AWARD NUMBER: W81XWH-20-1-0928

TITLE: Control Network Neuromodulation to Enhance Cognitive Training in Complex Traumatic Brain Injury (The CONNECT-TBI Trial)

PRINCIPAL INVESTIGATOR: Davin Quinn, MD

CONTRACTING ORGANIZATION: University of New Mexico Health Sciences Center
Albuquerque, NM

REPORT DATE: October 2022

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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4. TITLE AND SUBTITLE

Control Network Neuromodulation to Enhance Cognitive Training in Complex Traumatic Brain Injury (The CONNECT-TBI Trial)

5a. CONTRACT NUMBER
W81XWH-20-1-0928

5b. GRANT NUMBER
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5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Davin Quinn, MD

E-Mail: dquinn@salud.unm.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of New Mexico Health Sciences Center
MSC09 5030
1 University of New Mexico
Albuquerque, NM 87131

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release, Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The objective of this application is to conduct a clinical trial of APT-3 combined with targeted neuromodulation to treat cognitive control deficits in cmplex mTBI. Veterans and Servicemembers with mTBI and cognitive symptoms will be recruited from the New Mexico and Minneapolis VA Polytrauma clinics. Participants will undergo baseline demographic, neuropsychological, and quality of life testing, as well as resting/task-related fMRI. They will be randomized to 4 weeks of computer-based APT with concurrent rTMS, HD-tDCS, or sham stimulation delivered to the dorsolateral prefrontal cortex (DLPFC). Lastly, they will repeat all baseline tests, and report on 3- and 6-month recovery levels. Our central hypotheses are: (Aim 1) targeted neuromodulation applied to the DLPFC, when paired with APT-3, will facilitate the greatest improvement in cognitive control for the rTMS group (rTMS>HD-tDCS>sham); (Aim 2) these interventions will result in improvements in functional measures and quality of life; (Aim 3) fMRI will identify changes in CCN activation associated with cognitive control deficits and recovery.

15. SUBJECT TERMS

Traumatic brain injury; cognitive rehabilitation; transcranial direct current stimulation; transcranial magnetic stimulation

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
				33	USAMRDC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified	Unclassified		

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1. Accomplishments

	Timeline	% Completed
Major Task 1: Prepare Protocol for Submission and Approvals	(Mos.)	
Subtask 1: Prepare Regulatory Documents and Research Protocol		100%
Coordinate with Sites for Data Use Agreements (DUAs) clinical trial agreements (CTAs) submission, nondisclosure agreements (NDAs)	1-3	100%
Finalize eligibility, exclusions, screening, master consent and protocol	1-3	100%
Coordinate with Sites for local IRB submission/review	1-3	100%
Coordinate with Sites for Military 2nd level IRB review (ORP/HRPO)	4-6	100%
Submit amendments, adverse events and protocol deviations as needed	As needed	100%
Coordinate with Sites for annual IRB report for continuing review	Annually	100%
Milestone Achieved: Local IRB and ORP/HRPO approval for all protocols.	6	100%
Major Task 2: Harmonize Sites and Establish Cores for MRCTN		
Subtask1: Hiring and Training of Study Staff		100%
Coordinate with Sites for job descriptions, advertising, interviewing	1-4	100%
Coordinate for space and equipment allocation for new staff	1-4	100%
Milestone Achieved: Research staff hired	4	100%
Subtask 2: Coordinate Study Initiation Visits #1 and #2, with in-person trainings for NRC Core Technicians and Coordinators	5-6	100%
Subtask 3: Conduct human phantom imaging tests, disseminate methods and scripts, create and test pipelines for data capture, storage, and analysis	5-6	100%
Milestone Achieved: Trained and maintained Study Staff, equipment, and analytic tools throughout duration of clinical trial	6	100%
Major Task 3: Protocol Setup, Recruitment, Scanning, Assessments, Neuromodulation, Cognitive Training, Followup		
Subtask 1: Establish Protocol Structure		
Coordinate with Sites to map out all study steps, data collection, data transfer, and analytic tasks	4-6	100%
Finalize screening tool, assessment measures, sequence of tests	1-6	100%
Milestone Achieved: 1st participant consented, screened and enrolled	6-36	100%
Subtask 2: Run Protocol, Submit Regular Reports	6-36	
Participants complete baseline testing (surveys, cognitive testing, fMRI)	6-36	6%
Participants complete intervention (training + sham/rTMS/HD-tDCS)	6-36	6%
Participants complete post-testing (surveys, cognitive testing, fMRI)	6-36	6%
Participants complete follow-up assessments (symptoms, quality of life, function surveys) 3, 6 months after completion of post-testing	12-36	0%
Submit quarterly safety reports to DSMB, scientific reports to CDMRP, annual continuing reviews to IRBs/HRPO	6-36	50%
Milestone Achieved: Met recruitment and protocol completion goals	34-36	6%
Major Task 4: Data Analysis, Dissemination, Uploading		
Subtask 1: Report all analyses according to specifications, share output and finding with all investigators	36-48	0%
Work with MRCTN team members to disseminate findings (abstracts, presentation, publications, DOD)	36-48	0%
Upload data to FITBIR for data sharing	36-40	0%
Milestone Achieved: Report results from data analyses	36-48	0%

1.1 Major Activities

1.1.1 Administrative: All-Investigator meetings and Core meetings occur virtually on Zoom teleconference platform on a weekly basis, with attention to the following:

A) Subawards: Subawards have been structured, finalized, and awarded for Year 2. Minor adjustments to subaward for University of Minnesota were made to account for Dr. Mo Chen changing institutions, from University of Minnesota to Gillette Children's Specialty Care.

B) Protocol and Consent modifications and IRB submissions: Protocol and consent documents for each site have undergone several modifications to add study team members, ensure that sham procedures are identical at each site, and to include language regarding Certificate of Confidentiality. Each of these modifications was drafted with vetting by the Administration and Oversight Core (AOC), approved by all site investigators, and submitted along with all other relevant study materials to each local IRB with oversight of the study activities, ie. Minneapolis VAHCS, New Mexico VAHCS, and University of New Mexico (overseeing Mind Research Network and University of Minnesota).

C) Testing, quality assurance, and maintenance of equipment: Updated TMS equipment capable of delivering theta burst stimulation through the necessary dose ranges was purchased and installed at University of Minnesota, to ensure harmonization with the New Mexico site. The StarStim 8 HD tDCS device was found to have a flaw in its software that did not permit impedance monitoring of very low current levels such as those used in the individualized electrode montages for CONNECT-TBI. Therefore, updated software that permits this function was designed and deployed by Starstim for the CONNECT-TBI team. The Attention Process Training (APT-3) computer-based materials were found during administration to participants to have several flaws resulting in confusing or erroneous test performance. Replacement APT-3 flash drives with flaws corrected were sent to each site by the manufacturer. Stimulation sensation questionnaires were created and deployed to ensure that side effect monitoring is standardized across sites.

D) FITBIR: The process of FITBIR upload pipeline construction has been initiated with Rakib Zaman. Both the New Mexico and the Minnesota teams have experience with FITBIR upload processes from previous federally funded TBI grants. The sites participated in a training with Mr. Zaman in the second quarter. FITBIR account creation is pending necessary documentation and institutional approval. The study measures will be sent upon study account creation for data definition and validation.

E) Data Safety Monitoring Board: The first two DSMB meetings were convened, with discussion of overall protocol and agenda setting for future meetings at the first meeting. At the second DSMB meeting, protocol enrollment and side effects were discussed. The DSMB reviewed the prepared reports and approved the continued performance of the study.

F) Recruitment and retention: Challenges in recruitment of participants were identified early on, and additional weekly meetings to discuss enrolled participants and ongoing recruitment strategies. These strategies now include expanded queries of polytrauma registries to identify qualifying participants; monthly research tables;

social media advertisements targeted to Veterans; face to face meetings with polytrauma staff; modifications to inclusion/exclusion criteria; funds to pay for increased travel expenses, hotel accommodations for participants.

1.1.2 Personnel:

A. NMVAHCS: Tiana Maple, Chelsey Smith, and Joann Harner were both hired as study staff and added to the IRB as study team members. A fourth person is currently in the process of being hired.

B. U. Minnesota/Minneapolis VAHCS: Sloan Davidson, Rebecca Hiltner, and Alana Lieske were hired as study staff and added to the IRB as study team members. Mia Kellman and Cassie Nelson on the Minnesota side joined the study team in the past year.

C. UNM/MRN: Lindsay Worth, Cidney Robertson-Benta and Jessica McQuaid were hired as study staff and added to the IRB as study team members.

D. All key personnel, site PIs, and collaborators have completed necessary trainings and certifications to perform study tasks, including CITI, HIPAA, and FCOI certifications, MRI performance and safety training.

E. Certifications: All study staff have been granted access to study databases such as COINS. Study staff are all trained in brain stimulation performance and safety training, neuropsychological testing, assessment, and rehabilitation task training.

1.1.3 Scientific:

A) A poster describing the study design, harmonization activities, and standardization/optimization activities was presented at the 2022 MHSRS conference in Orlando, FL.

B) APT-3 standardization procedure: As the APT-3 is intended to be optimized for each subject according to effort, performance, and challenge level, an algorithm to guide this optimization process was created with the input of co-investigator Dr. Jessica Richardson. Concrete steps for increasing/decreasing difficulty and variety of tasks were mapped out. Metacognitive strategies that are taught at each session were standardized and made relevant for TBI patients.

C) Image acquisition, processing, and targeting: Virtual containers of all image processing scripts were created, and updated to include the latest versions of software such as MATLAB and SIMNIBS. Every participant's scan results from both sites were processed by the Image and Assessment Core (IAC) team, and targeting solutions from the first six subjects were compared between sites to ensure that comparable results are obtained.

Figure 1. Image processing algorithm contained in the virtual container constructed by the IAC.

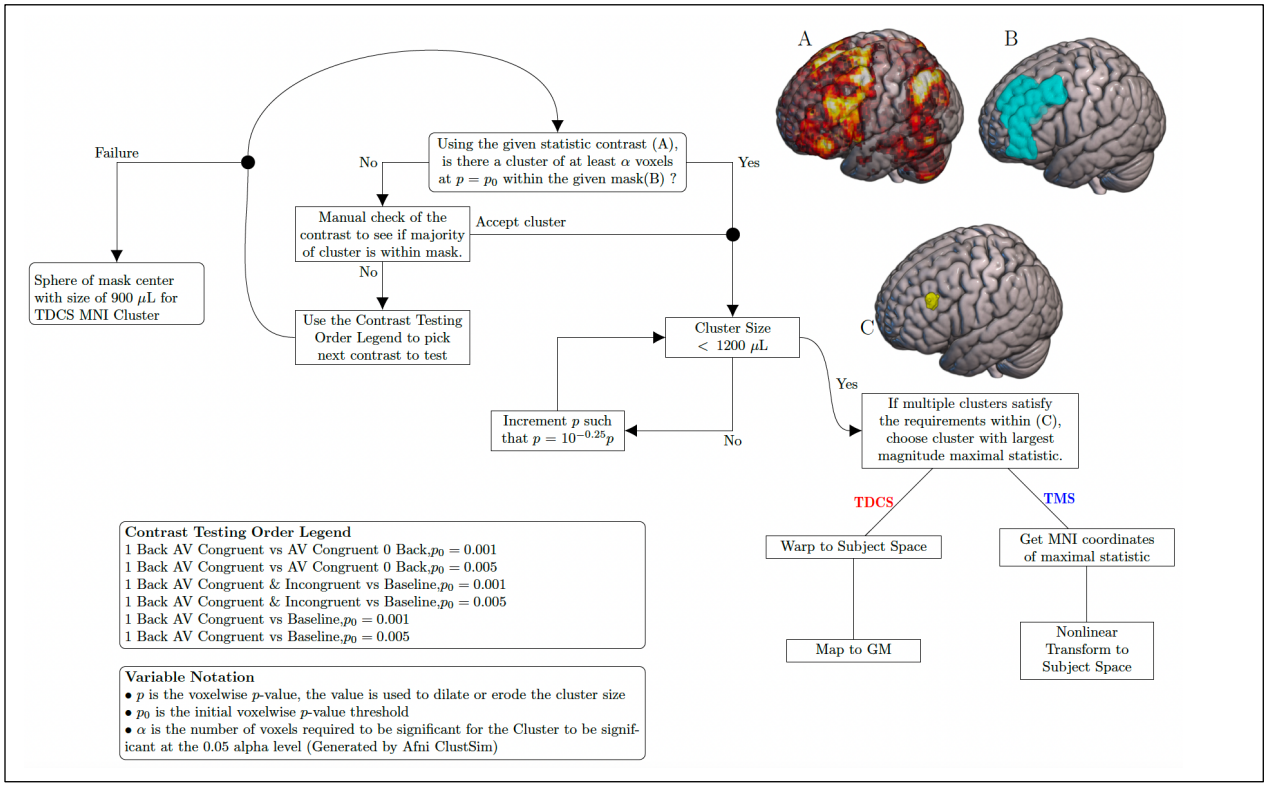


Figure 2. APT-3 optimization daily schedule.

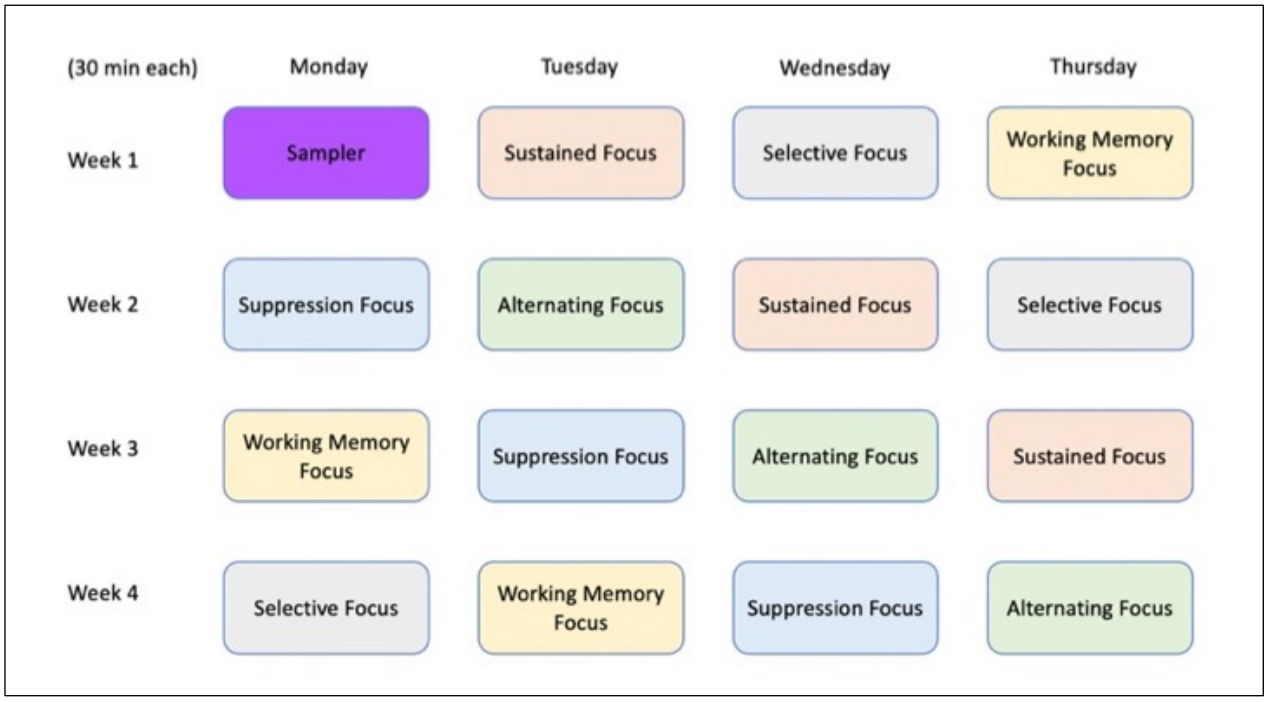
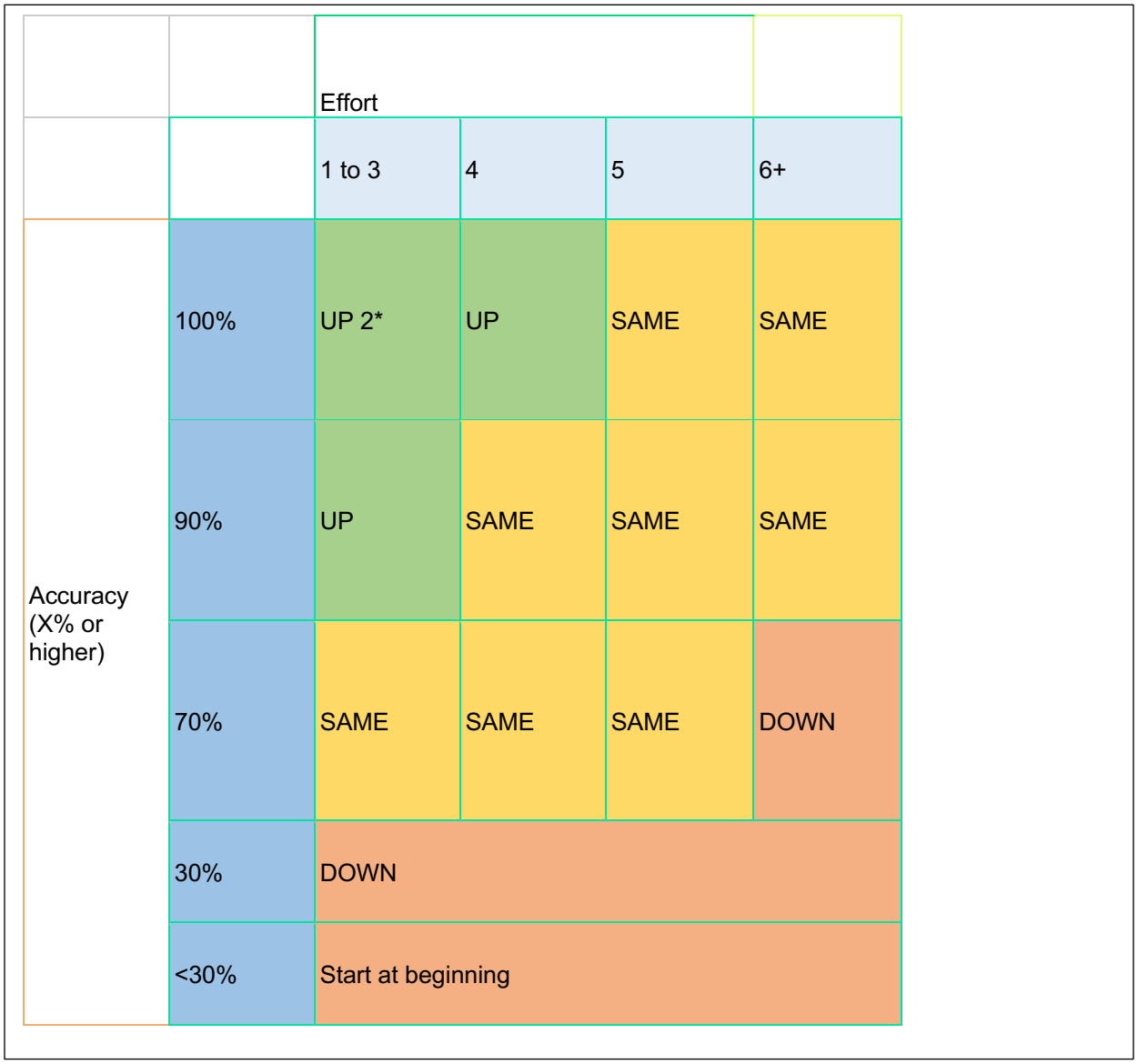
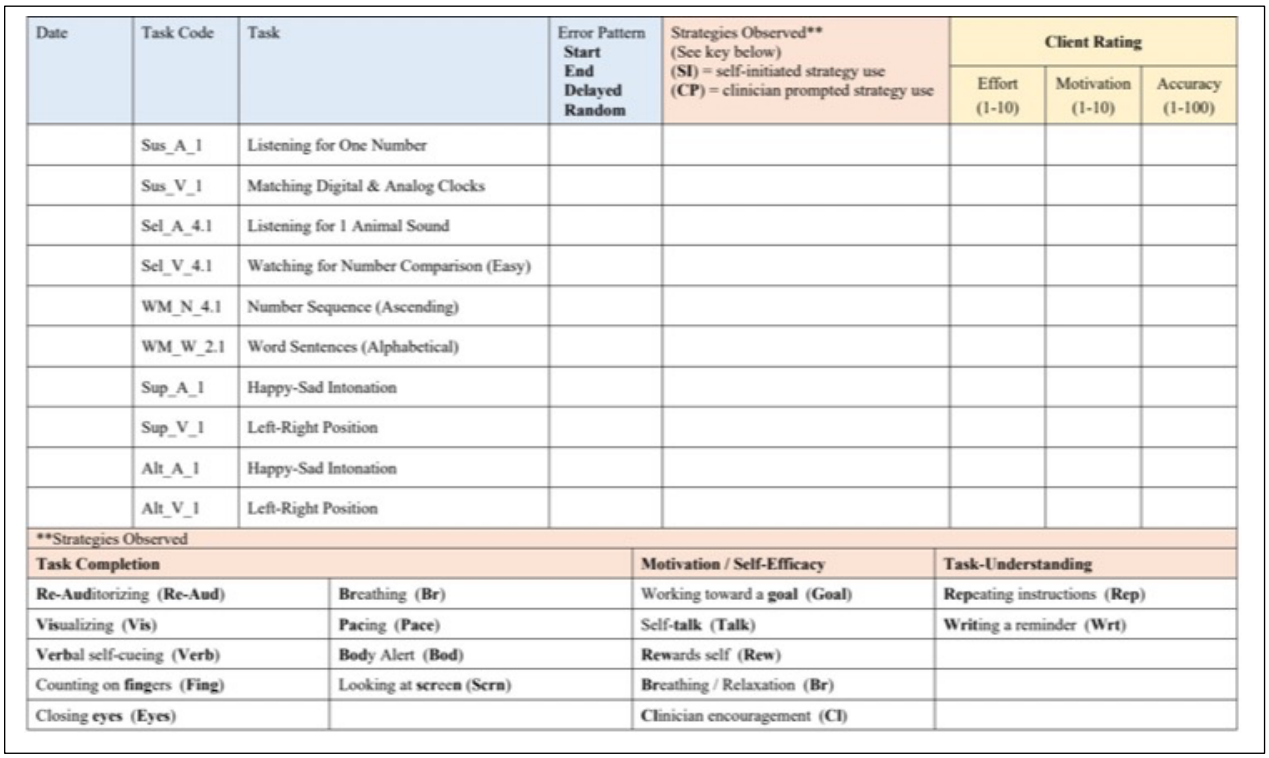


Figure 3. APT-3 algorithm for task progression.



		Effort			
		1 to 3	4	5	6+
Accuracy (X% or higher)	100%	UP 2*	UP	SAME	SAME
	90%	UP	SAME	SAME	SAME
	70%	SAME	SAME	SAME	DOWN
	30%	DOWN			
	<30%	Start at beginning			

Figure 4. APT-3 session record sheet with metacognition prompts.



Date	Task Code	Task	Error Pattern **Start** **End** **Delayed** **Random**	Strategies Observed** (See key below) (**SI**) = self-initiated strategy use (**CP**) = clinician prompted strategy use	**Client Rating**		
					Effort (1-10)	Motivation (1-10)	Accuracy (1-100)
	Sus_A_1	Listening for One Number					
	Sus_V_1	Matching Digital & Analog Clocks					
	Sel_A_4.1	Listening for 1 Animal Sound					
	Sel_V_4.1	Watching for Number Comparison (Easy)					
	WM_N_4.1	Number Sequence (Ascending)					
	WM_W_2.1	Word Sentences (Alphabetical)					
	Sup_A_1	Happy-Sad Intonation					
	Sup_V_1	Left-Right Position					
	Alt_A_1	Happy-Sad Intonation					
	Alt_V_1	Left-Right Position					

**Strategies Observed

Task Completion		**Motivation / Self-Efficacy**	**Task-Understanding**
Re-Auditorizing (**Re-Aud**)	**Br**eathing (**Br**)	Working toward a **goal** (**Goal**)	**Rep**eating instructions (**Rep**)
Visualizing (**Vis**)	**Pac**ing (**Pace**)	Self-**talk** (**Talk**)	**Writ**ing a reminder (**Wrt**)
Verbal self-cueing (**Verb**)	**Bod**y Alert (**Bod**)	**Rew**ards self (**Rew**)	
Counting on **fing**ers (**Fing**)	Looking at **scrn** (**Scrn**)	**Br**eathing / Relaxation (**Br**)	
Closing **eyes** (**Eyes**)		**Cl**inician encouragement (**Cl**)	

1.2 Specific Objectives

CONNECT-TBI is a randomized, double-blinded, sham-controlled clinical trial of neuromodulation to accelerate cognitive training in military mTBI. There are three treatment arms: 36 patients will receive rTMS + training; 36 patients will receive HD-tDCS + training; and 36 patients will receive sham + training. As outlined above, the specific objectives of the study are:

Aim 1 (HD-tDCS): To assess the efficacy of APT-3 combined with HD-tDCS to improve subjective PCS, objective cognitive control, and quality of life in Veterans and Active Duty Personnel with complex TBI.

Aim 2 (rTMS): To assess the efficacy of APT-3 combined with rTMS to improve subjective PCS, objective cognitive control, and quality of life in Veterans and Active Duty Personnel with complex TBI.

Aim 3 (Imaging): To identify baseline characteristics and longitudinal changes in activity within the CCN that correlate with clinical recovery and predict response to the interventions.

1.3 Significant Results or Key Outcomes

Nothing to report.

1.3.1 Other Achievements

Nothing to report.

Stated Goals Not Met
To date, the only study goals not met at the time of this annual report are the stated recruitment goals: we are aiming for recruitment of 108 mTBI subjects. To date we have enrolled 8 subjects across the sites. This lag in recruitment is attributable to several factors:

a) Delays in full HRPO approval to begin the study, due to required necessary modifications to UNM, Minneapolis VA, and NM VA IRB protocols.
b) Delays in equipment acquisition, underperformance of existing equipment needing to be replaced, and troubleshooting of equipment leading to need for the manufacturer to design software fixes.
c) Lack of published standards for conduct of Attention Process Training-3 in research and in clinical care, necessitating the study team to review literature, consult with experts, and build algorithms for this purpose.
d) Slower than expected intake of potential patients from the Minneapolis VAHCS and NMVAHCS Polytrauma Support Clinics.

Please see next section for description of efforts to meet this goal.

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

Nothing to report.

1.5 How were the results disseminated to communities of interest?

Nothing to report.

1.6 Planning

During the next reporting period, we plan to accomplish the following goals:

1) Recruit, enroll, and conduct participants through the protocol.
2) Bolster recruitment efforts via expanded inclusion/exclusion criteria, polytrauma registry review, polytrauma team engagement, allied health service team engagement, monthly research tables, targeted social media advertisements.
3) Continue hiring and training staff necessary to perform the protocol at each site.

2. Impact

2.1 What was the impact on the development of the principal discipline of the project?

Nothing to report.

2.2 What was the impact on other disciplines?

Nothing to report.

2.3. What was the impact on technology transfer?

Nothing to report.

2.4 What was the impact on society beyond science and technology?

Nothing to report.

3. Changes/Problems

3.1 Changes in approach and reasons for change

None at this time.

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

Three actual problems occurred in the past year that significantly delayed study activities:

A) Harmonization: Ensuring that the APT-3 can be conducted in a comparable fashion at both sites required significant literature review, consultation with content experts, and pilot testing of strategies to optimize APT-3. This led to delays in start of enrollment of participants. This harmonization is complete and we have initiated enrollment since May 2022.

B) Brain stimulation equipment: it was discovered that the TMS equipment at U. Minnesota was not powerful enough to deliver the type and intensity of stimulation needed in the study; therefore, a more powerful TMS unit capable of delivering above the necessary dose for CONNECT-TBI was purchased and installed. Due to the COVID pandemic, the delivery of this device was delayed. It is now installed and operational in the U. Minnesota Noninvasive Neuromodulation Lab.

C) Recruitment lag: Recruitment of participants between May 2022 and October 2022 has not achieved the projected rate in the Scope of Work. Identified causes of this recruitment lag include the following: COVID and economic concerns of participants leading to reluctance to enroll; increased costs associated with participation in the study (i.e., increased gas prices); time-intensive nature of the study difficult for potential participants who are currently employed to accommodate; search strategies for polytrauma registry queries not effectively identifying potential participants; direct engagement of polytrauma clinicians being restricted due to personnel and communication barriers. To address these issues, we are instituting a new set of robust recruitment methods that have shown success in our group's other studies recruiting Veterans. These include monthly research tables at the VAHCS sites; direct engagement of polytrauma clinicians via face to face meetings; targeted advertising strategies using social media channels such as Facebook; review of disqualifying factors and relaxation of inclusion/exclusion criteria.

Anticipated Problems/Issues

Given ongoing infectious disease/COVID effects on workforce health, staff availability, and participant retention, and ongoing economic challenges and hardships affecting attitudes about participation in research, we anticipate that achieving enrollment rates sufficient to meet our scientific goals will be the top challenge that our study team will face.

A) Staff/workforce health: Each team has redundancies built into staff roles, so that sickness or absence of any one team member does not lead to inability to conduct the protocol at the particular site. Meticulous hygiene and safety standards will be maintained with regard to COVID and other endemic infectious diseases such as influenza. Standard operating procedures and automated scripts will ensure that centralized Core functions

can be carried out even if data analysts or principle/site investigators must be absent from work. COVID symptom screening and ad hoc testing will continue to be carried out according to each institution's local guidelines. Recruitment, consenting, and followup methods will be contactless and virtual whenever possible.

B) Economic/travel hardship: Feedback from potential participants who were unable to enroll has revealed that costs associated with study participation (gas costs, parking costs, housing costs) have been negatively impacting enthusiasm to enroll in the study. Therefore we are allotting available study budget to reimburse participants for mileage according to the federal approved rate, as well as providing support for accommodations when participants are traveling long distances to the study sites.

C) Recruitment rates: In addition to the above outreach activities to spread awareness of the study and recruit Veterans from the community, we will also be modifying the inclusion and exclusion criteria to increase the pool of qualifying participants, without altering the ability to test the scientific hypotheses. These changes include: increasing allowable time since injury from 20 years to 30 years, increasing age at study entry to 69, and reducing duration of sobriety from ETOH/substance use to 6 months. This is based on identification of trends in disqualified individuals during the screening process.

3.3 Changes that had a significant impact on expenditures

Nothing to report.

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

Nothing to report.

3.5 Other Achievements

None at this time.

Human Use Regulatory Protocols

TOTAL PROTOCOLS: 3

PROTOCOL (1 of 3 total):

Protocol [HRPO Assigned Number]: UNM HRRC #: 21-026

Title: **Control Network Neuromodulation to Enhance Cognitive Training in Complex Traumatic Brain Injury (The CONNECT-TBI Trial)**

Target required for clinical significance: 108 (combined from both NM and MN sites)

Target approved for clinical significance: 108 (combined from both NM and MN sites)

SUBMITTED TO AND APPROVED BY:

- **Submitted: 12/11/2020**
- **Reviewed: 02/12/2021**
- **Approved: 04/29/2021**

STATUS:

(i) Number of subjects recruited/original planned target:33/500 (combined from both NM and MN sites)

Number of subjects screened/original planned target: 33/500 (combined from both NM and MN sites)

Number of patients enrolled/original planned target: 6/54 (combined from both NM and MN sites)

Number of patients completed/original planned target: 0/54 (combined from both NM and MN sites)

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:

Type of Submission	Summary of Submission	Site	Date of Approval
Modification	Changed ramp up and down time for all protocols; changed consent and protocol to reflect receipt of CoC	UMN, UNM	7/12/2022
Modification	Adding study team member McQuaid	MRN	8/22/2022
RNI	Older version of consent used on 07/28/22 and 08/10/22; Both participants reconsented with correct version of consent at post-treatment visit. No further action needed.	MRN	10/02/22
Modification	Adding study team member Richardson	UNM	9/19/2022

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:

PT ID	6001D	
Site	U. Minnesota	
Event Term	Amnesia	
AE Onset Date	6/12/22	
AE Stop Date	6/13/22	
Reported to IRB?	Yes	
IRB Determination	No increased risk, no action needed	
Study Period	Intervention	
Severity	Mild	
Related to Study?	No	
Unanticipated?	Yes	
Outcome	Resolved	
Action Taken	None	

Narrative of AE
6001D MN 06/12/22: Before beginning Treatment Session 14 on Tuesday 6/14/2022, Participant 6001D reported experiencing amnesia for 8 hours on Sunday 6/12/2022. He reported that he and his girlfriend watched a movie, and he does not remember the next 8 hours after that. He was told by his girlfriend that he drove to the store alone to buy bacon and eggs, came home, and cooked for himself and his girlfriend, and then fell asleep. His girlfriend told him that he was acting normally but was sweating profusely while he was asleep. He reported that he was not under the influence of alcohol or drugs.
Once the participant reported this to study staff, the Study Coordinator, immediately called the site PI, Dr. Davenport to report this incident. Based on the information provided, Dr. Davenport determined that the reported experiences were unlikely to be causally linked to the neuromodulation intervention, especially considering no stimulation had occurred in the 5 days prior to the event, and that the participant should be allowed to continue participation if willing and interested in doing so. Dr. Davenport discussed this adverse event with the full multi-site study team, including Drs. Pirio Ricahrdson, Chen, and Quinn, who concurred that this event was not consistent with common or rare side effects of transcranial direct current stimulation. Dr. Davenport recommended that the participant be reminded that all participation is voluntary and given the opportunity to discontinue or delay subsequent visits if concerned about safety. The Study Coordinator communicated this to the participant, who said “I’m here aren’t I?”. The

participant reported no concern about safety issues, and that he felt that we should know about the amnesia. The visit proceeded without further incident.
This was reported to the UNM IRB and it was determined that this did not increase the overall risk and no further action was required (06/06/22)

PROTOCOL (2 of 3 total):

Protocol [HRPO Assigned Number]: NMVAHCS IRB #: H3588

Title: **Control Network Neuromodulation to Enhance Cognitive Training in Complex Traumatic Brain Injury (The CONNECT-TBI Trial)**

Target required for clinical significance: 54

Target approved for clinical significance: 54

SUBMITTED TO AND APPROVED BY:

- **Submitted: 12/04/2020**
- **Reviewed: 02/09/2021**
- **Approved: Main IRB approval on 04/02/2021, R&D and IT approval on 05/14/2021**

STATUS:

(i) Number of subjects recruited/original planned target: 25/250
Number of subjects screened/original planned target: 25/250
Number of patients enrolled/original planned target: 3/54
Number of patients completed/original planned target: 0 / 54

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:

Type of Submission	Summary of Submission	Site	Date of Approval
Modification	Changed ramp up and down time; changed consent and protocol language to reflect receipt of CoC	VA	9/13/2022
Modification	Adding study team member, Worth and removing study team member - Allsop	VA	9/14/2022

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:

PT ID	M87187742	
Site	New Mexico VAHCS	
Event Term	Motor vehicle accident	

AE Onset Date	9/7/22	
AE Stop Date	9/17/22	
Reported to IRB?	Yes	
IRB Determination	Pending	
Study Period	Intervention	
Severity	Mild	
Related to Study?	No	
Unanticipated?	Yes	
Outcome	Pending	
Action Taken	Discontinued study intervention	

Narrative of AE:

M87187742 NMVAHCS 09/07/2022: Before beginning treatment Session 15 on Thursday 9/8/2022, participant reported he was involved in a motor vehicle accident at approximately 9:00 p.m. on 9/7/2022. He reported severe headache, dizziness, and less than 2 hours of sleep. Study Coordinator referred the participant to the ER and reported the incident to the P.I., Dr. Pirio-Richardson. The participant was seen at ER on 9/8/2022 and told that he had experienced a concussion and he was instructed to rest for 7 days. The PI met with study team and determined that it was not safe to continue the study intervention. The incident was reported to the NMVAHCS IRB and no further action is required per IRB. The participant will complete research post intervention visits.

PROTOCOL (3 of 3 total):

Protocol [HRPO Assigned Number]: Minneapolis VAHCS IRB #

Title: **Control Network Neuromodulation to Enhance Cognitive Training in Complex Traumatic Brain Injury (The CONNECT-TBI Trial)**

Target required for clinical significance: 54

Target approved for clinical significance: 54

SUBMITTED TO AND APPROVED BY:

- **Submitted: Feb. 2021**
- **Reviewed: 04/05/2021**
- **Approved: Main IRB approval on 05/06/2021, R&D and IT approval on 05/24/2021**

STATUS:

(i) Number of subjects recruited/original planned target: 8/250
Number of subjects screened/original planned target: 8/250
Number of patients enrolled/original planned target: 3/54
Number of patients completed/original planned target: 0/54

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:

None at this time

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:

None at this time

Use of Human Cadavers for Research Development Test & Evaluation (RDT&E), Education or Training

TOTAL ACTIVITIES: *No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW).*

ACTIVITIES: *No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW).*

Animal Use Regulatory Protocols

TOTAL PROTOCOL(S): *"No animal use research will be performed to complete the Statement of Work."*

4. Products

4.1 Journal Publications

Nothing to report.

4.2 Books or other non-periodical, one-time publications

Nothing to report.

4.3 Other publications conference papers and presentations

Quinn DK, Maple T, Lieske A, Cunningham S, Hiltner R, Worth L, Ojeda C, Jones TR, Upston J, Lehud E, Chen M, Pirio Richardson S, Sponheim S, Mayer AR, Davenport N. Control network neuromodulation to enhance cognitive training in complex traumatic brain injury (CONNECT-TBI). Poster abstract accepted at the Military Health System Research Symposium, Kissimmee, FL, September 12-15, 2022.

4.4 Websites or other Internet sites

Nothing to report.

4.5 Technologies or techniques

The study team developed a containerized, virtual method of processing MRI images and determining ideal targets in the region of interest for individual subjects based on a novel task developed by the study investigators. The team also developed an algorithm for standardized Attention Process Training-3 individualization based on rules for increasing/decreasing difficulty across separate cognitive domains. These will be described in separate research papers to be published in 2023.

4.6 Inventions, patent applications, and/or licenses

Nothing to report.

4.7 Other products

Nothing to report.

5. Participants & Other Collaborating Organizations

Name	**Davin Quinn, MD**
Project Role	Coordinating PI (New Mexico), AOC Co-Director
Research Identifier	**0000-0002-1613-8018**
Nearest person month worked	**24**
Contribution to Project	Dr. Quinn is a Neuropsychiatrist at the University of New Mexico. With Dr. Nicholas Davenport, he is Co-Director of the Administration and Oversight Core, and runs meetings and conference calls, and assists the site PIs and Core Co-Directors in oversight and training of study staff. Dr. Quinn with Dr. Davenport oversees the creation and management of regulatory binders, written updates, progress reports, data safety and monitoring reports, and random audits of the research data performed by the USAMRMC Human Research Protection Office, and maintains compliance with the IRBs of record for the study.

Name	**Nicholas Davenport, PhD**
Project Role	Co-PI (Minnesota), AOC Co-Director
Research Identifier	
Nearest person month worked	**24**
Contribution to Project	As the Minneapolis site PI, Dr. Davenport will be responsible for carrying out the study tasks at UM/MAVHCS, and will coordinate closely with Dr. Quinn and collaborators regarding protocol harmonization, IRB submission, data management, and results dissemination. With Dr. Quinn, he will co-direct the Administration and Oversight Core (AOC).

Name	**Andrew Mayer, PhD**
Project Role	Co-PI, IAC Co-Director (New Mexico)
Research Identifier	
Nearest person month worked	**24**
Contribution to Project	Dr. Mayer is the Director of Trauma and En-route Care, as well as a Professor of Translational Neuroscience at The Mind Research Network (MRN) and an Adjunct Professor of Neurology at the University of New Mexico. He will assist in the development of the study and will be involved in all aspects of the neuropsychological and imaging components, including data quality assurance and analysis of data. He will work with Drs. Quinn, Pirio Richardson, Davenport, Chen, and Sponheim, to interpret results of MRI in relation to cognition, attention processing performance and behavioral data. He will serve as the co-Director of the Imaging and Assessment Core (IAC), along with Dr.

	Sponheim, and will provide oversight and leadership in the harmonization and consistency of the multi-site imaging component of the protocol.

Name	**Scott Sponheim, PhD**
Project Role	Co-I, IAC Co-Director (Minnesota)
Research Identifier	
Nearest person month worked	**24**
Contribution to Project	Dr. Sponheim is a Professor of Psychiatry at the University of Minnesota, and a Staff Psychologist at the Minneapolis VAHCS. He will provide input on the recruitment, imaging, and neuropsychological testing components of the planned clinical trial. He will co-direct, with Dr. Mayer, the Imaging and Assessment Core (IAC).

Name	**Sarah Pirio Richardson, MD**
Project Role	Co-PI, NRC Co-Director (New Mexico)
Research Identifier	
Nearest person month worked	**24**
Contribution to Project	Dr. Pirio Richardson is a Neurologist and an Attending Physician in the Neurology Section at the New Mexico VAHCS. She will provide expertise on harmonization of stimulation techniques, safety and individualization of stimulation, and clinical trial design and management. Along with Dr. Mo Chen, Dr. Pirio Richardson will be co-Director of the Neuromodulation and Rehabilitation Core (NRC).

Name	**Mo Chen, PhD**
Project Role	Co-Investigator, NRC Co-Director
Research Identifier	
Nearest person month worked	**24**
Contribution to Project	Dr. Chen is a Research Scientist in the University of Minnesota Department of Psychiatry, and Manager of the Noninvasive Neuromodulation Laboratories. He will contribute his expertise in neuromodulation methods and safety, as well as inform the targeting of cognitive control networks with rTMS. With Dr. Pirio Richardson, he will co-direct the Neuromodulation and Rehabilitation Core (NRC).

Name	**Orrin Myers, PhD.**
Project Role	Biostatistician
Research Identifier	

Nearest person month worked	**24**
Contribution to Project	Dr. Myers is the Director of Biostatistics in Department of Family and Community Medicine and a faculty member in the Biostatistics, Epidemiology and Research Design Core of the UNM Clinical and Translational Sciences Center. He will provide biostatistical consultation and input for the CONNECT-TBI MRCTN, including for study design and sample size calculations, data analysis approaches and safety monitoring. He will coordinate closely with Drs. Quinn and Davenport as a member of the Administration and Oversight Core, as well as with Drs. Mayer and Sponheim as a member of the Imaging and Assessment Core.
Name	**Lindsay Worth**
Project Role	Clinical Program Manager
Research Identifier	
Nearest person month worked	**4**
Contribution to Project	Ms. Worth, as the Clinical Research Manager (CRM), will assist the AOC Co-Directors Drs. Quinn and Davenport in ensuring site integration and harmonization. Weekly AOC meetings run by the CRM will review each component of the study, discussing updates, modifications, protocol deviations or violations, expected and unexpected study-related events, regulatory reporting, recruitment, and data capture. Monthly meetings with all six Core Co-Directors and all study staff will review each of these components, as well as data analysis updates and plans for dissemination, presentations, and publications.

Name	**Elijah Lahud**
Project Role	Study Coordinator (Minnesota)
Research Identifier	
Nearest person month worked	**21**
Contribution to Project	As the site study coordinator, Mr. Lahud is responsible for regulatory submissions and reporting, personnel management, participant payments, recruitment, consenting, and coordination between the Minnesota and New Mexico teams.

Name	**Sloan Davidson, MS**
Project Role	Study Coordinator (U. Minnesota)
Research Identifier	
Nearest person month worked	**21**

Contribution to Project	As the site study coordinator, Ms. Davidson is responsible for regulatory submissions and reporting, personnel management, participant payments, recruitment, consenting, and coordination between the New Mexico and Minnesota teams.

Name	**Rebecca Hiltner**
Project Role	Recruitment Coordinator (U. Minnesota)
Research Identifier	
Nearest person month worked	**21**
Contribution to Project	As the recruitment coordinator, Ms. Hiltner is responsible for coordinating recruitment efforts at the UMN site. This will entail creation/dissemination of recruitment materials, acting as liaison/point of contact for patient referrals between the UMN site and the Minn. VAHCS, screening potential subjects, tracking all recruitment efforts, and coordination between the New Mexico and Minnesota teams.

Name	**Alana Lieske**
Project Role	Research Assistant (U. Minnesota)
Research Identifier	
Nearest person month worked	**16**
Contribution to Project	As a research assistant, Ms. Lieske is responsible for the administration of the study interventions at the University of Minnesota, including TMS, tDCS, and APT. Ms. Lieske will assist Dr. Chen in his lab with all parts of the neuromodulation component of the research protocol. Ms. Lieske will also provide comprehensive training to the study team on the StarStim 8 HD tDCS device.

Name	**Mia Kellman**
Project Role	Research Assistant (U. Minnesota)
Research Identifier	
Nearest person month worked	**2**
Contribution to Project	As a research assistant, Ms. Kellman is responsible for the administration of the study interventions at the University of Minnesota, including TMS, tDCS, and APT. Ms. Kellman will assist Dr. Chen in his lab with all parts of the neuromodulation component of the research protocol. Ms. Kellman will also provide comprehensive training to the study team on the StarStim 8 HD tDCS device.

Name	**Cassie Nelson**

Project Role	Research Assistant (U. Minnesota)
Research Identifier	
Nearest person month worked	**2**
Contribution to Project	As a research assistant, Ms. Nelson is responsible for the administration of the study interventions at the University of Minnesota, including TMS, tDCS, and APT. Ms. Nelson will assist Dr. Chen in his lab with all parts of the neuromodulation component of the research protocol. Ms. Nelson will also provide comprehensive training to the study team on the StarStim 8 HD tDCS device.

Name	**Alana Lieske**
Project Role	Research Assistant (U. Minnesota)
Research Identifier	
Nearest person month worked	**16**
Contribution to Project	As a research assistant, Ms. Nelson is responsible for the administration of the study interventions at the University of Minnesota, including TMS, tDCS, and APT. Ms. Nelson will assist Dr. Chen in his lab with all parts of the neuromodulation component of the research protocol. Ms. Nelson will also provide comprehensive training to the study team on the StarStim 8 HD tDCS device.

Name	**Tiana Maple**
Project Role	Study Coordinator (New Mexico VAHCS)
Research Identifier	
Nearest person month worked	**15**
Contribution to Project	As the study coordinator, Ms. Maple is responsible for the administration of the study interventions at the New Mexico VAHCS, including TMS, tDCS, and APT. Ms. Maple will assist Dr. Pirio Richardson in her lab with all parts of the neuromodulation component of the research protocol.

Name	**Chelsey Smith**
Project Role	Study Coordinator (New Mexico VAHCS)
Research Identifier	
Nearest person month worked	**1**
Contribution to Project	As the site study coordinator, Ms. Smith is responsible for regulatory submissions and reporting, personnel management, participant payments, recruitment, consenting, and coordination between the New Mexico and Minnesota teams.

Name	**Cidney Robertson-Benta**
Project Role	Study Technician (MRN)
Research Identifier	
Nearest person month worked	**13**
Contribution to Project	As a study technician, Ms. Robertson-Benta is responsible for the administration of the study interventions at the MRN, including consent, baseline demographic, symptom, and cognitive assessment, and MRI.

Name	**Jessica McQuaid**
Project Role	Study Technician (MRN)
Research Identifier	
Nearest person month worked	**3**
Contribution to Project	As a study technician, Ms. McQuaid is responsible for the administration of the study interventions at the MRN, including consent, baseline demographic, symptom, and cognitive assessment, and MRI.

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

Davin Quinn, MD

New support starting:

- **Co-Principal Investigator** on "Individualized Targeting and Neuromodulation of Late Life Depression." Mind Research Network CoBRE Pilot Program. PI: Quinn/Abbott. FTE: 0.01 FTE/0.12 calendar months. Total direct costs: . 5/01/2022 – 04/30/2023. Purpose: this project is a renewal of a pilot study of structural and functional MRI (sfMRI) to validate patient-specific targets for TMS to treat late life depression.

- **Site Principal Investigator**, "Eye Recovery Automation for Post-Injury Dysfunctions (iRAPID)" (PI: Yaramothu). Department of Defense CDMRP FY21 TBIPHRP Clinical Trial Award. FTE: 0.10/1.2 calendar moths. Total Costs: 09/01/2022-08/31/2026. Purpose: to conduct a clinical trial of VERVE, a virtual reality platform for delivering automated vision therapy for post-concussion convergence insufficiency in Veterans with mild traumatic brain injury.

- **Co-Investigator**, "A Prospective Observational Study on Therapeutic and Adverse Effects of Medical Cannabis for Chronic Traumatic Brain Injury." Department of Defense CDMRP FY221 TBIPHRP Clinical Research Award. FTE: 0.05/0.6 calendar months. Total Costs: 10/01/2022-09/30/2025. Purpose: To use advanced

neuroimaging techniques to quantify changes in brain function in Veterans with traumatic brain injury taking medical cannabis.

Old support ended:

- **Coordinating Principal Investigator** on “High-Definition Transcranial Direct Current Stimulation for Sensory Deficits in Complex Traumatic Brain Injury.” W81XWH-17-1-0432, “Department of Defense, Congressionally Directed Medical Research Programs: Complex Traumatic Brain Injury Rehabilitation Research Award.” PI: Quinn. FTE: 0.3/3.6 calendar months. 11/1/2017-9/30/2022. Purpose: to characterize and ameliorate cognitive control deficits underlying multisensory postconcussive symptoms using magnetoencephalography and high-definition transcranial direct current stimulation in Veterans and Servicemembers with mild traumatic brain injury.

- **Co-Principal Investigator** on "Individualized Targeting and Neuromodulation of Late Life Depression.” Mind Research Network CoBRE Pilot Program. PI: Quinn/Abbott. FTE: 0.01 FTE/0.12 calendar months. 10/01/2020 – 04/30/2022. Purpose: a pilot study of structural and functional MRI (sfMRI) to identify individual-specific targets for TMS to treat late life depression.

Nicholas Davenport

New Support

- None since Oct 2021

Decrease in Support

- **Co-Investigator** Advancing Mechanisms of Resilience (decrease of .6 calendar months)

Andrew Mayer

New Support

- None since Oct 2021

Old support ended:

- **Co-Investigator** on “High-Definition Transcranial Direct Current Stimulation for Sensory Deficits in Complex Traumatic Brain Injury.” W81XWH-17-1-0432, “Department of Defense, Congressionally Directed Medical Research Programs: Complex Traumatic Brain Injury Rehabilitation Research Award.” PI: Quinn. FTE: 0.3/3.6 calendar months. 11/1/2017-9/30/2022. Purpose: to characterize and ameliorate cognitive control deficits underlying multisensory post concussive symptoms using magnetoencephalography and high-definition transcranial direct current stimulation in Veterans and Servicemembers with mild traumatic brain injury.

Scott Sponheim

New Support

- None since Oct 2021

Old Support Ended

- Principal Investigator of U01MH108150 entitled "Neural Disconnection and Errant Visual Perception in Psychotic Psychopathology". Major Goals: The overarching goal of this project is to use psychophysical tasks and neural connectivity data derived from the Human Connectome Project (HCP) to develop and test a biologically realistic model of basic and complex functions of the brain in order to understand the origins of visual misperception in psychosis. Name of PD/PI: Sponheim, Scott. Source of Support: NIH. Primary Place of Performance: University of Minnesota. Project/Proposal Start and End Date: 08/05/2016 - 07/31/2022 NCE . Person Months (Calendar/Academic/Summer) per budget period: 0.23 TPE calendar.

Sarah Pirio-Richardson

New Support

- Michael J Fox Foundation Grant Zabetian (PI) 9/1/22-8/30/24
  "Veterans Parkinson's Disease Genetics Initiative (Vet-PD)"
  Veterans and individuals of non-European ancestry are remarkably underrepresented in genetic studies.
  Role: Site PI

- Dystonia Coalition Pilot Project Martino (PI) 8/1/22-7/31/23
  "MOODSCREEN for Dystonia: a diagnostic accuracy study of depression and anxiety in people with adult-onset isolated dystonia"
  Role: Site PI

- R03AG075408 Ryman (PI) 2/15/22-1/31/24
  "Cerebrovascular contributions to cognitive impairment in Lewy body dementias"
  Leverage multimodal imaging to evaluate which cerebrovascular functions are altered and their association with cognition Parkinson's disease dementia and Dementia with Lewy bodies.
  Role: Co-I (0.10 FTE)

What other organizations were involved as partners?

Organization Name	**University of New Mexico Health Sciences Center**
Location of Organization	Albuquerque, New Mexico, USA
Partner's Contribution to Project	Financial support; in-kind support; facilities; collaboration.

Organization Name	**University of Minnesota**
Location of Organization	Minneapolis, Minnesota, USA
Partner's Contribution to Project	Financial support; in-kind support; facilities; collaboration.

Organization Name	**Mind Research Network**
Location of Organization	Albuquerque, New Mexico, USA
Partner's Contribution to Project	Financial support; in-kind support; facilities; collaboration.

Organization Name	**New Mexico VA Health Care System**
Location of Organization	Albuquerque, New Mexico, USA
Partner's Contribution to Project	Financial support; in-kind support; facilities; collaboration.

Organization Name	**Minneapolis VA Health Care System**
Location of Organization	Minneapolis, Minnesota, USA

Partner's Contribution to Project	Financial support; in-kind support; facilities; collaboration.

6. Special Reporting Requirements

Quad Charts: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

7. Appendices

None.