Individualized Resting-State fMRI-Guided Transcranial Magnetic Stimulation Treatment for Depressive Symptoms in Military Traumatic Brain Injury Patients

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DISCLOSURES

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USU Disclaimer Statement: The opinions and assertions expressed herein are those of Dr. David Brody and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of Defense
Objectives

• 1) To understand the relationship between depression, post-traumatic stress disorder, and traumatic brain injury in military service members injured in wartime.

• 2) To appreciate the role of individualized resting-state fMRI in guiding transcranial magnetic stimulation treatment for depressive symptoms in the context of traumatic brain injury.
Research studies of US Military Personnel with blast-related and non-blast-related traumatic brain injury

Photograph from LRMC public website, 2011

Landstuhl Regional Medical Center (LRMC)
Geographical Orientation

Image from C. Mac Donald, with permission

Brody in Kandahar, Jan, 2011

Photograph by C. Giza with permission
Concussion Clinic
Kandahar Air Field, Afghanistan

Photograph by D. Brody

Concussion Care in Theater

1. Scheduled Sleep
2. Non-narcotic pain medications
3. Concussion education
4. Strict regulation of caffeine use
5. Acupuncture
6. Physical Therapy
Clinical outcomes in concussive blast-related vs non-blast TBI

- Prospective evaluation of patients with
  - blast + impact TBI (n=53),
  - non-blast related TBI (n=29),
  - blast-exposed controls evacuated for other reasons (n=27),
  - non-blast exposed controls (n=69)
- Objective: determine similarities and differences in clinical outcome between blast and non-blast TBI

MacDonald et al., 2014 JAMA Neurology

Clinical Outcomes in concussive blast vs nonblast TBI

6-12 month outcome

Mac Donald et al., 2014 JAMA Neurology
Clinical outcomes in concussive blast vs nonblast TBI

Multivariate correlates of clinical outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td><strong>−0.9477 (−1.5376 to −0.3578)</strong></td>
<td><strong>.0016</strong></td>
</tr>
<tr>
<td>MADRS</td>
<td><strong>0.0689 (0.0190 to 0.1178)</strong></td>
<td><strong>.0059</strong></td>
</tr>
<tr>
<td>No. of neuropsychological</td>
<td><strong>0.4381 (0.1173 to 0.7588)</strong></td>
<td><strong>.0024</strong></td>
</tr>
<tr>
<td>covariates</td>
<td><strong>0.02349 (0.00092 to 0.04696)</strong></td>
<td><strong>.0498</strong></td>
</tr>
<tr>
<td>Model 2†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td><strong>−0.7573 (−1.3837 to −0.1309)</strong></td>
<td><strong>.178</strong></td>
</tr>
<tr>
<td>MADRS</td>
<td><strong>0.0663 (0.0162 to 0.1163)</strong></td>
<td><strong>.0094</strong></td>
</tr>
<tr>
<td>No. of neuropsychological</td>
<td><strong>0.4077 (0.0755 to 0.7399)</strong></td>
<td><strong>.0181</strong></td>
</tr>
<tr>
<td>covariates</td>
<td><strong>0.0182 (−0.0055 to 0.0418)</strong></td>
<td><strong>.1323</strong></td>
</tr>
<tr>
<td>TBI vs control groups</td>
<td><strong>−0.3546 (−0.7273 to 0.0182)</strong></td>
<td><strong>.0623</strong></td>
</tr>
</tbody>
</table>

Abbreviations: GOS-E, Glasgow Outcome Scale—Extended; MADRS, Montgomery-Åsberg Depression Rating Scale; MDAS, Migraine Disability Assessment; TBI, traumatic brain injury.

* The overall Akaike information criterion was 2025, and the likelihood ratio by χ² test was 54.04.
** Model 1 includes the GOS-E, MADRS, number of neuropsychological abnormalities, and MDAS.
† Model 2 includes the GOS-E, MADRS, number of neuropsychological abnormalities, MDAS, and TBI vs control groups.
Clinical outcomes in concussive blast-related vs non-blast TBI

• Both TBI groups had higher rates of moderate to severe overall disability
• Self-reported combat exposure intensity was higher in the blast + impact TBI group than in the non-blast TBI group
• Global outcomes, headache severity, neuropsychological performance, and PTSD severity and depression were indistinguishable between the TBI groups
• One potential interpretation is that TBI itself is the driver of outcome, independent of injury mechanism or combat exposure intensity
• Headache severity and PTSD symptoms were worse in blast-exposed controls than non-blast exposed controls:
  • ongoing research is focused on effects of sub-concussive blast-exposures.
• Depression severity was the strongest correlate of overall clinical outcome, irrespective of mechanism of injury or other factors.

McDonald et al., 2014 JAMA Neurology

Acute (0-7 days) predictors of 6-12 month outcome
Acute predictors of 6-12 month outcome

- Prospective observational study of US military service members with blast concussive TBI (n = 38) and controls (n = 34). Patients were evaluated 0-7 days following injury and again 6-12 months later.
- Objective: determine if acute clinical measures predict 6-12 month outcome.
- Acute assessments revealed heightened post-concussive, post-traumatic stress, depressive symptoms, and worse cognitive performance in those with blast TBI.
- At 6-12 months, 63% of those with blast TBI had moderate overall disability, compared with 20% of controls.
- Acute (0-7d) predictors of later global adverse outcome include TBI diagnosis, older age, and more severe post-traumatic stress symptoms.

Mac Donald* Adam* et al, Brain 2015

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Initial Clinical Assessments

1. Concussion Symptoms
2. Balance-Postural Stability
3. Post-TRA Symptoms
4. Depression Symptoms

Global Outcome 6-12 months post-injury

Mac Donald et al, Brain 2015
Acute predictors of 6-12 month outcome

Neurobehavioral outcome in blast TBI vs controls

Neuropsych test abnormalities in blast TBI vs controls

Mac Donald et al, Brain 2015

Acute predictors of 6-12 month outcome

Depression and PTSD severity in blast TBI vs controls

Mac Donald et al, Brain 2015
Acute predictors of 6-12 month outcome

- At 6-12 months, 63% of those with blast TBI had moderate overall disability, compared with 20% of controls.
- Acute (0-7d) predictors of later global adverse outcome include TBI diagnosis, older age, and more severe post-traumatic stress symptoms.

Mac Donald* Adam* et al, Brain 2015

6-12 month outcomes across multiple cohorts

...the 2010 Directive Type Memorandum

Mac Donald et al, J Neurotrauma 2016
6-12 month outcomes after blast-related TBI

Much higher rates of disability than observed in concussive TBI in other circumstances

Mac Donald et al, J Neurotrauma 2016

6-12 month outcomes after blast-related TBI

Mostly normal neuropsychological test performance, with a subset of patients performing poorly

Mac Donald et al, J Neurotrauma 2016
6-12 month outcomes after blast-related TBI

Substantial burden of depression and post-traumatic stress disorder, with some reduction in severity in later cohorts after Directive-Type Memorandum (DTM) 09-033 issued in 2010

Mac Donald et al, J Neurotrauma 2016

Global disability was more common in those with TBI, those evacuated from theater, and those with more severe depression and PTSD.

Mac Donald et al, J Neurotrauma 2016
6-12 month outcomes after blast-related TBI

- Global disability was more common in those with TBI, those evacuated from theater, and those with more severe depression and PTSD.
- Disability was not significantly related to neuropsychological performance, age, education, self-reported sleep deprivation, injury mechanism, or date of enrollment.
- Imaging findings did not predict disability or specific outcomes.

Mac Donald et al, J Neurotrauma 2016

Acute (0-7 days) and early (1yr) predictors of 5 year outcome
5 year outcome after blast TBI

**PTSD and depression at 5yrs**

- **Anxiety, sleep, and alcohol use at 5yrs**

Acute (0-7d) predictors of 5 year outcome

- Prospective evaluation of blast TBI (n=45) and combat deployed controls (n=45)
- Objective: characterize 5 yr outcome and identify clinical measures collected acutely in theater associated with 5 yr outcome
- Blast TBI patients fared poorly at 5 yrs compared to controls on global disability, neurobehavioral impairment, and psychiatric symptoms, but not cognitive impairment
- **PCL-M scores increased** 54% between 0-7d and 5yr post-injury in blast patients, compared to 30% in controls
- **PCL-M was also the most informative measure in predicting long-term functional outcome**
5 year outcomes

Acute (0-7d) predictors of 5 year outcome

McDonald et al, JAMA Network 2019
Acute (0-7d) predictors of 5 year outcome

- Blast TBI patients fared poorly at 5 yrs compared to controls on global disability, neurobehavioral impairment, and psychiatric symptoms, but not cognitive impairment.
- Self-reported PTSD symptom severity (PCL-M) at 0–7 days is almost as good as a multivariate model for predicting 5 year outcomes.
- Recall that these were all service members who had prospectively diagnosed TBI and nearly all returned to duty within 28 days.
- Screening based on early PTSD symptoms would be a logical approach for future interventions designed to improve outcomes after blast-related TBI.

McDonald et al, JAMA Network 2019

Overall Summary

- Blast-related concussive TBI in US Military personnel is associated with advanced MRI abnormalities, adverse clinical outcomes.
- There is evolution – not resolution – of brain injury pathology and clinical symptoms over time.
- Both acute (0-7d) and early (1 yr) clinical measures can inform long-term clinical outcome, up to 5 years, with implications for early intervention strategies especially focused on mood dysregulation (depression, post-traumatic stress).
- Wartime TBI itself, independent of mechanism of injury, appears to drive clinical outcome. Further work is required to distinguish blast and impact TBI.
- New methods will be required to directly assess the precise relationships between structural brain injury and specific neurological sequelae.
- Ongoing work in the laboratory involves development of molecular contrast MRI methods that promise to reveal blast-related TBI pathophysiological processes with greater sensitivity and specificity.
Treatments for Depression and PTSD in the context of TBI

- Evidence-based psychotherapy: most likely similarly effective in TBI vs. non-TBI populations.
  - Challenges have been availability of appropriate therapists and commitment of patients to full courses of therapy.

- Pharmacotherapy: relatively little evidence-based practice
  - RCTs of sertraline have not shown efficacy in the context of TBI
  - Methylphenidate may be effective in reducing PTSD symptoms in the context of TBI

- Transcranial Magnetic Stimulation:
  - Traditionally TBI was considered a contraindication due to seizure risk.
  - Recent appreciation that seizure risk is not significantly different from general population after concussion/“mild” TBI (>85% of military TBI, and 100% of our studies)
Transcranial Magnetic Stimulation

Siddiqi, Brody, et al. unpublished

Resting State fMRI Network Mapping: Individual Subject

Shan Siddiqi, MD. Beth Israel Deaconess, Harvard University.

Resting State fMRI-based Individualized Target Selection

Hot spots:
High likelihood of membership in Dorsal Attention Network and Low likelihood of membership in Default Mode Network (including subgenual anterior cingulate)

Dorsal Attention and Default Mode Networks are anti-correlated.
By stimulating Dorsal Attention Network, we hope to reduce the activity in Default Mode Network.

Siddiqi et al., Journal of Neuropsychiatry and Clinical Neurosciences 2019

Alternative Stimulation Targeting

Siddiqi et al., Journal of Neuropsychiatry and Clinical Neurosciences 2019 and unpublished data
Test-retest reliability of connectivity & targeting

Siddiqi et al. Journal of Neurotrauma 2019

TMS effects on clinical status

Siddiqi et al., Journal of Neuropsychiatry and Clinical Neurosciences 2019
TMS effects on brain network connectivity

Siddiqi et al., Journal of Neuropsychiatry and Clinical Neurosciences 2019

Enrollment
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)
  - Lost to follow-up (n = 0)
  - Did not complete full course of treatment within the 5-week timeframe (n = 1)
- Allocated to sham (n = 6)
  - Received sham sessions (n = 5)
  - Withdrew prior to first session (n = 1)
  - Lost to follow-up (n = 0)
  - Did not complete full course of treatment within the 5-week timeframe (n = 1)

Allocation

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. Journal of Neurotrauma 2019
<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Sham</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>43 ± 13</td>
<td>50 ± 18</td>
</tr>
<tr>
<td>Sex</td>
<td>7 M, 2 F</td>
<td>4 M, 2 F</td>
</tr>
<tr>
<td>Duration since TBI (yrs)</td>
<td>8.4 ± 8.2</td>
<td>8.1 ± 11.3</td>
</tr>
<tr>
<td>TBI mechanism</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>Duration of depression (yrs)</td>
<td>4.8 ± 4.2</td>
<td>7.7 ± 9.9</td>
</tr>
<tr>
<td>Treatment trials</td>
<td>4.8 ± 3.0</td>
<td>5.4 ± 3.4</td>
</tr>
<tr>
<td>(antidepressants, augmentation,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or CBT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid PTSD</td>
<td>4/9</td>
<td>3/6</td>
</tr>
</tbody>
</table>

Siddiqi et al. Journal of Neurotrauma 2019

Primary Outcome: Depression

Siddiqi et al. Journal of Neurotrauma 2019
Individualized rTMS for depression in TBI – Results

Change in MADRS subscores with treatment

Subscale

Siddiqi et al. Journal of Neurotrauma 2019

Secondary Outcomes

Siddiqi et al. Journal of Neurotrauma 2019
What about TMS treatment for military service members?

- A major priority for the CNRM
2 SITE TMS: A randomized, sham-controlled, blinded study of bilateral prefrontal individual connectome-targeted repetitive transcranial magnetic stimulation (ICT-rTMS) to treat the symptoms of depression associated with concussive TBI

- **PI:** David Brody, MD, PhD
- **Status:** Study Closeout
- **Total Enrolled:** 10
- **Start:** June 28, 2019
- **Projected End:** October 27, 2020
- **Study activities placed on hold due to COVID-19 restrictions as of March 2020. Study close out underway.**
- **Key Study Team Members:** Charline Simon, Dr. Lindsay Oberman, Diana Nora and Alexander Koosman
- **Participating Sites:**
  - Walter Reed National Military Medical Center
  - Fort Belvoir Community Hospital

ADEPT: “Adaptive Trial for the treatment of Depression associated with Concussion using repetitive Transcranial magnetic stimulation protocols”

- **PI:** David Brody, MD, PhD
- **Status:** Approved at Core IRB, Site approvals and agreements in process
- **Projected Start:** estimate Spring 2021 enrollment start
- **Projected End:** Estimate December 2025
- **Key Study Team Members:** Dr. Xochitl Ceniceros, Charline Simon, Dr. Lindsay Oberman, Diana Nora, Alex Koosman, Dr. Shan Siddiqi, Tad Haight, Dr. Dzung Pham, Yi-yu Chou, and Dr. Holly Lisanby,
- **Participating Sites:**
  - Walter Reed National Military Medical Center
  - Fort Belvoir Community Hospital
  - Brooke Army Medical Center, Joint Base San Antonio
  - Naval Medical Center San Diego + Camp Pendleton (joint site)
  - Ft Gordon
  - Ft. Bliss
### Brody lab and Collaborative Research Group

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COL Raymond Fang, MD (2009 – 2010)  
COL Stephen Flaherty, MD (2007-2009)  
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Yi-yu Chou  
Holly Lisanby, MD

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Thank you!