Clinical Applications and Depression Evidence

Berenson-Allen Center for Noninvasive Brain Stimulation
Beth Israel Deaconess Medical Center
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Disclosure of Financial Relationships

• Magstim LTD - Consultant
• NeoSync – Research Support
• Cervel Neurotech – Research Support
• Neuronetics – Research Support
• Medtronic (DBS) – Research support

Off-label use of TMS devices will be discussed
### Table 10: Leading global causes of YLD by sex, 2004

<table>
<thead>
<tr>
<th>Males</th>
<th></th>
<th></th>
<th>Females</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>YLD (millions)</td>
<td>Per cent of total YLD</td>
<td>Cause</td>
<td>YLD (millions)</td>
<td>Per cent of total YLD</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------</td>
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<td>-------------------------------</td>
<td>----------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>1 Unipolar depressive disorders</td>
<td>24.3</td>
<td>8.3</td>
<td>1 Unipolar depressive disorders</td>
<td>41.0</td>
<td>13.4</td>
</tr>
<tr>
<td>2 Alcohol use disorders</td>
<td>19.9</td>
<td>6.8</td>
<td>2 Refractive errors</td>
<td>14.0</td>
<td>4.6</td>
</tr>
<tr>
<td>3 Hearing loss, adult onset</td>
<td>14.1</td>
<td>4.8</td>
<td>3 Hearing loss, adult onset</td>
<td>13.3</td>
<td>4.3</td>
</tr>
<tr>
<td>4 Refractive errors</td>
<td>13.8</td>
<td>4.7</td>
<td>4 Cataracts</td>
<td>9.9</td>
<td>3.2</td>
</tr>
<tr>
<td>5 Schizophrenia</td>
<td>8.3</td>
<td>2.8</td>
<td>5 Ostearthritis</td>
<td>9.5</td>
<td>3.1</td>
</tr>
<tr>
<td>6 Cataracts</td>
<td>7.9</td>
<td>2.7</td>
<td>6 Schizophrenia</td>
<td>8.0</td>
<td>2.6</td>
</tr>
<tr>
<td>7 Bipolar disorder</td>
<td>7.3</td>
<td>2.5</td>
<td>7 Anaemia</td>
<td>7.4</td>
<td>2.4</td>
</tr>
<tr>
<td>8 COPD</td>
<td>6.9</td>
<td>2.4</td>
<td>8 Bipolar disorder</td>
<td>7.1</td>
<td>2.3</td>
</tr>
<tr>
<td>9 Asthma</td>
<td>6.6</td>
<td>2.2</td>
<td>9 Birth asphyxia and birth trauma</td>
<td>6.9</td>
<td>2.3</td>
</tr>
<tr>
<td>10 Falls</td>
<td>6.3</td>
<td>2.2</td>
<td>10 Alzheimer and other dementias</td>
<td>5.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease.

**Depression is the #1 GLOBAL CAUSE OF DISABILITY**
Unresolved Symptoms Following Adequate Trial (Dose and Duration) of Antidepressant Medication

STAR*D = Sequenced Treatment Alternatives to Relieve Depression

Percent

- Remission ~33%
- Mild symptoms ~28%
- Moderate symptoms ~23%
- Severe symptoms ~12%
- Very severe symptoms ~4%

Depressive Symptoms (QID-SR Score) After Up to 12 Weeks Antidepressant Treatment

STAR*D Study (N=2,876)
Historical Perspective....
Electroconvulsive Therapy (ECT)

- Treatments 2 – 3 times/week
- Course of Treatment = 6 - 12
- General anesthesia, Ventilation
- Succinyl Choline – neuromuscular block
- EEG monitoring
- Brief Pulse (.5 – 2 msec pulse width)
- Sine Wave Pulse (8.33 msec phase period)
- Dose= % output of ECT device
- Titrate to above Seizure Threshold
- Goal= Seizure (EEG) at least 30 seconds
Historical Perspective

1896: D’Arsonval - demonstrates electromagnetic stimulation

1910: Sylvanus – demonstrates retina stimulation magneto-phosphenes

1982: Polson – Sheffield UK Peripheral Nerve Stimulation

1985: Jalinous, Freeston, Barker - First TMS Device

1985: Barker & Cain - publish TMS to cortex

2018: Carpenter teaches how to find Barker’s Motor Threshold
FDA-Cleared TMS Devices for Depression

Neuronetics

MagVenture

NeuroSoft

Brainsway

Magstim

Nexstim
Other TMS Devices...

magandmore.com

deymed.com

kejianmed.com

eNeura
Spring TMS

axilumrobotics.com
TMS Coil Size/Shape: Depth vs. Focality

Deng Z et al, 2012
Different Pulse Patterns: Effect on Synaptic Efficiency (Plasticity)

<table>
<thead>
<tr>
<th>Paradigm</th>
<th>Net Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Pulse TMS (spTMS)</td>
<td>None</td>
</tr>
<tr>
<td>1 hz rTMS</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>10 hz rTMS</td>
<td>Excitatory</td>
</tr>
<tr>
<td>Continuous Theta Burst (cTBS)</td>
<td>LTD-like</td>
</tr>
<tr>
<td>Intermittent Theta Burst (iTBS)</td>
<td>LTP-like</td>
</tr>
</tbody>
</table>

- **Paradigm**
  - Single Pulse TMS (spTMS)
  - 1 hz rTMS
  - 10 hz rTMS
  - Continuous Theta Burst (cTBS)
  - Intermittent Theta Burst (iTBS)

- **Net Effect**
  - None
  - Inhibitory
  - Excitatory
  - LTD-like
  - LTP-like

- **Temporal Patterns**:
  - 20 msec (50hz)
  - 200 msec (5hz)
“Fast” versus “Slow” Pulsing: Opposite Effects on Neuronal Activity

rTMS over Left DLPFC (100% MT) x 2 weeks

20 Hz increased rCBF
- prefrontal cortex (L>R)
- cingulate gyrus (L >> R)
- left amygdala
- bilateral insula, basal ganglia, uncus, hippocampus
- bilateral parahippocampus, thalamus, and cerebellum

1-Hz decreased rCBF (in small areas)
- right prefrontal cortex
- left medial temporal cortex
- left basal ganglia
- left amygdala

rCBF not related to degree of clinical change

Speer AM et al. 2000
Stimulation Protocols: FDA-Cleared Devices

*Demonstrated Efficacy and Safety for MDD in Large RCTs*

**Figure-8 coils: Left DLPFC**
- 3000 pulses daily
- 10 Hz
- Four-second trains
- 75 trains of 40 pulses
- 26 sec interval*
- 5 days/wk x 6 weeks = 30
- 6 sessions for tapering (3/wk=>2/wk=>1/last week)
- 9 wks of care

*(O’Reardon et al. 2007)*

**H-coil: L>R DLPFC**
- 1980 pulses daily
- 18 Hz
- Two-second trains
- 55 trains of 36 pulses
- 20 sec interval
- 5 days/wk x 4 weeks
- Tapering: 2 days/wk x 12 wks
- 16 wks of care

*(Levkovitz et al. 2015)*
In USA... The FDA-Cleared Indication for TMS:
“...for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.”

In USA... TMS is considered “Off-Label” for:
- Adults who have not tried antidepressants
- Depression in Children or Adolescents
- Bipolar I or II Depressive Episodes
- Primary Anxiety Disorders, PTSD, OCD, ADHD
- Psychotic MDD, Schizoaffective DO, Schizophrenia
- Autism, Tinnitus, TBI, Parkinson’s
- Other neuropsychiatric disorders or indications

National Institute for Health and Care Excellence (NICE)
“Depression” (not limited to specific disease or course qualifiers)

“In rTMS, repetitive pulses of electromagnetic energy are delivered at various frequencies or stimulus intensities. Conventional rTMS is a repetition of individual pulses at a pre-set interval (train of pulses), whereas theta-burst rTMS is a repetition of short bursts of pulses at a pre-set interval (train of bursts). Stimulation can either be delivered unilaterally, over the left or right dorsolateral prefrontal cortex, or bilaterally over both cortices. Bilateral stimulation may be done sequentially or simultaneously. Treatment with rTMS usually comprises daily sessions lasting about 30 minutes, typically for 2 to 6 weeks.”
Other rTMS Protocols for Depression

Demonstrated Efficacy and Safety for MDD in Large Patient Samples, but not associated with FDA clearance

**Figure-8 coil: L then R DMPFC**
- 6000 pulses daily (3000 each side)
- 10 Hz stim (5-second trains)
- 10-second intertrain interval
- 5 days/week x 4-6 weeks
- 120% MT extensor hallucis longus-foot/toe
- DMPFC=25% of the nasion-inion distance posteriorly along the midline
- Coil orientation perpendicular to midline; current flow directed toward L or R hemisphere
  (Downar et al 2014)

**Figure-8 coil: Right DLPFC**
- 1800 pulses daily
- 1Hz (“Slow”)
- 1-second train
- No intertrain interval
- 5 days/week
- 120% (right) MT
- 4 weeks in “OPT TMS”
  (McDonald et al 2011)
Neuronetics’ RCT Design

Randomized, Double-blind, Sham-Controlled

Phase I
Drug-Free Lead-In
7-10 days

Phase II
Acute Treatment Phase
6 weeks

Phase III
Taper Phase
3 weeks

**Neurostar TMS Therapy (N=155)**
- 120% MT
- 10 pulses per second
- 4 sec on-time/26 sec off-time
- 3000 pulses/session

**Sham (N=146)**
- <10% field exposure at cortex

Primary Efficacy @ 4 weeks
Secondary Efficacy @ 6 weeks
Durability of Effect @ 9 weeks

[+ Open-label AD Mono-Rx]
Patient Characteristics for Neuronetics TMS Trial

Diagnosis, Disease Severity & Illness Course
- DSM-IV Diagnosis: Major Depressive Disorder, unipolar, unipolar, non-psychotic
- Average age ~50 years
- Largely (~95%) recurrent illness course
- Approximately 50% unemployed due to illness
- Moderate to severe symptom burden
  - Avg HAMD24 ~30, MADRS ~32 at study entry

Antidepressant Treatment History
- Moderate to severe treatment resistance in current episode
  - Nearly all received multiple ineffective treatments in current episode (range: 1 to 23 attempts, avg: 4)

Demitrack, MA, Thase, ME, 2009
Neuronetics’ Clinical Trial
Acute Study Outcomes

A. MADRS
(p=.057)

B. HAMD17
(p=.006)

O’Reardon et al, 2007
TMS Response and Remission Rates in Neuronetics’ Controlled Acute Study

O’Reardon et al, 2007
Extended TMS Acute Course for Nonresponders (n=71)
Open Cross Over Trial (n=85, former sham)

Avery DH et al, 2008
FDA Approval based on Subset (n=164) from Overall Study Sample (n=301)

<table>
<thead>
<tr>
<th>DSM-IV Diagnosis</th>
<th>Unipolar, non-psychotic Major Depressive Disorder (MDD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Previous MDD Episodes</td>
<td>97%</td>
</tr>
</tbody>
</table>
| Treatment History in Current Episode | # of median treatments attempted: 4  
Range of treatments attempted (#): 1 - 23  
# of treatments at adequate dose and duration: 1 |
| Patients Unemployed due to MDD | 48% |
| Patients with Co-morbid Anxiety Disorder | 35% |
| Symptom Severity | Baseline MADRS=33, HAMD24=30 (moderate to severe) |

This analysis lead to the original FDA indication for NeuroStar TMS therapy for patients with only 1 antidepressant medication failure in the current episode.
TMS Response and Remission Rates in *FDA-Indicated Population*

**HAMD-24 Response Rates**
(>50% Improvement from Baseline)

- Week 2: 23%
- Week 4: 37%
- Week 6: 54%

**HAMD-24 Remission Rates**
(HAMD-24 Total Score <11)

- Week 2: 7%
- Week 4: 19%
- Week 6: 33%

Demitrack MA & Thase ME, 2009
Highly Significant Outcomes in Subset (n=164) who failed ONE Adequate Antidepressant Trial

**P < .01.; LOCF analysis of evaluable study population.

Demitrack & Thase, 2009
Table 3. Adverse Events Occurring in the Active Treatment Group at a Rate of 5% or More and at Least Twice the Rate for Sham (with ME-Coded Preferred Terms Shown)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Active TMS (n = 165)</th>
<th>Sham TMS (n = 158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred term</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye pain</td>
<td>10 (6.1)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders Toothache</td>
<td>12 (7.3)</td>
<td>1 (.6)</td>
</tr>
<tr>
<td>General Disorders and Site Administration Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site discomfort</td>
<td>18 (10.9)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Application site pain</td>
<td>59 (35.8)</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td>Facial pain</td>
<td>11 (6.7)</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle twitching</td>
<td>34 (20.6)</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain of skin</td>
<td>14 (8.5)</td>
<td>1 (.6)</td>
</tr>
</tbody>
</table>

MedDRA, Medical Dictionary for Regulatory Activities.

O’Reardon J et al, 2007
NIH Optimization of TMS for Depression Study (OPT-TMS)

4 University Hospital TMS Clinics

Novel Sham (more effective blind)

Same device and stim parameters as Neuronetics clinical trial but no Industry sponsorship

MRI-guided coil placement

Large Sample N=190 (ITT)

George M et al, 2010
OPT-TMS Improved Sham

- Active TMS - scalp sensation, noise
- Developed system for producing electrical tickle, noise cancellation
- Patients less able to guess which group

Table 6. Spontaneous Adverse Events With rTMSa

<table>
<thead>
<tr>
<th></th>
<th>Active rTMS Group (n=92)</th>
<th>Sham rTMS Group (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>29 (32)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Discomfort at the stimulation site</td>
<td>17 (18)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 (7.6)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Worsening of depression or anxiety</td>
<td>6 (7)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6 (7)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (5)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>4 (4)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Skin pain</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Facial muscle twitching</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (20)</td>
<td>15 (15)</td>
</tr>
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</table>

George MS et al, 2010
### Table 3. Remission Status (Primary Outcome)

<table>
<thead>
<tr>
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<th>ITT (n=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active (n=92)</td>
</tr>
<tr>
<td>Remission</td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>13 (14)</td>
</tr>
<tr>
<td>95% CI</td>
<td>8.5-22.7</td>
</tr>
<tr>
<td>No remission</td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>79 (86)</td>
</tr>
<tr>
<td>95% CI</td>
<td>77.3-91.5</td>
</tr>
<tr>
<td>Logistic regression model (df)</td>
<td>Wald $\chi^2$</td>
</tr>
<tr>
<td>Treatment (1)</td>
<td>5.93</td>
</tr>
<tr>
<td>Site (3)</td>
<td>6.05</td>
</tr>
<tr>
<td>Age (1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Duration (1)</td>
<td>1.90</td>
</tr>
<tr>
<td>Medication resistance (1)</td>
<td>2.12</td>
</tr>
<tr>
<td>Treatment Odds ratio (95% CI)</td>
<td>4.18</td>
</tr>
</tbody>
</table>

George MS et al, 2010

**Replicated Neuronetics’ Trial Results**

$^b$ Adjusted odds ratio - adjusted for site, age duration of current depressive episode, and medication resistance
# OPT- TMS Continuous Outcomes

**Table 5. Continuous Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of Phase 1</th>
<th>Modeled^b</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>95% CI Effect Estimate^c</td>
<td>Cohen d^d</td>
<td>P Value^e</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients, No.</td>
<td>Patients, No.</td>
<td>Estimate^c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D: active TMS</td>
<td>26.26 (4.95)</td>
<td>21.61 (9.26)</td>
<td>-4.23 to 0.10</td>
<td>-0.42</td>
<td>.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D: sham TMS</td>
<td>26.51 (4.83)</td>
<td>23.38 (7.43)</td>
<td>-6.10 to -0.76</td>
<td>-0.51</td>
<td>.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADRS: active TMS</td>
<td>29.48 (6.91)</td>
<td>24.59 (11.44)</td>
<td>-0.68 to -0.09</td>
<td>-0.55</td>
<td>.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADRS: sham TMS</td>
<td>29.81 (6.42)</td>
<td>27.75 (9.06)</td>
<td>-10.04 to -2.62</td>
<td>-0.66</td>
<td>.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-S: active TMS</td>
<td>4.62 (0.70)</td>
<td>3.96 (1.14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-S: sham TMS</td>
<td>4.63 (0.69)</td>
<td>4.30 (0.87)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDS: active TMS</td>
<td>40.98 (9.27)</td>
<td>32.56 (15.40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDS: sham TMS</td>
<td>40.07 (9.81)</td>
<td>36.70 (13.91)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Confirmed efficacy as reported by Neuronetics’ Sponsored Trial

George MS et al, 2010
OPT – TMS
Open Extension/Cross-over Study

N=61 Prior Active
31% Remitted

N=80 Prior Sham
30% Remitted

DURATION OF ACUTE COURSE:
Mean 5.2 weeks to Remission
Some needed 6-9 wks

LATERALITY:
Of those who did not improve
To 10 Hz Left TMS, 26%
Remitted with Right 1 Hz TMS

(START*D patients with 3 failed medication trials had remission rates with new medication trials of 10% to 20%)

McDonald W et al (2011)
MRI – Guided Adjustment of Coil Placement

“5 cm Rule” not over DLPFC for many Better TMS Outcome
• More Anterior
• More Lateral (within 5-cm rule area)


<table>
<thead>
<tr>
<th>Brodmann Area (%)</th>
<th>9 *</th>
<th>46 *</th>
<th>6</th>
<th>8</th>
<th>44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined (n = 54)</td>
<td>31 (57.4)</td>
<td>3 (5.6)</td>
<td>10 (18.5)</td>
<td>5 (9.3)</td>
<td>5 (9.3)</td>
</tr>
<tr>
<td>Active TMS (n = 28)</td>
<td>13 (46.4)</td>
<td>3 (10.7)</td>
<td>5 (17.9)</td>
<td>2 (7.1)</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Sham TMS (n = 26)</td>
<td>18 (69.2)</td>
<td>0 (0)</td>
<td>5 (19.2)</td>
<td>3 (11.5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex; TMS, transcranial magnetic stimulation.
*BA 9 and BA 46 comprise DLPFC.
Acute Efficacy Outcomes in Naturalistic Settings
58% Responders, 37% Remitters

- n=307 Clinical results matched those reported in controlled research trials.
- Confirmed that TMS therapy is safe and well tolerated in a nonresearch population.
- 54% of the patients had ATR>1 but, resistance level NOT a predictor of response

Carpenter et al 2012
Brainsway “Deep TMS” RCT (H1 Coil)

- 21 clinical sites (14 US, 4 Israel, 2 Germany, 1 Canada)
- 233 medication free unipolar depressed enrolled
- mild treatment resistance
- Left prefrontal predominant target
- 120% MT, 18 Hz, 2 sec on, 20 off, 15 min, 1680 pulses/day
- 5/week x 4 weeks, then 2/week
- Continued blind until week 12
- US FDA Approval Jan 2013

Primary Outcome=week 5 (22 sessions)

Levkovitz et al 2015
**Brainsway - Acute TMS Results**

*6.39 vs 3.28 mean improvement on HRSD (p=0.008; n=212)*
ITT (n=181), 6.17 vs. 3.94 point change (p=.058)

*Response 38.4% versus 21.4% (p=0.01)*
*Remission 32.6% versus 14.6% (p=0.005)*

* Per-Protocol (PP); n= rather than ITT

Levkovitz et al 2015
PRESSING CLINICAL QUESTION: Long-Term Durability of TMS?
For Comparison with Relapse Following TMS: Relapse During Follow-Up in STAR*D Treatment with the Best Medication Algorithms

The greater the level of treatment resistance (prior to remission), the more quickly a patients with TRD will relapse

Neuronetics Trial: Durability of Response (n=99 followed 24 weeks)

- **10% Relapsed**
  (Kaplan-Meier survival estimate=12.9%)
- **38% had “symptom worsening”**
  - TMS re-introduction “rescue"
  - 2 session/week x 2 weeks, then daily

- **84.2% who got “booster” TMS re-achieved response**

Janicak PG et al, 2010
Brainsway dTMS Trial: 16 weeks Continuation
Scheduled 2 Sessions/Week

- 5/week TMS x 4 weeks (acute)
- 2 TMS/Week from weeks 5 to 16
- 12 week Continuation Remained Blind

n=33 Nonresponders to 4 week Acute (20)
Continue to Receive Active TMS 2/week

61% of unmedicated treatment resistant depression patients who did not respond to acute TMS treatment responded after four weeks of twice weekly deep TMS in the Brainsway pivotal trial

Yip et al 2017
Naturalistic Settings: Long-Term Outcomes

63% Acute TMS Responders Remained Responders Throughout Follow up

36% Required Additional TMS Treatments

Mean Number of Additional Treatments = 16

Dunner et al, 2014
“Maintenance” (Continuation) dTMS
Bipolar or Unipolar MDE

n=24

Standard Acute dTMS
4 weeks = 20 sessions
(18 Hz H1-coil,
1980 pulse/session)

Randomize:
Maintenance TMS (16 total)
twice/week x 1 month
once/week x 2 months
versus
Observation (Naturalistic)
HAMD: 6 months and 12 months after end acute phase

Rapinesi et al 2015

Table 2 | Within-groups HDRS changes after dTMS, at the 6-month follow-up, and at the 12-month follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Patients with dTMS maintenance, mean ± SD</th>
<th>P</th>
<th>Patients without dTMS maintenance, mean ± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HDRS</td>
<td>23.83 ± 3.27</td>
<td></td>
<td>23.50 ± 3.28</td>
<td></td>
</tr>
<tr>
<td>Post-dTMS HDRS</td>
<td>9.83 ± 1.27</td>
<td>0.002</td>
<td>9.92 ± 2.35</td>
<td>0.002</td>
</tr>
<tr>
<td>Wilcoxon-Z Test</td>
<td>-3.070</td>
<td></td>
<td>-3.083</td>
<td></td>
</tr>
<tr>
<td>Post-dTMS HDRS at 6-month follow-up</td>
<td>9.83 ± 1.27</td>
<td>0.002</td>
<td>9.92 ± 2.35</td>
<td>0.002</td>
</tr>
<tr>
<td>HDRS at 6-month follow-up</td>
<td>9.33 ± 2.23</td>
<td>0.441</td>
<td>13.75 ± 5.53</td>
<td>0.046</td>
</tr>
<tr>
<td>Wilcoxon-Z Test</td>
<td>-0.770</td>
<td></td>
<td>-1.995</td>
<td></td>
</tr>
<tr>
<td>Post-dTMS HDRS at 12-month follow-up</td>
<td>9.83 ± 1.27</td>
<td>0.441</td>
<td>9.92 ± 2.35</td>
<td>0.046</td>
</tr>
<tr>
<td>HDRS at 12-month follow-up</td>
<td>12.92 ± 5.78</td>
<td>0.252</td>
<td>16.17 ± 7.11</td>
<td></td>
</tr>
<tr>
<td>Wilcoxon-Z Test</td>
<td>-1.146</td>
<td></td>
<td>-2.050</td>
<td>0.040</td>
</tr>
</tbody>
</table>
Can Medication Free, Treatment-Resistant, Depressed Patients Who Initially Respond to TMS Be Maintained Off Medications? A Prospective, 12-Month Multisite Randomized Pilot Study

Noah S. Philip\textsuperscript{a,b,*}, David L. Dunner\textsuperscript{c}, Sheila M. Dowd\textsuperscript{d}, Scott T. Aaronson\textsuperscript{e}, David G. Brock\textsuperscript{f}, Linda L. Carpenter\textsuperscript{b}, Mark A. Demitrack\textsuperscript{f}, Sarit Hovav\textsuperscript{g}, Philip G. Janicak\textsuperscript{d}, Mark S. George\textsuperscript{h,i}

![Image of survival curves and table]

**Figure 2.** Survival curves for time to first retreatment. Kaplan–Meier survival curves for time to first retreatment. Log-rank $\chi^2 = 1.01$, df = 1, $p > 0.1$. Key: OBS, observation-only group; SCH, scheduled TMS group. * indicates participant drop outs.
Targeting: Resting State Functional Connectivity to Guide Targeting TMS coil position?

Differences in functional connectivity related to clinical efficacy of TMS

DLPFC TMS sites with better clinical efficacy were more negatively correlated (anticorrelated) with the subgenual cingulate.

Fox MD et al, 2012
TMS Coil Placement: Neuronavigation

• Visualization of TMS coil in relation to brain in real time on a screen

• Anatomic landmarks “co-register” the head and the coil in the coordinate system of the brain MRI

Herwig U, et al 2003
Both Groups Improved Over Time (p<.0001)
Neuronavigated DLPFC Coil Placement:
Numerically Greater Improvement
42% vs. 18% Responders (p=.07)

*Trend Difference; Not Statistically Superior to “5-cm Rule”*

P. Fitzgerald et al. 2009
Alternate Stimulation Protocols?
5 Hz TMS to Left DLPFC: Open Label/Naturalistic


Research report

5 Hz Repetitive transcranial magnetic stimulation to left prefrontal cortex for major depression

Noah S. Philip a,b,*, S. Louisa Carpenter a, Samuel J. Ridout b, George Sanchez a, Sarah E. Albright a, Audrey R. Tyrka b, Lawrence H. Price b, Linda L. Carpenter b

a Center for Neuron restoration and Neurotechnology, Providence VA Medical Center, Providence, RI, United States
b Butler Hospital Mood Disorders Research Program, Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, United States

Philip N et al 2015
Right-Sided (DLPFC) 1 Hz TMS Appears Effective for MDD

*Meta-Analysis: Randomized, Double-Blind, Sham Controlled Trials*

Subjects from 8 RCTs, n=263

Response Rate After 12.6±3.9 rTMS sessions: 38.2% (Active) and 15.1% (Sham)

Odds Ratio=3.35; 95% CI 1.4–8.02; p=0.007

Berlim et al 2013
Bilateral (DLPFC) TMS Appears Effective in Randomized Trials

...But not superior to Unilateral (Left)

n=410
Bilateral TMS not superior to Unilateral TMS for MDD

n=278
Bilateral TMS superior to SHAM (RR=3.29; p=.0004)
1 Hz rTMS for Postpartum Depression

Table 2

<table>
<thead>
<tr>
<th>Scale</th>
<th>Mean/SD</th>
<th>Mean/SD</th>
<th>Mean/SD</th>
<th>Mean/SD</th>
<th>χ² value</th>
<th>Significance level (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline score</td>
<td>2-wk score</td>
<td>4-wk score</td>
<td>6-mo score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRSD-24</td>
<td>23.43 (6.00)</td>
<td>9.00 (3.70)</td>
<td>2.14 (3.19)</td>
<td>2.00 (3.32)</td>
<td>19.50</td>
<td>&lt; .0005</td>
</tr>
<tr>
<td>IDS-SR</td>
<td>42.43 (11.89)</td>
<td>20.71 (7.48)</td>
<td>7.29 (6.42)</td>
<td>4.29 (5.25)</td>
<td>19.97</td>
<td>&lt; .0005</td>
</tr>
<tr>
<td>EPDS</td>
<td>18.29 (4.68)</td>
<td>9.14 (2.12)</td>
<td>3.43 (3.21)</td>
<td>2.71 (2.43)</td>
<td>19.35</td>
<td>&lt; .0005</td>
</tr>
<tr>
<td>CGI-S</td>
<td>4.00 (0.00)</td>
<td>2.57 (0.79)</td>
<td>1.14 (0.38)</td>
<td>1.29 (0.49)</td>
<td>19.82</td>
<td>&lt; .0005</td>
</tr>
</tbody>
</table>

HRSD-24 = Hamilton Rating Scale of Depression-24-point scale; IDS-SR = Inventory of Depressive Symptomatology-Self-Report; EPDS = Edinburgh Postnatal Depression Scale; CGI-S = Clinical Global Impressions-Severity; SD = standard deviation. Data are given as mean (SD).
1 Hz rTMS for Postpartum Depression

Neuronetics’ PPD Trial (n=19)
postpartum onset
TMS monotherapy
Active, “on-label” protocol
Results presented @ APA 2016
Edinburgh Postnatal Dep Scale
*Mean Decreased 20.6 from 8.2
74% Remission Rate
Safety Established for PPD

www.clinicaltrials.gov, listing number NCT 01842542; manuscript in preparation
What About TMS for Bipolar Depression?

n=49 (Bipolar I and II, Depressive Episodes)

MRI Neuronavigation-Targeted DLPFC
Sequenced Protocol:
- Right: 1 Hz x 1000 pulses (110%MT)
- Left: 10 Hz (5 sec/25 sec) x 1000 pulses (110%MT)

This is largest trial of TMS in Bipolar Depression.
No group difference in reduction on HAMD
No group difference in reduction on IDSSR
No group difference in Response or Remission

P. Fitzgerald et al. 2016
TMS for Bipolar II Depressive Episodes?

Randomized, Sham-Controlled Trial: TMS + Quetiapine

Hu et al. 2016

1200 pulses/session for 4 Weeks (20 sessions)

TMS Intensity = 80% MT

(N=12) 10 Hz TMS to left DLPFC + Quetiapine

(N=13) 1 Hz TMS to Right DLPFC + Quetiapine

(N=13) SHAM TMS (10 Hz Left) + Quetiapine

- No differences between groups on any outcome measure.
- Possible limitation: subthreshold (80% MT) stimulation.

Hu et al. 2016
More pulses per session?
6800 stimuli per session (34,000 stimuli per week)

Confirmed **tolerability** of increased number pulses/session/day

Prospective data support **extension of acute phase** with additional daily treatments for nonresponders

**Data are still lacking** to support the notion that increased number of pulses per session (above standard protocol) produces better outcome

D. Hadley et al, 2011
Accelerated TMS – High Daily “Dose” of Pulses and Sessions

Research Article

ACCELERATED REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR TREATMENT-RESISTANT DEPRESSION

Paul E. Holtzheimer, III M.D.,1 William M. McDonald, M.D.,1 Mustafa Mufti, M.D.,1 Mary E. Kelley, Ph.D.,2 Sinéad Quinn, B.A.,1 German Corso, M.D.,1 and Charles M. Epstein, M.D.3*

14 Treatment Resistant Depressed Patients on medications
Open-Label TMS, 15 sessions over 2 days, 15,000 total pulses
10 Hz, 5 sec, 25 rest, 100% MT
Safe, well-tolerated
More Sessions Per Day?
Retrospective Chart Review n=130

Bilateral 10 Hz to DMPFC
N=65 Once-daily (6000 pulses) compared with n=65 who got twice per day (3000 pulses each session)
80 minutes between sessions
Response/Remission Rates did not differ
once/day: 35.4%/33.8%
twice/day: 41.5%/35.4%

“Therapeutic gains tracked the cumulative number of sessions, not pulses”

L. Schulze et al. 2017
Intermittent Theta-Burst TMS for MDD

*iTBS: ‘Quicker’ but Not Superior to Standard 10 Hz Protocol*

10 Hz x 30 minutes to DMPFC
3000 Left PLUS 3000 Right
120% MT; 5 sec train/10 sec rest;
n=98
40.6% Response,
29.2% Remission

*iTBS x 6 minutes to DMPFC*
600 Left PLUS 6 --Right
120% MT  n=87
43.0% Response,
31% Remission

No Significant Differences
Biological Mechanism of rTMS Effects on Neuropsychiatric Disorders is Unknown

- Changes in blood flow and metabolism at the stimulation site
- Brain-derived neurotrophic factor upregulation
- Increase in grey matter volume
- Reductions in GABA/glutamate concentrations
- Enhancements in synaptic plasticity
- Change in neural oscillations (EEG)
- Changes in connectivity/activity of neural circuitry, e.g., DLPFC-anterior cingulate cortex

...Probably not one single mechanism for rTMS therapeutic action
Neuronal Entrainment to Reset Cortical Oscillatory Rhythms

*Theoretical Mechanism of rTMS Action*

| MDD: Hypersynchronous Alpha Rhythm | rTMS: Entrain Alpha Rhythm | After rTMS: Reset Oscillators; Reduced Alpha Synchrony |

Leuchter A et al, 2013
TMS Acutely Increases ACC Connectivity Within One Specific Meso-Cortical-Limbic Network

Sham-controlled, Single session rTMS in N=60 healthy adults

Whole-Brain Resting State Network Analysis based on 20 independent components from worldwide sample (n>1000): pre- versus post treatment change

RSN#17 includes dorsal cingulate, posterior DMPFC, DLPFC, inferior parietal lobule, inferior frontal cortex, and posterior temporal lobes.

Tik et al 2017
rTMS Normalizes Depression-Related Hyperconnectivity of Subgenual ACC

Baseline subgenual cingulate connectivity predicted Positive rTMS treatment response

Liston C et al. 2014
rTMS-Induced Morphological Changes in Brain Regions: Reversal of Gray Matter Deficits?

MRI T1 scans (structural)

N=27 MDD patients got rTMS to left DLPFC

N=27 healthy volunteers (no rTMS)

Anterior Cingulate Cortex Smaller in MDD vs. Healthy at Baseline And Significantly Increased (Normalized) Following rTMS

Lan et al 2016
fMRI Connectivity Predictors of Response to TMS

A) anticorrelations between sgACC and regions of DMN
B) more positive connectivity between prefrontal cortex and basolateral amygdala
C) pos connectivity between BL amygdala – medial PFC
## Professional Practice Guidelines Following Failure of Initial Treatment

<table>
<thead>
<tr>
<th>Guideline Source</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>World Federation of Societies for Biological Psychiatry (2009)</td>
<td>“...There is sufficient class I evidence of acute efficacy for TMS in depression in medication-free unipolar depressed patients...”</td>
</tr>
<tr>
<td>Canadian Network for Mood and Anxiety Treatments (2009)</td>
<td>“...There is most evidence to support ECT as a first-line treatment under specific circumstances and rTMS as a second-line treatment...”</td>
</tr>
<tr>
<td>Institute for Clinical Systems Improvement (2010)</td>
<td>“...At this time it appears there probably is enough evidence to consider rTMS (as implemented with a protocol that utilizes a six-week standardized protocol) an evidence-based treatment for treatment-resistant depression in adults...”</td>
</tr>
<tr>
<td>American Psychiatric Association (2010)</td>
<td>“...Acute phase treatment may include pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or light therapy...”</td>
</tr>
</tbody>
</table>

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**PLEASE DO NOT COPY**
Shinjuku Mental Clinic in Tokyo, Japan

- Opened in June, 2013 to treat Major Depressive Disorder
- 60 NeuroStar Devices
- Staff of physicians, clinical psychologists and treaters.
Future Applications of Neuromodulation Therapeutics…

Could brain stimulation inhibit Donald Trump’s Tweats?
1 Hz rTMS to DLPFC for Cigarette Smoking/ Nicotine Craving

Results:
- Better Abstinence @ week 2
- But no Sustained Effect

Limited Effect on Craving

<table>
<thead>
<tr>
<th>Time period from quitting attempt (weeks)</th>
<th>Active rTMS + NRT</th>
<th>Sham rTMS + NRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>88.8</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>44.4</td>
<td>44.4</td>
</tr>
<tr>
<td>12</td>
<td>38.8</td>
<td>38.8</td>
</tr>
<tr>
<td>12</td>
<td>27.7</td>
<td>27.7</td>
</tr>
</tbody>
</table>

Changes in craving scale scores at the end of 2 weeks of active and sham rTMS (10 sessions) combined with NRT in participants quitting smoking.

<table>
<thead>
<tr>
<th>rTMS</th>
<th>Active</th>
<th>Sham</th>
<th>Active vs Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MD (SD)</td>
<td>WSRT</td>
<td>MD (SD)</td>
</tr>
<tr>
<td>VAS</td>
<td>-2.6 ± 3.5</td>
<td>0.009*</td>
<td>-3.0 ± 3.5</td>
</tr>
<tr>
<td>QSU</td>
<td>-12.0 ± 13.2</td>
<td>0.004*</td>
<td>-9.8 ± 14.2</td>
</tr>
<tr>
<td>Desire (factor 1)</td>
<td>-14.1 ± 15.2</td>
<td>&lt;0.001*</td>
<td>-12.0 ± 13.2</td>
</tr>
<tr>
<td>Relief (factor 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trojak et al. 2015
Summary

- rTMS has evolved to a Standard of Care for Depression
- Infinite Stimulation Parameter Space to be Investigated
- Much ongoing research to optimize rTMS for depression and establish rTMS evidence base for other disorders
- Putative Mechanism of rTMS Therapeutic Mechanism is Unknown
- Findings from Scientific Studies Should Guide Clinical Practice