Treatment for Key Sequelae of Military Traumatic Brain Injury: The USUHS/NIH Military TBI Research Group Program

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Disclosures

• Neither I nor any member of my family have a financial arrangement or affiliation with any corporate organization offering financial support or grant monies for this research, nor do I have a financial interest in any commercial product(s) or service(s) I will discuss in the presentation or publication.

• The opinions or assertions contained herein are the private ones of David Brody’s and are not to be construed as official or reflecting the view of the DoD or the USUHS.
Learning Objectives

At the end of this activity, the participant will be able to:

• To discuss potential interventional trial approaches for military Service Members with late neurological sequelae of TBI

• To analyze the interactions between sleep disorders, mood dysregulation, and migraine in military Service Members with TBI

• To weigh the pro’s and con’s of inclusive vs restrictive inclusion/exclusion criteria for clinical trials
MISSION: To do great science that improves outcomes for military traumatic brain injury patients.

VISION

• In 2 years, CNRM will run multiple studies that test treatments in human patients, and test new therapies in animal models that closely mimic studies in human patients.

• In 5 years, CNRM will fully implement a scientifically rigorous, well organized, and highly focused military TBI research program that has twice the funding of its existing program.

• In 10 years, CNRM will develop a substantial body of knowledge about what is effective and what is ineffective when treating military TBI patients.
Values

• **Urgency**: We maintain a sense of urgency towards improving outcomes for military TBI patients

• **Solutions-focused**: We focus our efforts on research that makes a difference in the lives of those with TBI

• **Collaborative**: We partner with other leading research groups in the National Capital Area and around the world

• **Transparency**: We publish and disseminate all findings, regardless of whether the treatments work or not

• **Fiscally responsible**: We generate real world value for taxpayer money
Strategic Objectives by Domain

**Education and Training:**

- Initiating a new joint USU/NIH/University of Maryland fellowship program to train post-MD and post-PhD scientists to become future leaders in military-relevant TBI research.
- Training USU medical students and graduate students through research opportunities.

**Research and Scholarship:** Large, ambitious, collaborative projects. Strategic priorities (in order)

1. Interventional trials of new treatments in humans relevant to military TBI patients.
2. Clinically realistic trials of new treatments in animal models relevant to military TBI.
3. Development of new tools and new treatments to support future trials in humans.
4. Development of better animal models and better ways to directly link outcomes in animals to outcomes in human patients, to support future clinically realistic animal trials.
5. Other projects related to TBI.

**Leadership and Service:**

Creating collaborations with military treatment facilities around the world to implement high quality, strategically-focused research. Key partners include DVBIC, the Intrepid Spirit Centers, and the USU national faculty.
# Clinical Trials “Pipeline”

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Early Planning</th>
<th>Protocol Development</th>
<th>Regulatory Review</th>
<th>Enrollment</th>
<th>Follow-up</th>
<th>Analysis &amp; Publication</th>
</tr>
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<tbody>
<tr>
<td>TMS for depression: pilot</td>
<td></td>
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<td>TMS for depression: Capital area</td>
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<td>Internet CBT for insomnia</td>
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<td>CGRP antagonist for acute migraine</td>
<td></td>
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</table>
Transcranial Magnetic Stimulation

Siddiqi, Brody, et al. unpublished
Resting State fMRI Network Mapping: Individual Subject

Siddiqi, Brody, et al. under review
Dorsal Attention and Default Mode Networks are **anti-correlated**. By stimulating Dorsal Attention Network, we hope to reduce the activity in Default Mode Network.
Assessed for eligibility (n = 32)
- Excluded (n = 17)
  - Not meeting inclusion criteria (n = 7)
  - Declined to participate (n = 8)
  - Other reasons (n = 2)

Randomized (n = 15)

Allocated to active treatment (n = 9)
- Received active sessions (n = 9)
- Withdrew prior to first session (n = 0)

Allocated to sham (n = 6)
- Received sham sessions (n = 5)
- Withdrew prior to first session (n = 1)

Follow-Up
- Lost to follow-up (n = 0)
- Did not complete full course of treatment within the 5-week timeframe (n = 1)

Analysis
- Analyzed (n = 9)
  - Excluded from analysis (n = 0)
- Analyzed (n = 5)
  - Excluded from analysis (n = 0)

Siddiqi et al., in preparation
<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>43 ± 13</td>
<td>50 ± 18</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>7 M, 2 F</td>
<td>4 M, 2 F</td>
</tr>
<tr>
<td><strong>Duration since TBI (yrs)</strong></td>
<td>8.4 ± 8.2</td>
<td>8.1 ± 11.3</td>
</tr>
<tr>
<td><strong>TBI mechanism</strong></td>
<td>4/9 MVC</td>
<td>3/6 MVC</td>
</tr>
<tr>
<td></td>
<td>2/9 military/fire</td>
<td>3/6 sports</td>
</tr>
<tr>
<td></td>
<td>1/9 sports</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/9 other</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of depression (yrs)</strong></td>
<td>4.8 ± 4.2</td>
<td>7.7 ± 9.9</td>
</tr>
<tr>
<td><strong>Treatment trials</strong></td>
<td>4.8 ± 3.0</td>
<td>5.4 ± 3.4</td>
</tr>
<tr>
<td>(antidepressants, augmentation, or CBT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comorbid PTSD</strong></td>
<td>4/9</td>
<td>3/6</td>
</tr>
</tbody>
</table>

Siddiqi et al., *in preparation*
Primary Outcome: Depression

Siddiqi et al., in preparation
Secondary Outcomes

Siddiqi et al., *in preparation*
Resting State fMRI Predictors of Primary Outcome

Siddiqi et al., in preparation
Total Randomized = Overall N

Stage 1: Targeting Strategy
- 5cm Rule/Scalp Localization
- Anatomical MRI
- ICT-rTMS
- Sham

Optimized Targeting Strategy

Stage 2: Laterality and Frequency
- Unilateral 10 Hz LDLPFC
- Bilateral 10 Hz LDLPFC/1 Hz RDLPFC
- Unilateral iTBS LDLPFC
- Bilateral iTBS LDLPFC/cTBS RDLPFC

Optimized Targeting and Protocol

Stage 3: Combined rTMS + Psychotherapy
- rTMS + Control Relaxation Therapy
- Sham rTMS + CBT
- Active rTMS + CBT

Oberman et al., unpublished
Alternative Stimulation Targeting

Siddiqi et al., in preparation
Goals for the Multicenter Adaptive Trial Design

• **Create a network of trial sites:** Goal ≥10 sites enrolling ≥ 10 patients each per year.
  - NICoE/Walter Reed [Central Coordinating Site]
  - Intrepid Spirit Centers: Traumatic Brain Injury Treatment Facilities
  - DVBIC Military Treatment Facilities
  - DVBIC Veterans Administration Sites
  - Additional VA sites
  - Regulatory review through the Regional Health Command-Atlantic and VA Central IRB

• **Test the relative efficacy of several TMS targeting strategies, assess several stimulation protocols, and explore the potentially synergistic interaction between TMS and cognitive behavioral therapy.**

• **Move quickly and efficiently, fueled by a sense of urgency. Every week an average of 2 military TBI patients commit suicide.** (>383,000 military TBI patients, suicide rate of 30 per 100,000 per year = >110 per year)
Internet – Delivered Cognitive Behavioral Therapy for Insomnia in TBI patients

Primary outcome: change in insomnia severity index (ISI)

Team Leader: Tom Swanson
Anti-CGRP Monoclonal Antibody for TBI-related Migraine

**Objective:** Determine the safety and efficacy of an anti-CGRP monoclonal antibody administered within 24 hours following a concussive TBI for the acute treatment of post-traumatic headache (PTH) and prevention of persistent PTH

- Randomization will be stratified according to the presence of meningeal enhancement identified on post-contrast FLAIR images. The specific aims are to:

1. Determine the efficacy (i.e. 2-hour pain-free and 24-hour sustained pain free) of an anti-CGRP monoclonal antibody for the **acute treatment** of post-traumatic headache. [co-primary outcome]

2. Determine the efficacy of an anti-CGRP monoclonal antibody for the **preventive treatment** of post-traumatic headache (frequency of moderate-severe headache days during weeks 5-8). [co-primary outcome]

3. Identify **predictors of acute and preventive treatment response** to an anti-CGRP monoclonal antibody including patient demographics, injury mechanism, specific post-TBI symptoms, patient medical history, brain MRI findings, and blood biomarkers.

4. Determine the **tolerability and safety** of an anti-CGRP monoclonal antibody when administered within the first 24 hours following concussive TBI.

- Lead Consultants: Todd Schwedt and David Dodick, Mayo Scottsdale.
- CNRM Cores: Acute Studies (Latour & Turkso), Imaging (Butman & Pham), Biomarkers (Gill & Cox), Phenotyping (Chan & French), Recruitment (Roy)
- Sites: Suburban Hospital (level 2 trauma center), Medstar Georgetown (level 1 trauma center), plus several military treatment facilities with high volume acute concussion patients.
Translational Therapeutic Trials Criteria

1. Preregistration of the protocol, including primary outcome measure and sample size (e.g. Open Science Framework at https://osf.io, analogous to clinicaltrials.gov)

2. Authentication of biological reagents such as antibodies, recombinant proteins, and cell lines.

3. Randomization

4. Blinding

5. Accounting for each animal in a CONSORT diagram

6. Time from injury to intervention realistic relative to what would be achieved in human trials (e.g. 6-8 hours for acute studies, 3-6 months after injury for late sequelae)

7. Pharmacodynamic markers of therapeutic target engagement that could be implemented in human trials (e.g. MRI, blood biomarkers, physiological tests)

8. Long-term (6-12 month) behavioral outcome measures analogous to those used in human trials

   Safety/toxicity assessments

9. Consideration of secondary injury factors (hypoxia, hypotension, elevated ICP, other trauma)

10. Exploration of age and sex as biological variables

11. Replication within the same lab, and in an independent lab

12. Testing in a larger animal model for studies performed initially in rodents
Models for Translational Therapeutic Trials

1. Mouse model of combined blast + impact + stress under development with long-term (6-12 month) behavioral assessments as primary outcomes.

   Social Behavior
   Depression and anxiety-like Behavior
   Sleep disruption
   Impulsivity/attention deficit
   Headache-related behavior

2. Ferret model of combined blast + impact + stress under development with long-term (6 month) behavioral assessments as primary outcomes.

   Behavioral assays for social behavior, headache-related behavior, anhedonia, sleep, and activity under development.

Efficient study design such than multiple therapeutic trials can be run in a staggered fashion.
Summary

• Treatment for military TBI-related depression with individualized brain network-guided Transcranial Magnetic Stimulation

• Treatment for military TBI-related insomnia with internet-based cognitive behavioral therapy

• Treatment for military TBI-related headache with anti-CGRP monoclonal antibody

• Development of new animal models relevant to military TBI
Extra Slides
<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>TBI Mechanism</th>
<th>TBI severity</th>
<th>Structural MRI abnormalities</th>
<th>Duration since TBI (yr)</th>
<th>Duration of depression (yr)</th>
<th>Antidepressant Trials</th>
<th>Augmentation trials</th>
<th>Psychiatric comorbidities</th>
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<tbody>
<tr>
<td>20</td>
<td>M</td>
<td>Assault</td>
<td>Concussive</td>
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<td>1</td>
<td>3-4</td>
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<td>44</td>
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<td>8</td>
<td>3</td>
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<tr>
<td>38</td>
<td>M</td>
<td>Sports</td>
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<td>2-3</td>
<td>3</td>
<td>0</td>
<td>Anxiety</td>
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<tr>
<td>58</td>
<td>M</td>
<td>Firefighting injury</td>
<td>Concussive</td>
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<td>15</td>
<td>15</td>
<td>5</td>
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<tr>
<td>34</td>
<td>M</td>
<td>MVC</td>
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<td>0.5</td>
<td>0.5</td>
<td>4</td>
<td>0</td>
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<tr>
<td>64</td>
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<tr>
<td>38</td>
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<td>1</td>
<td>0</td>
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<tr>
<td>39</td>
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<td>Moderate</td>
<td>Focal atrophy</td>
<td>5</td>
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<td>3</td>
<td>1</td>
<td>Anxiety</td>
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</table>

**SHAM**

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>TBI Mechanism</th>
<th>TBI severity</th>
<th>Structural MRI abnormalities</th>
<th>Duration since TBI (yr)</th>
<th>Duration of depression (yr)</th>
<th>Antidepressant Trials</th>
<th>Augmentation trials</th>
<th>Psychiatric comorbidities</th>
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<tr>
<td>61</td>
<td>F</td>
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<td>0.5</td>
<td>1</td>
<td>1</td>
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<tr>
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<td>None</td>
<td>2.5</td>
<td>2.5</td>
<td>3</td>
<td>1</td>
<td>PTSD</td>
</tr>
<tr>
<td>65</td>
<td>M</td>
<td>MVC</td>
<td>Concussive</td>
<td>None</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>PTSD, resolved</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>Sports</td>
<td>Concussive (multiple)</td>
<td>None</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>Anxiety; cannabis use disorder</td>
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<tr>
<td>51</td>
<td>M</td>
<td>Sports</td>
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<td>2</td>
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<td>20 to 40</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>PTSD</td>
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</table>

Siddiqi et al., *in preparation*
Pre-specification of Primary Outcome

• **Primary Outcome Measure**: Montgomery-Asberg Depression Rating Scale (MADRS)

• **Primary Hypothesis Stage 1**: ICT-rTMS will lead to greater depressive symptom reduction than structural, 5 cm, or sham stimulation.

• **Primary Hypothesis Stage 2**: Bilateral stimulation will lead to greater depressive symptom reduction than unilateral stimulation with no superiority or inferiority of efficacy of theta burst stimulation over standard protocols.

• **Primary Hypothesis Stage 3**: Combined CBT + rTMS will lead to greater depressive symptom reduction than either CBT or rTMS alone.

• **Primary Analysis of Primary Outcome Measure**: Compare change in MADRS scores from baseline to post-treatment (defined as within 10 days following the final course of treatment in the randomization stage) between groups, in an intention to treat analysis.

• **Secondary Analyses of Primary Outcome Measure**:
  • Compare change in MADRS scores from baseline to 6-month follow-up in an intention to treat analysis to assess durability of effects.
  • Compare proportion of subjects in each condition achieving treatment response (≥50% improvement in MADRS) or remission (final MADRS ≤10) at post-treatment
  • Compare proportion of subjects in each condition achieving sustained treatment response, or sustained remission over 6 months of follow-up.
  • Assessment of heterogeneity between sites in terms of treatment efficacy.
Pre-specified Secondary Outcomes

A. To assess changes in TBI-related symptoms as reflected by the TBI Quality of Life Scale.
   1. Primary Analysis: Compare change in TBI-QOL subtest scores from baseline to post-treatment between those randomized to the treatment arms.
   2. Secondary Analysis: Compare change in TBI-QOL subtest scores from baseline to 6-month follow-up.

B. To assess changes in PTSD-related symptoms as reflected by the PTSD Checklist for DSM-5 (PCL-5).
   1. Primary Analysis: Compare change in PCL-5 scores from baseline to post-treatment between those randomized to the treatment arms.
   2. Secondary Analysis: Compare change in PCL-5 scores from baseline to 6-month follow-up intention to treat analysis to assess durability of effects.

C. To compare the feasibility, tolerability, and acceptability of the treatment arms.

D. To compare the frequency and severity of adverse effects between those randomized to the treatment arms.

E. To compare the number, dose, and type of adjunctive treatments, including psychotherapy, lifestyle modification, and psychotropic medications undertaken by those randomized to the treatment arms.

F. To assess changes in rsfMRI connectivity from baseline to post-treatment.
Exploratory Analyses

To evaluate initial clinical predictors of the magnitude of the effects of rTMS on change in MADRS from baseline to post-treatment for development of potential future subject selection strategy. Candidate predictors include:

1. baseline depression severity,
2. duration of depressive symptoms,
3. change in MADRS from baseline to mid-treatment,
4. initial rsfMRI between DLPFC, DMN, and CEN/CCN (defined by the algorithm below),
5. concussive TBI diagnostic criteria (e.g., number of TBIs, duration of loss of consciousness, alteration of consciousness, post-traumatic amnesia)
6. expectation of benefit
7. medical/psychological comorbidities
Sample Size and Power Analysis

The precise sample size is not determined in advance in a Bayesian adaptive design. Rather, the study continues enrolling participants in each stage until pre-specified stopping criteria are reached. As outcome data from each subject becomes available, probabilities of randomization to each arm are adjusted, so that more effective arms have increased randomization probabilities and less effective arms have reduced randomization probabilities. This approach allows optimal use of accumulated information and minimization of sample size without sacrificing statistical rigor.

Initial estimates indicate that approximately 400 participants total will be enrolled across the 3 stages of the trial, assuming effect sizes similar to those reported in prior studies. Based on clinical judgement, the minimum number of participants in each arm will be 20; we won’t exclude any therapeutic approach with less than 20 patients. There will be a total of 11 arms (4 in stage 1, 4 in stage 2, 3 in stage 3), thus the minimum total sample size will be 220. The maximum sample size will be 60 per arm, 660 total. Effects requiring sample sizes larger than 60 per arm to demonstrate statistical significance are not likely to be clinically meaningful in the estimation of the Principal Investigator, a clinician with 17 years of experience in caring for TBI patients.

Estimated effect size 0.25 (“moderate”) at 80% power for p<0.04 = 47 subjects per group, 188 subjects total for 4 groups. Estimated effect size 0.4 (“large”) at 80% power for p<0.01 = 26 subjects per group, 104 subjects total for 4 groups.
Inclusion / Exclusion Criteria

Inclusion Criteria:
1. Age 18-45
2. Current or former US military service member
3. Able to provide written, informed consent in English
4. History of concussive TBI:
   a. >6 months, but <20 years prior to consent
   b. Documented previously in medical records and/or as confirmed by the TBI Screener
5. Must meet Criterion A of the DSM-5 criteria for Major Depressive Disorder as determined by a trained assessor
6. Baseline MADRS >10

Exclusion Criteria:
1. Elevated risk of seizures:
   a. Prior history of unprovoked seizures other than within 24 hours of concussive TBI
   b. History of TBI resulting in penetrating trauma or intraparenchymal hemorrhage
   c. History of intracranial tumor
2. Contraindications to awake 3T MRI without contrast:
   a. Ferromagnetic implants or metallic shrapnel
   b. Severe claustrophobia
   c. Unable to lie awake, supine, stationary, with reasonable comfort in the scanner for approximately 45 minutes
   d. Markedly distorted functional brain anatomy such that rsfMRI targeting cannot be performed
3. Life expectancy of less than 6 months
4. Presence of rapidly progressive illnesses such as late stage cancer, neurodegenerative conditions, major organ failure, etc.
5. History of Bipolar Disorder, Schizophrenia Spectrum Disorders, or Moderate/Severe Substance Use Disorders, with the exception of nicotine and cannabis use disorders
6. Current evidence of substance-induced mood disorder, active psychosis, or depression secondary to general medical illness
7. Concomitant or previous history of receiving open-label TMS, other neurostimulatory treatment, or electroconvulsive therapy
8. Pregnancy as confirmed by urine testing during baseline visit
9. Unilateral or bilateral upper extremity amputation or other condition precluding motor threshold calibration
10. History of severe or recent uncontrolled heart disease
11. Other considerations that may adversely affect patient safety, participation, or the scientific validity of the data being collected (e.g., planned hospitalization halfway through the initial treatment period)