The use of non invasive brain stimulation in the treatment of mood and cognitive disorders

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Epworth
Psychiatric illness and Treatment Resistance

Depression is:
- Common (~7% of Australians every year)
- Highly disabling
- Costly to treat
- Frequently unable to be treated or respond poorly to treatment (30% TRD)

Neuropsychiatric Drug development:

"This is hardly a rich pipeline...It suggests a sad dearth of ideas and involves lots of attempts at patent extensions and new indications for old drugs."

(Steven Hyman, former NIMH director, Provost Harvard)

*Figure and data cited from Science 30 July 2010:Vol. 329. no. 5991, pp. 502 - 504*
Table 1
Rate of acute remission, likelihood of completing 12-months without relapse, and probability of sustained benefit at each level of STAR*D [19].

<table>
<thead>
<tr>
<th></th>
<th>Acute remission rate</th>
<th>Probability of remaining well for 12 months after acute remission</th>
<th>Probability of sustained benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>36.80%</td>
<td>69.90%</td>
<td>25.72%</td>
</tr>
<tr>
<td>Level 2</td>
<td>30.60%</td>
<td>44.70%</td>
<td>13.68%</td>
</tr>
<tr>
<td>Level 3</td>
<td>13.70%</td>
<td>35.40%</td>
<td>4.85%</td>
</tr>
<tr>
<td>Level 4</td>
<td>13.00%</td>
<td>28.90%</td>
<td>3.76%</td>
</tr>
</tbody>
</table>
The answer... ask Magnus
Novel Brain Stimulation Treatments in Psychiatry

**Established**
- TMS - depression
- Deep TMS - depression
- tDCS - depression

**Undergoing clinical trials**
- TMS – other disorders: e.g. OCD, Alzheimer’s disease
- tDCS – cognitive enhancement
- Trigeminal nerve stimulation - PTSD
- Caloric nerve stimulation - mania
- EMF pulse stimulation – depression
- External vagal nerve stimulation – multiple applications

**Early stage development**
- Ultrasound stimulation
- Optogenetics

**Non Invasive**

**Convulsive**
- ECT
- MST - depression
- FEAST

**Surgical**
- Vagal nerve stimulation - depression
- DBS – neurological, OCD
- DBS – Depression
- Epidural cortical stimulation
Changing Electrical Current $\rightarrow$ Time Variable Magnetic Field $\rightarrow$ Induced Electrical Field $\rightarrow$ Neuronal depolarization / Firing

Repeated stimulation (rTMS) $\rightarrow$ High frequency $\rightarrow$ Increased local cortical activity $\rightarrow$ Changes in cortical – subcortical connectivity

Low frequency $\rightarrow$ Decreased local cortical activity
What does TMS for depression involve?

• Daily, Monday to Friday treatment
• 20-45 minutes a day, for a number of weeks
• Sitting in reclining chair
• Coil placed on head
• ‘Tapping’ sensation
Non invasive electrical stimulation

- Existing technology:
  - tDCS – direct current stimulation
  - tACS – alternating current stimulation
  - tRNS – random noise stimulation
Transcranial Direct Current Stimulation

- tDCS involves the application of a weak electrical current (1-2mA) to the scalp via two surface electrodes,
  - Anode = hyperpolarisation leading to increases in neuronal activity
  - Cathode = depolarisation leading to decreases in neuronal activity
Transcranial Alternating Current Stimulation: entraining brain waves

Fröhlich & McCormick
rTMS as a Therapeutic Tool in Depression

- Initial case reports in early 1990’s: vertex then Left DLPFC stimulation
- First controlled studies mid 90’s [Pascual-Leone, 1996] [George, 1997]
- Initial studies for 1 week, cross over designs
- Gradually longer duration and increased pulse number
- Predominant focus on Left DLPFC
Evidence for Efficacy of Left PFC rTMS in adults

- 30 + clinical trials
- Numerous meta-analyses
- Greater effects in more recent studies
  - Longer duration of treatment
  - Increased intensity
  - Increased pulse number
- Most recent
  - 34 individual trials, 1383 patients and found
  - rTMS to be more effective than sham rTMS
  - Large effect size = 0.55.
  (Slotema et al 2010)

- Moderate effect sizes
- Increase in efficacy over time

Slotema et al 2010
rTMS in Depression: what are the overall outcomes?

A STUDY OF THE PATTERN OF RESPONSE TO rTMS TREATMENT IN DEPRESSION


TABLE 1. Demographic and baseline clinical variables

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non-responders</th>
<th>t/p²</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.7</td>
<td>45.1</td>
<td>3.2</td>
<td>.001</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>189/309</td>
<td>202/357</td>
<td>0.18</td>
<td>.67</td>
</tr>
<tr>
<td>Diagnosis (number of subjects)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD—single episode</td>
<td>121</td>
<td>209</td>
<td>2.19</td>
<td>.000</td>
</tr>
<tr>
<td>MDD—relapse</td>
<td>287</td>
<td>277</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPAD</td>
<td>78</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of failed antidepressant trials</td>
<td>5.7</td>
<td>6.1</td>
<td>0.48</td>
<td>.49</td>
</tr>
<tr>
<td>Age of illness onset</td>
<td>28.7</td>
<td>26.1</td>
<td>2.4</td>
<td>.02</td>
</tr>
<tr>
<td>Illness duration (years)</td>
<td>5.9</td>
<td>5.0</td>
<td>1.0</td>
<td>.32</td>
</tr>
<tr>
<td>Baseline HAMD/MADRS</td>
<td>21.6</td>
<td>23.7</td>
<td>4.3</td>
<td>.000</td>
</tr>
<tr>
<td>Right-sided resting motor threshold</td>
<td>52.9</td>
<td>53.7</td>
<td>0.5</td>
<td>.62</td>
</tr>
<tr>
<td>Concurrently taking antidepressant medication (yes/no)</td>
<td>421/70</td>
<td>437/121</td>
<td>9.7</td>
<td>.002</td>
</tr>
<tr>
<td>Concurrently taking mood stabilizer medication (yes/no)</td>
<td>176/289</td>
<td>154/351</td>
<td>5.8</td>
<td>.02</td>
</tr>
<tr>
<td>Concurrently taking antipsychotic medication (yes/no)</td>
<td>203/232</td>
<td>279/255</td>
<td>0.02</td>
<td>.88</td>
</tr>
<tr>
<td>Comorbid diagnoses (number of subjects)</td>
<td>36</td>
<td>67</td>
<td>18.9</td>
<td>.002</td>
</tr>
<tr>
<td>Type of TMS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left-sided</td>
<td>121</td>
<td>188</td>
<td>13.1</td>
<td>.02</td>
</tr>
<tr>
<td>Right-sided</td>
<td>232</td>
<td>256</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>132</td>
<td>132</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MDD, major depressive disorder; BPAD, bipolar affective disorder; OCD, obsessive-compulsive disorder; GAD, generalized anxiety disorder; HAMD, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.
Pattern of Response

Data from 11 clinical trials (n = 1132)
TMS vs Medication

Treating with TMS early is more effective than adding a 3rd antidepressant

Efficacy of TMS or medication in MDD

- Rush 2004 (addition of a 3rd antidepressant)
  - Response: 31%
  - Remission: 14%

- Carpenter 2012
  - Response: 58%
  - Remission: 37%

- Fitzgerald 2016
  - Response: 46%
  - Remission: 31%

- TMSA 2018
  - Response: 55%
  - Remission: 35%

* TMS Australia Preliminary Internal Data (n=130)
Future Targets

Efficacy
Utility
Application
Does improved treatment targeting enhance response to rTMS?

- Randomised double blind
- 52 subjects
- Targeted or ‘5 cm method’
- Target = Middle FG / border BA 48 and 9
- x,y,z=-45, 45,35

Sign time vs group p<0.05
Future Targets: Applications of TMS

- Depression
  - Schizophrenia: Treatment of Auditory Hallucinations
  - Alzheimer’s Disease
  - Obsessive Compulsive Disorder
  - Post Traumatic Stress Disorder
  - Autism Spectrum Disorder
  - Chronic Pain - Fibromyalgia

- Eating Disorders
- Addictions
Cognitive functions are represented by dynamic activity occurring throughout neural networks, both locally and globally.

Activity of interconnected networks of synapses throughout the brain is crucial.

There are number of ‘index’ ways in which these fundamental processes can be disturbed...
rTMS in Dementia

• Multi-focal versus critical node
• Frequency specific activation of task related oscillations
• Interaction of stimulation with cognitive activation
Repetitive transcranial magnetic stimulation (rTMS) combined with cognitive training is a safe and effective modality for the treatment of Alzheimer’s disease: clinical experience

Jose Martin Rabey*2 - Evgenia Dobrovolsky*2

Table 4 ADAS-Cog percentile improvement (%) per ADAS-Cog improvement points

<table>
<thead>
<tr>
<th>ADAS-Cog improvement (points)</th>
<th>Patients’ improvement percentile (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>−5</td>
<td>21.4</td>
</tr>
<tr>
<td>−4</td>
<td>25.0</td>
</tr>
<tr>
<td>−3</td>
<td>42.9</td>
</tr>
<tr>
<td>−2</td>
<td>60.7</td>
</tr>
<tr>
<td>−1</td>
<td>71.4</td>
</tr>
<tr>
<td>0</td>
<td>78.6</td>
</tr>
</tbody>
</table>

Fig. 1 ADAS-Cog results for the first and second treatment course (5 patients)
Similar clinical improvement and maintenance after rTMS at 5 Hz using a simple vs. complex protocol in Alzheimer’s disease.
RCT of Theta Burst Stimulation for Mild to Moderate Alzheimer's
Alzheimer’s RCT: Preliminary data

% Performance Gain in Episodic Memory: from baseline to end of treatment

ADASCog Scores at 3 months
Alzheimer’s RCT: Preliminary data

Resting EEG data from 13 patients in active and 13 in sham.

Active iTBS significantly reduced theta connectivity at rest, from bilateral frontal regions to left and central occipital regions (p = 0.025). No change in sham group.

*Image of the endpoint network differences, right*
Conclusions

- rTMS is an established, safe and effective treatment for depression
- rTMS shows evidence of preliminary efficacy in cognitive disorders
- rTMS presages the use of potentially a wide range of non invasive brain stimulation techniques
Thanks
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Beyond Blue
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Monash University
Weston Foundation