Transcranial Magnetic Stimulation: What has experience told us?

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Repetitive Transcranial Magnetic Stimulation:
A Quick Overview
rTMS: What is it?

• Non-invasive brain stimulation therapy
• Powerful, focused magnetic field pulses applied to target brain regions through the scalp via a handheld electromagnet
• Induces lasting changes in brain activity and synaptic connection strength via the mechanisms of neuroplasticity
• Targets frontal lobe regions involved in self-regulation of thoughts, emotions, and behaviour - NOT pressing “happy button”
rTMS: What are its uses?

- FDA-Approved (2008) for major depression resistant to ≥1 adequate medication trial
- Broader approval in Canada (2002)
- Studies supporting efficacy in bipolar depression, PTSD, OCD, eating disorders, addiction, tinnitus, chronic pain
- Several large meta-analyses (N>1000) support efficacy for major depression
- Most common clinical use is major depression; we will focus on this indication today
rTMS: What is it like?

- Patient awake, seated, not sedated
- rTMS device on scalp for 5-20 min
- MRI/CT-guided positioning system
- Must hold still during treatments
- Static electricity sensation: forehead, (sometimes eyes, nose, teeth)
- Typical treatment course: need 20 - 30 daily sessions (4 - 6 weeks)
rTMS: What are the outcomes?

- After failing ≥2 medication trials = treatment-resistant depression (2% prevalence)
- Add’l med trials: 10-15% remission
- Therapy (eg CBASP): ~15-20% remission
- Berlim et al. 2014: N=1371, 29 trials
  29.3% response 18.6% remission vs
  10.4% response 5.0% remission (sham)
- NB mean only 12.9 sessions (50% of full course)
- Gaynes et al. 2014: N=764, 18 trials, 14.1 sessions:
  odds ratios: 3.38 for response, 5.07 for remission
- Outcomes for rTMS favorable over additional meds or psychotherapy after 1-2 failed medication trials, even with most early trials underdosed (10-15 sessions rather than 20-30).
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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<tr>
<td>Fitzgerald et al., 2010</td>
<td>219</td>
<td>20</td>
<td>117</td>
<td>69</td>
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<td>31.5</td>
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<td>McDonald et al., 2011</td>
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<td>26</td>
<td>58</td>
<td>43</td>
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<td>Galletly et al., 2012</td>
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<td>19</td>
<td>33</td>
<td>25</td>
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<td>32.5</td>
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<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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<td>Downar et al., 2013</td>
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<td>20</td>
<td>24</td>
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<tr>
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<td>22</td>
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<td>35</td>
<td>30</td>
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<td>35.3</td>
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<tr>
<td>Carpenter et al., 2012</td>
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<td>28</td>
<td>178</td>
<td>114</td>
<td>58.0</td>
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<tr>
<td><strong>POOLED</strong></td>
<td>1010</td>
<td>21.6</td>
<td>515</td>
<td>348</td>
<td>51.0</td>
<td>34.5</td>
</tr>
</tbody>
</table>

*Table A1: Response and remission rates in trials of rTMS in TRD with n>40, 2010-present*
rTMS: ? Trimodal Outcomes

Bakker et al., 2015
Brain Stimulation
Current Active Issues in rTMS Research
rTMS: Current Research Issues

• Optimizing Treatment Parameters

- Site of stimulation:
  - Conventional is left / right / bilateral DLPFC
  - Newer sites: DMPFC, OFC, Insula

- Protocol (pattern) of stimulation:
  - Conventional is 10 Hz for 38 minutes
  - Recent evidence suggests theta-burst stimulation may achieve same effect in 3 min
  - 1 Hz may achieve same effect in 8 min (Brunelin et al., 2014 “French protocol”)
  - Shorter sessions would allow several-fold improvements in capacity and cost
rTMS: Current Research Issues

• Optimizing Treatment Parameters

- Number of sessions per day
  - Conventional is once daily
  - Accelerated rTMS: 2, 3, 5, 10 sessions per day
    (e.g., Holtzheimer et al. 2010; 15 sessions in 2 d
     achieved sustained remission x 6 wks in 4/14 pts)
  - Preliminary evidence: ? Full course in 5-10 days
  - Large formal RCTs not yet complete on this issue

- Interval between sessions of stimulation:
  - Conventional is 24h (once daily)
  - Preclinical evidence: minimum inter-session interval exists
    2 sessions w 30 min interval 2x potency
    2 sessions w 15 min interval: no additional effect
    (Nettekoven et al. 2014/15)
  - Currently, minimal / optimal inter-session interval unknown
  - Short inter-session intervals (30-60 min) could help accelerate rTMS
rTMS: Current Research Issues

• Relapse Prevention / Maintenance rTMS

- rTMS has acute effects: median relapse ~ 120 d

- Relatively few studies on maintenance protocols to prevent or reverse relapse following acute course

- Clinical experience suggests maintenance sessions or “booster” treatments are effective in majority of rTMS responders

- Unclear issues:
  - Do all patients need maintenance?
  - When should maintenance be offered?
  - Clustered course versus sporadic (e.g. once weekly)
  - How often to do sessions? (2x weekly, 1x weekly, biweekly)
rTMS: Current Research Issues

• Integration with other Rx modalities
  - Medications: do any of them help or hinder rTMS effects?
    - Antiepileptics: Reduce efficacy of rTMS
    - Benzodiazepines / GABAerics: Reduce efficacy
    - Dopaminergics (antipsychotics / stimulants)
    - If maintenance rTMS, can antidepressants be discontinued?
    - If so, when?

  - Cognitive Manipulations During rTMS:
    - Craving induction in addiction
    - Trauma script reading (PTSD)
    - Negative / Positive Ruminations (Major depression)

  - Psychotherapies After rTMS:
    - Mindfulness-Based Cognitive Therapy: relapse prevention
    - Group CBT or other therapies to leverage rTMS-enhanced capacity for cognitive control
Current Challenges in rTMS Trial Design
rTMS trials: Current Challenges

**Patient Selection**

- RTMS of DLPFC does not target “depression” or “mood”
  - Some current evidence suggests strengthening of cognitive control capacity via “salience network”
  - Cognitive Control Deficiency:
    A transdiagnostic feature in many Axis I disorders but not present in all patients with a given disorder
    - Notable bimodal / trimodal outcomes suggest “MDD patients” are heterogeneous, good/bad rTMS candidates might be identifiable pre-Rx
  - Preliminary evidence of an “rTMS phenotype”:
    Cluster B, ADHDish, binge eating, “bipolar NOS”

- Research Domain Criteria (RDoC):
  - Cognitive control / response selection is an RDoC domain
  - Specific circuits/markers: fMRI, EEG, behavioral
  - RDoC formulation may be better than DSM for rTMS
rTMS trials: Current Challenges

- **Outcome Assessment**
  - Conventional measures: *clinician vs self-rated*
    - Hamilton Depression Rating Scale (clinician-rated)
    - Inventory of Depressive Symptoms (clinician-rated)
    - Quick Inventory of Depressive Symptoms (self-rated)
    - Beck Depression Inventory-II (self-rated)
    - Patient Health Questionnaire-9

- What about accelerated protocols (2-10 days)?
  - Are daily mood ratings valid?
  - Can existing scales be modified (1 week -> 1 day)?
  - Clinical experience suggests daily ratings (eg BDI) may be helpful for tracking progress - few studies yet!
rTMS trials: Current Challenges

• Valid Sham Controls for Stimulation
  - Conventional approach: “hold coil sideways” for sham
    - Widely used in 1990s > 2000s > less today
    - Sensations are different than with verum rTMS
    - Patients now better informed – potential unblinding
    - Technicians are aware – certain unblinding
    - Better sham techniques are needed
  - Newer Approaches:
    - Sham coils: generate noise and sensation, but field mostly blocked by shielding or far from head
    - Scalp electrodes: generate rTMS-like “zap” sensations
    - Computer-controlled active vs sham: technician blinding
    - rTMS sensation cannot be exactly replicated however
    - Unblinding of patients / techs remains problematic
rTMS trials: Current Challenges

• Effect of Cognitive State During Stimulation

  - Conventional approach: no control of cognition during rTMS
    - Techs often instructed not to talk to patients (artificial)
    - Patients may ruminate / focus on pain / ???

  - Cognitive state now known to affect rTMS outcome
    - Addiction Rx: more efficacy with craving induction during rTMS
    - PTSD Rx: more efficacy when reading trauma script vs neutral
    - MDD Rx: more / less effective with positive / negative scripts

  - New trials could constrain cognition during rTMS
    - MBCT: “3 min Breathing Space” = 3 min duration of theta-burst
    - CBT: scripts of automatic thoughts vs balanced thoughts
    - EMDR: rTMS sensations may play analogous non-specific role

  - A neglected, fruitful approach to improving rTMS outcomes
    - Formal RCTs will be needed to assess whether this is useful
Q & A
and Discussion