper Hansen, OTD, OTR/L	Neurobehavioral test administration and training rTMS provision
Northwestern University	Joshua Rosenow, MD	Medical safety oversight
Adler University	Vanessa Silva, MS Konner Nelson	Neurobehavioral data preparation
TIRR	Katherine O'Brien: CRS-R data collection procedures in clinical practice	CRS-R data collection to enable co-calibrating outcome measures
Spaulding Rehabilitation Hospital	Joseph Giacino: DRS and CRS-R data from the amantadine trial	Data sharing to enable Co-calibrating outcome measures

How were the results disseminated to communities of interest?

We disseminated to communities of interest via peer-reviewed publications, and international, national, and local conference presentations. We specifically disseminated to communities that were discipline-specific and interdisciplinary to tailor our messaging and reach a broader audience.

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

Not applicable, final report.

IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Objectives and aims of this project have contributed substantially to the field of rehabilitation in four major knowledge areas: rTMS specific seizure risk in patients with severe TBI, minimal competency for patients with DoC, behavioral outcomes, and TMS targeting. After completing Aims 2 and 3 analyses as well as our analyses where we are examining miRNA changes relative to neurobehavioral gains, we will also likely advance knowledge of how rTMS induces neural plasticity.

rTMS Specific Seizure Risk

Given the complex clinical management of patients with DoC and an incidence rate of 20% for post-traumatic seizures as late as five years after TBI (Annegers, Hauser et al. 1998, Ritter, Wagner et al. 2016), seizures remain the complication of utmost concern when considering rTMS as a neurorehabilitation intervention. The numbers represented here are small. However, considering the challenges in conducting clinical trials for persons with DoC due to TBI and that these patients have widespread lesions that affect normal anatomical relationships and function and, in turn, are likely to make rTMS much less precise relative to individuals without TBI, our comparison of seizure occurrences between Active rTMS and Placebo rTMS groups advances understanding rTMS related seizure incidence and risk factors. Also,

Based on these seizure risk findings (Appendix 27), a manuscript is being submitted for peer review and the findings as well as recommendations will be made to the FDA for the safe use of rTMS with patients in a severe state of disordered consciousness, either vegetative or minimally conscious.

Minimal Competency Recommendations

This project also made a significant contribution to the minimal competency recommendations for persons who have DOC. The Brain Injury Interdisciplinary Special Interest Group of the ACRM, in collaboration with the Disorders of Consciousness Special Interest Group of the NIDILRR-Traumatic Brain Injury Model Systems convened a multidisciplinary panel of experts to address this need through the present position statement. Content area-specific workgroups reviewed relevant peer-reviewed literature and drafted recommendations which were then evaluated by the expert panel using a modified Delphi voting process. The process yielded 21 recommendations on the structure and process of essential services required for effective DoC-focused rehabilitation, organized into 4 categories: diagnostic and prognostic assessment (4 recommendations), treatment (11 recommendations), transitioning care/long-term care needs (5 recommendations), and management of ethical issues (1 recommendation). With few exceptions, these recommendations focus on infrastructure requirements and operating procedures for the provision of DoC-focused neurorehabilitation services across subacute and post-acute settings (Public dissemination and peer reviewed publication (Giacino, Whyte et al. 2020) are both provided in Appendices 3 and 5).

Behavioral Outcomes

Behavioral outcomes were addressed throughout the study and through the development of a behavioral recovery hierarchy without gaps. Examining the psychometric properties of each of the assessment scales used in the clinical trial led to the identification of the need to develop a hierarchy without gaps, which was only possible with a larger than anticipated data set to conduct a co-calibration analysis. Thus, we assembled data sets from eight additional studies that each have a unique sample of patients in DoC due to TBI. Co-calibration requires some linkages in the data set, which was provided by the rTMS trial (ID #

W81XWH-14-1-0568) as it includes all four assessments (Table 4) being co-calibrated. That is, to link the data sets across studies, some of the patients in the co-calibration data set must be scored on more than one of the four assessments. We leveraged the data from this rTMS clinical trial and eight additional databases to complete the analyses, creating data use agreements with each organization sharing the data. We supplemented the clinical trial data with previously collected assessment data from Dr. Pape's FAST clinical trial (Pape, Rosenow et al. 2015) and observational post-acute care study (Pape, Mallinson et al. 2014). We leveraged existing relationships with Kelsey Watters and Piper Hansen to receive DOCS and CRS-R data from Shirley Ryan Ability Lab and Katherine O'Brien at TIRR Memorial Hermann to receive additional CRS-R data. We also entered into a data use agreement with Dr. Giacino and Dr. Whyte to receive DRS and CRS-R data from the amantadine trial. Each data set required IRB amendments and data use agreements.

Table 1 Co-Calibration dataset: Combined data from nine studies

	Data Sets	**Assessments Being Co-calibrated**			
	n/r	**DRS**	**CRS-R**	**CNC**	**DOCS**
**rTMS Trial	18/126	X	X	X	X
FAST Clinical Trial	30/354			X	X
PACS (Observational)	175/851			X	X
R21 Clinical Trial	4/62			X	X
Open Label Trial	3/31			X	X
SRAL	52/876		X		X
Amantadine trial	184/1288	X	X		
TBIMS	2107/2312	X			
TIRR	19/25		X		

The rTMS clinical trial (ID # W81XWH-14-1-0568) included all four assessments (DOCS, CRS-R, CNC, and DRS) thereby creating the necessary linkage across the co-calibration data set. **Abbreviations: n/r-sample of unique patients and total records**; rTMS trial** (ID # W81XWH-14-1-0568; 2016-2022); **FAST**-Familiar Auditory Sensory Training clinical trial; **PACS-** Post Acute Care Study data that collected at Hines VA as part of DOCS validation observational study. **R21**: clinical trial data collected at Hines VA; **Open Label:** Data collected at Hines VA; **SRAL:** clinical data from Shirley Ryan Ability Lab 2014-2018; **Amantadine trial**:-Clinical trial testing effect of Amantadine 2003-2010; **TBIMS**: NIDILRR TBI Model Systems Data 2012-2018; **TIRR**: Clinical data from Texas Institute of Rehabilitation Research 2019-2020.

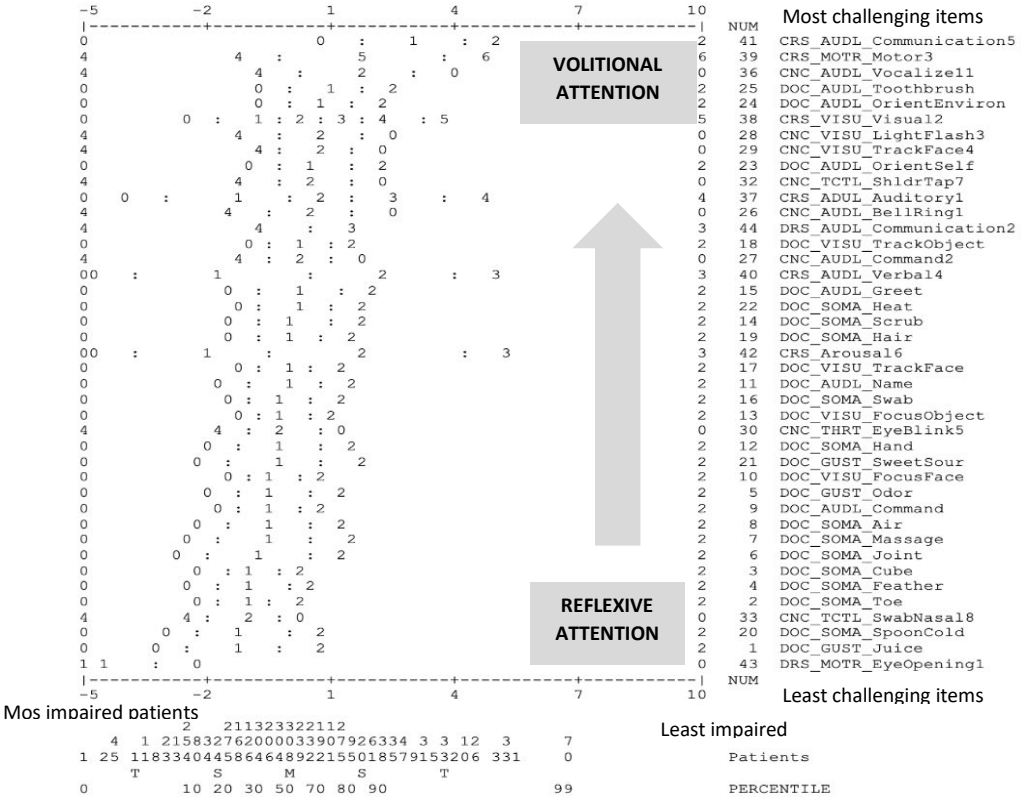
To arrive at the final co-calibration of 49 items across the four assessments of neurobehavioral function, we conducted a series of analyses, as follows:

1. Examined all 49 items and rating scale steps for DOCS, CNC, CRS, DRS.
2. Removed DRS items 44-49 (Awareness, Communication, and Global Function items).
   a. The rationale for removing these items described above under DRS analyses.
3. Removed Pain items and rating scale steps from the CNC (CNC9-Pain to Finger; CNC10-Pain to ear), CRS pain rating scale steps of the motor item (CRS3 Motor Function steps 3, 2, 1, 0), and the DRS pain rating scale categories (DRS1 Eye Opening step 3, 2; DRS3-Motor Response to Pain steps 5,4,3,2,1).
   a. The rationale for removing these items/step categories was evidence (fit statistics, principal component analysis of residuals) that pain is a distinct construct from neurobehavioral function.

The resulting item hierarchy (**Figure 5**) shows that DRS eye-opening is the easiest item as it is the first to be seen in the recovery of patients in states of DoC after TBI. Communication, orientation, and purposeful object use are the most challenging and align with eMCS. Next, many of the DOCS somatosensory items capture very low levels of function in patients classified as being in the VS and provide an important means of capturing change in this difficult-to-measure population. CNC items, which were originally designed to capture very low levels of patient function are, however, seen towards the top of the hierarchy. This is consistent with findings reported in our aforementioned CNC publication when the CNC items were examined separately (Weaver, Liu et al. 2021). As found with our analyses of the CRS-R items separately (Weaver, Cogan et al. 2022), the wider range of these seen here with the CRS-R is related to the six CRS-R items being comprised of multiple stimuli levels within a single item domain.

In summary, the co-calibration of the CNC, CRS-R, DOCS, and DRS indicates that the DOCS somatosensory items are easier for patients to respond to while CRS-R and DOCS auditory and visual items are the most challenging. The CRS-R arousal item appears higher in the hierarchy than expected, likely due to the rating scale step 3 (attention). This aligns with other items of similar challenge (e.g., DOCS-25 face tracking, and responding to name called aloud). This is the first time that the alignment of major assessment tools has been empirically described. Notably, each of these four assessments captures different areas of the recovery spectrum for patients in states of DoC. Our findings clearly illustrate that no assessment in isolation can effectively measure DoC after TBI.

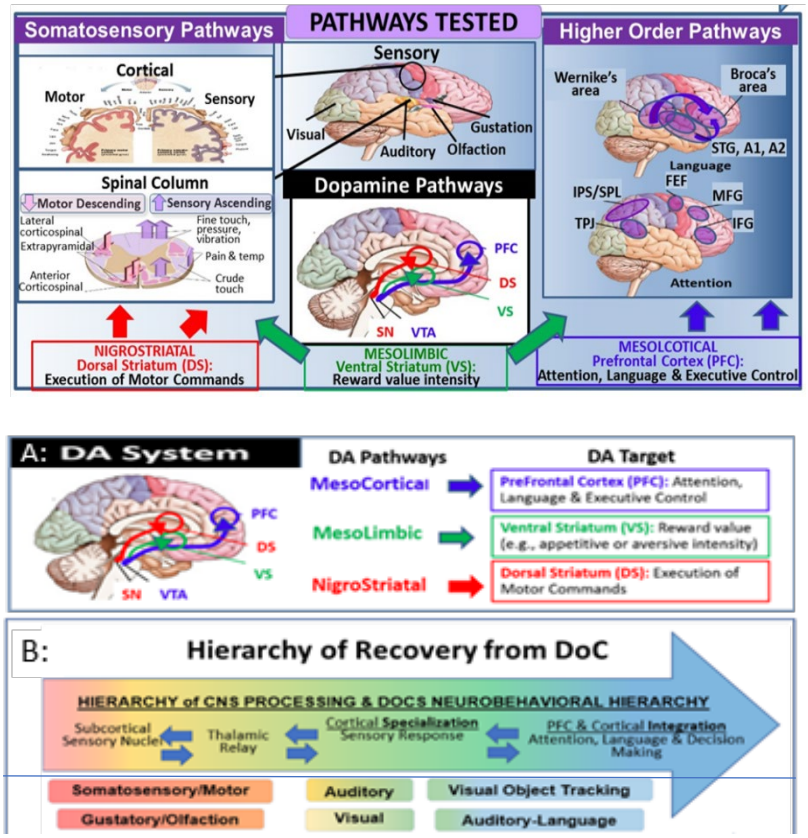
Figure 5 Co-Calibrated Person-item Hierarchy (abbreviation DOC=Disorders of Consciousness Scale)



rTMS Targeting Framework

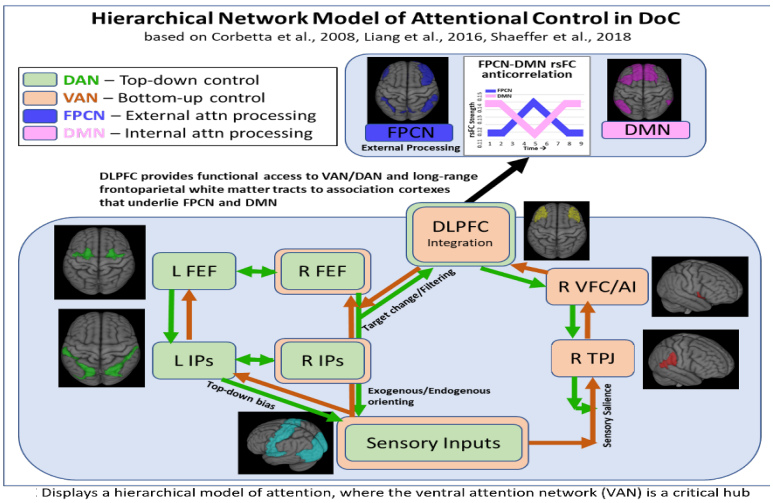
In the context of the primary goal of the treatment, to restore cortical activity to higher-order cognitive functions in patients with DoC due to TBI, we evaluated the neuroscience methodologies and outcome measures available to use with a non-communicative population. We evaluated these methods and measures to develop the above described a neurobehavioral hierarchy of recovery from disorders of consciousness, that we used to inform us about treatment effects and how we can optimize these effects by improving rTMS treatment targeting. The behavioral recovery hierarchy (Figure 5) indicates that as volitional attention (vs reflexive attention or orienting) comes online, behavioral recovery improves. Based on the evidence that the hierarchy of neurobehavioral recovery manifests as a progression from reflexive abilities to volitional attention abilities, we sought to advance our understanding of how to optimize rTMS targeting to enable attention-processing skills. We integrated the new knowledge created with the behavioral recovery hierarchy with the established knowledge that the dopaminergic anterior forebrain mesocircuit effectively achieves subcortical and cortical modulation to improve attention processing with the behavioral hierarchy. We integrated this knowledge to develop a framework (Figure 6) that can be used to inform us of rTMS targeting in DoC patients to improve attention skills.

Figure 6 Targets for DoC Recovery: Subcortical Dopamine Pathways



To our knowledge, we developed the first neuroscience probes for different levels of neural processing (Figure 6) that can be collected from a non-communicative population. For neuroimaging, we developed a model of attention control (Figure 7) that reflects the behavioral hierarchy of DoC recovery above (Figure 5); and changes in the attention networks that can be measured using both resting state fMRI in addition to two passive-listening task fMRI paradigms.

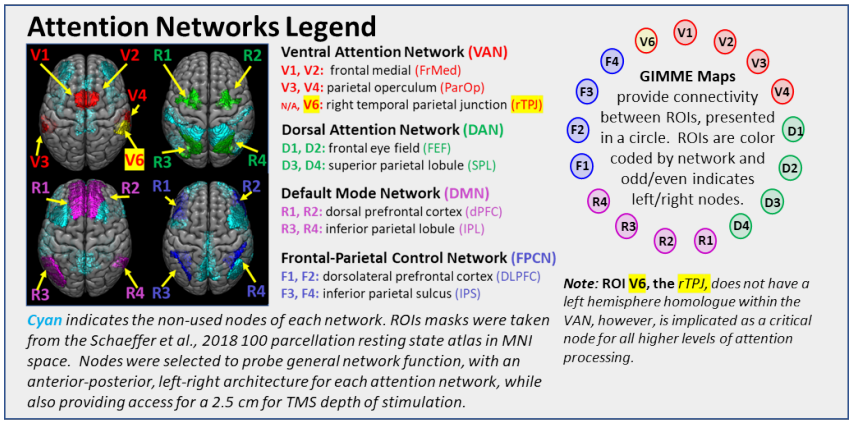
Fig 7 Hierarchical Model of Attention Control in DoC Recovery



Displays a hierarchical model of attention, where the ventral attention network (VAN) is a critical hub that supports function within the dorsal attention network (DAN), and together the VAN & DAN engage the frontoparietal control network (FPCN) and default mode network (DMN) via the = dorsolateral prefrontal cortex (DLPFC). *R VFC/AI= right ventral frontal cortex/anterior insula; R TPJ= right temporal-parietal junction; R L FEF= right & left frontal eye fields; R L IPs= right & left intraparietal sulcus; Sensory Inputs=Occipital cortex & somatosensory cortex.*

Based on the Hierarchical Model of Attentional Control in DoC presented in Figure 7, we identified network nodes of attention (Figure 8 below) that optimize resting state probes in severely damaged brains and that are accessible to rTMS. The nodes were chosen to provide the best opportunity to measure network function at a group level when lesions and damage are heterogeneous across the population. For example, probe the anterior, posterior, and left and right nodes of the same network, to gain a distributed probe that increases the likelihood of accessing viable substrate within each network.

Figure 8 rTMS accessible Probes of the Attention Neural System



By integrating established knowledge with evidence created with the co-calibrated neurobehavioral recovery hierarchy, we can now choose neural targets based on the behavioral skills targeted for remediation. Also, we can select outcome measures that will capture the targeted skill. These scientific capabilities will support future research in the development of rTMS, paired with targeted pharmacology and/or learning-based interventions, to enable DoC recovery.

What was the impact on other disciplines?

The funded work had a significant impact on the field of neuroimaging. We were successful in advancing the following areas: imaging vulnerable populations, controlling for motion artifacts, and improving scanner harmonization. Additionally, we made advancements in personalized targeted TMS with improvements in hand knob motor hot spot location and the creation of a treatment target algorithm. These developments can be used across multiple scientific and clinical disciplines.

<u>Imaging Vulnerable Populations and Controlling Motion Artifact</u>

Medically complex patients with DoC, as well as other populations, can pose unique challenges for MRI acquisition due to uncontrollable motion. However, procedures developed for this study can be used to minimize motion across allstudies. These motion minimization procedures include using blanket cocooning, rigidly positioning patient's head using inflatable pads and/or Caseforge helmets molded to

each patient and the 64-channel coil. detecting signs of participant discomfort or distress that will exacerbate motion. A research nurse and research therapist also continuously monitor each patient's vital signs and the patient via live video, and the nurse and/or therapist will enter the MRI at the next available break in sequences to reposition and provide intervention (i.e., stretching, suctioning, etc.) to minimize motion in the scanner. However, interruptions and interventions are minimized as able to prevent overstimulation of the participant due to frequent repositioning and interventions, if they are not needed in the clinical judgment of the providers present during the scan. The participant is positioned in the scanner with their head in a 64-channel coil, but towels, padding, and foam are used within the coil around the head to provide comfort and minimize abnormal or end-range postures. Padding is also utilized around extremities to reduce the risk of pressure injury and reduce discomfort. The participant is covered in a blanket, and straps are used to secure the participant to the table and minimize motion. Relaxation techniques utilized during the scan may include stretching, massage, or reorientation. In one clinical case, where head motion was not maintained with the standard positioning described above, a customized foam helmet was trialed to further improve positioning and reduce motion artifact. The customized helmets developed by CaseForge are constructed of rigid foam and molded based on mapping via the iPhone app of an individual's unique anatomy. This trial was the first to use this technology in individuals with Disorders of Consciousness. The unique patterns of posturing, hypertonicity, and range of motion restrictions that present in this patient population limited the fit of the helmet as manufactured. However, with manual modifications done by clinicians while positioning the participant within the head cage of the scanner, motion was able to be reduced significantly. For example, the CaseForge helmet improved the useable data from 589/1100 (53%) useable volumes without the helmet, to 1040/1100 (94%) useable volumes with the helmet, producing a roughly 41% increase in useable data.

Scanner Harmonization

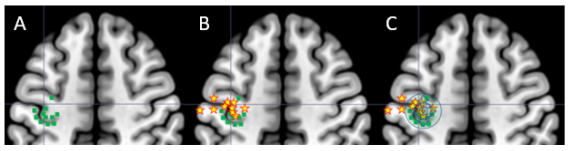
As collaborations continue to add more power to neuroscience research, we worked to resolve issues with scanning across different sites, scanners, software, and scanner peripherals, such as different head coils. Our study spanned two scanner sites with a range of software and technical capabilities. Our team radiologist harmonized the scans across our two sites – Northwestern Center for Translational Imaging and Santa Clara VA Hospital Clinical MRI scanner. We also incorporated emerging methodologies such as COMBAT(Fortin, Parker et al. 2017), to statistically harmonize a large number of data points across known fixed site variables, such as software version number, coil type, and site location, to reduce the potential variance introduced by site, scanner, and software differences.

Personalized TMS Targeting

Advancing personalized targeted TMS treatments can significantly impact the way TMS is prescribed and delivered, not only to patients with severe DOC but to all patients with neurologic conditions prohibiting their ability to reliably communicate. As localizing the motor hotspot is necessary to define each participant's Motor Threshold (MT) that is used as the basis for defining their treatment intensity, we addressed the challenges of spatially locating the motor hot spot for DoC patients. For DoC patients, we made modifications to the traditional hand knob hot spot location procedure. The location of participant's APB on their primary motor cortex (M1) was demarcated using stereotaxic neuro-navigation of each participant's structural neuroimages (T1) (Brain Sight, Rogue Research, Montreal, Quebec, Canada; Localite Neuronavigation, MagVenture, Alpharetta GA, USA). According to previously reported procedures, the hand knob on M1 was pre-marked and used as the initial location to locate the APB using single-pulse TMS with EMG (Pape, Rosenow et al. 2009). After locating each participant's APB, single-pulse TMS with EMG was also used to delineate their APB-MT; however, methods were modified in response

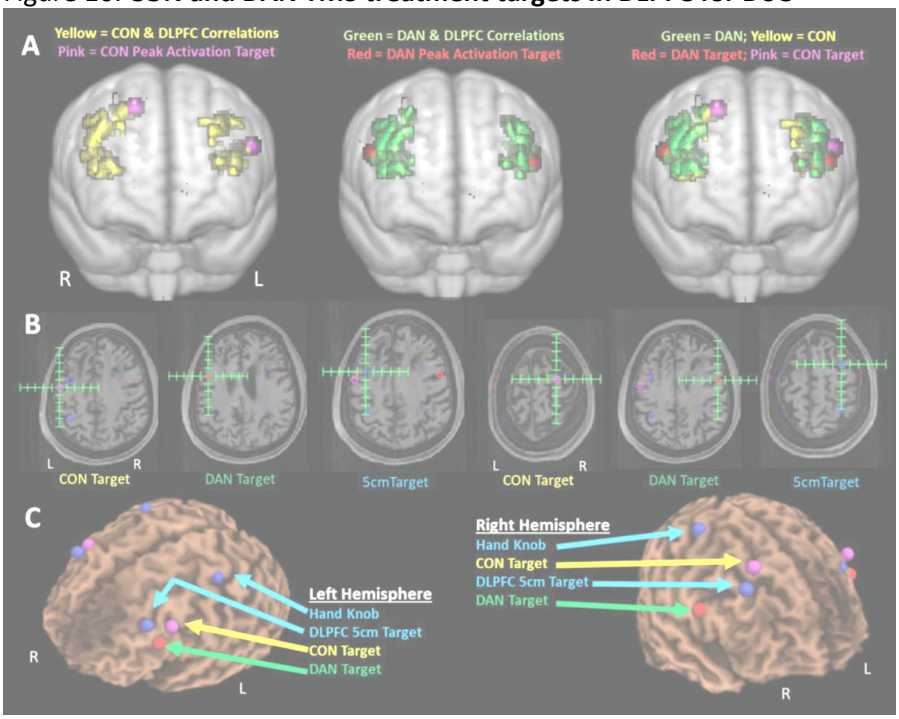
to the significant damage to the neurologic substrate present in the DoC. Figure 9 demonstrates that a 2-4 cm search radius (employed by methods that use anatomical measures of the skull) is sufficient to isolate the MT in healthy controls but is insufficient for severely damaged brains. Going beyond the standard search radius requires neuronavigation to probe a medial-to-lateral search path of the patient's motor and sensory motor cortex, which may be displaced by lesions or enlarged ventricles commonly occurring in severe TBI. In addition, we observed in several patients that a lip or face twitch was the first and only neural response to MT stimulation along the medial-lateral path of the motor or sensorimotor strip. We speculated the displaced response is due to either extensive motor cortex damage, rendering the face map the first to respond, or cortical reorganization placing hand responses within the facial map identified the shape and location of the hand knob in healthy controls using fMRI and a finger movement task. In our clinical trial, neuronavigation is used to identify the hand knob targeting the abductor pollicis brevis muscle. TMS is used to stimulate while EMG and visual confirmation are used to confirm MT location and strength.

Figure 9. Spatial distribution of MT coordinates: Severe TBI vs. Healthy Controls



Panels above show the relative spatial distribution of motor thresholding (MT) coordinates on an MNI brain. Panel A shows 11 healthy controls (adapted from Yoursy, 1997) in green squares. Panel B shows 10 severe TBI patients from the clinical trial in red/yellow stars (all outliers were verified by a neurosurgeon at the time of MT). Panel C demonstrates that a 2-4 cm search radius employed by methods that use anatomical measures of the skull is sufficient to isolate the MT in healthy controls

Figure 10. **CON and DAN TMS treatment targets in DLPFC for DoC**



Panel A: Correlation map masks and a 5-mm sphere designating the coordinates for peak correlations are presented in MNI space. From left to right, the CON (yellow and pink) and DAN (green and red) and both are overlaid on the MNI brain. **Panel B:** The bilateral CON, DAN, and 5-cm treatment targets in 2-dimensional native space**. Panel C:**The hand knob in the motor cortex and the subsequent 5-cm rule target, as well as the CON and DAN targets in a 3-dimensional model of the patient's brain, in native space. Results are based upon 20 minutes of rs-fMRI data from one patient with DoC. CON indicates cingulo-opercular network, DAN indicates dorsal attention network.

Individualized rs-fMRI TMS treatment targets in severe TBI with DoC

In a pilot case study(Herrold, Siddiqi et al. 2020), we demonstrated the viability of creating individualized treatment targets for severe TBI and DoC, based on neurological function, in contrast to the standard clinical targets which are selected anatomically (Figure 10).

Methods: "rs-fMRI data were analyzed using a custom machine learning algorithm that identifies rs-fMRI networks based on each voxel's seed-based connectivity profile to extract the top 20 network parcellation maps, which were then identified through correlations with canonical rs-fMRI

network maps. Target networks (CON and DAN) were then correlated with bilateral DLPFC, and coordinates for peak clusters of activation were identified."

What was the impact on technology transfer?

In conjunction with advancing neuroscience methodologies to produce meaningful outcome measures for a non-communicative population, we developed a custom piece of hardware to turn an older clinical EEG system into an auditory time-locked research EEG system. The auditory time-locking device enabled us to capture brain activity in response to passive-listening auditory stimulation that was designed to evoke a range of low-level to high-level cognitive processing. The potential impact is that hospitals and rehab centers can now use the low-cost device added to legacy clinical EEG systems to measure neural response to auditory stimuli, for clinical or research purposes, for any population. We are submitting a patent application for the novel piece of hardware.

In terms of FDA pathway to obtaining approval for physician's to prescribe rTMS for use in specialty inpatient rehabilitation settings with patient sin states of DoC due to TBI, the regulatory strategy for is to identify an industry sponsor to work with the study team to engage the FDA pre-submission process. An industry partner has been approached and Dr. Pape is actively in discussion with this partner. Once the final safety paper (Appendix 27) is accepted for peer review publication and the primary efficacy paper has been developed and submitted for peer review, Dr. Pape and the industry sponsor will, in advance of the pre-submission, use the safety and efficacy data derived from this study to develop a rationale justifying FDA clearance of the use of rTMS as a specialty rehabilitation treatment, relative to standards of care, for patients remaining in states of DoC 3 months after TBI (510k) and who do not have active management of seizure activity. The strategy takes into account that the safety and/or efficacy outcomes may warrant an additional study to validate the results with an independent and larger study sample.

What was the impact on society beyond science and technology?

While TMS is not yet ready to be used in a specialty inpatient rehabilitation setting and does not have FDA clearance for clinical use with the population studied, this data collected on the use of rTMS has led to the availability of new treatment options for DOC patients, pending FDA clearance, as well as opened new avenues for research. Through the future integration of the principles of plasticity with advances in technology, treatment-induced consciousness is possible.

CHANGES/PROBLEMS

Change in approach and reasons for change

Initial inclusion and exclusion criteria for this approved protocol specified eligible enrollment for participation at least 3 months up to 12 months post severe TBI and stipulated participants be seizure-free for at least 3 months before study enrollment. These stringent and narrow criteria proved limiting and inherently challenging for recruitment. With the guidance of study physicians and current literature, the inclusion criteria were ultimately expanded, first to include patients up to 2 years post-injury. Recruitment efforts found that the majority of families and LARs elected to trial and exhaust all rehabilitation avenues before engaging in research-related activity. Expanding the criteria to 2 years

helped to widen the recruitment pool and allow participants to complete rehabilitation services first while remaining eligible based on time post-injury. However, the study team continued to run into challenges with the 3-month seizure-free window. As is common practice in TBI management, a large number of patients with severe injury are often prescribed anti-seizure medication, if not for active seizure history, then as prophylaxis. If patients were identified as eligible but were also taking anti-seizure medication, the next steps included consultation with the LAR and prescribing physician. If medically safe and LAR agreed, participants could be weaned off antiseizure medication for inclusion into the study, but they would be required to have a 3-month seizure-free waiting period before enrollment. Again, based on expert consensus with study physicians and current literature guidance, the seizure-free waiting period was decreased to 1 month. It was determined that 1 month was sufficient and safe to establish stability following weaning of anti-seizure medication.

The COVID-19 Pandemic forced multiple changes in approach for the study to remain financially solvent and still meet study goals. Northwestern Memorial Hospital notified us on 7/2/2020 that there would be a restructuring of the inpatient Clinical Research Unit (CRU), including an increase in the fee structure and elimination of 24-hour nursing support to care for this medically complex patient population. In response, the PI adjusted the study protocol to abbreviate the total length of stay and eliminate the morning EEG to attempt to find a financially viable solution. The protocol continued to include 30 rTMS sessions, however mid-week rest days were removed as well as a 24-hour observational period following baseline brain mapping/motor threshold testing to condense the protocol down to a 4-week length of stay. Additionally, the protocol was updated to remove a morning EEG that was performed at the start of each study day, as that was redundant considering an EEG was completed at the end of each study day and only standard care was provided after the evening EEG until the next day's rTMS session. These changes were completed to reduce overall costs and to improve the feasibility of moving the study to a new site.

When the study was initially conceptualized, and over the first 6 years of the study, an enrolled participant was randomized to an active treatment or placebo group. According to that protocol, all participants randomized to the placebo rTMS group had the opportunity to continue with study participation and transition to the active rTMS group. This study design, based on the risk-benefit ratio, also facilitated subject recruitment. However, as of December 2021, only two participants had been randomly assigned to the placebo group and had completed both the placebo and active arms of the protocol. The PI consulted with the chair of the DSMB to discuss possible solutions to obtain sufficient placebo data, and subsequently decided to modify the protocol to assign all future enrollments to the placebo condition first while keeping the legally authorized decision maker and study team blind to this elimination of the randomization protocol. Participants continued to be offered the option to re-enroll in the study under the active arm following completion of their enrollment in the placebo arm of the study.

Actual or anticipated problems or delays and actions or plans to resolve them

Recruitment

Strict eligibility criteria limited many potential enrollments. The most common reason for exclusion was that patients were admitted to standard acute rehabilitation first and then referred to the study. During acute rehabilitation, many patients emerged from the minimally conscious state (i.e., are classified as conscious). Thus, at the time of acute rehabilitation discharge, they were no longer eligible for study enrollment. Patients who did remain in a state of disordered consciousness were often referred to us after the 1-year cut-off, which was later even extended to a 2-year cut-off however with the same limitation persisting. Due to the risk of post-traumatic seizures, many patients were on an anti-epileptic medication and could not be titrated off of the medications safely. We worked to address these recruitment barriers

by extending the initial exclusion criteria of greater than 1-year post-injury, to greater than 2 years post-injury. Additionally, we later reduced the required period to be off anti-epileptic medications from 3 months to 1 month before enrollment.

Throughout the project, we also considered multiple approaches to bolster recruitment. Initial recruitment strategies focused on VA system referrals and referrals from clinical partners. 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 ICD-9-CM and ICD-10-CM codes which allowed us to search by three eligibility criteria. This national search yielded a list of 33,398 unique Veterans, unfortunately after further filtering and screening none of these were ultimately eligible.

We sought direct referrals from VA PRC through collaboration with the VA Central Office PM&R and Polytrauma Medical Director. During monthly leadership meetings with the PRC Chiefs (medical directors of the emerging consciousness programs at each PRC), the importance of referrals to the study was emphasized. However, this did not result in any PRC referrals. Thus, we continued to receive lists from the VA CO emerging consciousness program database as the method for identifying study candidates from PRC admissions, unfortunately with no resulting enrollments.

We further sought referrals nationally and locally through the distribution of study flyers with national Defense and Veterans Brain Injury Centers (DVBIC) sites and salient websites. Study team members sent email reminders to specialty providers and provided in-services at Level I trauma centers and extended care facilities throughout the Chicagoland area.

In 2019 we sought to further bolster recruitment through the services of PatientWing, an online interface for potential families searching for clinical trials. Families and caregivers could search for clinical trials based on conditions and geography. The clinical trial had a “landing page” that provided trial-specific information, such as inclusion criteria, as well as a contact form. The page also linked to “pre-screener” questions to collect further information about participant eligibility. When a potential participant’s family entered contact information and answered the pre-screener questions, an email notification was sent to the study coordinator for further follow-up. We significantly increased inquiries regarding study enrollment with the addition of PatientWing, however caregivers and family members who initially contacted us would become less responsive to follow-up communication, change their position on participation, or further screening would determine that patients did not meet inclusion criteria often due to anoxic brain injury or being conscious at the time of screening.

Direct referrals of civilians from physicians at emerging consciousness programs at the Shirley Ryan Ability Lab and the Texas Institute for Rehabilitation Research, along with inquiries from PatientWing, were the most successful strategies with most of our enrolled patients coming from these referral sources.

Equipment

Throughout this project, from startup and continuing through active study participation, we encountered a variety of equipment problems that were inhibitory to study procedures and required active problem-solving for a quick resolution.

The initial barrier we faced was the need for a placebo system. As one was not available to us for use in the project as intended and the manufacturer would not develop one for us, we were tasked with developing our own system to look, sound, and feel like real TMS. This required extensive, time-consuming QA testing for consistent output within the specifications of materials that were being employed.

Additional barriers included overheating coils during the provision of TMS, which would cause the entire system to self-shut down and was therefore nonoperational until cooled. One of our TMS generators fried and needed to be sent back to the manufacturer for repairs. We ran into a variety of cable issues including fraying, compatibility, and general non-function. The EMG system we were using to assist with motor threshold testing and motor hotspot determination presented a host of compatibility challenges, often not returning active data points. Finally, the EEG equipment on hand for use in this project was considered geriatric.

To remedy these setbacks, the study team devised a series of solutions. While the generator was out for repair, the manufacturer was able to send us a generator on loan for continued use. Study funds were used to purchase additional coils and the team created a coil rotation and cooling system to be adopted into every TMS session for prevention of overheating. Finally, if the EMG system was not providing data points, the study team used visual observation to determine the motor threshold and hotspot location.

Site Closure

Santa Clara Valley Medical Center (SCVMC) received initial IRB approval as a study site on 06/14/16. A PI was identified for this site, and they were provided with equipment and training by the primary study team. Successful enrollment and study completion for one participant was completed without adverse events and recruitment efforts were ongoing at SCVMC. A potential participant, with a Codman VP shunt was being considered for study inclusion. This shunt would require frequent monitoring and re-setting during MRI and rTMS procedures. Before initiating additional screening procedures, the local PI was being taught to manage and reset the shunt to determine the feasibility of study inclusion. Approximately 8 hours after the shunt was being manipulated by the local PI and the patient's neurosurgeon, the patient experienced a seizure event. Despite expert opinion to the contrary, this event was considered by the local IRB to be a study-related SAE and the study was suspended pending further investigation. Following the local IRB's decision to suspend this study and ultimately require a change in PI at this site, Dr. Pape was decided that SCVMC would be closed as a study site for this protocol.

Transportation

Due to the unique nature of the condition of Disorders of Consciousness following traumatic brain injury and stringent inclusion/exclusion criteria, recruitment for the study expanded nationally in an attempt to meet recruitment goals. Initially, air ambulance support was anticipated through philanthropic endeavors; however, due to a range of circumstances (e.g., COVID-19), various avenues for air transportation fell through. The study team did identify Wings of Hope as one organization that would provide air ambulance transportation, Wings of Hope; however, this transportation option was limited to the Midwest region. Subjects were identified outside of the radius of transportation for Wings of Hope and required fundraising efforts to secure transport of the participants to Chicago or SCVMC to enroll in the study. The time required to raise sufficient funds to allow travel extended beyond study inclusion criteria with one participant exceeding 2 years post-injury and another recovering consciousness.

Impact of COVID-19 Pandemic

The Illinois governor's Stay-at-Home order was effective March 21, 2020, through May 29, 2020. Although the Stay-at-Home order was lifted on May 29, 2020, IRB approval to resume research activities was not immediately granted by either of our study sites, Edward Hines Jr. VA (Hines VA) or Northwestern University (NU). For the Hines VA site, the requirements for re-starting were issued on 6/2/2020, and we submitted our Hines VA-specific plan on 6/22/2020. To date, we have not received approval to reactivate research activities and enroll Veterans for this study at Hines due to COVID surges making an inpatient bed unavailable for a research admission.

Civilian enrollment at Northwestern was also put on hold due to the Stay-at-Home order. This study population required an inpatient admission within a Clinical Research Unit at Northwestern Memorial Hospital, and additional research visits for imaging at Northwestern University. Therefore, approval to restart research activities was needed from both institutions to resume enrollment. Northwestern University instituted a phased re-opening plan.

In response to the financial impact on the hospital, Northwestern Memorial Hospital notified us on 7/2/2020 that there would be a restructuring of the inpatient Clinical Research Unit (CRU), including an increase in the fee structure. Despite having a contract in place that listed a daily per diem that was budgeted to meet the recruitment goals of the grant, the new daily rate was a three-fold increase. Further, as we continued to work with the leadership of the hospital to find a resolution to the budgeting problem, the fall COVID surge pulled all available nursing resources to immediate acute care nursing needs. We were subsequently notified that there would be no internal support for nursing staff for research admissions and that the only option would be for the study to hire agency nurses at an estimated rate of $40,000/participant admission.

As we continued to receive more information about compounding costs at Northwestern Memorial Hospital, the PI began pursuing options for other study sites to allow affordable enrollments to achieve the study goals. Shirley Ryan Ability Lab was considered as an admission site, but costs were similar to the new CRU rates and new non-essential research activities were considered to be too risky to the existing vulnerable inpatient population. Further investigation presented an option to consider a subacute rehabilitation facility located in the greater Chicagoland area. Initial meetings to pursue the viability of HealthBridge Complex Care and Rehabilitation (HB) as a research site occurred in October 2020. Multiple meetings were required to thoroughly vet the site with leadership of the facility and the study PI, to ensure that staffing and safety monitoring needs of the study could be met. Additionally, a private EEG company needed to be identified to provide bedside EEGs as part of the FDA IDE requirements of the parent study. Contractual negotiations between the study team and HB, and HB and EEG companies took place over the ensuing months.

As negotiations were finalized, the research team began the regulatory work necessary to move the study location to a new site. The protocol modifications were submitted to the NU IRB on 1/21/2021 with approval to add HB as a site provided on 4/12/2021. As modifications were finalized with the IRB, a revision to the FDA IDE was prepared and ultimately submitted on 4/7/2021 with approval received on 5/10/2021. The final regulatory approval needed through HRPO was submitted on 4/15/2021 with approval granted on 6/1/21.

In addition to the COVID-19 pandemic forcing a change in study site, it also impacted our ability to recruit and retain participants. Without a feasible plan for a study site, any participants who were in the screening process prior to the pandemic could not be enrolled while a new site was vetted, and regulatory approval

was obtained. At the start of the pandemic, 4 candidates were being screened for enrollment. One candidate withdrew from consideration in February 2021 due to family concerns about additional COVID-19 exposure risk for the participant with the necessary travel required for study participation. Another participant withdrew in June 2021 as they had identified home nursing support that they had been pursuing for over a year and could not lose as a result of traveling to the Chicago area to participate in the study. A third participant was scheduled to begin research procedures in July 2021; however, as final screenings were completed to schedule transport, it was determined that the participant had regained consciousness and therefore no longer met study eligibility criteria.

Changes that had a significant impact on expenditures
New recruitment was limited during the COVID-19 Pandemic in the interest of protecting remaining funds to support study procedures (e.g., MRI, EEG). All of the above-referenced participants who were being screened and prepped for enrollment during the pandemic were obtained through Patient Wing, a web-based recruitment platform. While an effective recruitment tool, the cost (approximately $5,000 per quarter) was considered to be too high risk to continue while we did not have an approved site to complete study procedures and considering the candidates we already had in the queue. Therefore, PatientWing services were discontinued in June 2021.

Funding to support staffing levels necessary to meet recruitment and study goals was also impacted by the delays due to the COVID-19 pandemic. More affordable staffing solutions via fellowship opportunities and recruiting new volunteers to support the study were pursued to accomplish the goals of the project.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Not applicable

Significant changes in use or care of human subjects

As outlined above, this project was met with significant problems and delays in recruitment. To mitigate some of the challenges faced with trying to recruit a medically complex disordered consciousness population, changes were made to our inclusion/exclusion criteria in an attempt to bolster enrollment. Prior to making the changes, safety research was re-examined, and the expert opinion of several study physicians was gleaned to make the most informed and safest changes possible. All proposed changes were approved by the necessary regulatory bodies (local IRB, HRPO, and FDA) prior to implementation. These changes included extending the time post-injury inclusion period up to 2 years and decreasing the seizure-free window before initiating study procedures from three months to one month. Participants were still required to be seizure-free without the use of antiseizure medication. It was determined that these changes to inclusion did not significantly change the risk profile of this protocol but did allow for a broader recruitment pool.

Significant changes in use or care of vertebrate animals

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

PRODUCTS

Publications, conference papers, and presentations

Journal Publications

1. Ripley D et al Seizure risk Pape to be submitted in December of 2023
2. Foecking et al miRNA changes relative to behavioral gains paper in development.
3. Weaver J Pertsovskaya V Tran J Kozlowski A Guernon A Bender Pape T Mallinson T (under review) Comparing indices of responsiveness for the Coma Near-Coma Scale with and without pain items: An Exploratory study. Clinical Rehabilitation
4. Zilliox M* Foecking E* Kuffel G Conneely M Saban K Herrold A Kletzel S Radke J Walsh E Guernon A Ripley D Patil V Pacheco M Rosenow, J Bhaumik D **Bender Pape T** (in press, 2023). miRNA profiles of persons with chronic neurobehavioral impairments and remaining in states of Disordered Consciousness after Severe Traumatic Brain Injury, Journal of Head Trauma Rehabilitation (*authors contributed equally).(PMID: 36350037)
5. **Bender Pape T** Herrold A Livengood S Guernon A Weaver J Higgins J Rosenow J Walsh E Bhaumik R Pacheco M Patil V Kletzel S Conneely M Bhaumik D Mallinson T Parrish T (2020) A Pilot Trial Examining the Merits of Combining Amantadine and Repetitive Transcranial Magnetic Stimulation as an Intervention for Persons with Disordered Consciousness after TBI. Journal of Head Trauma Rehabilitation, 35(6): 371–387 (PMID: 33165151).
6. Kletzel S Aaronson A Guernon A Carbone C Chaudhry N Walsh E Conneely M Patil V Roth E Steiner M Pacheco M Rosenow J **Bender Pape T** (2020) Safety considerations for the use of transcranial magnetic stimulation as treatment for coma recovery in people with severe traumatic brain injury. Journal of Head Trauma Rehabilitation, 35(6): 430–438 (PMID: 33165155).
7. Herrold A Siddiqi S Livengood S **Bender Pape T** Higgins J Adamson M Leung A Raij T (2020) Customizing TMS applications in traumatic brain injury using neuroimaging. Journal of Head Trauma Rehabilitation, 35(6): 401-411 (PMID: 33165153).
8. **Bender Pape T** Livengood S Blabas B Kletzel S Guernon A Bhaumik DK Bhaumik R Mallinson T Weaver J Wang X Herrold A Rosenow JM Parrish T (2020) Treatment Induced Changes in Structural Connectivity occurring in Parallel with Neurobehavioral Recovery from Disordered Consciousness after TBI. Frontiers in Neurology, 11: 1027 (doi: 10.3389/fneur.2020.01027).
9. **Bender Pape T** Herrold A Aaronson A Guernon A Rosenow J (2020) Preface, JHTR Topical Issue on Neuromodulation Interventions in TBI. Journal of Head Trauma Rehabilitation, 35(6): 365–370 (PMID: 33165150).
10. **Bender Pape T** and Zasler N (2020) Provider Competencies for Disorders of Consciousness: Minimum Competency Recommendations Proposed by the ACRM-NIDLRR Workgroup. Brain Injury Professional, 17(2): 28.
11. Giacino J Whyte J Nakase-Richardson R Rosenbaum A Yablon S Weintraub A Katz D **Bender Pape T** Seel R Greenwald B Zasler N Zafonte R Blum S Day K Hammond F Arciniegas D (2020) Minimal Competency Recommendations for Programs that Provide Rehabilitation Services for Persons with Disorders of Consciousness: A Position Statement of the American Congress of Rehabilitation Medicine and the National Institute on Disability and Rehabilitation Research Traumatic Brain Injury Model System. Archives of Physical Medicine and Rehabilitation, 101(6): 1072-1089 (PMID: 32087109).

Abstracts/Poster Presentations

1. *Weaver J Maisano K Cogan A Harrod T **Pape T** Mallinson T (2020) Rehabilitation Interventions for Adults with Disorders of Consciousness Following a Brain Injury: A Scoping Review. GW Research Days, Washington, DC., Accepted Poster, page 359, Conference cancelled due to COVID-19. Retrieved from: https://cpb-us-e1.wpmucdn.com/blogs.gwu.edu/dist/7/135/files/2020/05/2020-Abstract-Submissions-Booklet-FINAL-3.pdf
2. *Rosenow J **Pape T** Blabas B Kletzel S Herrold A Guernon A Mallinson T Bhaumik B Bhaumik R Walsh E Conneely M Pacheco M Patil V Steiner m Roth E (2018) rTMS and Amantadine for Persons in Chronic States of Disordered Consciousness after TBI, North American Neuromodulation Society, Poster, Las Vegas.

Books or other non-periodical, one-time publications

1. **Bender Pape T** Barrington N Webber E Stutzmann G (in press, 2024) Exogenous Induction of Neuroplasticity: Non-Invasive Neurostimulation, In Encyclopedia of Human Brain, 2nd edition, Jordan Grafman (Editor), Section: Neuroplasticity, A.M. Barrett and Keith McGregor (Section Editors).

Other publications, conference papers, and presentations

Oral Presentations

1. 2023: Oral Presentation, "Seizure Risk Associated With the Use of Transcranial Magnetic Stimulation for Coma Recovery in Individuals With Disordered Consciousness After Severe Traumatic Brain Injury," International Brain Injury Association, Dublin, Ireland.
2. 2023: Oral Presentation, "Clinical and research utility of miRNA as neurobiological markers of responsiveness to rTMS treatment provided to persons remaining in states of Disordered Consciousness 1 to 2 years after Traumatic Brain Injury" International Brain Injury Association, Dublin, Ireland.
3. **Bender Pape T** (2022) Neuromodulation for Neurologic Recovery, Transcranial Magnetic Stimulation for TBI. North American Neuromodulation Society's Annual Conference, Symposia, Orlando FL.
4. 2022: Symposia, "rTMS RCT trial results for DoC after TBI. " 12th World Congress for Neurorehabilitation, World Federation for Neurorehabilitation" symposium on Brain injury rehabilitation from diagnosis to the treatment with new tools and technologies, Vienna, Austria.
5. 2022: Symposia, "CNS Injury and Repair, Re-imagining Neurologic Recovery: The role of micro-RNA in a Circuitry- and Metaplasticity-Based Neuromodulation Approach to Severe TBI Neurorehabilitation," Chicago Chapter of the Society for Neuroscience Annual Meeting, DePaul University Student Center, Chicago, IL.
6. Foecking M Zilliox M Saban K Herrold A Kletzel S Walsh E Guernon A Pape A Bhaumik D ***Bender Pape, T** (2021) Preliminary evaluation of the clinical utility of miRNA as neurobiological markers of TBI diagnosis and rTMS treatment responsiveness, 4th International Brain Stimulation Conference, Symposia, Charleston, SC, Brain Stimulation: 14 (2021) e1721 (FS4F.07).
7. 2021: Symposia, " "Neuromodulation Techniques for Disorders of Consciousness after Severe TBI," Brain Injury Association of IL Annual Educational Conference, Virtual.
8. *Herrold A Livengood S Siddiqi S **Bender Pape T** (2021) Customizing rTMS treatment targeting for co-occurring alcohol use disorder and mild traumatic brain injury using multi-modal neuroimaging data as neurobiological markers. , 4th International Brain Stimulation Conference, Symposia, Charleston, SC, Brain Stimulation: 14 (2021) e1721 (FS4F.06).

9. Kletzel S **Bender Pape T** Herrold A Livengood S Guernon A Parrish T Mallinson T Higgins J Rosenow J Bhaumik D (2021) A Pilot Trial Examining The Merits Of Combining Amantadine and Repetitive Transcranial Magnetic Stimulation As An Intervention For Persons with Disordered Consciousness after TBI, 4th International Brain Stimulation Conference, Symposia, Charleston, SC, Brain Stimulation: 14 (2021) e1721 (FS4F.05).
10. 2020: Keynote Address, "Neuromodulatory Interventions for Traumatic Brain Injury," Mitch Rosenthal Research Webinar series, Brain Injury Association of America.
11. 2020: Symposia, "Neuromodulation Techniques in DoC patients after TBI-to study or to treat?" 11th World Congress for Neurorehabilitation, World Federation for Neurorehabilitation" symposium on Brain injury rehabilitation from diagnosis to the treatment with new tools and technologies, Lyon, France, COVID-19 Virtual platform.
12. 2018: Key Note Address, "Management of Disordered Consciousness: Standard Practices and New Evidence Ready for Clinical Implementation," Shirley Ryan Ability (SRAL, Formerly Rehabilitation Institution of Chicago) Brain Injury Course, Chicago, IL.
13. 2018: Keynote Address, "Precision Neurorehabilitation for Severe TBI during Acute and Sub-acute Recovery," Northwestern University Clinical and Translational Sciences (NUCATS) Research Impact workshop, Chicago, IL.
14. **Pape T** Blabas B Kletzel S Bhaumik D Wang X Parrish T Guernon A Bhaumik R Herrold A Rosenow J Mallinson T (2017) Resting State Functional Connectivity Evidence of Familiar Auditory Sensory Stimulation Promoting Plasticity in Disordered Consciousness, 12th World Congress on Brain Injury, International brain Injury Association, Oral Paper, Abstract # 523.
15. **Pape T** Rosenow J Kletzel S Herrold A Parrish T Guernon A Mallinson T Bhaumik D Bhaumik R Walsh E Conneely M Pacheco M Patil V Steiner M Roth E Reilly J Brooks M Riordan P Maiertisch K Narechania A (2017) Precision Neurorehabilitation for Severe TBI during Acute and Sub-acute Recovery, Oral Presentation, Abstract # MHSRS-17-1429 - TBI Treatment & Emerging Care.

Website(s) or other Internet site(s)

None to report

Technologies or techniques

1. Using multimodal MRI to capture neurological changes in DoC with TBI
2. Using GIMME modeling to gain refined insight to network changes in neural communication in DoC with TBI
3. Custom auditory time-locking hardware developed to convert legacy EEG system into research EEG system

Inventions, patent application, and/or licenses

None to report; Patent application in process for converting (as described previously) legacy EEG systems to collect time locked research data.

Other Products

None to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Hines VA

Name: Theresa Pape, Dr. PH
Project Role: Principal Investigator
Responsibilities: Dr. Pape has overseen protocol development, staffing, and training at each study site and overall project flow.

Name: Ann Guernon, MS, PhD
Project Role: Clinical Research Manager
Responsibilities: Provided oversight of regulatory submissions, recruitment, screening, scheduling, and clinical data collection. She acted as a treatment provider and assisted with outcome assessment, data collection, and data entry.

Name: Elyse Walsh, DPT
Project Role: Research Coordinator/Therapist
Responsibilities: Served as the study coordinator for this project. She oversaw recruitment, screening, all regulatory submissions, scheduling, and basic project management. She also contributed as a treatment provider and outcome assessor. She was integral in establishing the electronic RedCap database for data entry and has been responsible for overseeing data management and entry.

Name: Amy Herrold, PhD
Project Role: Research Scientist
Responsibilities: Assisted with data collection as a treatment provider and has been integral in data analysis and dissemination.

Name: Sandra Kletzel, PhD
Project Role: Co-Investigator
Responsibilities: Assisted with data collection and analysis.

Name: Vijaya Patil, MD
Project Role: Co-Investigator/Neurologist
Responsibilities: Served as the project neurologist at Hines VA responsible for EEG oversight and safety.

Name: Monica Steiner, MD
Project Role: Co-Investigator/Medical Monitor
Responsibilities: Served as medical oversight for Hines VA participants.

Name: Marilyn Pacheco, MD
Project Role: Co-Investigator
Responsibilities: Served as the admitting physician, providing medical oversight and monitoring for participants at Hines VA.

Name: Mark Conneely, MD
Project Role: Radiologist

Responsibilities: Provided safety oversight for fMRI

Name: Dulal Bhaumik, PhD
Project Role: Biostatistician
Responsibilities: Statistical analysis support for articles and presentations

Name: Ilse Salinas, BS
Project Role: Research Assistant
Responsibilities: Assisted with treatment provision, data collection and data entry.

Name: Lisel Kwartnik, MBA
Project Role: Project Manager
Responsibilities: Development and monitoring of study budgets and ensuring all financial allocations and expenditures were in accordance with the grant and VA requirements for the currently funded research clinical trial and the supplemental projects. She provided daily operational assistance to project staff.

Name: Brett Blabas, MS
Project Role: Research Assistant/Biomedical Engineer
Responsibilities: Provided research support for coordinating and documenting of collected data. Initially responsible for all equipment and technical support including creation, testing, and management of novel placebo system. Acted as a treatment provider, collected data, and assisted with the creation of the RedCap database for data entry.

Name: Franco Laghi, MD
Project Role: Pulmonologist
Responsibilities: Assessment and monitoring of pulmonary status for Hines VA participants

Name: Lynnea Vis, MS
Project Role: Doctoral student
Responsibilities: Assisted with treatment provision and data collection

Name: Christina Carbone, MS
Project Role: Doctoral student
Responsibilities: Assisted with treatment provision and data collection

Name: Emily Sullivan, MS
Project Role: SLP
Responsibilities: Assisted with treatment provision and data collection

Name: Laura Chalcraft, MS
Project Role: SLP
Responsibilities: Assisted with treatment provision and data collection

Name: Bella Etigen, PhD
Project Role: Post-doctoral fellow
Responsibilities: Data analysis and dissemination

Name: Elizabeth Miskiel, BS
Project Role: Research Assistant
Responsibilities: Assisted with treatment provision and data collection

Name: Juan Manuel Hernandez, BS
Project Role: Research Assistant
Responsibilities: Assisted with treatment provision and data collection

Name: Vanessa Jessie, BS
Project Role: Research Assistant
Responsibilities: Assisted with treatment provision and data collection

Name: Sherri Livengood, PhD
Project Role: Post-Doctoral Fellow/Imaging Specialist
Responsibilities: Equipment and technical management, imaging protocol creation and management, imaging analysis

Name: Andrea Billups, MS
Project Role: Research Assistant
Responsibilities: Research support for coordinating and documenting of collected data

Name: Kenneth Blank, MS
Project Role: Research Assistant
Responsibilities: Assisted with treatment provision and data collection

Name: Alexandra Aaronson, MD
Project Role: Psychiatrist
Responsibilities: TMS and EEG oversight

Name: Catherine Kestner, DPT
Project Role: Research Therapist
Responsibilities: Provided research support for coordinating and documenting of collected data. Assist with documentation of reporting requirements and acted as a treatment provider and outcome assessor. She also assisted in data management and organization as well as recruitment and screening.

Name: Kelly Krese, DPT
Project Role: Research Therapist
Responsibilities: Provided research support for coordinating and documenting of collected data. She acted as a treatment provider and outcome assessor. She also assisted in data management and organization.

Name: Jack Lennon
Project Role: Research Assistant
Responsibilities: Assisted with treatment provision and data collection

Name: Zhiping (Jenny) Huo
Project Role: Data programmer
Responsibilities: Data analysis

Name: Lishan Cao
Project Role: Data analyst
Responsibilities: Data analysis

Name: Konnor Nelson
Project Role: Research Assistant
Responsibilities: Assisted with treatment provision and data collection

Name: Noor Chaudhry
Project Role: Research Assistant
Responsibilities: Assisted with data collection and entry.

Name: Andre Lindsey SLP, PhD
Project Role: Post-Doctoral Fellow
Responsibilities: Assisted with treatment provision and data collection, EEG management and oversight, data analysis and dissemination.

Name: Renee Ecklund
Project Role: Research Assistant
Responsibilities: Assist with regulatory and scheduling as needed

Name: Julie Schwertfeger, PT, PhD
Project Role: Post-Doctoral Fellow
Responsibilities: Assisted with treatment provision and data collection

Name: Sadie Walker, OTD
Project Role: Research Assistant
Responsibilities: Assisted with treatment provision and data collection

Name: Cheryl Odle
Project Role: Project Manager
Responsibilities: Fiscal oversight, contract management, assist with data collection as needed.

Name: Naail Chaudhry
Project Role: Research Assistant
Responsibilities: Assisted with data entry

Northwestern University

Name: Joshua Rosenow, MD
Project Role: Site PI
Responsibilities: Medical management and oversight of participants admitted to Northwestern Memorial Hospital for TMS treatment and fMRI procedures, assist with brain mapping and motor threshold testing as needed and assist with pre-screening for inclusion and enrollment.

Name: Todd Parrish, PhD
Project Role: Director of Neuroimaging
Responsibilities: fMRI and neuroimaging oversite for the project

Name: Lauren Cimino, APRN
Project Role: Medical oversight
Responsibilities: Assist with medical management and oversight of participants admitted to Northwestern Memorial Hospital.

Rehabilitation Institute of Chicago (now Shirley Ryan Ability Lab)
Name: David Ripley, MD, MS, CRC, FAAPM&R
Project Role: Site PI
Responsibilities: Recruitment from Shirley Ryan Ability Lab, transitioned to assist with medical oversight at HealthBridge.

Name: Kelsey Watters, OTD
Project Role: Research Assistant
Responsibilities: Assisted with treatment provision and data collection

Santa Clara Valley Medical Center
Name: Linda Issac, PhD, ABPP
Project Role: Site PI
Responsibilities: Initial project management at SCVMC, regulatory oversight, staffing, recruitment, screening, and scheduling.

Name: Reza Ehsanian, MD, PhD
Project Role: Study coordinator
Responsibilities: Responsible for staffing, recruitment, screening, consenting, scheduling, data collection and management, data entry.

Name: Thao Duong, MD
Project Role: Site PI
Responsibilities: Continued project management at SCVMC, medical monitoring and oversight of participants at SCVMC, TMS treatment provision.

Name: Marco Lee, MD, PhD
Project Role: Neurosurgeon
Responsibilities: Oversight of brain mapping at SCVMC.

Name: Ben Dirlikov, MA
Project Role: Research Coordinator
Responsibilities: Responsible for staffing, recruitment, screening, consenting, scheduling, data collection and management, and data entry.

Name: Michael Prutton, MS
Project Role: Research Assistant
Responsibilities: Responsible for regulatory management at SCVMC, data collection and entry.

Name: Jyodi Mohole
Project Role: Research Assistant

Responsibilities: Assisted with data collection and entry.

George Washington University
Name: Trudy Mallinson, PhD
Project Role: PI of Supplemental Project # 2
Responsibilities: Neurobehavioral Outcomes Measurement

Name: Jen Weaver, PhD, OTR/L
Project Role: Research Associate
Responsibilities: Neurobehavioral Outcomes Measurement

What other organizations were involved as partners?

Organization Name: George Washington University
Location of Organization: Washington, DC, USA
Partner's Contribution to the Project: Collaboration

Organization Name: Northwestern University
Location of Organization: Chicago, IL, USA
Partner's Contribution to the Project: Collaboration

Organization Name: Santa Clara Valley Medical Center **(STUDY SITE CLOSED-5/10/2019)**
Location of Organization: San Jose, CA, USA
Partner's Contribution to the Project: Collaboration

Organization Name: HealthBridge Complex Care and Rehabilitation Facility
Location of Organization: Arlington Heights, IL, USA
Partner's Contribution to the Project: Collaboration

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: None to report

QUAD CHARTS: Submitted separately, as a separate attachment

APPENDICES

Appendix 1	Cited References in this Final Report
Appendix 2	Manuscript 'A Pilot Trial Examining the Merits of Combining Amantadine and Repetitive Transcranial Magnetic Stimulation as an Intervention for Persons with

	Disordered Consciousness After TBI' *Journal of Head Trauma Rehabilitation 35(6): 371-387*
Appendix 3	Manuscript 'Provider Competencies for Disorders of Consciousness: Minimum Competency Recommendations Proposed by the ACRM-NIDLRR Workgroup'. *Brain Injury Professional, 17(2): 28*
Appendix 4	Manuscript 'Neural Connectivity Changes Facilitated by Familiar Auditory Sensory Training in Disordered Consciousness: A TBI Pilot Study' *Frontiers in Neurology Oct 2020 (11).*
Appendix 5	Manuscript 'Minimum Competency Recommendations for Programs That Provide Rehabilitation Services for Persons With Disorders of Consciousness: A Position Statement of the American Congress of Rehabilitation Medicine and the National Institute on Disability, Independent Living and Rehabilitation Research Traumatic Brain Injury Model Systems' *Archives of Physical Medicine and Rehabilitation 2020;101:1072-89*
Appendix 6	Manuscript 'Customizing TMS Applications in Traumatic Brain Injury Using Neuroimaging' *Journal of Head Trauma Rehabilitation 35(6): 401-411*
Appendix 7	Manuscript Preface 'Neuromodulatory Interventions for Traumatic Brain Injury' *Journal of Head Trauma Rehabilitation 35(6): 365-370*
Appendix 8	Manuscript 'Safety Considerations for the Use of Transcranial Magnetic Stimulation as Treatment for Coma Recovery in People With Severe Traumatic Brain Injury' *Journal of Head Trauma Rehabilitation 35(6): 430-438*
Appendix 9	Manuscript 'Comparing indices of responsiveness for the Coma Near-Coma Scale with and without pain items: An Exploratory study' *Brain and Behavior Brain and Behavior, 13(8):e3120.*
Appendix 10	Manuscript 'An Initial miRNA Profile of Persons with Persisting Neurobehavioral Impairments and States of Disordered Consciousness After Severe Traumatic Brain Injury' *Journal of Head Trauma Rehabilitation, 38(4):E267-E277.*
Appendix 11	Poster (2018) 'rTMS and Amantadine for Persons in Chronic States of Disordered Consciousness after TBI', North American Neuromodulation Society, Las Vegas.
Appendix 12	Poster (2020) Rehabilitation Interventions for Adults with Disorders of Consciousness Following a Brain Injury: A Scoping Review. GW Research Days, Washington, DC.
Appendix 13	Oral Presentation (2017) Resting State Functional Connectivity Evidence of Familiar Auditory Sensory Stimulation Promoting Plasticity in Disordered Consciousness, 12th World Congress on Brain Injury, International brain Injury Association, Oral Paper, Abstract # 523

Appendix 14	Oral Presentation (2017) Precision Neurorehabilitation for Severe TBI during Acute and Sub-acute Recovery, Oral Presentation, Abstract # MHSRS-17-1429 - TBI Treatment & Emerging Care
Appendix 15	Oral Presentation (2018) Management of Disordered Consciousness: Standard Practices and New Evidence Ready for Clinical Implementation, Keynote Address, Shirley Ryan Ability (SRAL, Formerly Rehabilitation Institution of Chicago) Brain Injury Course, Chicago, IL
Appendix 16	Oral Presentation (2018) Precision Neurorehabilitation for Severe TBI during Acute and Sub-acute Recovery, Keynote Address, Northwestern University Clinical and Translational Sciences (NUCATS) Research Impact workshop, Chicago, IL
Appendix 17	Oral Presentation (2020) 'Neuromodulation in TBI Neurorehabilitation', Keynote Address, Mitchell Rosenthal Research Webinar series, Brain Injury Association of America.
Appendix 18	Oral Presentation (2020) Symposia: 'Neuromodulation Techniques in DoC Patients after TBI: to Study or to Treat?', 11th World Congress for Neurorehabilitation, World Federation for Neurorehabilitation symposium on Brain injury rehabilitation from diagnosis to the treatment with new tools and technologies, Lyon, France, COVID-19 Virtual platform
Appendix 19	Oral Presentation (2021) A Pilot Trial Examining The Merits Of Combining Amantadine and Repetitive Transcranial Magnetic Stimulation As An Intervention For Persons with Disordered Consciousness after TBI, 4th International Brain Stimulation Conference, Symposia, Charleston, SC, Brain Stimulation: 14 (2021)
Appendix 20	Oral Presentation (2021) Symposia, Neuromodulation Techniques for Disorders of Consciousness after Severe TBI," Brain Injury Association of IL Annual Educational Conference, Virtual
Appendix 21	Oral Presentation (2021) Preliminary evaluation of the clinical utility of miRNA as neurobiological markers of TBI diagnosis and rTMS treatment responsiveness, 4th International Brain Stimulation Conference, Symposia, Charleston, SC, Brain Stimulation: 14 (2021)
Appendix 22	Oral Presentation (2022) Symposia, rTMS RCT trial results for DoC after TBI. 12th World Congress for Neurorehabilitation, World Federation for Neurorehabilitation symposium on Brain injury rehabilitation from diagnosis to the treatment with new tools and technologies, Vienna, Austria.
Appendix 23	Oral Presentation (2022) Symposia, CNS Injury and Repair, Re-imagining Neurologic Recovery: The role of micro RNA in a Circuitry- and Metaplasticity-Based Neuromodulation Approach to Severe TBI Neurorehabilitation, Chicago Chapter of the Society for Neuroscience Annual Meeting, DePaul University Student Center, Chicago, IL.

Appendix 24	Oral Presentation (2022) Neuromodulation for Neurologic Recovery, Transcranial Magnetic Stimulation for TBI. North American Neuromodulation Society's Annual Conference, Symposia, Orlando FL
Appendix 25	Oral Presentation (2023) Seizure Risk Associated With the Use of Transcranial Magnetic Stimulation for Coma Recovery in Individuals With Disordered Consciousness After Severe Traumatic Brain Injury, International Brain Injury Association, Dublin, Ireland
Appendix 26	Oral Presentation (2023) Clinical and research utility of miRNA as neurobiological markers of responsiveness to rTMS treatment provided to persons remaining in states of Disordered Consciousness 1 to 2 years after Traumatic Brain Injury, International Brain Injury Association, Dublin, Ireland
Appendix 27	Draft of Seizure Risk Paper currently being formatted for submission to Peer review in December of 2023
Appendix 28	Manuscript under review in CRS-R responsiveness