SO STIMULATING! NON-PHARMACOTHERAPY FOR DEPRESSION
Learning Objectives

• Evaluate the efficacy of brain stimulation techniques for the treatment of a variety of mental disorders

• Examine the application of transcranial magnetic stimulation for treatment-resistant depression (TRD), and other mental disorders
History of Brain Stimulation Therapies

• Electroconvulsive therapy (ECT) 1938

• Cranial electrotherapy (CES) 1972

• Transcranial magnetic stimulation (TMS) 1985
ECT Efficacy

• Highest response/remission rates of any depression treatment
• Best data are for acute treatment
• Remission after one round of ECT:

51.5% for unipolar depression

50.9% for bipolar depression

• High relapse rates following remission:

50% relapse if followed by antidepressants

Twice as many relapse if given ECT alone

*No clear evidence to support any particular medicine for maintaining response after ECT; best research suggests nortriptyline, lithium, venlafaxine

Cranial Electrotherapy (CES)

- Noninvasive brain stimulation: applies a small, pulsed electric current across a person’s head

- Approved by the Food and Drug Administration (FDA) in 1976

- Electrodes placed on the ear lobes, maxilla-occipital junction, mastoid processes, or temples

- CES stimulation of 1mA (milliampere) has shown to reach the thalamic area at a radius of 13.30 mm

- Induces changes in EEG: Increases alpha relative power and decreases relative power in delta and beta frequencies

- In neuroimaging studies, CES has shown to reach cortical and subcortical areas of the brain

CES Efficacy

• CES treatments are cumulative; however, most patients show some improvement after the first treatment

• Depression can take up to 3 weeks for initial response
  • Insomnia varies widely (immediately–2 months into treatment)

• CES can also be used in conjunction with psychotherapy, medications, hypnosis, and biofeedback

• Side effects are mild and self-limiting: vertigo, skin irritation at electrode sites, and headaches

Transcranial Magnetic Stimulation (TMS)

- TMS is a neurophysiological technique that allows for non-invasive stimulation of the human brain.
- Can be combined with brain mapping methods (EEG, fMRI) to study brain plasticity.
- Trains of TMS pulses known as repetitive TMS (rTMS) transiently disrupt neuronal activity for periods exceeding stimulation duration.
- Used to treat a variety of neuropsychiatric illnesses.
History of TMS

• Physical principles of TMS discovered in 1831 by Faraday

• Pulse of electric current passing through a wire coil generates a magnetic field

• During TMS, the stimulating coil is held over the patient’s head and produces an electrical current in the brain through electromagnetic induction
Side effects? What side effects?

Kalu UG et al. Psychol Med 2012;42(9):1791-800.
Side effects? What side effects?

1. Magnetic field penetrates the skull by a few cm
2. Depolarizes neurons in superficial cortex
3. Through neural pathways, this local stimulation causes functional changes in other brain regions

History of TMS

- Efficacy
- FDA-approved in 2008 for treatment-resistant depression (TRD)

RCT = randomized controlled trial

2008 First FDA-Approved rTMS Procedure for TRD

- Electromagnetic coil is placed against the scalp: Delivers pulses of the magnetic field in 30-sec intervals
  - 4 sec each, 10 pulses/sec, with 26-sec rest intervals
  - Or 2 sec each, 18 pulses/sec with 20-sec rest intervals
  - Feels/sounds like light tapping on the scalp

- Therapeutic dose: 90–120% of resting motor threshold (RMT)

- Session length: typically 37.5 minutes
- Treatment duration: typically five treatments/week for 4–6 weeks
What About Coil Positioning Accuracy?

• Stimguide by MagStim is the first TMS navigation system that’s FDA approved (2019) for the clinical setting

• Guides you to your precise treatment location by aligning contact, XY location, tilt, and rotation

• Green indicator appears when all 4 parameters are aligned

• Not a complicated system that requires MRI

• Quality control- even with multiple technicians the treatment target for each patient remains the same

• Ensures simple, precise coil position

Deep TMS

- Deep TMS (dTMS) allows current to travel deeper into the brain because of special coil designs
- In 2013, the Brainsway H1 coil became FDA approved to treat patients with major depressive disorder (MDD)
- dTMS requires only five daily sessions of 20 min each, over 4–6 weeks
- H1 coil stimulates 1.7cm beneath the skull surface
- In 2018, the Brainsway H7 coil became FDA approved to treat obsessive compulsive disorder (OCD)
- H7 coil stimulates up to 4cm beneath the skull surface, reaching deep brain structures
Second FDA-Approved rTMS Procedure for TRD: Theta-Burst TMS

- FDA approved MagVenture’s theta-burst 3-minute protocol in **August 2018** for TRD

- Lower stimulation intensity than TMS (70% compared to 120% RMT)

- Shorter duration (1–3 minutes vs. 15–20 minutes for deep TMS)

- Typical theta-burst pattern consists of three bursts of pulses at 50Hz repeated every 200 milliseconds (ms)

- Based on results from the THREE-D clinical trial demonstrating similar efficacy to the original TRD rTMS protocol

Intermittent theta-burst stimulation (iTBS) = excitatory
Continuous theta-burst stimulation (cTBS) = inhibitory
Repetitive TMS (rTMS) and Major Depression

• Repetitive TMS (rTMS) disrupts neuronal activity for periods exceeding stimulation duration. Current rTMS treatment for major depressive disorder (MDD) uses one of the two most common protocols:

  **High**-frequency rTMS (HF-rTMS, >1.0 Hz) to the **left** dorsolateral prefrontal cortex (DLPFC)

  **Low**-frequency rTMS (LF-rTMS, <1.0 Hz) to the **right** DLPFC

• **High**-frequency stimulation **activates**, while **low**-frequency stimulation **inhibits** neural activities (when intensity is > MT)

• Altered cortical activity modulates interactions of different brain regions

• Meta-analysis: Both rTMS methods have been equally effective therapies for MDD

Recent meta-analysis examined HF-rTMS on MDD

- rTMS had a significant overall therapeutic effect on depression severity scores
- The higher the number of rTMS sessions, the greater the improvement
- Across the groups, the maximal mean effect size overall was obtained in the subgroup of 1200–1500 pulses per day (p<0.05)
- This pulse range may produce the best antidepressant effects, regardless of session numbers

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of trial</th>
<th>Protocol</th>
<th># of participants</th>
<th># of sessions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bystritsky et al. 2008</td>
<td>Open</td>
<td>1Hz to the right DLPFC, at 90% MT with 900 pulses/day</td>
<td>N=10</td>
<td>6 sessions</td>
<td>Significant reduction in anxiety symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2x/week for 3 weeks)</td>
<td></td>
</tr>
<tr>
<td>Diefenbach et al. 2013</td>
<td>Open</td>
<td>10Hz to the left DLPFC, at 130% MT</td>
<td>N=32 patients with MDD and GAD</td>
<td>31 sessions</td>
<td>Significant improvement in depression/anxiety symptoms</td>
</tr>
<tr>
<td>Diefenbach et al. 2016</td>
<td>RCT</td>
<td>1Hz to the right DLPFC, at 90% MT</td>
<td>n=12</td>
<td>32 sessions</td>
<td>Significantly greater response on anxiety rating scales posttreatment and 3 months later</td>
</tr>
<tr>
<td>Dilkov et al.</td>
<td>RCT</td>
<td>20 Hz to the right DLPFC, at 110% MT with 3600 pulses/day</td>
<td>N=15</td>
<td>25 sessions</td>
<td>Significant decrease in anxiety symptoms compared to sham</td>
</tr>
</tbody>
</table>
## rTMS for Depression in Bipolar Disorder

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Protocol/Parameters</th>
<th>Participants</th>
<th>Sessions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tavares et al.</td>
<td>2017</td>
<td>RCT H1 coil with 18Hz at 120% MT for 1980 pulses/day</td>
<td>n=50 (25 active; 25 sham)</td>
<td>20 daily sessions</td>
<td>Significant improvement in depression ratings at 4 weeks, but lost at 8-wk follow-up</td>
</tr>
<tr>
<td>Rapinesi et al.</td>
<td>2015</td>
<td>RCT H1 coil with 18Hz at 120% MT for 1980 pulses/day</td>
<td>N=24; n=12 maintenance (M)</td>
<td>20 sessions; M group: 16 additional sessions</td>
<td>Significant ↓ in HDMRS scores after first 20 sessions; scores stayed the same for the M group but significantly ↑ in the non-M group at 6 and 12-month follow-up</td>
</tr>
<tr>
<td>Pallanti et al.</td>
<td>2014</td>
<td>Open 1Hz to the right DLPFC at 110% MT</td>
<td>N=40 patients with mixed depression</td>
<td>15 sessions over 3 wks</td>
<td>Significant improvement in depressive and manic symptoms</td>
</tr>
</tbody>
</table>

**Kozel AF. Psychiatr Clin N Am 2018;41:433-46.**

**FDA Grants NeuroStar® Advanced Therapy System Breakthrough Device Designation to Treat Bipolar Depression: March 6th 2020**
### rTMS Alone for the Treatment of PTSD

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample size (n)</th>
<th>Procedure</th>
<th>Duration</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al. 2004</td>
<td>24 patients</td>
<td>LF(1Hz), HF(10Hz)-rTMS to right dLPFC (80% resting motor threshold; RMT)</td>
<td>10 sessions</td>
<td>HF-rTMS reduced PTSD core symptoms</td>
</tr>
<tr>
<td>Nam et al. 2013</td>
<td>18 patients</td>
<td>LF(1Hz)-rTMS to the right DLPFC (80% RMT)</td>
<td>15 sessions</td>
<td>Significant improvement in PTSD symptoms</td>
</tr>
<tr>
<td>Oznur et al. 2014</td>
<td>20 combat veterans with comorbid MDD</td>
<td>LF(1Hz)-rTMS to the right DLPFC (80% RMT)</td>
<td>20 sessions</td>
<td>Significant improvement in hyperarousal scale; no change in total PTSD scale</td>
</tr>
<tr>
<td>Phillip et al. 2016</td>
<td>10 veterans with comorbid MDD</td>
<td>5Hz rTMS to the left DLPFC (120% RMT)</td>
<td>36 sessions</td>
<td>Significant reduction in PTSD symptoms and depressive symptoms</td>
</tr>
</tbody>
</table>

## rTMS Combination for the Treatment of PTSD

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample size (n)</th>
<th>Procedure</th>
<th>Duration</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osuch et al. 2009</td>
<td>9 patients (civilian)</td>
<td>LF(1Hz)-rTMS to the right DLPFC with brief exposure therapy (80% RMT)</td>
<td>20 sessions</td>
<td>Significant reduction in PTSD symptoms</td>
</tr>
<tr>
<td>Boggio et al. 2010</td>
<td>30 patients (civilian)</td>
<td>HF(20Hz)-rTMS to the left DLPFC, HF(20Hz)-rTMS to the right DLPFC (80% RMT)</td>
<td>10 sessions</td>
<td>Both resulted in significant ↓ PTSD symptoms, right side had greater effect</td>
</tr>
<tr>
<td>Isserles et al. 2013</td>
<td>30 patients (civilian)</td>
<td>Deep transcranial magnetic stimulation (dTMS) to the mPFC at 120% RMT combined with brief exposure procedure</td>
<td>12 sessions</td>
<td>Significant improvement in intrusive component of CAPS-5 scale</td>
</tr>
<tr>
<td>Kozel et al. 2017</td>
<td>103 combat veterans</td>
<td>LF(1Hz)-rTMS to the right DLPFC (110% RMT) just prior to weekly CPT</td>
<td>12–15 sessions</td>
<td>Significantly greater improvements than CPT alone; even 6 months later</td>
</tr>
</tbody>
</table>

Using Brain Patterns to Predict Treatment Response to Exposure Therapy in PTSD

Concurrent TMS-fMRI: Right pMFG (ECN) vs. Right aMFG (Salience)

pMFG: Posterior middle frontal gyrus
ECN: executive control network
aMFG: anterior middle frontal gyrus

Using Brain Patterns to Predict Treatment Response to Exposure Therapy in PTSD

Concurrent TMS-fMRI: Right pMFG (ECN) vs. Right aMFG (Salience)

Those who showed the largest decrease in left amygdala activation in response to right pMFG TMS single pulses had greater reductions in PTSD symptoms.

Brainsway: H6 Coil and ADHD

75 Adults with ADHD (18–60 yrs old)

Randomly assigned to one of three conditions; underwent 15 dTMS sessions (1x day for 3 weeks)

- dTMS to right DLPFC (n=27)
- dTMS to left DLPFC (n=28)
- Sham control (n=20)

Underwent Conner’s Adult ADHD Rating Scale (CAARS) at baseline, after 3 wks treatment, and follow-up visits

6 Minutes of Cognitive Training, 3 min Immediate Recall Test, 3 min Sustained Attention Task at each session

One more treatment session 1 month later, and 2 months later

Results: significant improvements were observed in the Inattention/Memory Problems subscale of the CAARs in both right and left treatment groups compared to sham (p=0.033)

Interestingly, increased fMRI brain activation in the right DLPFC during a working memory task were only apparent following treatment in the right stimulation group (p=0.01)
rTMS for the Treatment of Obsessive-Compulsive Disorder (OCD)

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Procedure</th>
<th>Primary Measures</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right dorsolateral prefrontal cortex (DLPFC)</td>
<td>3 studies LF-rTMS (1Hz): 3x wk/6 wks; 5x wk/3 wks; 5x wk/2wks; 2 studies HF-rTMS (10 Hz): 30 sessions; 20 sessions</td>
<td>Improvement on Yale-Brown Obsessive Compulsive Scale (YBOCS)</td>
<td>Mixed results. 2/3 of the LF-rTMS showed significant improvement; 1/2 of the HF-rTMS showed significant improvement</td>
</tr>
<tr>
<td>Left DLPFC</td>
<td>1 study LF-rTMS (1Hz): 2 wks 1800 pulses/session 1 study HF-rTMS: 20 sessions</td>
<td>Improvement on the YBOCS</td>
<td>Not significant</td>
</tr>
<tr>
<td>Bilateral DLPFC</td>
<td>3 studies: HF-rTMS (20Hz): 2 wks 1 study: LF-rTMS (1Hz): 2 wks</td>
<td>Improvement on the YBOCS</td>
<td>HF-rTMS: significant improvement, LF-rTMS: not significant</td>
</tr>
<tr>
<td>Supplementary motor area (SMA)</td>
<td>5 studies: LF-rTMS (1Hz): 2 wks–8 wks</td>
<td>Improvement on the YBOCS</td>
<td>Mixed results: 2/5 studies showed significant improvement</td>
</tr>
<tr>
<td>Orbitofrontal cortex (OFC)</td>
<td>2 studies: LF-rTMS (1Hz): 15 sessions, 10 sessions</td>
<td>Improvement on the YBOCS</td>
<td>Significant improvement</td>
</tr>
</tbody>
</table>
Deep TMS for the Treatment of OCD

41 patients with treatment-resistant OCD at baseline

Yale-Brown Obsessive-Compulsive Scale (YBOCS)

HF 20 Hz dTMS to mPFC-ACC

LF 1 Hz dTMS to the mPFC-ACC

Sham to the mPFC-ACC

EEG

Stroop task

Five weeks

Yale-Brown Obsessive-Compulsive Scale (YBOCS)

EEG

Stroop task

Key:
mPFC=medial prefrontal cortex
ACC=anterior cingulate cortex
LF=low frequency; HF=high frequency

Deep TMS for the Treatment of OCD Results

Results:
YBOCS scores significantly improved following HF but not LF stimulation

EEG: Clinical response in the HF group correlated with error-related negativity (ERN) in the Stroop Task

Conclusion: HF dTMS over the mPFC-ACC alleviates OCD symptoms and may be used as a novel therapeutic intervention
## rTMS for the Treatment of Addiction

<table>
<thead>
<tr>
<th>Addiction</th>
<th>Procedure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Su et al. 2017</td>
<td>30 Methamphetamine-addicted patients received five sessions of 8 min sham or 10 Hz rTMS to the left DLPFC</td>
<td>Significantly reduced craving and improved verbal learning/social cognition after five sessions</td>
</tr>
<tr>
<td>Terraneo et al. 2016</td>
<td>32 cocaine-addicted patients received rTMS to the left DLPFC for 29 days</td>
<td>Significantly higher number of cocaine-free urine drug tests compared to control</td>
</tr>
<tr>
<td>Gay et al. 2017</td>
<td>22 patients with gambling disorder received a single session of HF-rTMS to the left DLPFC or sham</td>
<td>A single session of HF-rTMS significantly decreased cue-induced craving; however, it did not alter gambling behavior</td>
</tr>
<tr>
<td>Liu et al. 2020</td>
<td>118 male patients with heroin addiction were randomly assigned to three conditions (10 Hz rTMS, 1 Hz rTMS to the left DLPFC for for 20 daily sessions, or wait-list control condition)</td>
<td>10 Hz and 1 Hz rTMS were both effective in significantly reducing cue-induced craving scores in heroin users compared to the control</td>
</tr>
</tbody>
</table>

### Table 1

Studies that implemented TMS in the treatment of alcohol addicts. ACC, anterior cingulate cortex; ACQ-Now, alcohol craving questionnaire; AUQ, alcohol urge questionnaire; cTBS, continuous theta burst stimulation; dACC, dorsal anterior cingulate cortex; DMAI, days of maximum alcohol intake; dTMS, deep repetitive transcranial magnetic stimulation; DLPFC, dorsolateral prefrontal cortex; F, female; HF-rTMS, high frequency repetitive transcranial magnetic stimulation; M, male; mPFC, medial prefrontal cortex; NJ, not included; OCDS, obsessive compulsive drinking scale; rMT, resting motor threshold; rTMS, repetitive transcranial magnetic; VAS, visual analog scale; vmPFC, ventromedial prefrontal cortex.

<table>
<thead>
<tr>
<th>Study</th>
<th>REAL group (n)</th>
<th>SHAM group (n)</th>
<th>TMS</th>
<th>Sessions</th>
<th>Trains (pulses)</th>
<th>Coil</th>
<th>Frequency (Hz)</th>
<th>Intensity (% rMT)</th>
<th>Target Area</th>
<th>Assessment</th>
<th>Results (REAL vs. SHAM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addolorato et al., 2017</td>
<td>5 (all M)</td>
<td>6 (all M)</td>
<td>rTMS</td>
<td>12 (3/week)</td>
<td>20 (50/train)</td>
<td>H-shaped coil</td>
<td>10</td>
<td>100%</td>
<td>DLPFC</td>
<td>OCDS craving, VAS, Symptom Check List-90-R (SCL), Inhibitory control task (Stroop), Go/No-go task neuronal activation may serve as a protective mechanism regarding relapse</td>
<td></td>
</tr>
<tr>
<td>Del Felice et al., 2016</td>
<td>10 (3 F)</td>
<td>10 (1 F)</td>
<td>HF-rTMS</td>
<td>4 (2/week)</td>
<td>20 (50/train)</td>
<td>8-shaped coil</td>
<td>10</td>
<td>100%</td>
<td>left DLPFC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herremans et al., 2016</td>
<td>19 (11 M; 8 F)</td>
<td>19 (11 M; 8 F)</td>
<td>Accelerated HF-rTMS</td>
<td>14 over 3 consecutive days (4/5/5)</td>
<td>40 (1.9 s/train, 12 s inter-train interval)</td>
<td>8-shaped coil</td>
<td>20</td>
<td>110%</td>
<td>right DLPFC</td>
<td>OCDS craving, VAS, Symptom Check List-90-R (SCL), Inhibitory control task (Stroop), Go/No-go task neuronal activation may serve as a protective mechanism regarding relapse</td>
<td></td>
</tr>
<tr>
<td>Herremans et al., 2015</td>
<td>13 (4 F)</td>
<td>13 (5 F)</td>
<td>Accelerated HF-rTMS</td>
<td>15 (spread over 4 consecutive days)</td>
<td>40 (1.9 s/train, 12 s inter-train interval)</td>
<td>8-shaped coil</td>
<td>20</td>
<td>110%</td>
<td>right DLPFC</td>
<td>AUQ and OCDS</td>
<td></td>
</tr>
<tr>
<td>Ceccanti et al., 2015</td>
<td>9 (all M)</td>
<td>9 (all M)</td>
<td>dTMS</td>
<td>10 (5/week)</td>
<td>30 (50/train)</td>
<td>H-shaped coil</td>
<td>20</td>
<td>120%</td>
<td>mPFC</td>
<td>craving VAS, DMAI</td>
<td></td>
</tr>
<tr>
<td>Mishra et al., 2015</td>
<td>10/group targeted at left vs right DLPFC (all M)</td>
<td>NJ.</td>
<td>rTMS</td>
<td>10</td>
<td>20 (4.9 s/train, 30 s inter-train interval)</td>
<td>8-shaped coil</td>
<td>10</td>
<td>110%</td>
<td>right and left DLPFC</td>
<td>ACQ-Now</td>
<td></td>
</tr>
<tr>
<td>Herremans et al., 2012</td>
<td>15 (3 F)</td>
<td>16 (7 F)</td>
<td>HF-rTMS</td>
<td>1</td>
<td>40 (1.9 s/train, 12 s inter-train interval)</td>
<td>8-shaped coil</td>
<td>20</td>
<td>110%</td>
<td>right DLPFC</td>
<td>AUQ</td>
<td></td>
</tr>
<tr>
<td>De Riddler et al., 2011</td>
<td>1 F</td>
<td>NJ.</td>
<td>rTMS</td>
<td>21</td>
<td>1 (600 pulses)</td>
<td>double-cone coil</td>
<td>50</td>
<td>dACC</td>
<td>VAS</td>
<td>ACQ-Now in patients receiving either right or left rTMS No significant differences between groups = craving</td>
<td></td>
</tr>
<tr>
<td>Mishra et al., 2010</td>
<td>30 (M)</td>
<td>15 (M)</td>
<td>rTMS</td>
<td>10</td>
<td>20 (4.9 s/train, 30 s inter-train interval)</td>
<td>8-shaped coil</td>
<td>10</td>
<td>110%</td>
<td>right DLPFC</td>
<td>ACQ-Now</td>
<td></td>
</tr>
</tbody>
</table>

## Deep TMS (dTMS) for the Treatment of Addiction

<table>
<thead>
<tr>
<th># of studies</th>
<th>Addiction</th>
<th>Procedure</th>
<th># of sessions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Open-label</td>
<td>Alcohol use disorder (AUD)</td>
<td>H1 coil, 10–20Hz, 100-120%MT</td>
<td>10–12</td>
<td>Alcohol consumption was significantly reduced</td>
</tr>
<tr>
<td>1 RCT</td>
<td>AUD</td>
<td>H1 coil, 20Hz, 120%MT</td>
<td>20</td>
<td>Acute and longer term (6–12 months) cravings were reduced</td>
</tr>
<tr>
<td>1 RCT</td>
<td>Nicotine</td>
<td>H1 coil, 10Hz, 120%MT</td>
<td>13</td>
<td>Consumption reduced; abstinence increased</td>
</tr>
<tr>
<td>1 Open-label</td>
<td>Cocaine</td>
<td>H1 coil, 10Hz, 120%MT</td>
<td>12</td>
<td>Consumption reduced</td>
</tr>
<tr>
<td>1 RCT</td>
<td>Cocaine</td>
<td>H1 coil, 15Hz, 100MT</td>
<td>12</td>
<td>Cravings reduced</td>
</tr>
</tbody>
</table>

*Warning: Withdrawal from alcohol can lower the seizure threshold, and sobriety is strongly encouraged prior to starting TMS*

Brainsway: H4 Coil and Smoking Cessation

Multisite trial (14 sites) 168 participants highly addicted to smoking

dTMS (H4 coil) for 3 wks

Sham for 3 wks

Primary Endpoint: Continuous Quit Rate (CQR) (representing abstinence over four weeks)

The CQR was 28.4% compared to 11.7% in the sham group (p= 0.0063)

<table>
<thead>
<tr>
<th>Avg # Cigarettes/Week Before Treatment</th>
<th>Avg # Cigarettes/Week After 3 Wks of Treatment</th>
<th>Avg # Cigarettes/Week After 6 Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>132 vs. 127 (sham)</td>
<td>38 vs. 57 (sham) (p=0.0018)</td>
<td>31 vs. 48 (sham) (p=0.0125)</td>
</tr>
</tbody>
</table>

Large randomized pivotal study demonstrates exiting results: December 2019
Brainsway: H4 Coil and Smoking Cessation

*The FDA approved the H4 coil on August 24th, 2020 to treat smoking addiction.
Are we ready for TMS maintenance?

Three-Arm Open Label Study

(66 patients with TRD who had received either rTMS, venlafaxine, or combination, or sham, in a previous study were placed on a maintenance plan)

- For the rTMS group, 40.0% did not relapse
- For the venlafaxine group, 45.1% did not relapse
- For the combination group, 36.9% did not relapse

After 12-month follow-up, the rates of remitters were not significantly different between the three groups

3 Arm Study:
- (n=25) 1Hz rTMS to the right DLPFC [2x/week for 1 month, followed by 1x/week for 2 months, followed by 1x/2 weeks for 9 months]
- (n=22) Venlafaxine (Mean Dose 179± 36.6)
- rTMS [2x/week for one month, followed by 1x/week for 2 months, followed by 1x/2 weeks for 9 months] + venlafaxine (n=19)

Individualized Connectome-Targeted TMS for the Neuropsychiatric Sequelae of Repetitive TBI in a Retired NFL Player

Major depressive disorder

Traumatic brain injury can affect functional connectivity to the: DMN, DAN, anterior cingulate cortex (ACC), medial temporal lobe (MTL), and DLPFC

72% improvement in the Montgomery-Asberg Depression Rating Scale (MADRS)

Retired NFL player with multiple mTBIs

Resting-state network mapping (RSNM)

20 sessions of HF-rTMS (10Hz) to the left DLPFC and LF-rTMS (1Hz) to the right DLPFC at 120% RMT

Exploratory Studies With TMS

- Recent studies have aimed to reduce inter-individual variability and increase the efficacy of rTMS.

- One factor that remains overlooked is inter-train variability (ITI).

- Recent study: rTMS (20 Hz, 2s trains, 1200 pulses, 100% RMT) was applied to 14 healthy individuals with ITI of 4s (duration ~3 min), 8s (~5min), 16s (~9min), or 32s (16.5 min); sessions separated by ≥ 5 days.

- Disinhibition increased with shorter ITI duration.

- These findings provide the first evidence to suggest that ITI may be substantially shortened without loss of rTMS effects.

- Shorter ITI results in greater disinhibitory effects, which may be desirable for accelerated treatment paradigms.

• Electroconvulsive therapy (ECT)

• Cranial electrotherapy (CES)

• Transcranial direct current stimulation (tDCS)

• Trigeminal nerve stimulation (TNS)
Transcranial Direct Current Stimulation (tDCS)

- Non-invasive, non-convulsive
- Weak direct current passes into the cerebral cortex through two surface scalp electrodes
- Modulates cortical excitability dependent on the polarity of the stimulation

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Polarization</th>
<th>Neuronal firing</th>
<th>Cortical excitability</th>
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</thead>
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<tr>
<td>Anodal</td>
<td>Depolarized</td>
<td>↑</td>
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<tr>
<td>Cathodal</td>
<td>Hyperpolarized</td>
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Kalu UG et al. Psychol Med 2012;42(9):1791-800.
tDCS and Negative Symptom Treatment in Schizophrenia

95 patients with schizophrenia included in the double-blind Schizophrenia Treatment with Electric Transcranial Magnetic Stimulation (STARTS) conducted from Sept 2014–March 2018

10 sessions of tDCS 2x/day for 5 days, or sham

Patients in the tDCS condition demonstrated significant improvement in the Positive and Negative Symptoms Scale (PANSS) compared to sham

Response rates for negative symptoms (20% improvement or greater) were also higher in the active group (20 of 50 [40%]) compared to the sham (2 of 50 [4%])(p<0.01); results persisted at follow-up

Trigeminal Nerve Stimulation (TNS) for the Treatment of ADHD

In April 2019, the FDA approved the first medical device to treat attention deficit hyperactivity disorder (ADHD).

eTNS increases blood flow in brain regions associated with mood, attention, and executive function.

Monarch external trigeminal nerve stimulation

Indicated for children age 7–12 not currently taking prescription medication for ADHD.

Based on results from a clinical trial (n=62) in patients (7–12 years old) with moderate to severe ADHD,
eTNS significantly improved ADHD symptoms, compared to placebo device (a 10.7 point decrease vs. a 6.2 decrease).
Summary

• There are many types of effective brain stimulation techniques for treating neuropsychiatric disorders

• TMS has demonstrated promise in effectively treating several neuropsychiatric conditions, both on- and off-label

• Understanding which brain stimulation technique(s) is most appropriate for special populations is essential to effective treatment
Posttest Question 1

What kind of H coil was designed to target addiction circuits, and has recently demonstrated success in smoking cessation in a large trial?

1. H1
2. H4
3. H6
4. H7
In 2018, the Food and Drug Administration (FDA) approved the Brainsway H7 coil for the treatment of which mental disorder?

1. Attention Deficit Hyperactivity Disorder (ADHD)
2. Major Depressive Disorder (MDD)
3. Obsessive Compulsive Disorder (OCD)
4. Addiction