Clinical Applications of TMS & Evidence in Depression

Adam Stern, M.D.
Director of Psychiatric Applications
Berenson-Allen Center for Noninvasive Brain Stimulation, BIDMC

Instructor in Psychiatry
Harvard Medical School
Overview

- TMS Basics in Psychiatry
- TMS studies in depression
- Treatment program at BIDMC
Disclosures

Research has been supported by

Harvard Catalyst / The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102) and financial contributions from Harvard University and its affiliated academic health centers. The content is solely the responsibility of the author and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation
Disclosures (cont.)

• TMS has been approved for treatment in treatment-resistant depression though we may discuss other uses which have not been FDA approved.

• Some portion of the material has been shared by other members of the BA-CNBS and are used with permission.

• I have no financial conflicts to report.
What is the need for non-invasive brain stimulation?

STAR*D Study (N=2,876)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>~33%</td>
</tr>
<tr>
<td>Mild symptoms</td>
<td>~28%</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>~23%</td>
</tr>
<tr>
<td>Severe symptoms</td>
<td>~12%</td>
</tr>
<tr>
<td>Very severe symptoms</td>
<td>~4%</td>
</tr>
</tbody>
</table>

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

STAR*D = Sequenced Treatment Alternatives to Relieve Depression
Developments in Medical Treatment of Depression

1900

1st century

’30s ’40s ’50s ’60s ’70s ’80s ’90s

“Black Bile”

ECT

TCAs

MAOIs

SSRIs

Lithium

Heterocyclics

Pharmacologic Refinements

Courtesy of: ASCP Psychopharmacology Curriculum: “Electroconvulsive Therapy”
What about Electroconvulsive therapy (ECT)?

- Many decades of safety and efficacy data
- Gold Standard for treatment-resistant depression
- Invasive stimulation requiring anesthesia with frequent cognitive adverse effects
- Enormous stigma

Image courtesy of:
Electro-Magnetic Induction

“I think I got hold of a good thing”

M. Faraday
29 August 1831
Stimulation Coils
Equipment
Repetitive Stimulators
Topographic resolution
Figure 1. Transcranial magnetic stimulation coil placement over the dorsolateral prefrontal cortex and its connectivity to subcortical loops and associated functional neural networks, including the subgenual cingulate.

ACC: Anterior cingulate cortex; dlPFC: Dorsolateral prefrontal cortex; DL: Dorsolateral; LDM: Lateral dorsomedial; MD: Mediodorsal; NA: Nucleus accumbens; TMS: Transcranial magnetic stimulation; V: Ventral; VA: Ventral anterior; VM: Ventromedial.

Adapted with permission from [35].

Scalp to Brain Relation
TMS Parameters

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

20 msec (50hz)

200 msec (5hz)
rTMS: Lasting Modulation of Cortical Activity

Sham TMS

1 Hz TMS

20 Hz TMS

Valero et al. 2002
Therapeutic Applications of rTMS

- Depression
- Bipolar Disorder
- OCD
- PTSD
- Schizophrenia
- Auditory Hallucinoses
- Pain
  - Visceral pain
  - Atypical facial pain
  - Phantom pain
- PD
- Focal dystonia
- Epilepsy
  - Myoclonic epilepsy
  - Focal status epilepticus
- Stuttering
- Tics
- Neurorehabilitation
  - Neglect
  - Aphasia
  - Hand weakness
Potential Adverse Effects

- **Common:**
  - Headache
  - Auditory effects

- **Rare**
  - Seizure induction
  - Effects on Cognition
  - Mania
  - Endocrine effects

Safety Guidelines
Monitoring
TMS Timeline

1984
Cadwell Repetitive TMS (rTMS)
Anthony Barker Single Pulse TMS

1987

1996
Pascual-Leone, et. al.
George, et. al.
rTMS for depression

2007
FDA approval
Neuronetics Phase III trial of rTMS for Medication-resistant depression

2008
NHIC Medicare Approval (MA,NH,VT and RI)

2012
Brainsway DeepTMS
FDA cleared

2013
rTMS in Depression

- Kolbinger et al. 1993, 95
- Grisaru et al. 1994
- George et al. 1996

- Pascual-Leone et al. 1996
  - Double Blind
  - Multiple Control Conditions
  - 17 patients
  - 9/17 with ∂HDRS > 50%

Lancet 1996

Figure 1: Hamilton depression rating scale (HDRS) and Beck questionnaire (BQ) scores according to rTMS stimulation condition

Symbols represent mean score (and SD) of raw scores for all 17 patients at baseline (weeks before first rTMS session), and at end of each week of rTMS session. Stimulation condition A=real left DLPFC stimulation; B=real right DLPFC stimulation (control); C=sham left DLPFC stimulation (control); D=sham right DLPFC stimulation (control); E=real vertex stimulation (C, control). Order of different stimulation conditions was randomised across patients. To generate these analyses, months of the same stimulation condition were arranged together, therefore, sequence A–E does not represent a real ordering in time.
rTMS for depression treatment
Efficacy - Review

Neuronetics - NeuroStar

- Treatment Coil
- Display
- Mobile Console
Sen-Star Treatment Link

4 key functions:

* Contact sensing to ensure treatment coil is positioned correctly
* Magnetic field confirmation to ensure patient receives desired treatment
* Surface field cancellation to reduce stimulation of the scalp
* Charge approximately $100 per treatment
Stimulation Parameters

10 pulses/sec
120% of motor threshold
3000 pulses/session
4–6 weeks
Iron-core coil
Study 101 Patient Population

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

- **Treatment Resistance**
  - Moderate to severe treatment resistance in current episode
    - Nearly 50% failed to receive benefit from >2 adequate treatments (i.e., dose/duration)
    - Nearly all received multiple (avg > 4), ineffective treatments in current episode
# Comparison of TMS Study Population to ECT Reference Population

<table>
<thead>
<tr>
<th>Demographic Variables</th>
<th>Neuronetics Active TMS (N=155)</th>
<th>OPT-ECT Study (N=139)*</th>
<th>Community ECT Study (N=129)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(%) Female</td>
<td>86 (55.5)</td>
<td>95 (68.3)</td>
<td>82 (63.6)</td>
</tr>
<tr>
<td>Age in years (SD)</td>
<td>47.9 (11.0)</td>
<td>46.8 (13.2)</td>
<td>48.2 (11.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>Neuronetics Active TMS (N=155)</th>
<th>OPT-ECT Study (N=139)*</th>
<th>Community ECT Study (N=129)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent illness course N (%)</td>
<td>149 (95.5)</td>
<td>110 (79.1)</td>
<td>84 (65.1)</td>
</tr>
<tr>
<td>Duration of current episode in mos (median)</td>
<td>10.0</td>
<td>11.0</td>
<td>8.3</td>
</tr>
<tr>
<td>N (%) with current episode &gt; 2 years</td>
<td>36 (23.2)</td>
<td>21 (15.1)</td>
<td>10 (7.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment History</th>
<th>Neuronetics Active TMS (N=155)</th>
<th>OPT-ECT Study (N=139)*</th>
<th>Community ECT Study (N=129)*</th>
</tr>
</thead>
<tbody>
<tr>
<td># Adequate in Current Episode</td>
<td>1.6</td>
<td>1.4</td>
<td>1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Symptom Severity</th>
<th>Neuronetics Active TMS (N=155)</th>
<th>OPT-ECT Study (N=139)*</th>
<th>Community ECT Study (N=129)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAMD 24 total score (Mean [SD])</td>
<td>30.1 (5.0)</td>
<td>33.9 (6.7)</td>
<td>30.7 (6.6)</td>
</tr>
</tbody>
</table>

*Subset analysis provided by H. Sackeim
Study 101 Trial 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

Primary Timepoint @ 4 weeks

NeuroStar TMS Therapy
(N=155)

Secondary Timepoint @ 6 weeks

Sham TMS
(N=146)

Durability of Effect @ 9 weeks

[TMS Taper + Open-label AD Mono-Rx]

Randomization

n=325
Study 101 Efficacy Outcomes Continuous Measures

MADRS Total Score Baseline to Endpoint Change

- Change from Baseline (SEM)
- Baseline, Week 2, Week 4, Week 6
- NeuroStar TMS Therapy, Sham

P = .057
P = .058

Pre-specified LOCF analysis of evaluable study population
# Study 101: Significant Clinical Effects on HAMD Categorical Measures

**HAMD24 Response**

(≥50% Improvement from Baseline)

<table>
<thead>
<tr>
<th></th>
<th>Week 4</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>19.4</td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>11.6</td>
<td>15.9</td>
</tr>
</tbody>
</table>

P = .030

**HAMD24 Remission**

(HAMD Total Score < 11)

<table>
<thead>
<tr>
<th></th>
<th>Week 4</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>23.9</td>
<td>17.4</td>
</tr>
<tr>
<td>Sham</td>
<td>15.9</td>
<td>8.2</td>
</tr>
</tbody>
</table>

P = .042

P = .644

P = .012

---

PLEASE DO NOT COPY
Acute Effects in Study 101 are Sustained
Maintained Effect in Taper From TMS to Pharmacotherapy

91.9% of Acute Phase Responders Persist Through End of Taper Phase

LOCF analysis of evaluable study population
Clinical Benefit Varies by Prior Treatment Failure in Both STAR-D and TMS Study 102

Comparison of Monotherapy Outcomes: Pharmacotherapy vs TMS

- % Remission (HAMD 17)
  - No or Limited Prior Rx: 27.5%
  - One Prior Failure: 21.2% (STAR-D), 25.6% (Neuronetics)
  - Two Prior Failures: 16.2% (STAR-D), 17.9% (Neuronetics)
  - Three Prior Failures: 6.9% (STAR-D), 18.2% (Neuronetics)

Sample Size (N):
- No or Limited Prior Rx: 2876
- One Prior Failure: 727 (STAR-D), 43 (Neuronetics)
- Two Prior Failures: 221 (STAR-D), 28 (Neuronetics)
- Three Prior Failures: 58 (STAR-D), 11 (Neuronetics)

[Low] Treatment Resistance [High]
How does TMS compare to other approaches for treatment-resistant depression?

- Olanzapine/Fluoxetine (Thase, 2007): 0.33
- Aripiprazole (Marcus, 2008): 0.34
- Neurostar TMS Therapy (Demitrack, 2009): 0.52
- Brainsway DeepTMS (Levkovitz, 2015): 0.76
- Electroconvulsive Therapy (UK ECT Review Group, 2003): 0.91
Brainsway DeepTMS: A New Device
Over 900 phone screenings

Over 470 subjects excluded

428 consented

216 subjects excluded
Subjects did not meet eligibility criteria, withdrew consent or left the study before randomization

212 subjects (ITT sample)

31 subjects excluded
Subjects' average stimulation intensity was <118% of measured MT

181 subjects (PP sample)

89 dTMS
- 7 dropouts (baseline-5 weeks) (7.9%)
- 82 subjects reached the primary endpoint
- 39 dropouts (6-16 weeks) (43.8%)
- 43 subjects completed the study

92 sham treatment
- 15 dropouts (baseline-5 weeks) (16.3%)
- 77 subjects reached the primary endpoint
- 49 dropouts (6-16 weeks) (53.3%)
- 28 subjects completed the study
DeepTMS HDRS Change

Leykovitz, et al. World Psychiatry 2015;14:64–73
Is this as good as it gets? Probably Not.

What about Stim. Target?
Patient Referral

• For patients with medication resistant depression
• Must be under care of a psychiatrist
• Referral form on tmslab.org or call: 667-0307
Initial Evaluation

• Referral from treating psychiatrist
• Neurology
  – Contraindications
  – Effect of medication on TMS
• Psychiatry
  – Caution if: Psychotic depression, bipolar, personality disorders
  – At least one adequate trial of antidepressant medication
## BIDMC Treatment Protocols

<table>
<thead>
<tr>
<th>Site</th>
<th>Hemisphere</th>
<th>Frequency</th>
<th>Duration</th>
<th>Wait time</th>
<th>Repetitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLPFC (5.5 cm)</td>
<td>Left DLPFC (110% MT)</td>
<td>20 Hz</td>
<td>2 seconds</td>
<td>28 seconds</td>
<td>40 (1600 pulses)</td>
</tr>
<tr>
<td>Neuronetics</td>
<td>Left DLPFC (120% MT)</td>
<td>10 Hz</td>
<td>4 seconds</td>
<td>26 seconds</td>
<td>75 (3000 pulses)</td>
</tr>
<tr>
<td>DLPFC</td>
<td>Right (110% MT)</td>
<td>1 Hz</td>
<td>1600 seconds</td>
<td>N/A</td>
<td>1 (1600 pulses)</td>
</tr>
<tr>
<td>Brainsway</td>
<td>Left DLPFC (120% MT)</td>
<td>18 Hz</td>
<td>2 seconds</td>
<td>20 seconds</td>
<td>55 (1980 pulses)</td>
</tr>
</tbody>
</table>
Consent

• Discussion of on-label vs. off-label treatment

• Explanation of side-effects
  – Seizure
  – Headache
  – Neck pain
  – Scalp pain
Initiation Phase

- Treatments daily (excluding weekends)
- Various mood assessments daily/weekly/monthly
- Minimum 2 weeks
- Maximum 4-6 weeks
Assessment tools

- Beck, Hamilton, Analogue scale
- Target symptoms
- Clinician evaluation of patient
- Other sources of information (e.g. family, referring psychiatrist)
- Side effects questionnaire

- Weekly meeting of all staff to discuss progress
Alternatives being investigated

• Choosing protocol on clinical parameters (anxiety, risk of mania.sz)
• Using rs-fMRI guidance for targeting
• Using anatomical MRI to help with intensity of stimulation (particularly in elderly)
• Plasticity measures as guide
• Others: mood induction, more than one session/day
Maintenance Phase

• Minimal evidence *(absence of evidence, not evidence of absence)*

• Relapse prevention
  – Start with weekly treatment
  – Gradually space out sessions

• “Watchful Waiting”
  – Patient presents when feeling worse
Cost

• Insurance coverage depends on location
  – Medicare jurisdiction
  – Private payers
• Additional fee for assessments
• Helping with billing, talking with payers
rTMS in the clinical practice - Should we include this therapy in the depression decision tree? And where?

Based on the American Psychiatric Association guideline for depression treatment
Conclusions

• TMS can be used to affect brain circuitry
• TMS has potential therapeutic effects for certain neuropsychiatric disorders
• It is FDA cleared for treatment of medication resistant depression
• Our clinical program is on forefront of treatment (bidmc.org/tms or tmslab.org)
I am confident that I know how to refer patients for rTMS

- Mean 2.71 (3.5 is neutral)
- Disagree 69.9%, Agree 30.1%
I will likely refer patients for TMS in the future

- Mean 3.76
- Disagree 31.6%, Agree 68.4% (even though they don't know how!)
I am confident that TMS is covered by most insurance plans

- Mean 2.30
- Residents 2.05, Faculty 2.52 (p<0.01)
- Academic 2.20, Community 2.59 (p=0.092) approaches significance
I feel that TMS is an effective treatment for treatment-resistant depression:

- Mean 3.82
I know and understand the FDA indications for TMS use in treatment-resistant depression:

- Mean 2.89