Repetitive Transcranial Magnetic Stimulation for improvement of Executive Function in Traumatic Brain Injury in Veterans

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Disclosures

Presenter has no interests to disclose

Outline: My Journey from Diagnosis to Treatment of TBI Related Problems

- Detecting the neural signature of mild and moderate brain injury – some specifics before the techniques:
  - Diffusion Tensor Imaging
  - Resting State fMRI: Connectivity
- Repetitive Transcranial Magnetic Stimulation
  - Behavioral, neuroimaging and biomarker results from pilot study

Poll Question #1

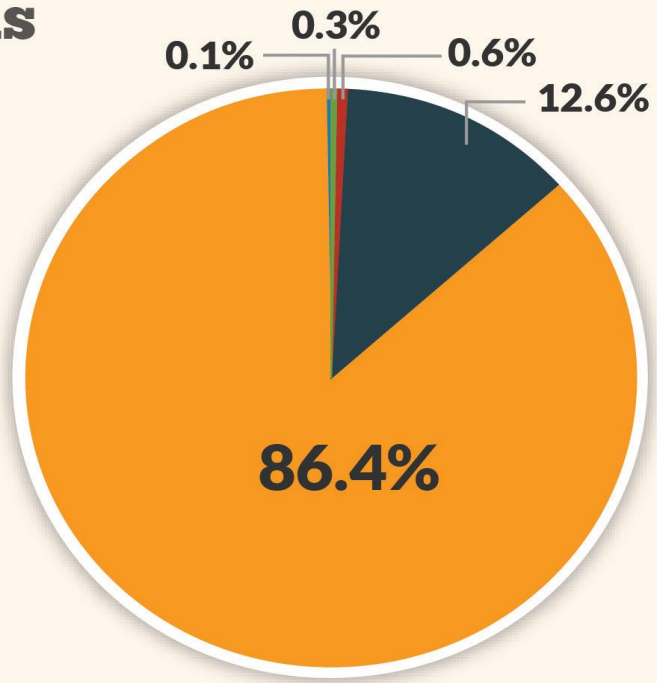
- What is your primary role in VA?
  - ❑ student, trainee, or fellow
  - ❑ clinician
  - ❑ researcher
  - ❑ administrator, manager or policy-maker
  - ❑ other

DVBIC Worldwide Numbers

DoD Numbers for Traumatic Brain Injury
Worldwide – Totals

2018 Q1

Penetrating	14
Severe	24
Moderate	540
Mild	3,716
Not Classifiable	6
Total - All Severities	**4,300**



Source: Defense Medical Surveillance System (DMSS), Theater Medical Data Store (TMDS) provided by the Armed Forces Health Surveillance Center (AFHSB)

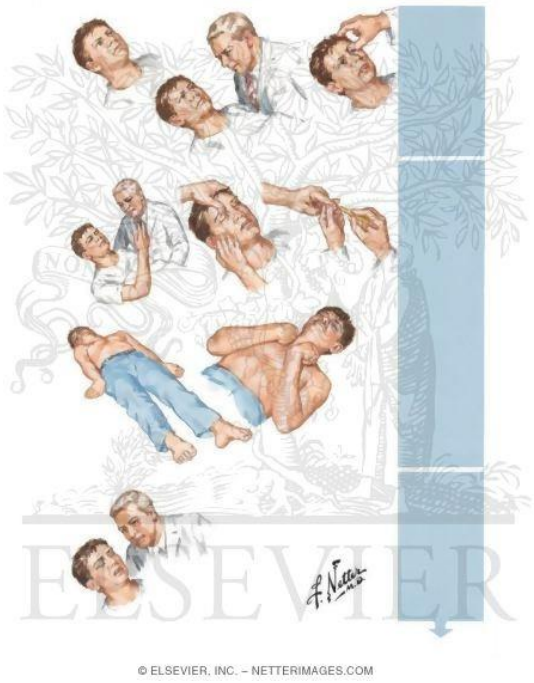
Prepared by the Defense and Veterans Brain Injury Center (DVBIC)

2018 Q1, as of June 21, 2018

*Percentages do not add up to 100% due to rounding

TBI Background - Classification

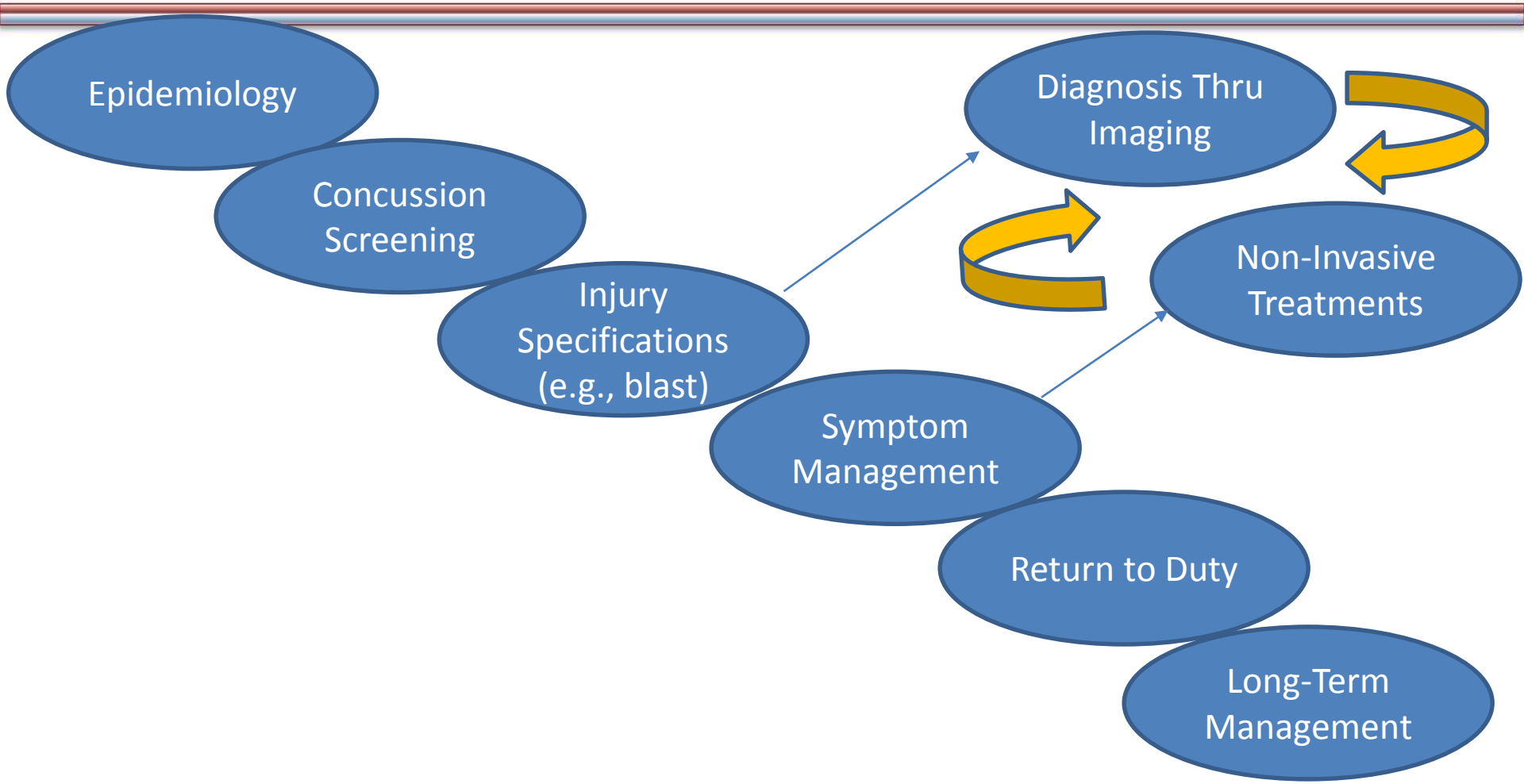
	GCS	PTA	LOC
Mild	13–15	<1 day	0–30 mins
Moderate	9–12	>1 to <7 days	>30 mins to <24 hours
Severe	3–8	>7 days	>24 hours



Poll Question #2

- Which best describes your research experience?
  - ❑ have not done research
  - ❑ have collaborated on research
  - ❑ have conducted research myself
  - ❑ have applied for research funding
  - ❑ have led a funded research grant

Our Daily Vocabulary in TBI Research:

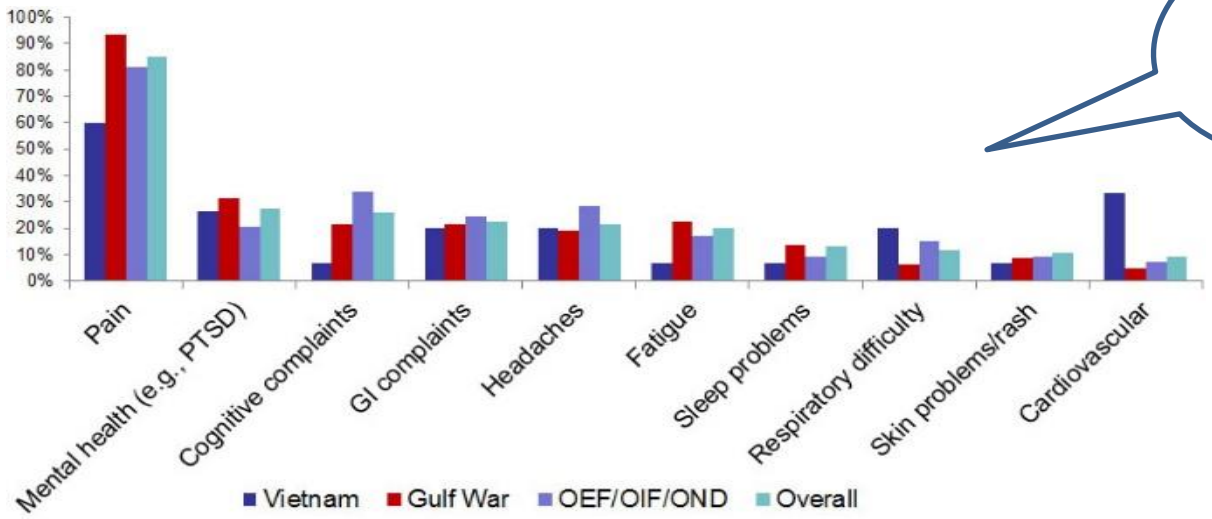


Detecting Mild TBI: The Challenge

- Heterogenous TBI – “you have seen one TBI, you have seen one TBI”
- Time to injury, type of injury (blast or concussion – *see Trotter et al., 2015*)
- Difficult to obtain in-theater documentation of defining symptoms at the time of injury. Need to rely on self report of TBI
- **Research Neuroimaging Goals:** Detection of mild & moderate TBI to compliment the gold standard diagnosis by a neurologist

TBI Detection in Veterans

2014-2015 alone, Veterans Affairs Healthcare System (VAHCS) evaluated 75,552 (outpatient) and 2,677 (inpatient) Veterans nationally for brain injury (ICD9 codes 850.0 & 907.0; source: *Praedico* software from Bitscopic® – OPH/VAPA (Holodniy))



Detecting TBI in this population

Distribution of primary chronic health complaints in War Related Illness and Injury Study Center (WRIISC) patient cohort (September 30th, 2014 – October 1st, 2015). Note: TBI is not one of them.

Outline

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  - Resting State fMRI: Connectivity
- Repetitive Transcranial Magnetic Stimulation
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Veteran Cohort Analysis

NeuroImage: Clinical 16 (2017) 1–16

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

DTI measures identify mild and moderate TBI cases among patients with complex health problems: A receiver operating characteristic analysis of U.S. veterans

Keith L. Main[a,b,c,*], Salil Soman[a,d,e], Franco Pestilli[f], Ansgar Furst[a,d,g], Art Noda[d], Beatriz Hernandez[d], Jennifer Kong[a], Jauhtai Cheng[a], Jennifer K. Fairchild[d], Joy Taylor[d], Jerome Yesavage[a,d], J. Wesson Ashford[a,d], Helena Kraemer[d], Maheen M. Adamson[d,h,i]

Sensitivity & Specificity Methods

Question: What is the sensitivity and specificity of such a measure in this population?

Answer: Use Signal Detection Theory (Receiver Operator Characteristics (ROC version 4.22; Yesavage & Kraemer, 2007)

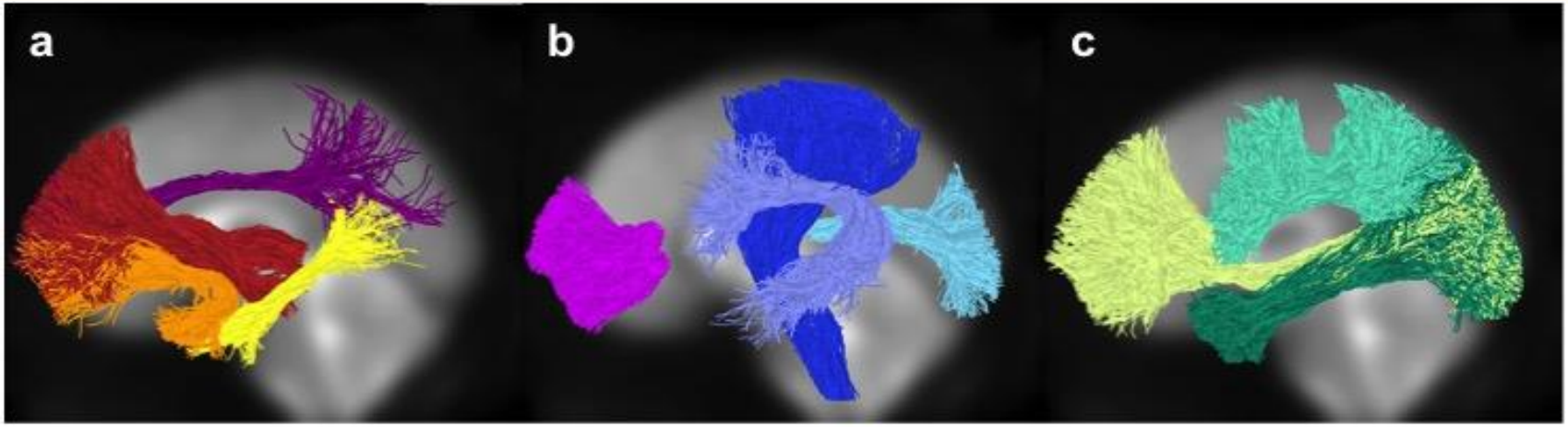
- Essentially, a radiologist/neurologist can investigate the most relevant fiber of interest in MRI scans of Veterans with similar medical histories

General Demographics

- N = 109; Age: M =47.2, SD=11.3; Male: 88%
- TBI: 67%
- Education: 15.0 ± 3.2
- Veterans: Deployed to various conflicts
- All TBIs are mild & moderate determined by a neurologist's exam (non-penetrating)
- No significant differences in neuropsychological measures (Digit Span, CVLTII, TMT-B)

Main … Adamson, 2017

DTI Tractography



- Anterior Thalamic Tract – L/R
- Uncinate Fasciculus – L/R
- Cingulum – L/R
- Cingulum-Hippocampus – L/R
- Forceps Anterior
- Cortico-Spinal Tract – L/R
- Superior Longitudinal Fasciculus-Temporal – L/R
- Forceps Posterior
- Inferior Fronto-Occipital Fasciculus – L/R
- Inferior Longitudinal Fasciculus – L/R
- Superior Longitudinal Fasciculus – L/R

Main … Adamson, 2017

Identifying Fibers – Finding Clues in the Brain

Table 1	Receiver Operator Characteristics (ROC) (*n*=109, df=1)						
Metric	Tract	Cutpoint	Sens.	Spec.	Kappa	χ^2	*p*
FA	LCG	0.433	74.0%	52.8%	0.264	7.60	<.01
MD*	LIF	0.837	68.5%	61.1%	0.278	8.72	<.01
RD	LIF	0.613	74.0%	55.6%	0.289	9.15	<.01
AD	LIF	1.272	72.6%	52.8%	0.249	6.76	<.01

FA = Fractional Anisotropy, MD = Mean Diffusivity, RD = Radial Diffusivity, AD = Axial Diffusivity

Main … Adamson, 2017

LCG = Left cingulum bundle is also implicated in depression

(Isaac … Adamson, 2015)

The Developing Story of Function

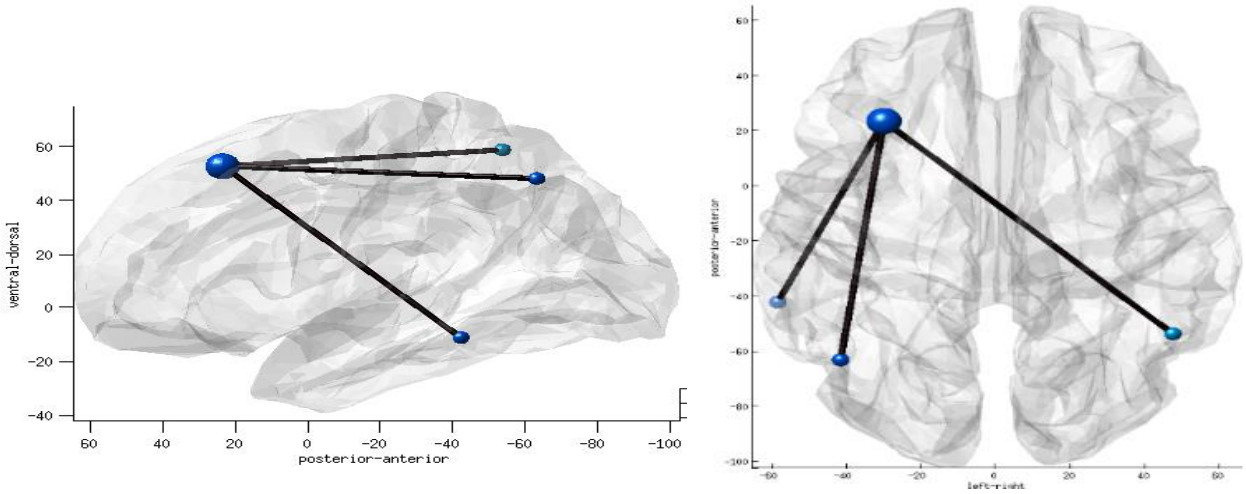
- Recent work indicates that changes in brain connectivity may partly explain the alterations in brain function years after mild to moderate TBI
- A model was constructed here to investigate the networks responsible for the most debilitating problems in chronic stage TBI
  - Executive Dysfunction

Functional Network Correlates of Executive Dysfunction in TBI

- Heterogeneous injury – mild and moderate TBI
- patients from Santa Clara Brain Injury Center
- Persistent symptoms
  - Emotional, memory, executive function, headaches
  - TBI + Chronic Symptom (CS): self-report memory problems

Milazzo … Adamson. In submission

Functional Connectivity (TBI + Self-report Memory Problems)

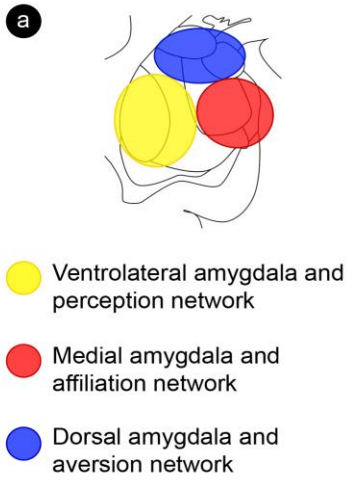


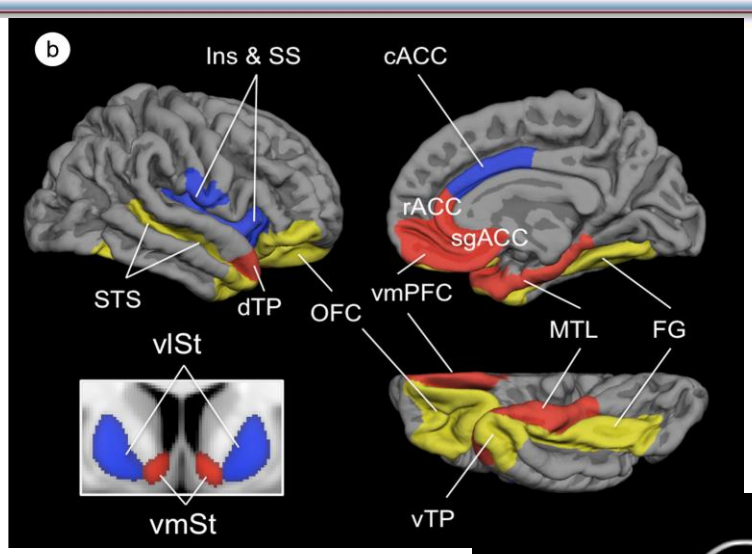
Three regions in the brain (left superior parietal cortex, right superior parietal cortex, and left medial temporal lobe) all show significantly reduced functional connectivity with the **left dorsolateral prefrontal cortex (LDLPFC)** in chronic symptom patients compared to controls.

Left dorsolateral prefrontal cortex is the hub of Central Executive Network, involved in planning, organization and cognitive control.

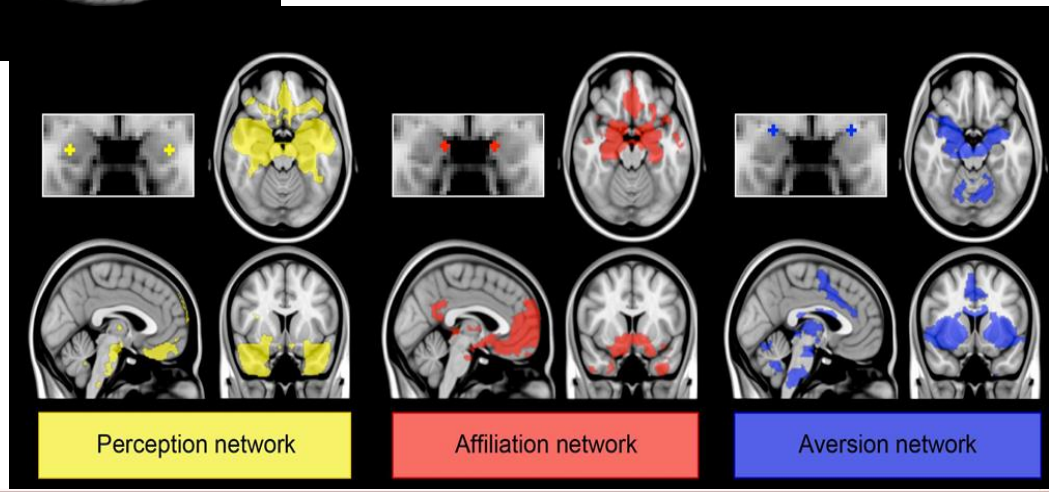
Milazzo … Adamson. In submission

Functional Connectivity in Emotional Networks: Two Independent Samples





Discovery and **replication** samples from two independent datasets containing resting-state fMRI in patients with moderate to severe TBI (n = 30 discovery, 14 replication) and healthy controls (n = 29 discovery, 20 replication).



Analysis done by Kevin Bickart, MD, PhD

Aberrant amygdala connectivity in traumatic brain injury from two independent samples

Crossing Imaging Platforms for TBI

- Structurally: LCG FA holds promise for detecting the TBI signature in patients years after injury

- Functionally:
  - Chronic symptoms was a significant predictor of decreased connectivity in the left executive control network
  - Aberrant amygdala connectivity in traumatic brain injury was validated in two independent samples

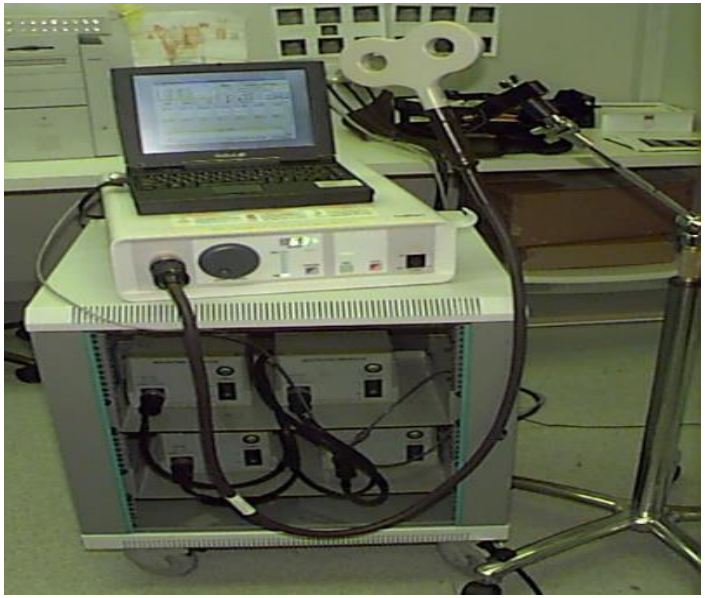
Innovative Treatments

Outline

- Detecting the neural signature of mild and moderate brain injury – What does each technique tell us?
  - Diffusion Tensor Imaging
  - Resting State fMRI: Connectivity
- Repetitive Transcranial Magnetic Stimulation
  - Behavioral, neuroimaging and biomarker results from pilot study

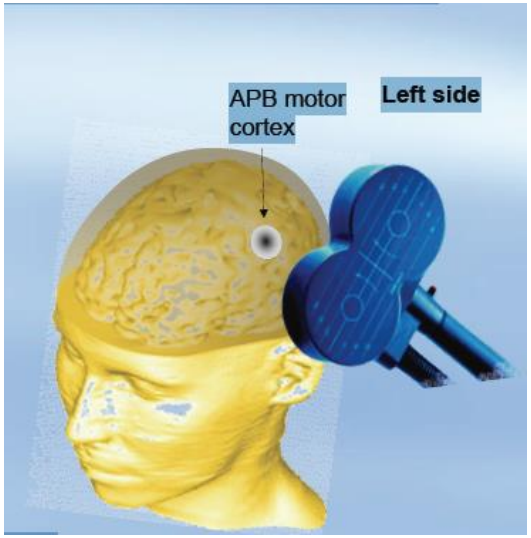
Repetitive Transcranial Magnetic Stimulation (rTMS)

Magnusson & Stevens, 1911



Magstim

Repetitive Transcranial Magnetic Stimulation[1] (rTMS)



Stimulating the Left Dorso Lateral Prefrontal Cortex (DLPFC)

- Electric energy within insulated coil induces MRI-strength magnetic fields
- Magnetic fields pass unimpeded through the cranium for 2-3 cm
- In turn inducing an electric current in the brain
- This stimulates the firing of nerve cells and the release of neurotransmitters as 5HT, NE, and DA (BDNF related mechanisms)

[1] Richelson, E. Mechanisms of Action of Repetitive Transcranial Magnetic Stimulation (rTMS) and Vagus Nerve Stimulation (VNS). *Psychiatric Annals*, 2007; Vol 37-No. 3, 181-187.

Repetitive TMS for Several Conditions

- Improvements reported after rTMS treatments for
  - Major Depressive Disorder(MDD; Connolly et al, 2012; George et al., 2010): FDA approved protocol
  - Various Stimulus Sites & Parameters:
    - PTSD (Kozel et al, 2018; Watts et al., 2012)
    - Pain (Leung et al,, 2018; Galhardoni et al., 2015)
    - Alzheimer's Disease (Rutherford e al., 2015)
    - Severe TBI (Pape et al., 2009)
    - Cognition (Bonnie et al., 2013)

RTMS for TBI

- Case study: rTMS leads to improved cognitive functioning in patients with TBI (Bonnie et al, 2013)
- A review (Herrold et al., 2014) of rTMS studies across various mental illnesses strongly suggests its use in TBI to promote recovery and minimize disabilities
- Siddiqi et al (2018): the use of rTMS targeted with individualized resting-state network mapping (RSNM) in subjects with treatment-resistant depression (TRMD) associated with TBI. This pilot study showed that RSNM-targeted rTMS is feasible in TBI patients with depression

Determining the Efficacy of rTMS in the Treatment of TRMD in Veterans:

- Nine VA centers – Corporate Studies Program
- In this randomized clinical trial of 164 US veterans with depression, the overall remission rate was 39%, with no significant difference between the active and sham groups
- **Patient comorbid posttraumatic stress disorder showed the least improvement with comorbid posttraumatic disorder**

Yesavage et al., 2018, JAMA Psychiatry

Poll Question #3

- #3: Challenges to intervention research conducted in the VA include (select all that apply):
  - ❑ Lack of funding
  - ❑ Need more first and second generation research first
  - ❑ Infeasible—potentially effective interventions are too big
  - ❑ Few well-researched interventions to test
  - ❑ Existing interventions don't effect meaningful outcomes

Study Design: Double-Blind Randomized Clinical Trial

Outcome Measure: Executive Function

Population: 20 – 65 years Veterans with mild & moderate TBI

Start Date – End Date:
10/01/2014 - 9/30/2018

Funding Agency: VA Rehab

Current Enrollment: 32 Veterans with mild & moderate TBI

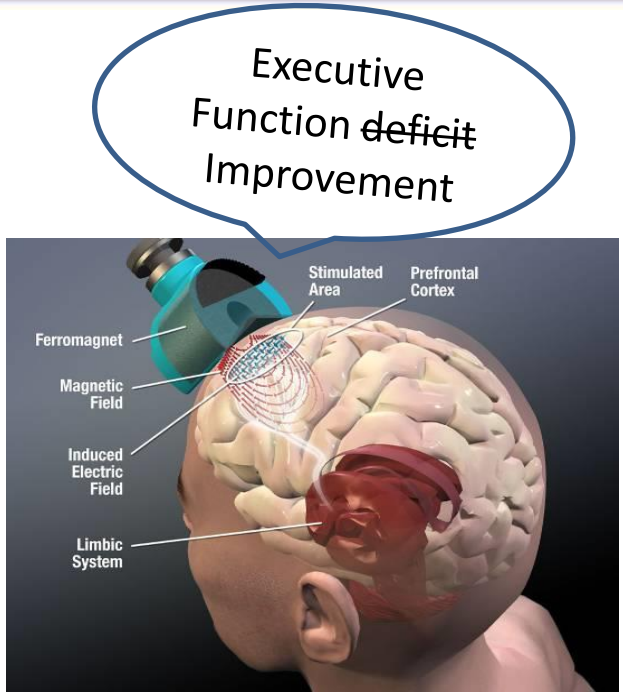
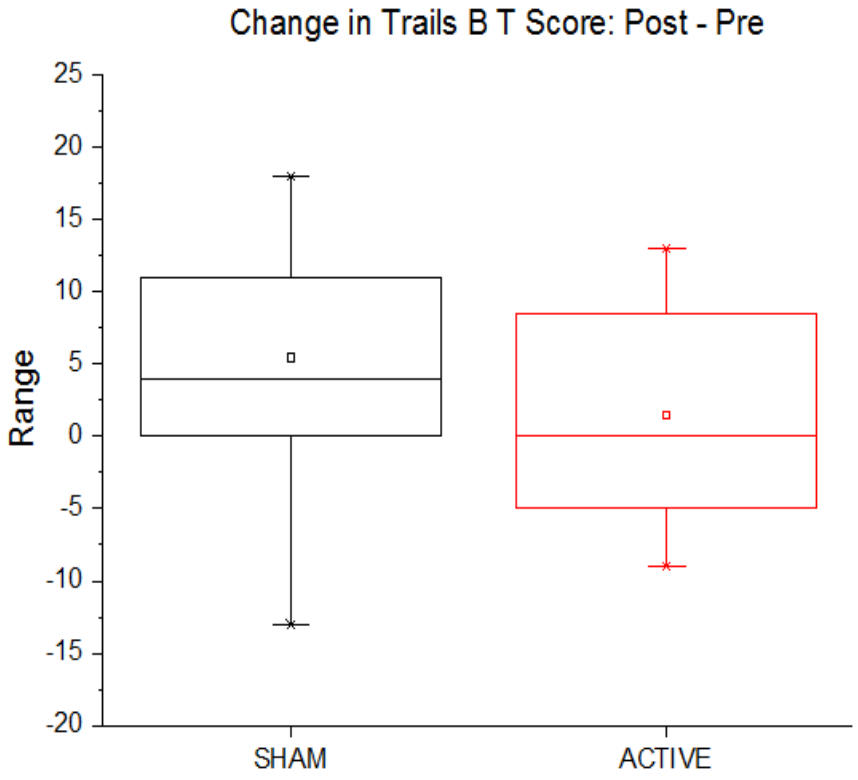


Diagram of simulated rTMS delivery (Machine, and area of stimulation (DLPFC) used in the proposed pilot study.

Demographics

Variables	Active rTMS (*n* = 17)	Sham rTMS (*n* = 16)	*P* - value
Age (yrs)	49.4 (13.3)	39.4 (11.9)	0.0299*
Education (yrs)	15.9 (2.0)	14.4(1.6)	0.0242
Female/Male	5/12	0/16	0.0185*
TBI Mild/Moderate	14/3	13/3	0.9346
Predicted FSIQ	104.9 (9.3)	98.4 (11.0)	0.0754

Behavioral Results



Treatment	n	Variable	Mean	SD
Sham	16	TRAILS B T_SCORE (Time 1)	45.3	14.9
		TRAILS B T_SCORE (Time 2)	50.8	13.7
		Change (Time 2 - Time 1)	5.5	7.9
Active	17	TRAILS B T_SCORE (Time 1)	52.1	8.2
		TRAILS B T_SCORE (Time 2)	52.9	10.3
		Change (Time 2 - Time 1)	1.5	7.3

- There is no difference between Sham and Active groups in the Executive Function change score ($p > .1$)
- Sham is showing a larger magnitude of difference compared to Active baseline to end of treatment

PTSD: The Explanation

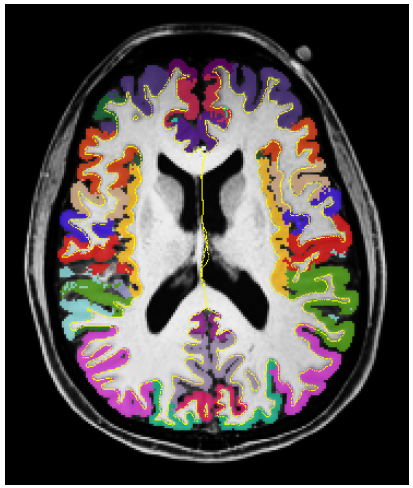
	SHAM	ACTIVE
NO PTSD (PCL < 38)	n=8 PCL score = 25.3 ± 4.9 Trail A T score = 40.0 ± 13.6 Trail B T score = 45.9 ± 13.0 Trails B/A Ratio = 2.1 ± 0.6 Trails A Errors = 0.1 ± 0.4 Trails B Errors = 0.1 ± 0.4	n=9 PCL score = 30.6 ± 5.0 Trail A T score = 50.2 ± 6.8 Trail B T score = 55.0 ± 8.6 Trails B/A Ratio = 2.1 ± 0.5 Trails A Errors = 0.0 ± 0.0 Trails B Errors = 2.3 ± 6.6*
PTSD (PCL ≥ 38)	n=8 PCL score = 58.3 ± 12.5 Trail A T score = 41.5 ± 18.7 Trail B T score = 44.6 ± 17.5 Trails B/A Ratio = 2.3 ± 0.8 Trails A Errors = 0.1 ± 0.4 Trails B Errors = 0.5 ± 0.8	n=7 PCL score = 49.1 ± 9.2 Trail A T score = 40.4 ± 6.0 Trail B T score = 48.9 ± 7.3 Trails B/A Ratio = 2.0 ± 0.6 Trails A Errors = 0.0 ± 0.0 Trails B Errors = 0.0 ± 0.0

- No significant difference between groups in terms of treatment-induced change in Trails B between baseline and immediately post-treatment ($p > .1$).
- After controlling for comorbid PTSD, active treatment appeared to be inferior to sham.
- This can be explained by randomization, which placed patients with higher PCL scores (by almost 10 points) in the sham group.
- Trail B T-score in Sham (no PTSD) group has an average that is 9 points lower than Active (no PTSD) group which can indicate lower performance.

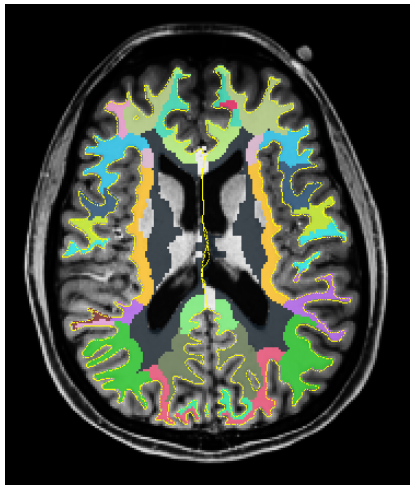
Defense Health Agency

Don’t get the tissues out yet!

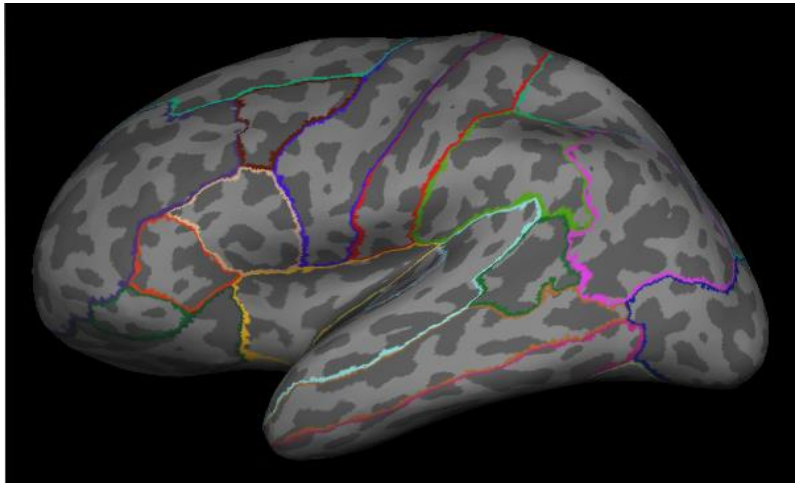
Diffusion Tensor Imaging Analysis:



(A) GM



(B) WM



(C) Inflated Surface

Desikan-Killiany (2006) (DK) parcellations in gray matter (GM) (A), white matter (WM) (B), and on the inflated GM/WM boundary of the left hemisphere of a subject. The yellow contour shows the GM/WM boundary in A and B. Light gray and dark gray shows the gyri and sulci structure in (C) along with the DK parcels in colored outline.

Correlation of FA/MD with Trails B

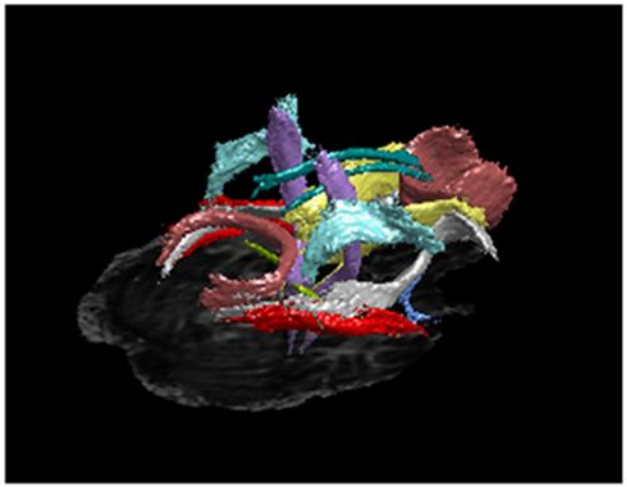
		FA vs Trails B		MD vs Trials B	
		LH	RH	LH	RH
Active	Session 1	0.32	0.40	-0.33	-0.20
	Session 2	0.50*	0.47*	-0.33	-0.27
Sham	Session 1	-0.26	-0.19	-0.48	-0.48
	Session 2	-0.41	-0.37	-0.47	-0.46

Table: Correlation coefficient between averaged overall FA and MD in WM with Trails B scores in two MR scan sessions for two subject groups. *$p < 0.1$.

Statistically, Trails B scores are not correlated with diffusion properties, i.e. FA and MD in WM, in all the test sessions, except session 2 for active subjects.

Tractography analysis is underway

Diffusion Tensor Imaging: Fiber tracks (JHU Template)



- Corpus Callosum - Forceps Major
- Corpus Callosum - Forceps Minor
- L/R Anterior Thalamic Radiations
- L/R Cingulum - Hippocampus
- L/R Cingulum - Cingulate Gyrus
- L/R Corticospinal Tract
- L/R Inferior Longitudinal Fasciculus
- L/R Inferior Fronto-occipital Fasciculus
- L/R Superior Longitudinal Fasciculus
- L/R Uncinate Fasciculus

Figure: The JHU Template probabilistic atlases of 18 association tract trajectories (TRS) [Oishi et al., 2008] was generated using the DTI data of 81 healthy subjects. The averages of Fractional Anisotropy (FA) and Mean Diffusivity (MD) were calculated in TRS for all the subjects. The percent changes of FA and MD were compared Active and Sham Groups.

JHU Fiber Tract	S2		
	LH		
	Active	Sham	(Active - Sham) [%]
Cingulum Hippocampus	0.34±0.03	0.30±0.07	12.5*

Table : Mean ± SD of FA in JHU fiber tracts. * $P < 0.1$.

Same fiber as in Main et al., 2017

Analysis done by Xiaojian Kang, PhD

Overall Change in Functional Connectivity in Active vs. Sham

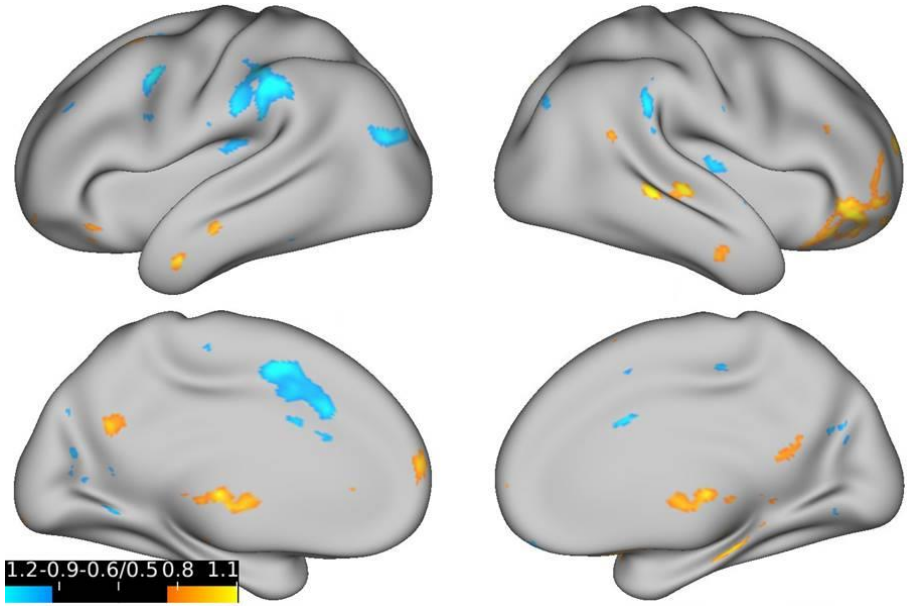
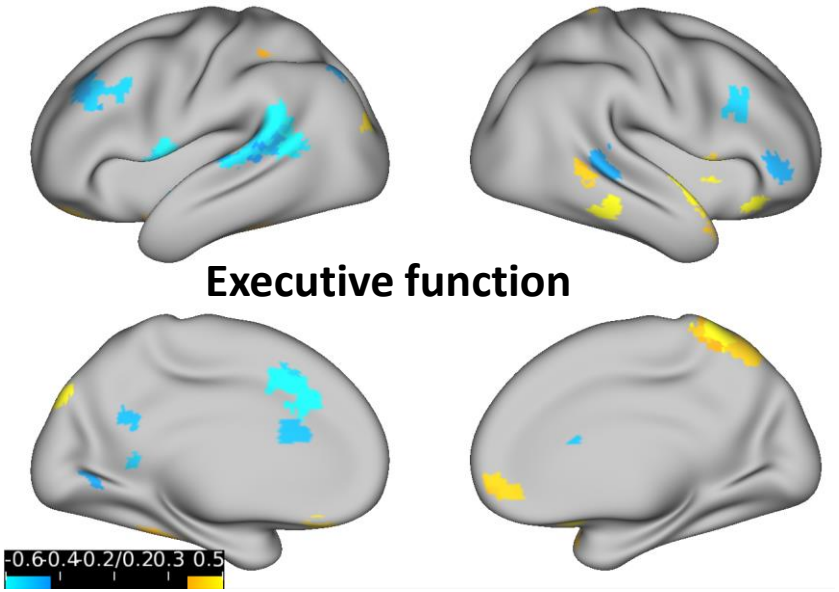


Figure: Difference in connectivity in Active vs. Sham (post-treatment). Yellow = Positive; Blue = Negative.

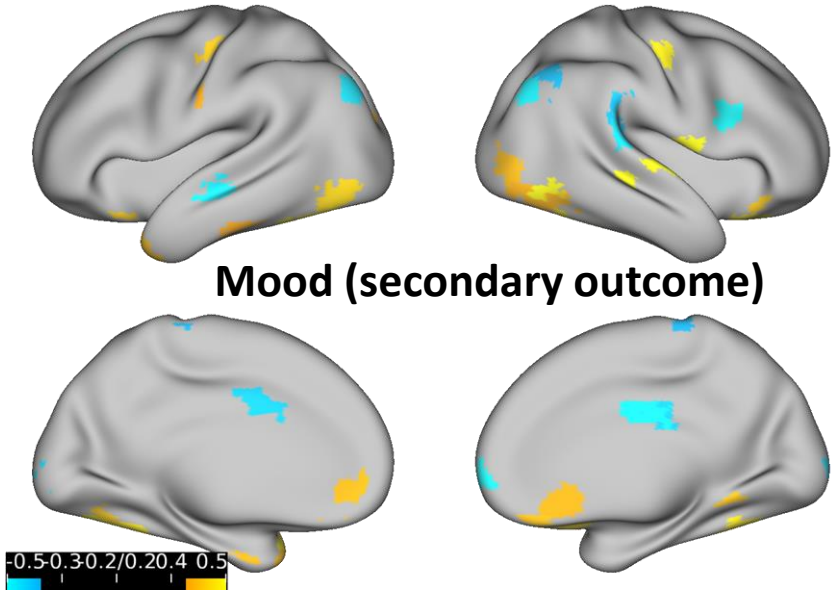
Preliminary Analysis conducted by Shan Siddiqi, MD Harvard Medical School

- There was a decrease in connectivity between stimulation site and cingulo-opercular network with a standardized beta effect size of -0.81 (p=0.036)
- Positive (yellow) areas overlap with lateral OFC, and the negative (blue) areas overlap quite precisely with the construct of "cingulo-opercular network."
- **Coding task**: cingulo-opercular network (CON) slightly associated with CON connectivity (p=0.046, beta=0.34)

Mood and Executive Changes show Distinct Connectivity Profiles



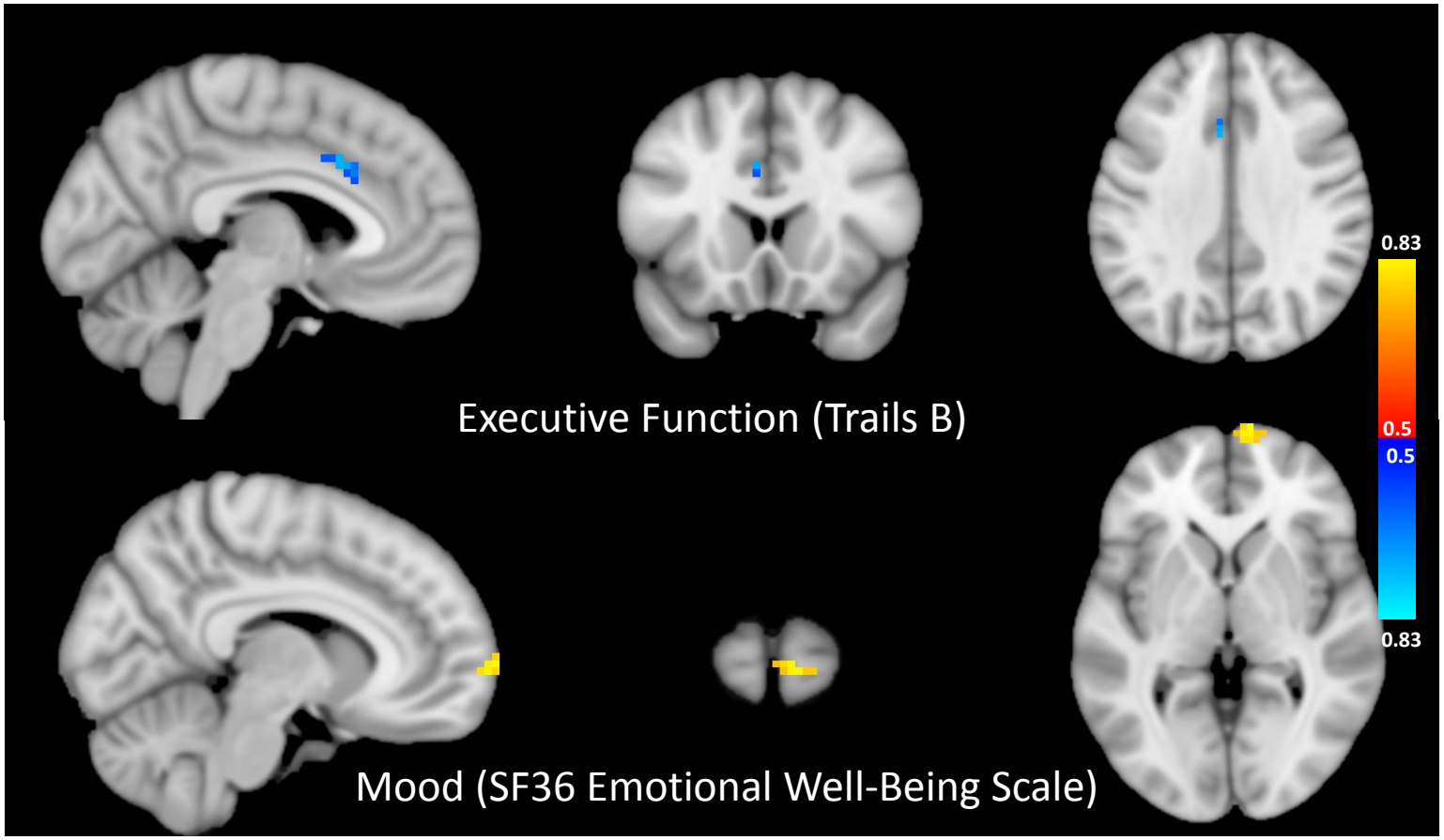
Executive function



Mood (secondary outcome)

Preliminary Analysis conducted by Shan Siddiqi, MD
Harvard Medical School

Regions most involved in Clinical Efficacy



Preliminary Analysis conducted by Shan Siddiqi, MD
Harvard Medical School

Mechanism underlying Repetitive TMS Treatment

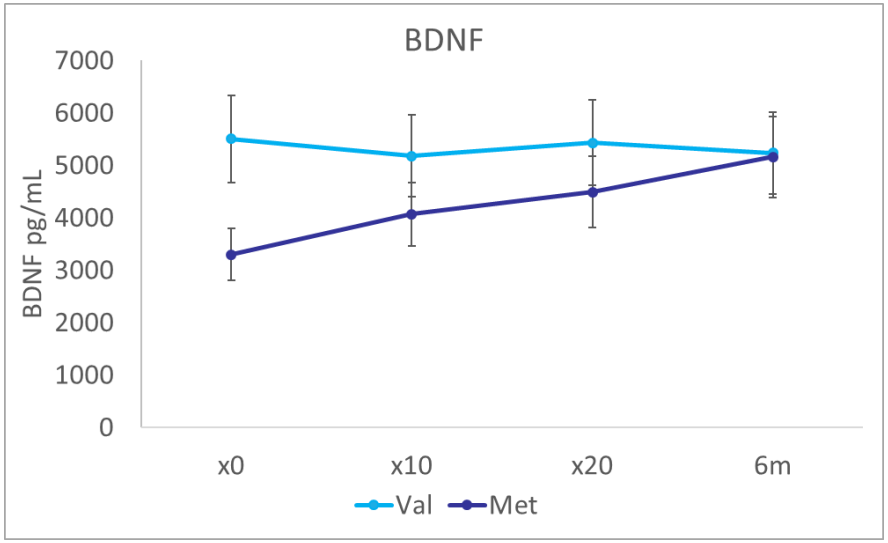
- Brain-Derived Neurotrophic Factor (BDNF) is a key signaling molecule for plasticity and regrowth following injury in the brain. BDNF is encoded by a gene that may contain a methionine (Met) substitution for valine (Val). Investigating the brain's powerful signaling mechanisms for neuroplasticity may be the key to facilitating recovery and optimizing treatment options for our Veterans.
- The goal of this project is to investigate the relationship between BDNF signaling and chronic mTBI symptoms during rTMS treatment.

Method

- Plasma was extracted and BDNF was measured using ELISA and Western Blot approaches. Blood draws for these analyses were taken prior to rTMS treatment, immediately following rTMS treatment, and at 6-month follow-up. DNA was extracted (Qiagen) for determination of BDNF polymorphisms via qPCR melting curve analysis (Sanchez-Ramero et al., 2009)

Preliminary Analysis conducted by M. Windy McNerney

BDNF Analysis and BDNF val66met Polymorphism



- At baseline, the Val/Val homozygotes had higher circulating BDNF levels than the met carriers.
- After 20 sessions of rTMS, there was an overall increase in BDNF, and this pattern continued at 6-month follow-up.
- The Val/Val individuals also had more proBDNF but overall levels did not change with treatment.

Results

1. Genotype was a significant factor in circulating BDNF levels.
   - This replicates previous findings
2. In chronic mTBI, rTMS does appear to increase BDNF
   - Met carriers may be more likely to respond to treatment than the Val/Val homozygotes
3. BDNF is an important factor in recovery from TBI, and genotype may moderate this effect. These findings pave the way for individualized treatment strategies for TBI.

Conclusions and Future Directions

- Findings have major implications for innovative treatments for mild & moderate TBI
- PTSD &/or Depression must be included in randomization – easier to accomplish in non-pilot studies
- A more comprehensive model that incorporates measures from different sources, including biomarkers, and considers their potential interactions will be valuable for precision targets for treatment

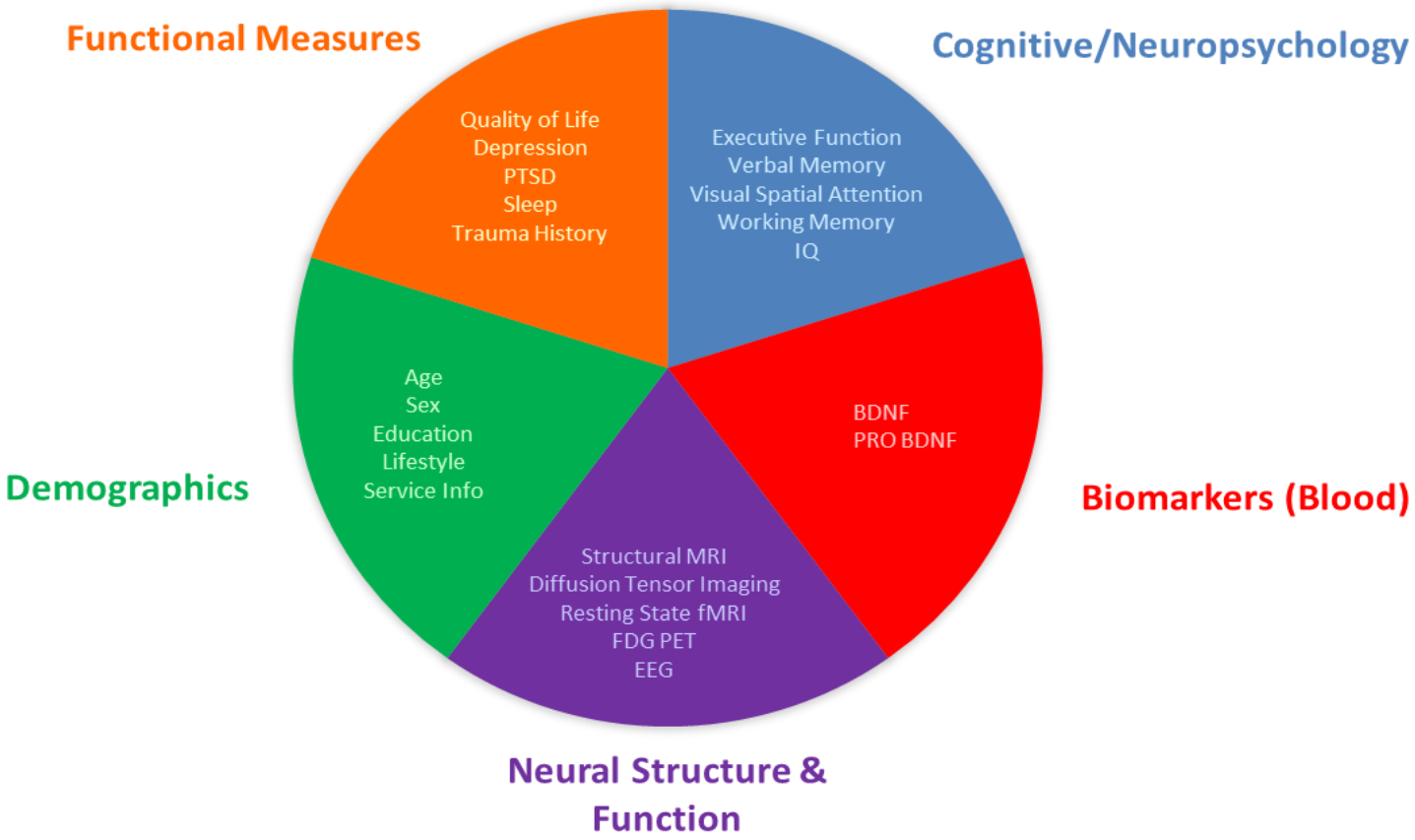
Current RCTs

- Repetitive Transcranial Magnetic Stimulation to Improve Cognitive Function in TBI (PI: Adamson)

  Status: In Analysis/Publication Mode
  https://med.stanford.edu/neurosurgery/research/clinicaltrials.html

- Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) for Improvement of Memory in Older Adults with TBI (PI: Adamson):
  - ❑Study funded by CDMRP/DOD
  - ❑Recruiting

New RCT: Data Sources



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