Neural Plasticity in Neurorehabilitation of TBI: rTMS in Facilitating Functional Repair

Theresa Pape, Amy Herrold, Ann Guernon & Brett Harton
Disclaimer and Conflict of Interest Statement

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- While I may mention specific equipment used in the conduct of my research, I do not endorse any specific commercial product or manufacturer.
SCVMC Plenary Objectives

Participants will be able to:

- Describe versatility of rTMS as an excitatory and inhibitory neurotherapeutic intervention.
- Describe rTMS in terms of global and focal neural effects.
- Explain conceptual differences between rTMS related modulation of and functional shaping of neural activity.
- Describe rTMS related effects on the functional and structural neural connectivity.
- Describe at least one other rTMS neurorehabilitation application.
Plenary Outline

1. Theresa: Neural Plasticity in Neurorehabilitation: Overview
2. Theresa: TMS Overview:
   • rTMS Neurotherapeutic applications: excitatory and inhibitory
   • Global and focal neural effects of TMS related
   • rTMS modulation of neural activity versus functional shaping of neural activity.
3. Theresa: TMS Neurotherapeutic example for Severe TBI
4. Amy: Example of use of rTMS with AUD with and without mTBI and PTSD
5. Ann: Describe Behavioral Effects of rTMS
6. Brett: Use of neuroimaging to describe rTMS effects
7. Q & A
Neural Plasticity in Neurorehabilitation

- **Neural Plasticity:**
  - The ability of the brain to adapt to new conditions
  - Ability of neurons & neuron aggregates to adjust activity and morphology to account for changes in the neural environment or use

- **Neural Repair:**
  - Restoration of or rerouting of neural circuits lost to injury or disease

- **Functional Neural Repair:**
  - Interventions target restoration to support functional repair/repair of functional skills

- **Neurorehabilitation:**
  - Clinical sub-specialty dedicated to restoration and maximization of function after an injury or disease to the nervous system
Neural Plasticity in the Adult CNS

- All plasticity is physiological but there are multiple manifestations:
  - Molecular & Cellular
  - Anatomical/Structural
  - Functional: Brain’s ability to shift function from
    ✓ Damaged to undamaged circuits or
    ✓ Restore function of damaged circuits

- Mechanisms of plasticity measurable indirectly and directly
  - Indirect measures are only useful if behavioral measures of change are included in analyses
  - fMRI is an example of indirect measures
Then why is neural repair after TBI limited?

- Plasticity can occur, but without coaxing it is very limited and does not occur to the extent necessary to support functional skill
  - New connections, for example, may be very short or spatially limited

- Barriers to Neural Repair after TBI
  - Many at different times post-injury
  - Examples
    - Nogo-A Protein
    - Glial Scarring

Brittis and Flanagan, Neuron, 2001
To Alter Disablement Three Scientific Areas are Necessary

- Modulation of Neural Activity
- Functional Skill
- A Healthy Neural Environment
- Shaping Neural Activity
Operational Definition

- A neural environmental ready and able to support repair of injured neural circuits or reassignment of functions to non-damaged neural circuits

- Opportunities to promote neural health include:
  - Steady states of healthy neural activity
  - Target barriers to plasticity, such as:
    - Anti-Nogo-A Antibody
    - Vitamin D & Antioxidants

Brittis and Flanagan, Neuron, 2001
Progressive modification of neural activity through successive approximations based on reinforcement:

- Contrasted with skill learning which uses feedback requiring cognitive processing (e.g., problem solving) for next practice session

Inducing and shaping are different

Shape the modulated activity so that it can support a functional skill

Shape via referencing and perhaps engaging targeted subsets of neural circuits or specific neural functions
Operational Definition

- Therapeutic alteration of neural activity including both excitation and inhibition in a group or population of neurons
  - Often reversible, but there is evidence of long lasting effects
  - A neuron uses 1 or > 1 neurotransmitter to regulate diverse groups of neurons
  - Is less direct than synaptic transmission and influences more than one neuron
  - Some neurotransmitters (e.g., dopamine, serotonin) are considered neuromodulators
Reality of TBI Treatment Development

Scientific Capacity to Measure Effects

- Modulation of Neural Activity
- Healthy Neural Environment
- Functional Skill
- Shaping Neural Activity

Medical Conditions Influence with Outcomes

Neurobehavioral Effects & Meaningful Change

Neurophysiological Effects (EEG, fMRI)

Methods to Define Neural Networks in Severe Injured Brains

Neural Network Effects & Change

Clinical Confounds/Covariates

Usual Care

Injury & Etiology Heterogeneity
1. Neural Plasticity in Neurorehabilitation: Overview
2. TMS Overview:
   • rTMS Neurotherapeutic applications: excitatory and inhibitory
   • global and focal neural effects of TMS related
   • rTMS modulation of neural activity versus functional shaping of neural activity.
3. TMS Neurotherapeutic example for Severe TBI
4. Example of use of rTMS with AUD with and without mTBI and PTSD
5. Describe Behavioral Effects of rTMS
6. Use of neuroimaging to describe rTMS effects
7. Q & A
Neural Modulation after TBI via Transcranial Magnetic Stimulation

TMS Overview:

- rTMS used as a Neurotherapeutic applications:
  - excitatory and inhibitory
- Global and focal neural effects
- rTMS modulation of neural activity versus functional shaping of neural activity
Transcranial Magnetic Stimulation

- Non-invasive technique to provide current to a cell that can inhibit or excite a cell
- If the cell is excitable, then an excitatory current can initiate an action potential
- Coil is held over the surface of the scalp then stimulator unit is discharged
- Current transferred into coil
- Pulse transcends scalp to tissue underlying the coil

TMS is Versatile

- **TMS Types**
  - Single-pulse = 1 pulse
  - Paired-pulse = 2 pulses
  - Rapid Rate TMS = > 2 pulses within 1 second
  - Theta Burst : Patterned
    - Continuous and Intermittent

- **Coil shape and size**

Fig. 2. The strength of the electric field induced in a spherical volume conductor below a circular (left) and a figure-of-eight coil (right). Reprinted from (Ilmoniemi et al., 1999), with permission of Begell House, Inc.
TMS Parameters

- Duration of pulse (micro seconds)
- Time between pulses (milliseconds)
- Time between trains of pulses (seconds)

1 Train =

<table>
<thead>
<tr>
<th>100μs pulse</th>
<th>100 ms rest</th>
<th>100μs pulse</th>
<th>5 s cortical rest</th>
</tr>
</thead>
</table>

Inter-pulse interval

Inter-train interval

Repetitive/Rapid Rate TMS (rTMS)
Theta Burst Stimulation (type or rTMS)

iTBS

2s

10s

cTBS
TMS Type & Parameters
Influence Neural Effects

- Initial excitation of a single pulse directly Beneath Coil
- Remote from coil/site of stimulation
- Within a distributed network
- Global/Across Hemispheres
rTMS Induced Neural Changes Outlast Period of rTMS Stimulation

- Local to and remote from the stimulation site

- Within specific neural networks related to specific behaviors
Net Neural Effects

- TMS-induced changes in excitatory and inhibitory neural processes occur at different levels, but the overall net effect is commonly measured in human research using:
  - electromyography (EMG),
  - electroencephalography (EEG),
  - Positron Emission Tomography (PET) and
  - functional Magnetic Resonance Imaging (fMRI).

- Mechanisms of rTMS induced neural plasticity measurable indirectly and directly
  - Indirect measures are only useful if behavioral measures of change are included in analyses.
Local & Remote Effects: Healthy

- Single TMS pulse to M1
- Rapid spread of neural activity to proximal site and remote homologous contralateral M1
- Reveals connectivity between local and remote brain areas
- Elicits muscle contraction contralateral to targeted M1
Local & Remote Effects for Severe TBI

- Successful elicitation of finger or hand muscle MEPs with severe TBI patients.
- Elicit MEPs in four subjects targeting the finger area of M1
  - 57%, 56%, 52% (Jaw) and 56%
- Indicates immediate TMS induced local neural activity that rapidly spread to remote brain areas. remote homologous contralateral M1
- Reveals connectivity between local and remote brain areas
rTMS Induced Neural Effects Remote from Sites of Stimulation

- ≈ 90 TMS-EEG studies report evidence of remote rTMS induced effects when TMS targets the Prefrontal regions.
- When rTMS is administered over frontal brain regions, PET data collectively indicate that remote neural activity is common in the anterior cingulate cortex, anterior insula premotor cortex, subcortical structures of the basal ganglia, parahippocampal gyrus, and cerebellum.
TMS as a Treatment for Severe TBI: Leveraging Remote & Distributed Effects

Figure 2. Dorsolateral Prefrontal Cortex Fibers Connected to Brainstem

atr = anterior thalamic radiation; cbt = corticobulbar tract; cst = corticospinal tract; ifo = inferior-fronto-occipital fasciculus; ilf = inferior longitudinal fasciculus; sfo = superior-fronto-occipital fasciculus; slf = superior longitudinal fasciculus;
rTMS # 2: Local & Remote Effects

Seed Based at Right DLPFC

Baseline

Mid-Point 18th TMS Session

30th TMS Session

Seed Based at Right Temporal

Baseline

Mid-Point 18th TMS Session

30th TMS Session
TMS Risks with TBI

- Seizure Induction
- Shifts in auditory threshold
  - Transient
  - Earplugs secured during stimulation
- Mild Transient Headache
- Skin Integrity
- Other unknown risks
- TMS with TBI is an experimental intervention
- In the United States it requires FDA (Food and Drug Administration) Investigational Device Exemption (IDE) for use over cortex
  - US FDA IDE # G040195

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rTMS # 3 Background

- Male
- Blunt trauma during a physical altercation
  - 23 years of age at injury
  - Hydrocephalus requiring programmable shunt
- Acute rehabilitation admission within first year of injury recovery
- At time of study enrollment
  - In VS/MCS for 9 Years at time of rTMS enrollment
  - No responses to SSEP at baseline

rTMS # 3 Neuroanatomical Injuries

- Right worse than left
- Contusions
  - Bilateral Frontal & Right Temporal Lobe
- Epi- & Sub- dural Hematomas (EDH & SDH)
  - Right Frontal, Temporal, Parietal
- Sub-arachnoid Hemorrhages (SAH)
  - Bilateral Frontal, Right Temporal & Parietal
- Diffuse Axonal Injuries (DAI)
  - Thalamus, hypothalamus, brainstem
Subject Relative to Healthy
rTMS Total Dose and Stimulation Site

- Stimulation Site:
  - LEFT Dorsolateral-Prefrontal-Cortex

- Dose:
  - 30 Sessions
  - 10 Additional Sessions

- Clinical Threshold (Jaw)
  - 52% MSO

- Intensity is 110%
  - 57%
rTMS Pulse Parameters & Dose

30 Sessions where Each Session:

1 Train =

100μs pulse  100 ms rest  100μs pulse  5 s cortical rest

Inter-pulse interval  Inter-train interval

300 Trains =

5 s cortical rest  5 s cortical rest  5 s cortical rest

Inter-train Interval  Inter-train Interval
Start rTMS 57% MSO

Verbalized on Command to say “Hi”, Command following, Visual tracking & focusing

Yes/no questions via eye gaze

"Seizure Like" Event

Re-start rTMS 55% MSO 200 Trains

End rTMS

Using alternative communication system: Eye gaze to answer yes/no questions with 80% to 90% accuracy
Summary of TMS # 3 Findings

- Neurobehavioral:
  - Gains correspond temporally with provision of rTMS and with Improved arousal, awareness, attention, visual skills and language comprehension/expression
  - Majority of gains maintained six weeks after stopping rTMS and after follow-up placed on amantadine then gains continued

- Neurobehavioral gains temporally correspond with
  - Increased Thalamo-cortical-structural connectivity (Superior Thalamic Radiata?)
  - Changes in structural connectivity in fiber tracts remote from site of stimulation

- Overall Net TMS Neural Effects
  - Direct effects evidenced with changes in correlations ipsilateral to stimulation site
  - Indirect Effects evidenced with changes in correlations in sites remote from stimulation
  - Global Effects evidenced with changes in correlations within inter-hemispheric areas and within areas contralateral to site of stimulation
  - Effects within DMN are increases in functional connectivity
Neurotherapeutic Potential of TMS with TBI

- Proof of Principle/Effects with severe TBI
  - Local, Remote and Distributed Effects within Networks & Across Hemispheres

- Efficacy Evidence with Severe TBI

- Evidence form other neurologic conditions
  - Medication-resistant depression, PTSD, neurodegenerative non-fluent aphasia, Stroke

- Two Ongoing Clinical Trials:
  - NIH NICHD NCMRR R21 HD075192-01AI
  - CDMRP Dept. of the Army W81XWH-14-1-0568
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rTMS for Complex Co-occurring Conditions

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Edward Hines Jr., VA Hospital

Research Assistant Professor
Northwestern University, Feinberg School of Medicine, Dept. of Psychiatry & Behavioral Sciences
Objectives

1. Population background: co-occurring conditions
2. Introduce a neurobiological model
3. Literature on rTMS for conditions alone
4. Neuroimaging methods are needed to inform rTMS treatment development for complex populations with co-occurring conditions
Population: MILD Traumatic Brain Injury

American Congress of Rehabilitation Medicine (ACRM) Definition of mTBI

<table>
<thead>
<tr>
<th>Loss of Consciousness (LOC)</th>
<th>Alteration of Consciousness (LOC)</th>
<th>Post-Traumatic Amnesia (PTA)</th>
<th>Glasgow Coma Scale (GCS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 min</td>
<td>Period Not Specified</td>
<td>&lt; 24 hours</td>
<td>13-15</td>
</tr>
</tbody>
</table>

DoD Numbers for Traumatic Brain Injury Worldwide – Totals

2000-2014 (Q1 - Q3)
- Penetrating: 4,577
- Severe: 3,126
- Moderate: 25,953
- Mild: 258,816
- Not Classifiable: 21,344

Total - All Severities: 313,816

Source: Defense Medical Surveillance System (DMSS), Theater Medical Data Store (TMDS) provided by the Armed Forces Health Surveillance Center (AFHSC)
Prepared by the Defense and Veterans Brain Injury Center (DVBIC)
Percentages do not add up to 100% due to rounding

Population: Co-occurring mTBI and PTSD

Prevalence Rates:
Veteran/Military: 26-44% (Brenner 2010, Hoge 2008)
Civilian US = 3-59% (Kim 2007)

Overlapping Symptoms:

[Diagram showing overlapping symptoms of PTSD and TBI]

Maguen et al., 2012, J Rehab Res Dev, 49(7):115-26
Population: Alcohol Use Disorder (AUD) Rates

- **Civilians (SAMHSA 2005)**: 7%
- **All Veterans (SAMHSA 2005)**: 8%
- **OEF/OIF/OND Veterans (Seal 2011, Burnett-Zeigler 2011, Polusny 2011)**: 13%, 36%, 42%
- **OEF/OIF/OND Veterans With mTBI (Heltemes 2011, Cernich 2012)**: 6%, 35%
Population:

mTBI and Addiction Risk

Risk for Addiction-Related Disorders Following Mild Traumatic Brain Injury in a Large Cohort of Active-Duty U.S. Airmen


FIGURE 1. Adjusted Hazard Ratios for Addiction-Related Disorders in Active-Duty U.S. Air Force Airmen With Mild Traumatic Brain Injury (TBI) and Other-Injured Comparison Subjects*

- Alcohol Dependence
- Drug Dependence
- Nondependent Abuse of Drugs/Alcohol
- Nicotine Dependence
- Opioid Dependence/Abuse
- Caffeine-Related Disorders
- Amphetamine Dependence/Abuse

Hazard Ratio

* Indicates statistical significance.
Neurobiological Model: AUD Alone

DMN = Default Mode Network, SN = Salience Network; Amg = Amygdala, CC = corpus callosum, Hipp = hippocampus, PFC = prefrontal cortex, rsFC = resting state functional connectivity, STR = striatum, Thal = thalamus, fDMN = frontal DMN, pDMN = posterior DMN

Herrold et al. 2014 *Neural Regeneration Research* Vol 9, Issue 19
Neurobiological Model: AUD Alone

De Ridder et al. 2011 Neuroscience Letters 496:5-10
Neurobiological Model: mTBI Alone

DMN= Default Mode Network, SN = Salience Network; Amg= Amygdala, CC= corpus callosum, Hipp= hippocampus, PFC= prefrontal cortex, rsFC= resting state functional connectivity, STR= striatum, Thal = thalamus, fDMN= frontal DMN, pDMN= posterior DMN

Herrold et al. 2014 Neural Regeneration Research Vol 9, Issue 19
Neurobiological Model: PTSD Alone

DMN = Default Mode Network, SN = Salience Network; Amg = Amygdala, CC = corpus callosum, Hipp = hippocampus, PFC = prefrontal cortex, rsFC = resting state functional connectivity, STR = striatum, Thal = thalamus, fDMN = frontal DMN, pDMN = posterior DMN

Herrold et al. 2014 Neural Regeneration Research Vol 9, Issue 19
Neurobiological Model: AUD+mTBI+PTSD

OVERLAPPING Networks & Dysfunction

DMN = Default Mode Network, SN = Salience Network; Amg = Amygdala, CC = corpus callosum, Hipp = hippocampus, PFC = prefrontal cortex, rsFC = resting state functional connectivity, STR = striatum, Thal = thalamus, fDMN = frontal DMN, pDMN = posterior DMN

Herrold et al. 2014 Neural Regeneration Research Vol 9, Issue 19
### Table 1 Summary of studies on repetitive transcranial magnetic stimulation (TMS) as a treatment among people with alcohol use disorder

<table>
<thead>
<tr>
<th>Citation</th>
<th>Sample size</th>
<th>Site</th>
<th>Coil</th>
<th>TMS parameters</th>
<th>#Sessions</th>
<th>Assessment</th>
<th>Immediate outcomes</th>
<th>Long-term outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mishra (2010)</td>
<td>n=45</td>
<td>Right DLPFC</td>
<td>Fig-8</td>
<td>10 Hz, 110%MT, 4.9 s/train, ITI=30 s, 20 trains/session, 1,000 pulses/session</td>
<td>10 daily</td>
<td>ACQ-NOW, GCI, relapse</td>
<td>• ACQ-NOW and GCI scores improved. Relapse rate was non-significantly reduced. • AE: seizure, scalp pain, transient headache, anxiety</td>
<td>• ACQ-NOW and GCI effects maintained 1 mo post-rTMS</td>
</tr>
<tr>
<td>De Ridder (2011)</td>
<td>n=1</td>
<td>mPFC, intended target dACC</td>
<td>Double Cone Coil</td>
<td>50% MO, 1 Hz</td>
<td>3 txt courses: txt1=3 wks daily, txt2=(after 3 mo)=1 wk daily, txt3=(after 3 wks)=single [−9 total sessions over −5 mo]</td>
<td>SLORETA EEG, fMRI, VAS, BAV, relapse</td>
<td>• VAS craving improved. BAV decreased. • Resting state EEG decreased activity in bilateral posterior insula, pregenual ACC, anterior PCC, and retrosplenial PCC. • Functional connectivity EEG is not changed for gamma but beta activity decreased between the PCC and NAc. • fMRI activation decreased in the PCC, ACC, and NAc. • AE: Not reported</td>
<td>• 3 mo post txt 1: BAV 1.9% • 3 wks post txt 2: BAV 1.45% time of relapse • Relapse associated with abnormal gamma band activity in the NAc, ACC, pregenual ACC, and PCC. • fMRI data obtained at relapse similar to pre-rTMS in the NAc, ACC, and PCC. Not conducted</td>
</tr>
<tr>
<td>Höppner (2011)</td>
<td>n=19</td>
<td>Left DLPFC</td>
<td>Not reported</td>
<td>20 Hz, 90%MT, 2.5 s/train, ITI=42.5 s, 20 trains/session, 1,000 pulses/session</td>
<td>10 sessions over 12 days</td>
<td>OCDS, HDRS, BDI, AB</td>
<td>• No differences in OCDS, BDI or HDRS • AB effect was increased after the rTMS session for alcohol-related pictures • AE: None observed</td>
<td>• No differences in OCDS, BDI or HDRS Not reported</td>
</tr>
<tr>
<td>Herremans (2012)</td>
<td>n=28</td>
<td>DLPFC</td>
<td>Fig-8</td>
<td>20 Hz, 110%MT, 1.9 s/train, ITI=12 s, 40 trains/session, 1,500 pulses/session</td>
<td>1 session repeated 1 wk later in cross-over design</td>
<td>OCDS</td>
<td>• No group differences in OCDS • AE: None observed</td>
<td>• No differences in OCDS, BDI or HDRS Not reported</td>
</tr>
<tr>
<td>Rapinesi (2013)</td>
<td>n=3</td>
<td>Bilateral DLPFC, Preference for left side</td>
<td>H1</td>
<td>20 Hz, 120%MT, 2 s/train, ITI=10 s, 55 trains/session</td>
<td>20 sessions over 28 days</td>
<td>OCDS, HDRS</td>
<td>• OCDS &amp; HDRS scores improved • Clinical condition improved allowing for reduction of antidepressant medications • AE: Not reported</td>
<td>• 6 mo follow-up: depression improved in all 3 subjects; alcohol craving was absent in 2 and minimal in 1 subject Not reported</td>
</tr>
<tr>
<td>Herremans (2013)</td>
<td>n=29</td>
<td>DLPFC</td>
<td>Fig-8</td>
<td>20 Hz, 110%MT, 1.9 s/train, ITI=12 s, 40 trains/session, 1,500 pulses/session</td>
<td>1 session repeated 1 wk later in cross-over design</td>
<td>OCDS, Go-Go task: Response inhibition, state of activation and consistency in cognitive performance</td>
<td>• Go-Go Task: Decrease of response inhibition, no differences between active and sham stimulation. No difference in state of activation between active and sham stimulation. Active stimulation increased consistency in cognitive performance • No differences in OCDS • AE: mild headache</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mishra (2014)</td>
<td>n=20</td>
<td>Right &amp; Left DLPFC</td>
<td>Fig-8</td>
<td>10 Hz, 110%MT, 4.9 s/train, ITI=30 s, 20 trains/session, 1,000 pulses/session</td>
<td>10 daily</td>
<td>ACQ-NOW</td>
<td>• Significant improvement in ACQ-NOW scores pre-v. post-rTMS for both Right &amp; Left DLPFC groups. No difference between groups • AE: nightmare and insomnia</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

**AB:** Attentional Blink paradigm; **ACQ-NOW:** Alcohol Craving Questionnaire; **AE:** adverse effects; **BAV:** Blood Alcohol Volume; **BDI:** Beck Depression Inventory; **dACC:** dorsal anterior cingulate cortex; **DLPFC:** dorsolateral prefrontal cortex; **Fig-8:** figure-of-eight TMS coil; **GCI:** General Craving Index; **HDRS:** Hamilton Depression Rating Scale; **ITI:** inter-train interval; **sLORETA EEG:** standardized low resolution brain electromagnetic tomography electroencephalography; **mPFC:** medial prefrontal cortex; **PCC:** posterior cingulate cortex; **min:** minutes; **MO:** machine output; **MT:** motor threshold; **NAc:** nucleus accumbens; **OCDS:** Obsessive Compulsive Drinking Scale; **txt:** treatment; **VAS:** Visual Analog Scale of alcohol craving wk(s); week(s); mo: month(s).
rTMS Treatment Literature: TBI Alone


  - **Population:** n=15 with mTBI, time since injury= 6mo – 28yrs, 60% with elevated depression symptoms
  - **Site of Stimulation:** Left DLPFC
  - **rTMS Parameters:** 10Hz, 110%MT, 20s train, ITI= 25s, Fig-8 coil
  - **rTMS Sessions:** 20 once daily sessions, 5 d/wk over 4 wks
  - **Initial Outcomes:**
    - Functional: Significant improvement in PCS scores pre-vs post-rTMS, significant improvement in Stroop task performance and category fluency, significantly increased activation in DLPFC with working memory tasks and significantly greater deactivation in ACC pre- vs post-rTMS
    - Adverse Events: 2 people withdrew because intervention was not tolerable, headache, vertigo, anxiety, increased sleep disturbance
  - **Long-term Outcomes:** 3 mo follow-up PCS scores improved for 2/8 completers

*TABLE 2, Herrold et al. 2014 Neural Regeneration Research Vol 9, Issue 19*
### SITE OF rTMS STIMULATION

<table>
<thead>
<tr>
<th>Left DLPFC</th>
<th>Right DLPFC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Citation</strong></td>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Rosenberg 2002</td>
<td>Immediate: improved depression and mood; all maintained at 2 mo follow-up</td>
</tr>
<tr>
<td>Boggio 2010</td>
<td>Immediate: reduced PTSD symptoms and improved depression; former maintained at 12 wk follow-up</td>
</tr>
<tr>
<td>Nakama 2013</td>
<td>Immediate: reduced suicidal ideations and most PTSD &amp; major depression symptoms; all maintained at 3 wk follow-up</td>
</tr>
</tbody>
</table>

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- **Population**: n=12 co-occurring PTSD and major depression
- **Site of Stimulation**: Left DLPFC
- **rTMS Parameters**: 90%MT, 600 pulses/session
  - compared 1Hz vs 5Hz
  - *Improved depression outcome 5Hz vs 1Hz group*

**TABLE 3 & Supplemental TABLE 1**, Herrold *et al.* 2014 *Neural Regeneration Research* Vol 9, Issue 19
Neuroimaging of These Networks Can Guide rTMS

Herrold et al. 2014 Neural Regeneration Research Vol 9, Issue 19
Multi-modal Neuroimaging Approach to Inform rTMS

**fMRI Task**
- Alcohol Images
- Neutral Images
- Craving Rating

**Functional Connectivity**
- Vollstädt-Klein et al. 2010

**Diffusion Tensor Imaging**

**GOAL: rTMS Protocol Development**
Funding Sources

- NIDRR Merit Switzer H133F130011
- VA RR&D CDA-II RX000949-01A2
- VA OAA Polytrauma and TBI Research Fellowship
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Neurobehavioral Measures

- Disorders of Consciousness Scale -25
- Coma Near Coma Scale (TMS # 1 & 2)
- Coma Recovery Scale-Revised (TMS #3 Only)
- Disability Rating Scale (TMS #3 Only)
Disorders of Consciousness Scale (DOCS-25)

- 25 item evaluation of neurobehavioral function

- Responses are scored on a 3 point scale based on the contextual appropriateness of the response to stimuli

- Best response profile

- Conducted weekly; used as safety monitoring and to measure neurobehavioral change

Coma Near Coma Scale (CNC)

- 9 items administered (skipped olfactory)
- Score ranges 0 – 36
- Lower scores = greater neurobehavioral function
- Average CNC Scores categorize a patient according to one of five levels describing levels of awareness/responsivity
- Conducted weekly during study participation

Coma Recovery Scale –Revised (CRS-R)

- 23 item neurobehavioral scale
- Responses to items scored based on prescribed definition of responses
  - (i.e. score of 4 on movement to auditory command requires 2 different commands followed on 4 trials)
- Screening Protocol
  - Classify state of disordered consciousness (insure VS or MCS upon enrollment)
  - Have recovered full consciousness at time of study screening as indicated by a Motor Function scale score of 6 and/or a Communication scale score of 2 on the CRS-R
- Administer weekly
  - Monitoring neurobehavioral change
  - Classification of state of consciousness

Disability Rating Scale (DRS)

- Developed to measure functional changes over time
- 8 items addressing functional abilities, overall level of function and employability
- Maximum score of 29; higher score reflects higher level of disability
- Used as an outcome measure

1. Eye Opening
2. Communication Ability
3. Motor Response
4. Feeding (Cognitive Ability Only)
5. Toileting (Cognitive Ability Only)
6. Grooming (Cognitive Ability Only)
7. Level of Functioning (Physical, Mental, Emotional or Social Function)
8. Employability (As a Full Time Worker, Homemaker or Student)

Neurobehavioral Measurement of Effect

- DOCS used weekly as a safety measure and measure of neurobehavioral change
  - Total DOCS score

- DRS

- CNC

- CRS-R completed weekly at the time of DOCS-25 (TMS #3)
# Safety Monitoring Using the DOCS

**SAFETY INDICATOR DATA COLLECTION FORM:** Adapted from the Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, Published December 12, 2003 ([http://ctep.cancer.gov](http://ctep.cancer.gov))

<table>
<thead>
<tr>
<th>Adverse Events / Safety Indicators</th>
<th>Data Source</th>
<th>Baseline Rating from: <em><strong>/</strong></em>/___</th>
<th>Daily Vital Signs or Safety Indicator Readings</th>
<th>Severity Rating for the Day</th>
<th>Comments</th>
<th>Severity Rating Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>8) Neurobehavioral Functioning</td>
<td>DOCS measures completed weekly</td>
<td>Total DOCS score</td>
<td>Weekly DOCS Score:</td>
<td>0 = No Change from Baseline 1 = Decrease of 5-10 DOC-units 2 = Decrease of 11-15 DOC-units 3 = Decrease of 16-25 DOC-units; Repeat Structural MRI indicated; check EEG data 4 = Decrease of &gt;25 DOC-units; Additional Neurodiagnostic indicated; medical intervention may be indicated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Severity Grades:**

0 = No change from Baseline; 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Life Threatening or Further Disability; 5 = Death related to AE
Figure 3. Weekly DOCS Measures by Group & TMS Subject

Control Group Averages (n = 22)

TMS # 2

15th TMS Session (Mid Point)

Acute Rehabilitation

TMS # 1

15th TMS Session Mid Point

Days After Injury DOCS Obtained

DOCS Neurobehavioral Findings
<table>
<thead>
<tr>
<th>Days after Injury for Baseline DOCS</th>
<th>TMS #1</th>
<th>TMS #2</th>
<th>TMS #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days after Injury for Baseline DOCS</td>
<td>287</td>
<td>188</td>
<td>9 YEARS</td>
</tr>
<tr>
<td>Total DOCS Measure: Baseline</td>
<td>50.7</td>
<td>44.0</td>
<td>56.0</td>
</tr>
<tr>
<td>DOCS Auditory Measure: Baseline</td>
<td>46.8</td>
<td>39.5</td>
<td>50.0</td>
</tr>
<tr>
<td>DOCS Tactile Measure: Baseline</td>
<td>48.5</td>
<td>52.0</td>
<td>54.1</td>
</tr>
<tr>
<td>DOCS Visual Measure: Baseline</td>
<td>57.2</td>
<td>20.8</td>
<td>78.9</td>
</tr>
<tr>
<td>Total DOCS Change (+ = Best Gain)</td>
<td>+16.1</td>
<td>+9.7</td>
<td>-4.6</td>
</tr>
<tr>
<td>DOCS Auditory Change (+ = Best Gain)</td>
<td>+26.3</td>
<td>+10.5</td>
<td>0.0</td>
</tr>
<tr>
<td>DOCS Tactile Change (+ = Best Gain)</td>
<td>+21.8</td>
<td>+9.3</td>
<td>-10.4</td>
</tr>
<tr>
<td>DOCS Visual Change (+ = Best Gain)</td>
<td>+21.8</td>
<td>+32.7</td>
<td>0.0</td>
</tr>
</tbody>
</table>
rTMS 1 Neurobehavioral Results using Disorders of Consciousness Scale measures.
rtMS 2 Neurobehavioral results using Disorders of Consciousness Scale Measures

- Keppra 500 mg BID
- Visual focus and tracking of objects, following simple 1-step commands
- Start rtMS 62% MSO
- End rtMS - 30 sessions
- Verbalizing appropriately with 1 to 2 word utterances

Baseline 1, Baseline 2, Baseline 3, Baseline 4, DOCS 2 (5 rTMS), DOCS 3 (10 rTMS), DOCS 4 (15 rTMS), DOCS 5 (20 rTMS), DOCS 6 (25 rTMS), Endpoint (30 rTMS), 6-Week Follow-Up
CNC TMS 1 and TMS 2

Less Responsiveness

More Responsiveness

Baseline 1 2 3 4 5 6

TMS 2
TMS 1
1. Eye Opening
   • Most of the time spontaneous eye opening
   • Varied from eye opening to speech and no eye opening

2. Communication Ability
   • Varied from no sounds to incomprehensible vocalizations

3. Motor Response
   • Consistently obey command

4. Feeding (Cognitive Ability Only)

5. Toileting (Cognitive Ability Only)

6. Grooming (Cognitive Ability Only)

7. Level of Functioning (Physical, Mental, Emotional or Social Function)
   • Totally Dependent

8. Employability (As a Full Time Worker, Homemaker or Student)
   • Not Employable
Comparison of Neurobehavioral Measures for TMS # 3
Compare performance and change with DOCS and CNC
Plenary Outline

1. Neural Plasticity in Neurorehabilitation: Overview
2. TMS Overview:
   • rTMS Neurotherapeutic applications: excitatory and inhibitory
   • global and focal neural effects of TMS related
   • rTMS modulation of neural activity versus functional shaping of neural activity.
3. TMS Neurotherapeutic example for Severe TBI
4. Example of use of rTMS with AUD with and without mTBI and PTSD
5. Describe Behavioral Effects of rTMS
6. Use of neuroimaging to describe rTMS effects
7. Q & A
Measuring the “TMS Effect”

- Neurobehavioral Assessments
- Neuropsychological Assessments
- Neurophysiological Assessments
Neurophysiological Measures

Mechanistic Measures

Direct
- EEG
- MEG

Indirect
- fMRI
TMS Evoked Potential

- Measure of cortico-cortical excitability

- Uses:
  - To determine treatment intensity
  - To measures changes in excitability due to:
    - TMS itself
    - Drugs
    - Treatments (TMS, therapy, drugs)
TMS & EEG

- Temporal profile of TMS effects
- Measure propagation of TMS stimulus to functionally and structurally connected regions
- Effective Connectivity
  - Description of causal interactions between regions
TMS & EEG

- Measure TMS treatment effect over time
TMS, EEG, Neurobehavioral

Subject #2 EEG Power vs. CNC Scores

- EEG Power
- CNC Score

- θ-CPz
- α-PO7
- α-PO8
TMS & Functional Connectivity

- Spatial profile of TMS effects
- Functional Connectivity
Healthy (n=7)  Sham (n=4)

TMS1_Baseline  TMS1_Endpoint  TMS2_Baseline  TMS2_Endpoint
TMS + Task-fMRI

- Use TMS to improve a certain function

- Stimulate region(s) responsible for that function to see if those regions are essential for task performance

- E.g., Attention or Working Memory
  - N-back
Diffusion Tensor Imaging

- Optimize site of stimulation
- Structural organization
- May explain observed transcallosal inhibition or motor excitability values
- Metrics: FA, MD, RD, AD
Neuroimaging & TMS

- Inform TMS Parameters
- Inform site of stimulation
- Inform on efficacy of treatment
- Inform on Disease State and Progression
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Xue Wang, PhD
Neuroradiology
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Thank You Veterans and Warriors!
Discussion, Questions & Hopefully Answers