Psychiatric Applications of Transcranial Magnetic Stimulation

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Overview

• TMS Basics in Psychiatry
• TMS studies in depression
• Treatment program at BIDMC
• Attitudes toward TMS
Disclosures

- 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.
Context of Noninvasive Brain Stimulation in Psychiatric Disorders

- **Diagnostic Applications**
  - TMS
  - Characterization of underlying neurobiology
  - Physiologic Biomarker
  - Predictor of Treatment

- **Therapeutic Applications**
  - TMS & tDCS
  - Stimulation alone or in combination with other interventions
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>

67%

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

1st century

Black Bile

ECT

TCAs

MAOIs

SSRIs

Lithium

Heterocyclics

Pharmacologic Refinements

1900

’30s

’40s

’50s

’60s

’70s

’80s

’90s

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

[Images of different stimulator coils and their corresponding 3D and 2D graphical representations]
Equipment Repetitive Stimulators
FDA approved for cortical brain mapping
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; dIPFC: 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
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
Pascual-Leone, et al.
George, et. al.
rTMS for depression

1996
MADRS Total Score
Baseline to End Point Change
Neuronetics Phase III trial of rTMS for Medication-resistant depression

2007
FDA approval

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

2012

2013
Brainsway DeepTMS

FDA approved
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%

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.

Lancet 1996
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 (ie, 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>
<tr>
<td>Clinical Variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<tr>
<td>Treatment History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Adequate in Current Episode</td>
<td>1.6</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Baseline Symptom Severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<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*

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**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**
**Secondary Timepoint @ 6 weeks**
**Durability of Effect @ 9 weeks**

- **NeuroStar TMS Therapy**
  - (N=155)

- **Sham TMS**
  - (N=146)

**Randomization**

n=325
Study 101 Efficacy Outcomes Continuous Measures

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

**HAMD24 Response**
(≥50% Improvement from Baseline)

- **Week 4:**
  - Active: 19.4
  - Sham: 23.9
  - *P = 0.030*

- **Week 6:**
  - Active: 11.6
  - Sham: 15.9
  - *P = 0.042*

**HAMD24 Remission**
(HAMD Total Score < 11)

- **Week 4:**
  - Active: 7.1
  - Sham: 17.4
  - *P = 0.644*

- **Week 6:**
  - Active: 6.2
  - Sham: 8.2
  - *P = 0.012*
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

<table>
<thead>
<tr>
<th>% Remission (HAMD 17)</th>
<th>No or Limited Prior Rx</th>
<th>One Prior Failure</th>
<th>Two Prior Failures</th>
<th>Three Prior Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27.5%</td>
<td>21.2%</td>
<td>16.2%</td>
<td>6.9%</td>
</tr>
<tr>
<td></td>
<td>25.6%</td>
<td>25.6%</td>
<td>17.9%</td>
<td>18.2%</td>
</tr>
<tr>
<td></td>
<td>30%</td>
<td>20%</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>40%</td>
<td>20%</td>
<td>20%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Sample Size (N): 2876  727  43  221  28  58  11

[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
# EXCLUSION CRITERIA

- Lifetime hx of psychosis
- Lifetime hx of bipolar d/o
- Lifetime hx of OCD
- Lifetime hx of PTSD
- Lifetime hx of eating disorders
- Significant neurological disorder or insult
- Increased risk of seizure
- Lifetime lack of response to ECT trial
- Prior rTMS or dTMS
- Vagus nerve stimulator implant
- Pregnancy
- Intracranial implants or metal object in/near head
- Present suicide risk or hx of attempt in past 3 yrs

## Dropouts by week 5:

<table>
<thead>
<tr>
<th>Reason</th>
<th>dTMS</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost to f/u</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Missed &gt; 2 tx days</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No improvement</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Developed SI</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Could not tolerate no meds</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Worsening of symptoms</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL:</strong></td>
<td><strong>7</strong></td>
<td><strong>15</strong></td>
</tr>
</tbody>
</table>

## Dropouts by week 16:

<table>
<thead>
<tr>
<th>Reason</th>
<th>dTMS</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sufficient improvement</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>Safety</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Missed &gt; 3 tx days</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Non-compliant</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>39</strong></td>
<td><strong>49</strong></td>
</tr>
</tbody>
</table>
Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>dTMS (N=101)</th>
<th>Sham (N=111)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean±SD)</td>
<td>45.1±11.7</td>
<td>47.6±11.6</td>
<td>0.1241</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>52.5</td>
<td>52.3</td>
<td>1.000</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>94.1</td>
<td>87.4</td>
<td>0.6866</td>
</tr>
<tr>
<td>Body mass index (mean±SD)</td>
<td>28.1±7.1</td>
<td>27.8±7.0</td>
<td>0.7837</td>
</tr>
<tr>
<td>Age at first episode (years, mean±SD)</td>
<td>25.3±11.5</td>
<td>26.9±12.7</td>
<td>0.3357</td>
</tr>
<tr>
<td>Duration of current episode (months, mean±SD)</td>
<td>21.7±16.3</td>
<td>19.5±15.2</td>
<td>0.3217</td>
</tr>
<tr>
<td>History of suicide attempts (% without any)</td>
<td>88.1</td>
<td>92.8</td>
<td>0.3471</td>
</tr>
<tr>
<td>Antidepressants in current episode (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>-</td>
<td>0.9</td>
<td>0.1880</td>
</tr>
<tr>
<td>One</td>
<td>24.8</td>
<td>24.3</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>33.7</td>
<td>31.5</td>
<td></td>
</tr>
<tr>
<td>Three</td>
<td>15.8</td>
<td>17.1</td>
<td></td>
</tr>
<tr>
<td>Four</td>
<td>10.9</td>
<td>19.8</td>
<td></td>
</tr>
<tr>
<td>Five or more</td>
<td>14.9</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Number of failed medications at ATHF level ≥3 (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>6.9</td>
<td>12.6</td>
<td>0.3838</td>
</tr>
<tr>
<td>One or two</td>
<td>71.3</td>
<td>66.7</td>
<td></td>
</tr>
<tr>
<td>Three or more</td>
<td>21.8</td>
<td>20.7</td>
<td></td>
</tr>
<tr>
<td>Baseline HDRS-21 score (mean±SD)</td>
<td>23.5±4.3</td>
<td>23.4±3.7</td>
<td>0.7641</td>
</tr>
<tr>
<td>Motor threshold at first treatment (mean ±SD)</td>
<td>59.8±8.3</td>
<td>61.1±8.9</td>
<td>0.2745</td>
</tr>
</tbody>
</table>

dTMS – deep transcranial brain stimulation, ATHF – Antidepressant Treatment History Form, HDRS – Hamilton Depression Rating Scale
1º Change in Hamilton Depression Rating Scale score at week 5
2º Response and remission rates at week 5
3º The above at week 16
DeepTMS HDRS Change

Leykovitz, et al. World Psychiatry 2015;14:64–73
Patient Referral

• For patients with medication resistant depression

• Must be under care of 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 MRI guidance for targeting
- Using anatomical MRI to help with intensity of stimulation (particularly in elderly)
- 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
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
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)