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

2021 Amygdala Conference

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1

• DISCLOSURES

- Research currently funded by NIH, Department of Defense.
- Previous research funded also by DARPA, National Football League, Cure Alzheimer's Fund, Health South, Thrasher Foundation, BrightFocus, F-Prime & Burroughs Wellcome.
- Consulting: Pfizer, Health Advances, Signum Nutralogix, Kypha, iPerian, Sage Therapeutics, St Louis Public Defenders Office, Avid Radiopharmaceuticals (Eli Lilly), Intellectual Ventures.
- Equity: Inner Cosmos LLC
- Royalties: Sales of *Concussion Care Manual* (Oxford University Press)
- Honoraria: Mary Ann Liebert, Inc. Publisher of ***Journal of Neurotrauma*** for services as Editor-in-Chief.
- Conflicts of Interest: None

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2

2

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

3

Brody lab and Collaborative Research Group

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LTC John Oh, MD (2010-2011)
COL Raymond Fang, MD (2009 – 2010)
COL Stephen Flaherty, MD (2007-2009)
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4

Research studies of US Military Personnel with blast-related and non-blast-related traumatic brain injury

5

Photograph from LRMC public website, 2011 Landstuhl Regional Medical Center (LRMC)

6

Geographical Orientation

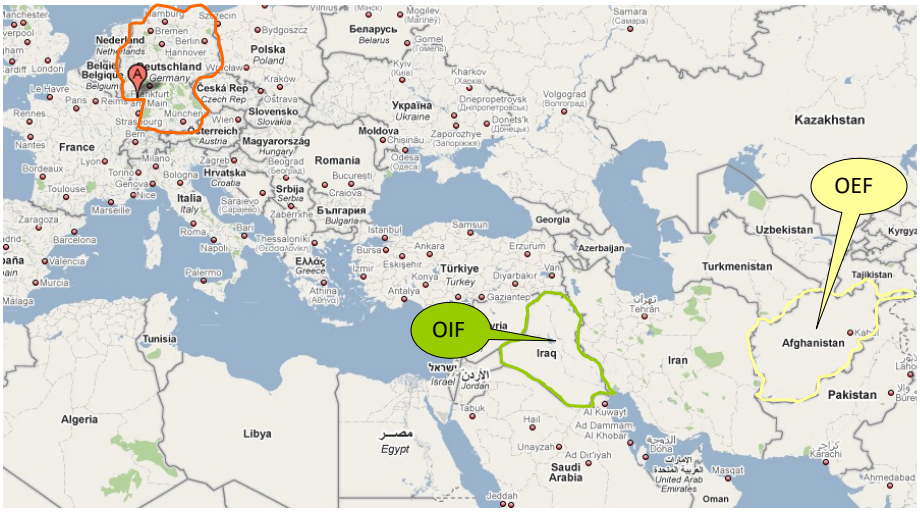


Image from C. Mac Donald, with permission

7

Brody in Kandahar, Jan, 2011

Photograph by C. Giza with permission

8

9

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

10

Clinical outcomes in concussive blast-related vs non-blast TBI

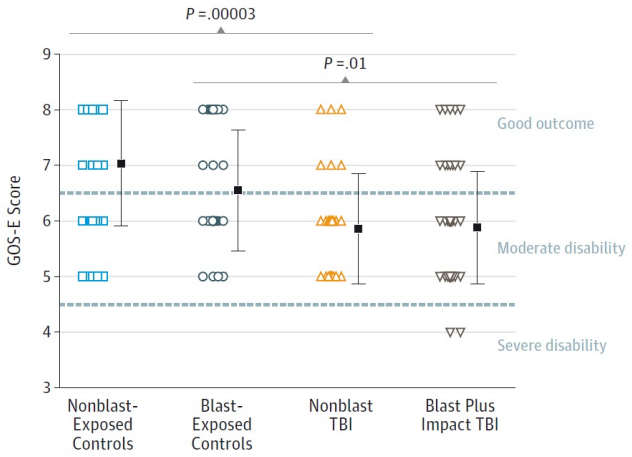
- Prospective evaluation of patients with
  - blast + impact TBI (n=53),
  - non-blast related TBI (n=29),
  - blast-exposed controls evacuated for other reasons (n=27),
  - non-blast exposed controls (n=69)
- Objective: determine similarities and differences in clinical outcome between blast and non-blast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

McDonald et al., 2014 JAMA Neurology

11

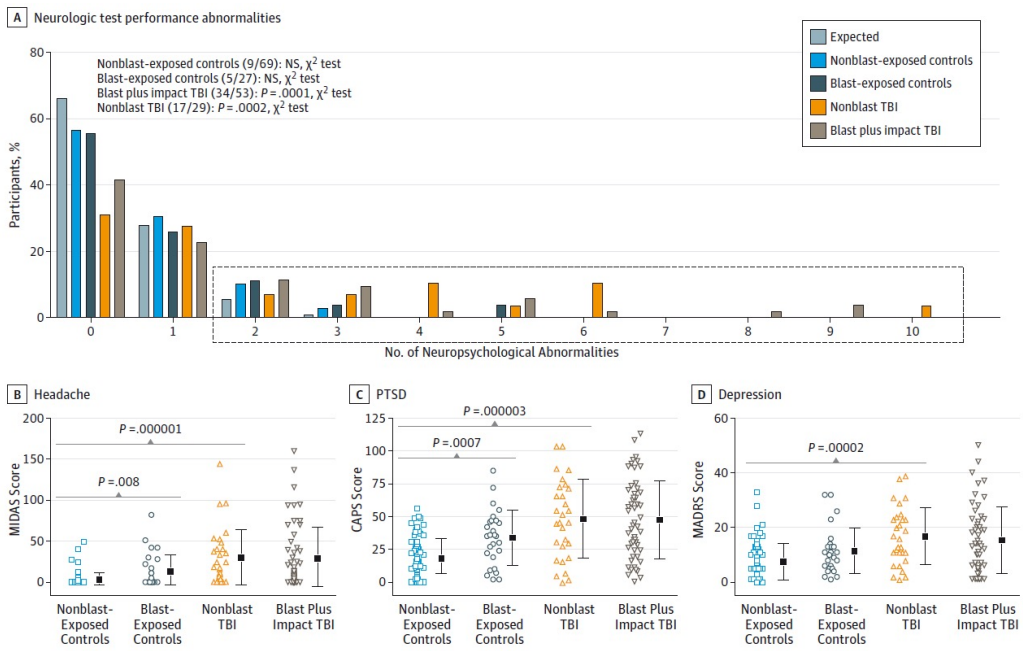
Clinical Outcomes in concussive blast vs nonblast TBI

6-12 month outcome



Mac Donald et al., 2014 JAMA Neurology

12



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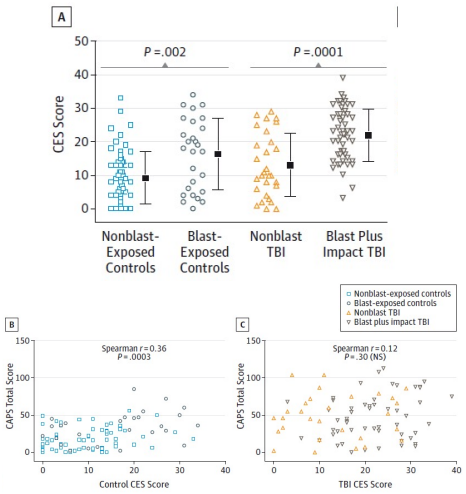
13

Clinical outcomes in concussive blast vs nonblast TBI

Combat exposure intensity and PTSD



Multivariate correlates of clinical outcome

Variable	Estimate (95% CI)	*P* Value
Model 1[a,b]		
Intercept	−0.9477 (−1.5376 to −0.3576)	.0016
MADRS	0.0689 (0.0199 to 0.1179)	.0059
No. of neuropsychological abnormalities	0.4381 (0.1173 to 0.7589)	.0074
MIDAS	0.02349 (0.00002 to 0.04696)	.0498
Model 2[c]		
Intercept	−0.7573 (−1.3837 to −0.1309)	.0178
MADRS	0.0663 (0.0162 to 0.1163)	.0094
No. of neuropsychological abnormalities	0.4077 (0.0755 to 0.7399)	.0161
MIDAS	0.0182 (−0.0055 to 0.0418)	.1323
TBI vs control groups	−0.3546 (−0.7273 to 0.0182)	.0623

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

[a] The overall Akaike information criterion was 202.5, and the likelihood ratio by χ^2 test was 44.04.

[b] Model 1 includes the GOS-E, MADRS, number of neuropsychological abnormalities, and MIDAS.

[c] Model 2 includes the GOS-E, MADRS, number of neuropsychological abnormalities, MIDAS, and TBI vs control groups.

McDonald et al., 2014 JAMA Neurology

14

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

15

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

16

Acute predictors of 6-12 month outcome

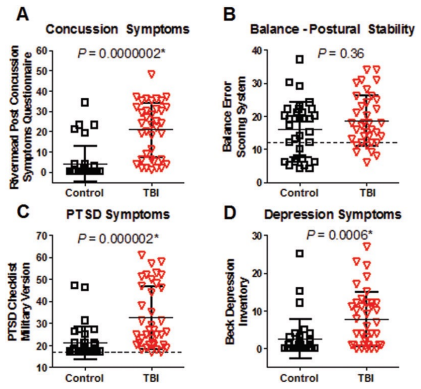
- Prospective observational study of US military service members with blast concussive TBI (n = 38) and controls (n = 34). Patients were evaluated 0-7 days following injury and again 6-12 months later
- Objective: determine if acute clinical measures predict 6-12 month outcome
- Acute assessments revealed 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

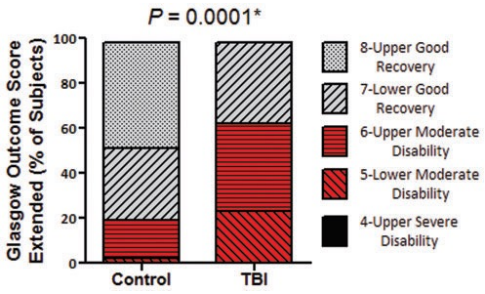
17

Acute predictors of 6-12 month outcome

Initial Clinical Assessments



Global Outcome 6-12 months post-injury

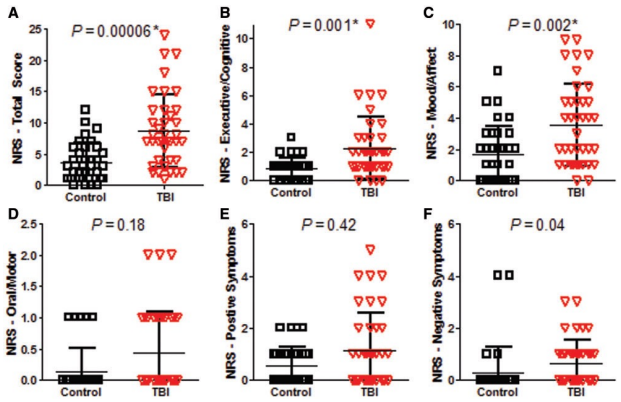


Mac Donald et al, Brain 2015

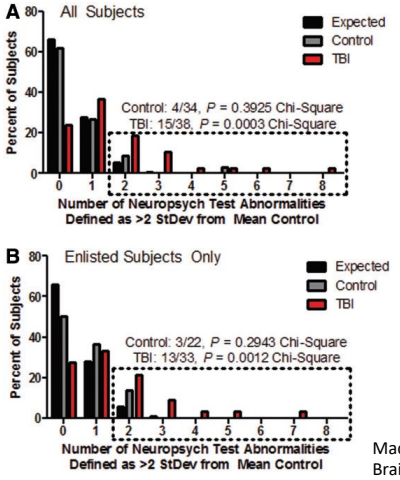
18

Acute predictors of 6-12 month outcome

Neurobehavioral outcome in blast TBI vs controls



Neuropsych test abnormalities in blast TBI vs controls

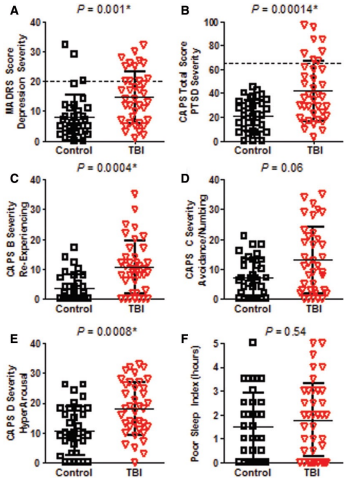


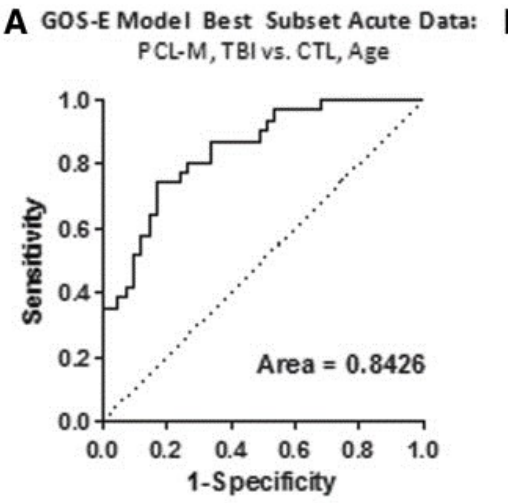
Mac Donald et al, Brain 2015

19

Acute predictors of 6-12 month outcome

Depression and PTSD severity in blast TBI vs controls





Mac Donald et al, Brain 2015

20

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

21

DEPUTY SECRETARY OF DEFENSE
1010 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-1010

June 21, 2010
Incorporating Change 1, November 19, 2010

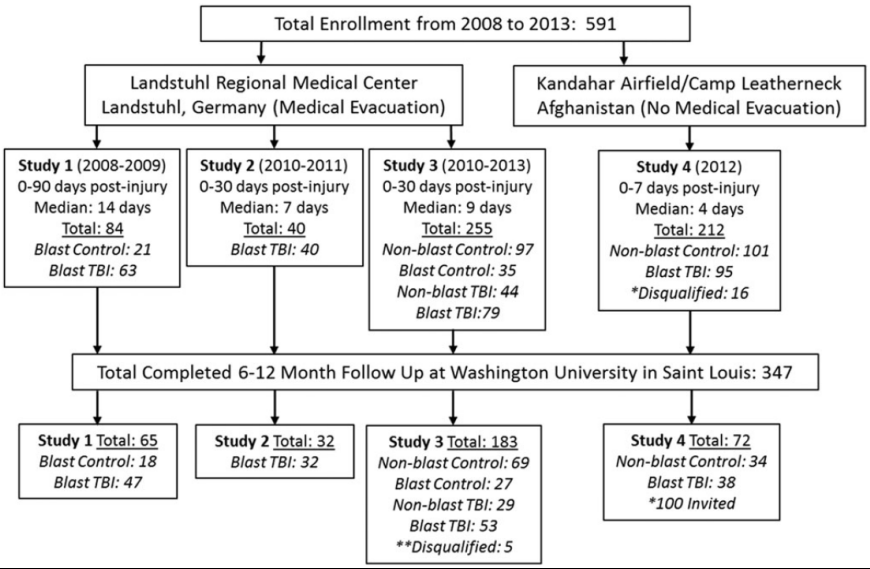
SUBJECT: **Directive-Type Memorandum (DTM) 09-033, "Policy Guidance for Management of Concussion/Mild Traumatic Brain Injury in the Deployed Setting"**

22

6-12 month outcomes across multiple cohorts
…the 2010 Directive Type Memorandum

23

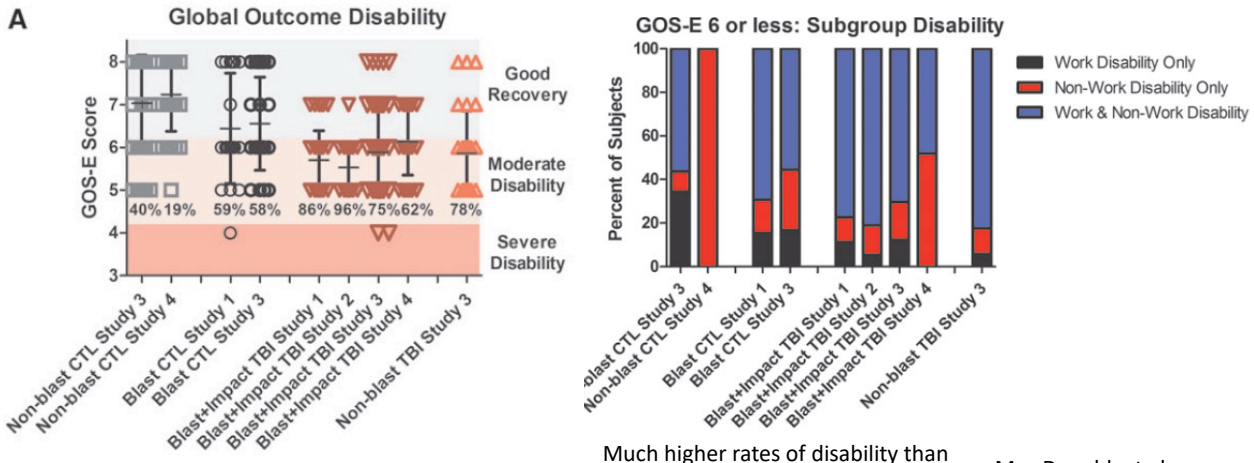
6-12 month outcomes across multiple cohorts



Mac Donald et al,
J Neurotrauma 2016

24

6-12 month outcomes after blast-related TBI

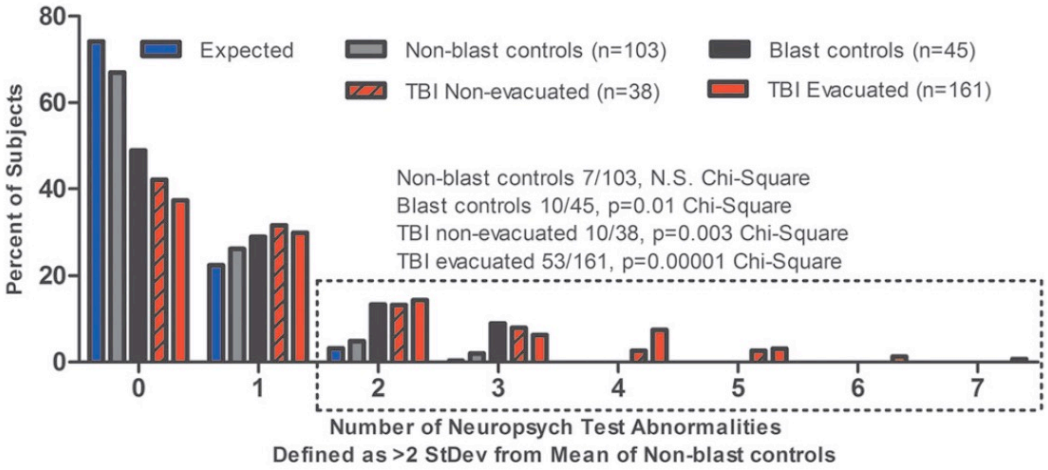


Much higher rates of disability than observed in concussive TBI in other circumstances

Mac Donald et al, J Neurotrauma 2016

25

6-12 month outcomes after blast-related TBI

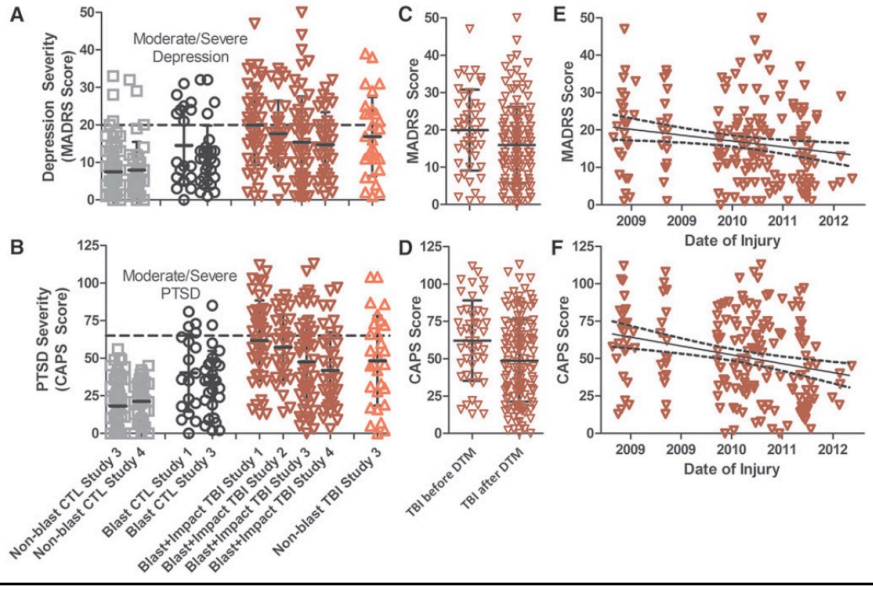


Mostly normal neuropsychological test performance, with a subset of patients performing poorly

Mac Donald et al, J Neurotrauma 2016

26

6-12 month outcomes after blast-related TBI



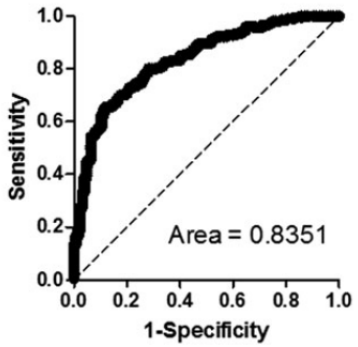
Substantial burden of depression and post-traumatic stress disorder, with some reduction in severity in later cohorts after Directive-Type Memorandum (DTM) 09-033 issued in 2010

Mac Donald et al, J Neurotrauma 2016

27

6-12 month outcomes after blast-related TBI

GOS-E Model Best Subset:
TBI vs. Control, Enrollment Site, MADRS, CAPS



Best Fit Model - Dichotomized GOSE				
Overall model : AIC 337.01, Likelihood ratio Chi square: 125.66				
Parameter	**Odds Ratio**	**95% Confidence Interval**	**P-value**	**Worse Outcome**
TBI /Control	1.73	(1.30 : 2.29)	0.0001	TBI
Enrollment Site: Medical-Evacuation vs. Non-Medically-Evacuated	1.76	(1.28: 2.43)	0.0005	Medical-Evacuation
MADRS (Depression Symptoms/10pts)	1.92	(1.14 : 3.24)	0.0133	Higher Score
CAPS (PTSD Symptoms/40pts)	2.49	(1.14 : 5.49)	0.0223	Higher Score

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

28

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

29

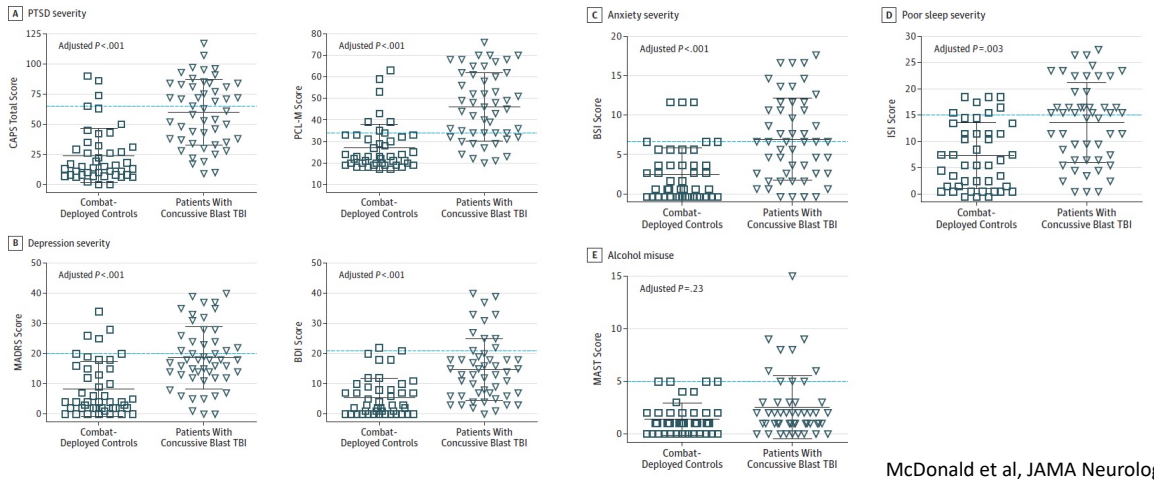
Acute (0-7 days) and early (1yr) predictors of 5 year outcome

30

5 year outcome after blast TBI

PTSD and depression at 5yrs

Anxiety, sleep, and alcohol use at 5yrs



McDonald et al, JAMA Neurology 2017

31

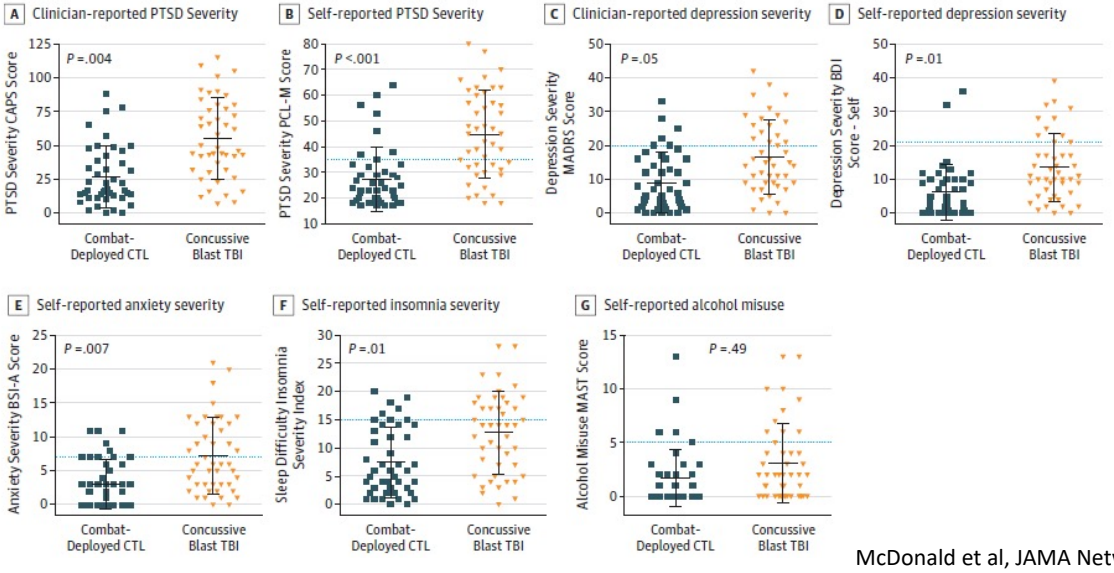
Acute (0-7d) predictors of 5 year outcome

- 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**

McDonald et al, JAMA Network 2019

32

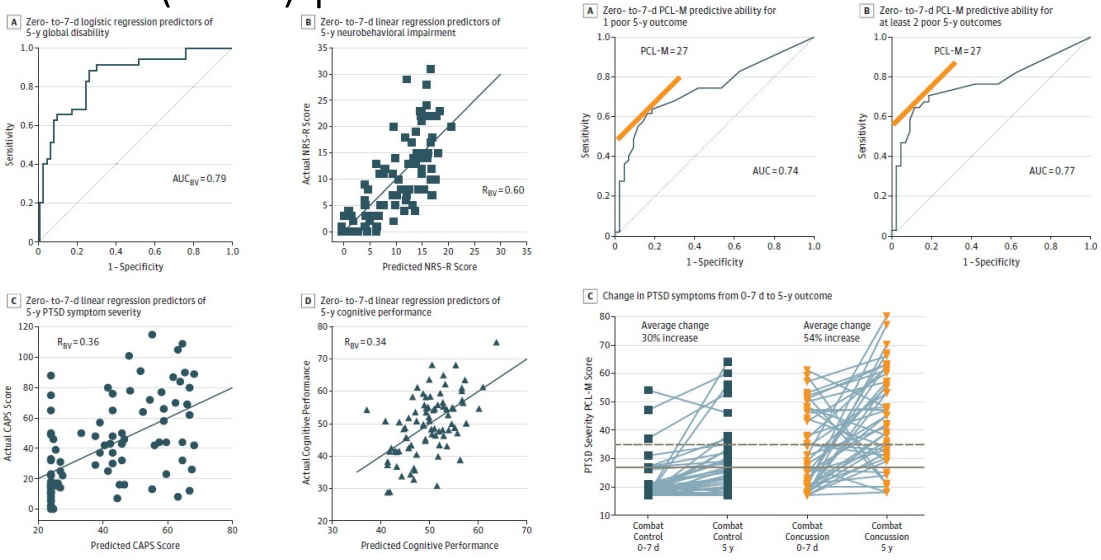
5 year outcomes



McDonald et al, JAMA Network 2019

33

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



McDonald et al, JAMA Network 2019

34

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

35

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

36

ate to severe sleep impairment. Of interest, between the 1- and 5-year study evaluations, 18 combat-deployed controls (41%) and 40 patients with concussive blast TBI (80%) endorsed seeking assistance from a licensed mental health care professional, defined as a psychologist, psychiatrist, therapist, social worker, or other licensed, credentialed mental health care professional. Only 9 combat-deployed controls (20%) and 9 patients with concussive blast TBI (18%) reported that the mental health programs helped.

McDonald et al, JAMA Neurology 2017

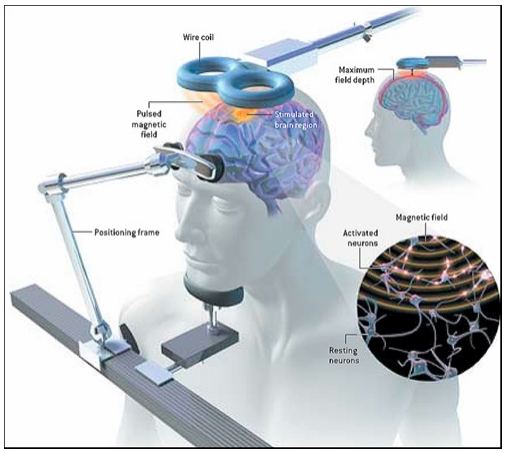
37

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)

38

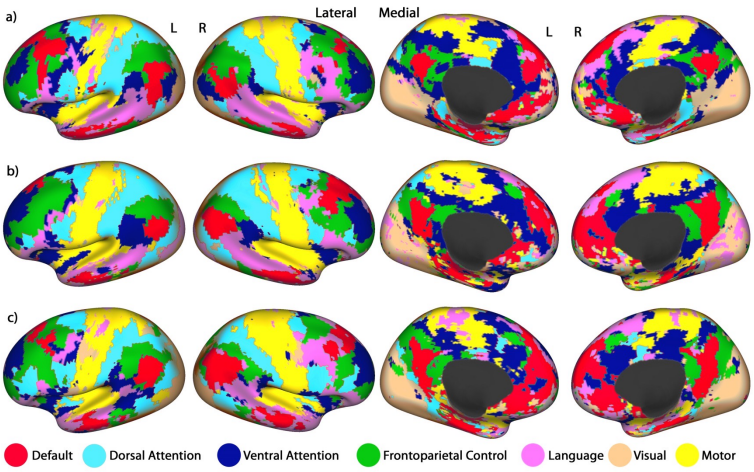
Transcranial Magnetic Stimulation



Siddiqi, Brody, et al. unpublished

39

Resting State fMRI Network Mapping: Individual Subject

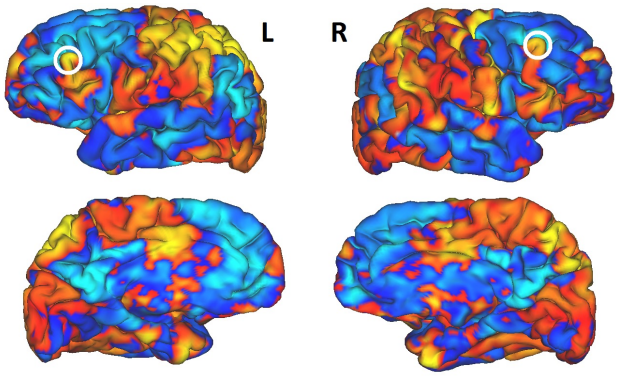


Shan Siddiqi, MD.
Beth Israel Deaconess, Harvard University.

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

40

Resting State fMRI-based Individualized Target Selection



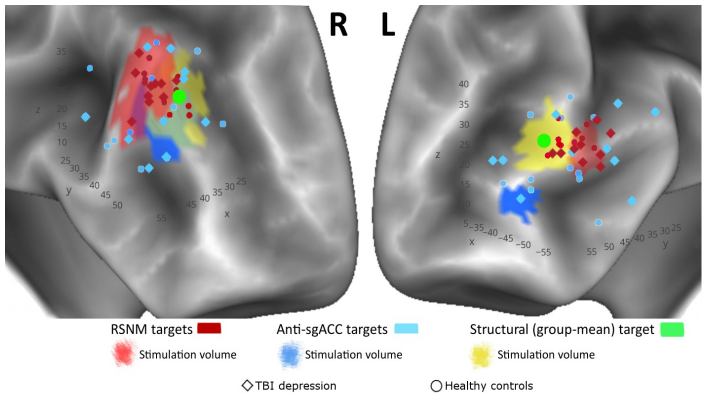
Hot spots:
High likelihood of membership in Dorsal Attention Network
<u>and</u>
Low likelihood of membership in Default Mode Network (including subgenual anterior cingulate)

Dorsal Attention and Default Mode Networks are <u>anti-correlated.</u>
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

41

Alternative Stimulation Targeting

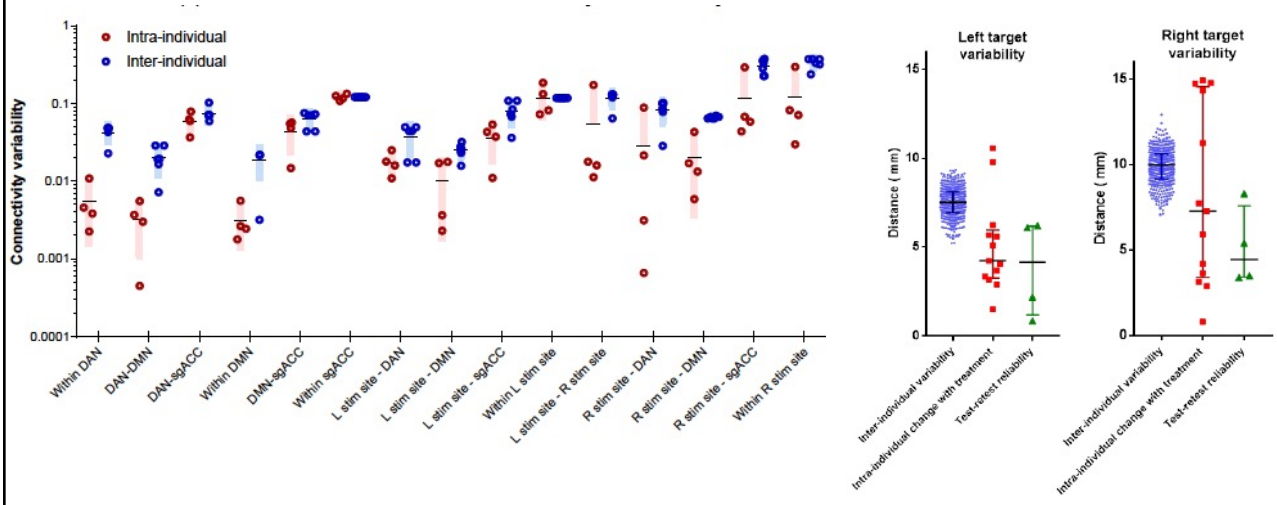


Siddiqi et al., Journal of Neuropsychiatry and Clinical Neurosciences 2019 and unpublished data

42

42

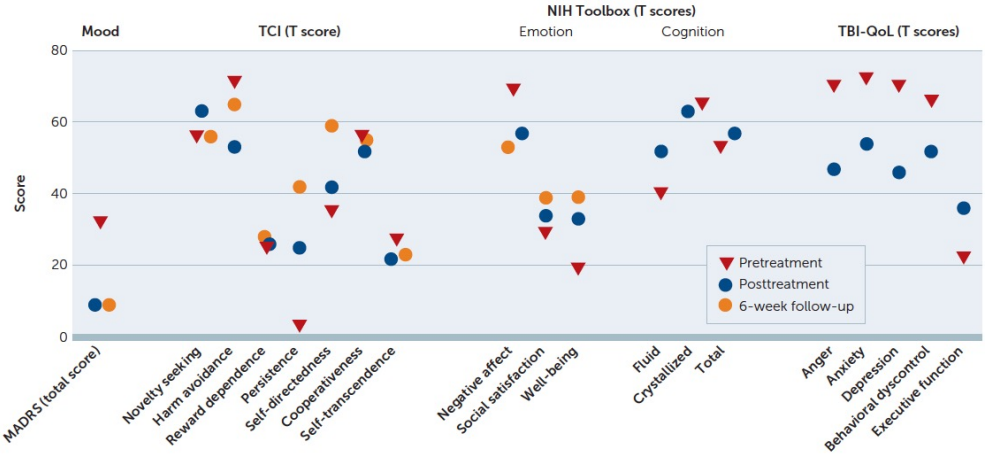
Test-retest reliability of connectivity & targeting



Siddiqi et al. Journal of Neurotrauma 2019

43

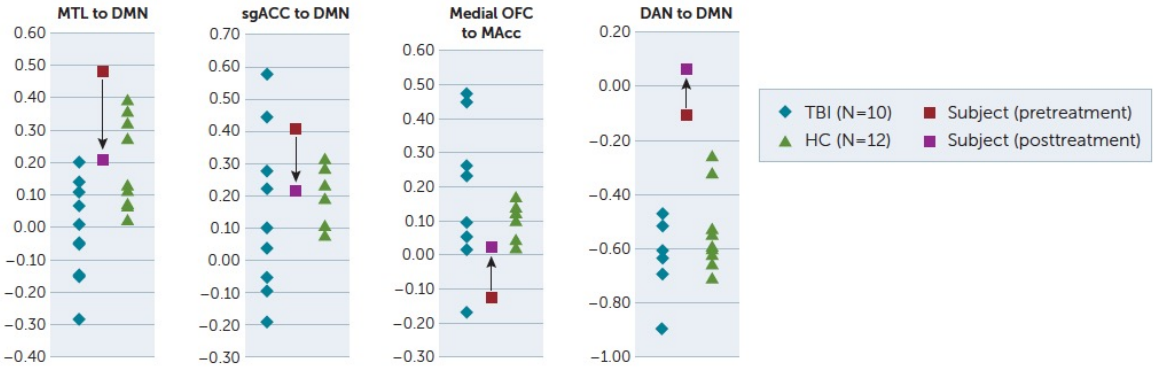
TMS effects on clinical status



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

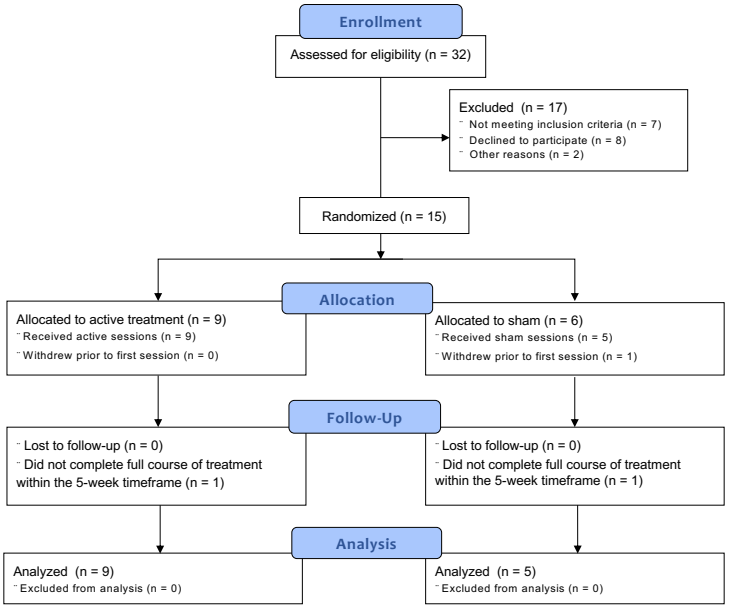
44

TMS effects on brain network connectivity



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

45



Siddiqi et al. Journal of Neurotrauma 2019

46

46

	Active	Sham
Age (yrs)	43 ± 13	50 ± 18
Sex	7 M, 2 F	4 M, 2 F
Duration since TBI (yrs)	8.4 ± 8.2	8.1 ± 11.3
TBI mechanism	4/9 MVC 2/9 military/fire 1/9 sports 3/9 other	3/6 MVC 3/6 sports
Duration of depression (yrs)	4.8 ± 4.2	7.7 ± 9.9
Treatment trials (antidepressants, augmentation, or CBT)	4.8 ± 3.0	5.4 ± 3.4
Comorbid PTSD	4/9	3/6

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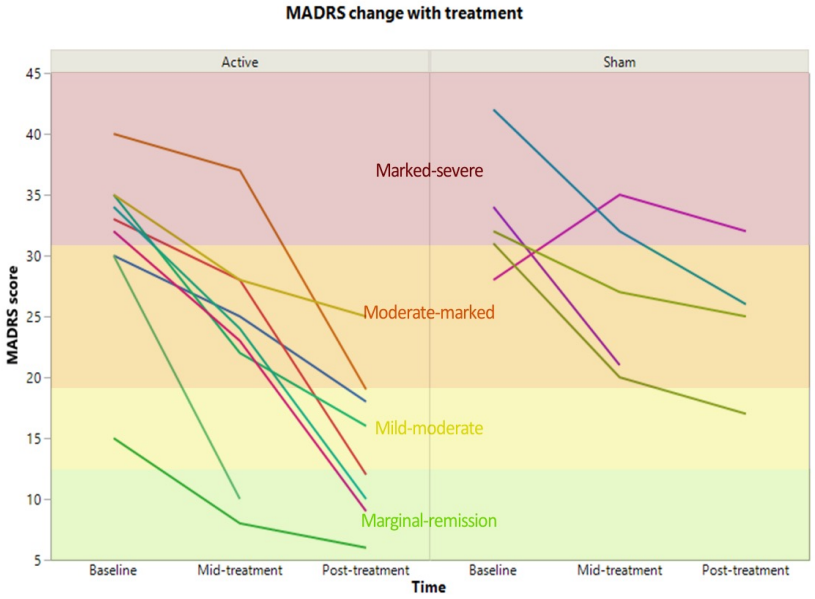
47

47

Primary Outcome: Depression



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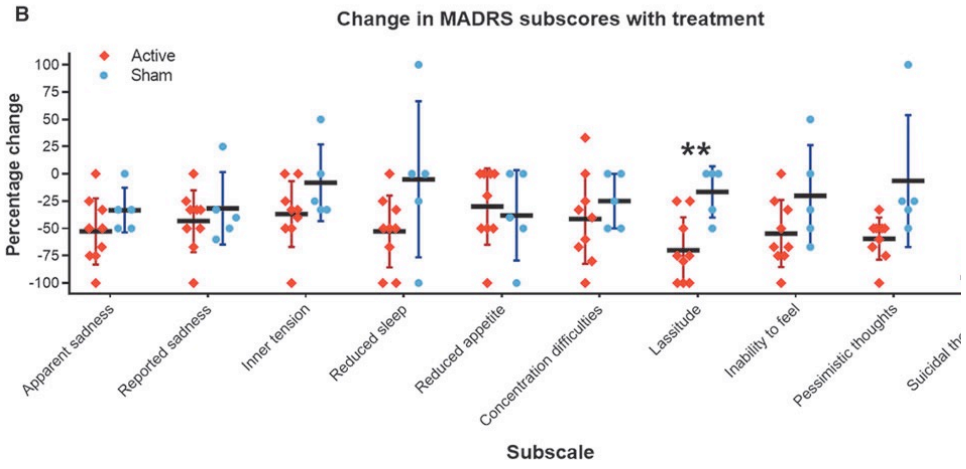
48

48

Individualized rTMS for depression in TBI – Results



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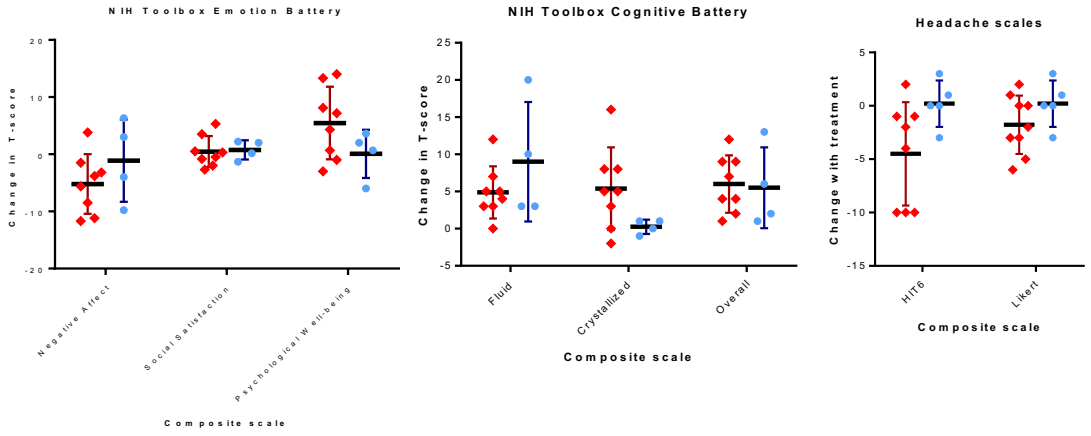
49

Secondary Outcomes

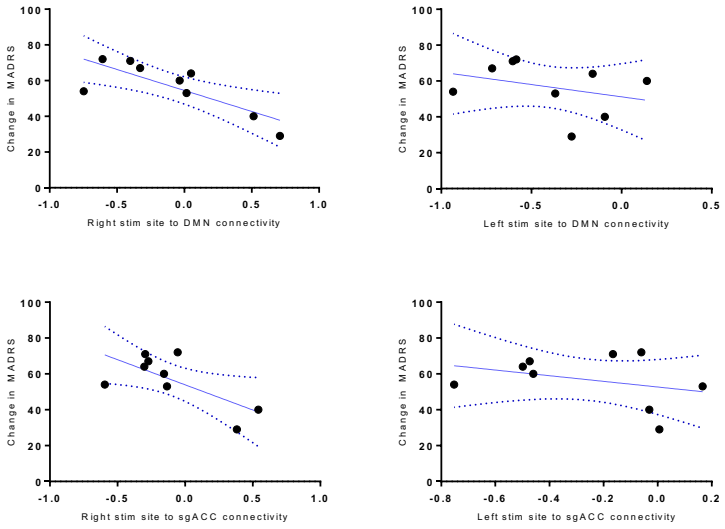


Siddiqi et al. Journal of Neurotrauma 2019

50

50

Resting State fMRI Predictors of Primary Outcome



Siddiqi et al. Journal of Neurotrauma 2019

51

51

What about TMS treatment for military service members?

- A major priority for the CNRM

52

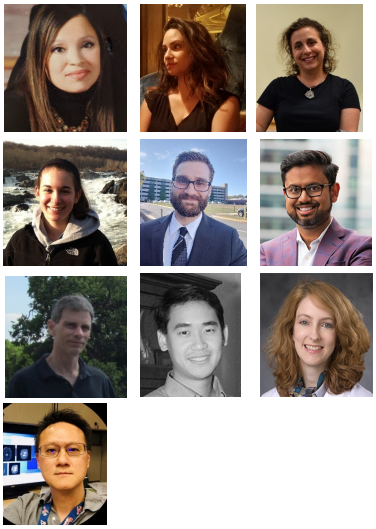
2 SITE TMS: A randomized, sham-controlled, blinded study of bilateral prefrontal individual connectome-targeted repetitive transcranial magnetic stimulation (ICT-rTMS) to treat the symptoms of depression associated with concussive TBI

- **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

53

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



54

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55

Thank you!

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56

56