Transcranial Magnetic Stimulation for the Treatment of Depression

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Mood/Thought/Behavior Circuits
Papez, 1937

Papez JW. Arch Neurol Psychiatry 38:725-743, 1937
Surgical Approaches: White Matter Disconnection

- Orbital undercutting
- Yttrium subcaudate tractotomy
- Cingulo-tractotomy

**Surgical Approaches:**

- **White Matter Disconnection**
  - 22-75% efficacy
  - No controlled studies
  - Not disorder specific
  - Adverse effects: seizures, pers Δ, cognitive abnorm.

- **Subcaudate Tractotomy**
- **Anterior Capsulotomy**
- **Anterior Cingulotomy**
Neuroimaging methods for the study of depression

- PET/SPECT
- Ligand imaging (PET/SPECT)
- Structural MRI
- EEG
- Functional MRI
- MEG
- MRS
- DTI

[Images and graphs illustrating various neuroimaging techniques and their applications in studying depression]
Putative “Depression” Network

Putative “Depression” Network

Four FDA-approved TMS devices:

- Neurostar (Neuronetics)
- Brainsway (“deep TMS”)
- Magstim
- Magventure
TMS/rTMS

- TMS can depolarize cortical neurons

- Repetitive TMS (rTMS) can modulate the tone of underlying cortex

- Distant effects in connected regions (e.g., dopamine release in striatum)

- Non-invasive, no anesthesia, patient awake during stimulation
Brief review of rTMS: Definitions

- **Frequency**: rate of rTMS pulses
  - Slow/low Hz: ≤ 1 Hz
  - Fast/high Hz: ≥ 5 Hz

- **Intensity**: strength of current induced in cortex
  - Defined as percent (%) of motor threshold (MT)
  - MT defined as intensity inducing motor evoked potential during stimulation of primary motor cortex

- **Train**: series of rTMS pulses
  - Train duration
  - Intertrain interval
TMS: Depth of stimulation

Relative depth reached by current TMS coils
Increasing neuropsychiatric interest

• Single pulse TMS used clinically and for research in neurology, rehab medicine

• rTMS as potential treatment for several conditions:
  – Depression
  – Mania
  – Schizophrenia
  – PTSD
  – Obsessive-compulsive disorder (OCD)
  – Generalized anxiety disorder
  – Addictions
  – Neurologic disorders (e.g., Parkinson’s, epilepsy, MS)
Side effects and contraindications

• Side effects:
  – Headaches (mild)
  – Pain during stimulation (mild)
  – Seizures (extremely rare with current settings)
  – No cognitive impairments; some patients may show cognitive improvements

• Contraindications:
  – Metal in body, especially head
TMS for Depression

• **Parameters:**
  - 5-20 Hz
  - 80%-120% motor threshold
  - ~30-40 min tx
  - 15-30 txs, daily, over 3-6 weeks

• **Location:**
  - Left dorsolateral prefrontal cortex (DLPFC)
  - ~5-6 cm anterior to motor cortex for hand muscles
rTMS: Antidepressant Efficacy

• Studied for depression since 1993

• Multiple meta-analyses confirm statistically significant antidepressant effects
  – Response rates ~20%-40%; up to 60% open-label

• Two large, multi-center trials (combined N=~500) demonstrate antidepressant effects
**Multi-Center Industry-Sponsored Trial (N=301)**

*(O’Reardon et al., *Biol Psychiatry, 2007)*

**MADRS Response Rates**
(50% Improvement from Baseline)

- Week 2: 8.4%
- Week 4: 18.1%
- Week 6: 23.9%

- Week 2: 6.2%
- Week 4: 11.0%
- Week 6: 12.3%

**MADRS Remission Rates**
(MADRS Total Score < 10)

- Week 2: 3.9%
- Week 4: 2.1%
- Week 6: 7.1%

- Week 2: 6.2%
- Week 4: 3.9%
- Week 6: 14.2%

*P < .05 vs sham,  **P < .01 vs sham*

- Black bars = Active TMS
- Gray bars = Sham TMS
More effective in less resistant pts

Lisanby et al., Neuropsychopharmacology, 2008
# OPT-TMS Multi-Center Trial (N=190)
*(George et al., Arch Gen Psychiatry, 2010)*

<table>
<thead>
<tr>
<th>Model</th>
<th>ITT N=190</th>
<th>Completers N=154</th>
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<tbody>
<tr>
<td></td>
<td>Active TMS N=92</td>
<td>Sham TMS N=98</td>
</tr>
<tr>
<td>Remission, N(%)</td>
<td>13 (14)</td>
<td>5 (5)</td>
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<table>
<thead>
<tr>
<th>Model</th>
<th>Wald Chi-Square</th>
<th>p value</th>
<th>Wald Chi-Square</th>
<th>p value</th>
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<tbody>
<tr>
<td>Treatment</td>
<td>5.93</td>
<td>0.02</td>
<td>5.45</td>
<td>0.02</td>
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<tr>
<td>Site</td>
<td>6.05</td>
<td>0.11</td>
<td>7.14</td>
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<td>Age</td>
<td>0.06</td>
<td>0.81</td>
<td>0.20</td>
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<tr>
<td>Duration</td>
<td>1.90</td>
<td>0.17</td>
<td>3.62</td>
<td>0.06</td>
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<tr>
<td>Tx-Resist</td>
<td>2.12</td>
<td>0.15</td>
<td>2.27</td>
<td>0.13</td>
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<table>
<thead>
<tr>
<th>Adj. Odds Ratio</th>
<th>95% CI</th>
<th>Adj. Odds Ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Treatment</td>
<td>4.18</td>
<td>1.32, 13.24</td>
<td>4.92</td>
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</table>
rTMS: What are the outcomes?

- **MDD**: if applying a full course (20-30 sessions): ~50% response, 35% remission

The outcomes of the most recent generation of large rTMS trials ($N$>40 subjects, post-2010) are summarized below:

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th># sessions</th>
<th>Responders</th>
<th>Remitters</th>
<th>% Response</th>
<th>% Remission</th>
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<tbody>
<tr>
<td>Fitzgerald et al., 2010</td>
<td>219</td>
<td>20</td>
<td>117</td>
<td>69</td>
<td>53.4</td>
<td>31.5</td>
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<tr>
<td>McDonald et al., 2011</td>
<td>141</td>
<td>26</td>
<td>58</td>
<td>43</td>
<td>41.0</td>
<td>30.5</td>
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<td>Galletly et al., 2012</td>
<td>77</td>
<td>19</td>
<td>33</td>
<td>25</td>
<td>42.9</td>
<td>32.5</td>
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<tr>
<td>Ciobanu et al., 2013</td>
<td>93</td>
<td>15</td>
<td>48</td>
<td>32</td>
<td>51.6</td>
<td>34.4</td>
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<tr>
<td>Downar et al., 2013</td>
<td>47</td>
<td>20</td>
<td>24</td>
<td>20</td>
<td>51.0</td>
<td>42.6</td>
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<tr>
<td>Bakker et al., 2013</td>
<td>41</td>
<td>20</td>
<td>22</td>
<td>15</td>
<td>53.7</td>
<td>36.6</td>
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<tr>
<td>Connolly et al., 2012</td>
<td>85</td>
<td>25</td>
<td>35</td>
<td>30</td>
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<tr>
<td>Carpenter et al., 2012</td>
<td>307</td>
<td>28</td>
<td>178</td>
<td>114</td>
<td>58.0</td>
<td>37.1</td>
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**POOLED**

<table>
<thead>
<tr>
<th>N</th>
<th>% Response</th>
<th>% Remission</th>
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<tbody>
<tr>
<td>1010</td>
<td>51.0</td>
<td>34.5</td>
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</table>

*Table A1: Response and remission rates in trials of rTMS in TRD with $n$>40, 2010-present*
Predictors of response to TMS

• Effects influenced by:
  – Intensity
  – Location
  – Frequency: slow (≤1 Hz) vs. fast (≥5 Hz)
  – Number of treatment sessions
  – Number of pulses?

• Subject/patient factors are also important:
  – Treatment resistance
  – Psychosis
  – Concomitant medications?
Remaining questions

• Target?
  – Left vs. right? Both?
  – DLPFC vs. DMPFC vs. VMPFC vs. ???
  – Neuronavigation?

• Patient selection/biomarkers?

• Dosing?
  – Theta burst?

• Combining with other treatments?

• Maintenance TMS?
“Deep” TMS

“Deep” TMS
Synchronized TMS

- Low magnetic field TMS
- Delivered at individual’s prefrontal alpha frequency
- Preliminary data suggest potential efficacy
- Practically no seizure risk
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 *

- 15 txs over 2 days
- Efficacy similar to 3-6 wk course
- No safety concerns
Oh, thank you so much for helping! We were on our way to terrorize the villagers when my monster just up and died on me... We'd still be stuck here if it wasn't for you.

Yeah, yeah... Another wet-behind-the-ears mad scientist.

THANK YOU