Non-Invasive Brain Stimulation and Behavioral Therapy

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How does repetitive behavior affect motor cortex?
**How does NIBS affect motor cortex?**

- **Simple repetitive finger movements increase excitability.**
- **Motor map changes with skilled practice.**

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**Physiology of TMS**

**Di Lazzaro et al. (1998)**

- Extensive training of elementary finger tapping movements changes the pattern of motor cortex excitability.

**Ziemann et al., 1998**

- Periodicity ~ 1.5 ms

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**“An excited neuron tends to decrease its discharge to inactive neurons, and increase this discharge to any active neuron, and therefore to form a route to it, whether there are intervening neurons between the two or not. With repetition, this tendency is prepotent in the formation of neural routes”**

(Hebb, 1932, p.13).

**Donald Hebb**

*The Organisation of Behaviour: A Neuropsychological Theory.* D.O. Hebb (1949)
Rate-dependent TMS protocols

- **Excitatory**
  - **Repetitive**
    - High-frequency (~10Hz)
  - **Intermittent**
    - Low-frequency (~1Hz)
  - **Continuous**

- **Inhibitory**

**Thetaburst**

**Long-term potentiation**

**Long-term depression**

Clinical application - rTMS, Stroke Motor Recovery
Functional Improvements
- sRT/eRT
- Pinch force acceleration
- Fingers/thumb AROM
- Movement accuracy
- Purdue Pegboard
- JTT

TMS correlates
- Resting MT
- Transcallosal Inhibition
- MEP Amplitude

How does combined intervention affect motor cortex?

Improved corticomotor output from ipsilesional M1 & improved motor behaviour

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Improvised corticomotor output from ipsilesional M1 & improved motor behaviour

Altering cortical excitability before repetitive synaptic activity

- 1mA 10mins tDCS
- rTMS at 5Hz 100stim train at AMT – decreases SICI, but not lasting change in excitability as tested by single pulse TMS
- Result: after effects of tDCS can generate opposite effects of rTMS or conversely can alter the after effects of tDCS


Motor systems example

If...

Motor Training = improvement in function ‘X’

and...

NIBS = improvement in function ‘X’

does...

Motor Training + NIBS = improvement in function 2X, X^2, or 0???
Anodal tDCS combined with robotic motor training

<table>
<thead>
<tr>
<th>Condition</th>
<th>Unconditioned</th>
<th>Conditioned</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-tDCS</td>
<td>1.5</td>
<td>2.0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Post-tDCS</td>
<td>2.5</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Post-Robot</td>
<td>3.5</td>
<td>4.0</td>
<td></td>
</tr>
</tbody>
</table>

Robotics for assessment of performance kinematics


Upper limb robotics at Burke-Cornell, New York

Edwards PI: R01 HD069776

Robotics with brain stimulation in patients with motor dysfunction

**TMS**

<table>
<thead>
<tr>
<th>Method</th>
<th>Author</th>
<th>Priming Method</th>
<th>Protocol</th>
<th>Effect</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>rTMS</td>
<td>lyer</td>
<td>rTMS</td>
<td>rTMS</td>
<td>increased inhibitory effect</td>
<td>&gt;60 min</td>
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<tr>
<td></td>
<td>Daskalakis</td>
<td>rTMS</td>
<td>rTMS</td>
<td>no change</td>
<td>20 min</td>
</tr>
<tr>
<td></td>
<td>Siebner</td>
<td>TDCS</td>
<td>rTMS</td>
<td>no change</td>
<td>20 min</td>
</tr>
<tr>
<td></td>
<td>Siebner</td>
<td>TDCS</td>
<td>rTMS</td>
<td>reversed results in MEP</td>
<td>&gt;30 min</td>
</tr>
<tr>
<td>TBS</td>
<td>lezzi</td>
<td>voluntary (finger abduction)</td>
<td>cTBS</td>
<td>reversed results in MEP</td>
<td>&gt;30 min</td>
</tr>
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<td>&gt;30 min</td>
</tr>
<tr>
<td>PAS</td>
<td>Müller</td>
<td>N20-5ms</td>
<td>N20-2ms</td>
<td>priming produced increase in MEP</td>
<td>&gt;30 min</td>
</tr>
<tr>
<td></td>
<td>Müller</td>
<td>N20-2ms</td>
<td>N20-2ms</td>
<td>change</td>
<td>&gt;30 min</td>
</tr>
<tr>
<td></td>
<td>Zienman</td>
<td>voluntary*</td>
<td>N20-5</td>
<td>enhanced inhibition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zienman</td>
<td>voluntary*</td>
<td>N20-2ms</td>
<td>no change</td>
<td></td>
</tr>
</tbody>
</table>

* presumed excitation

**Inhibitory***

**Excitatory***

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**Nexstim NICHE Trial 2014-16**

Clinicaltrials.gov # NCT02089464

PI: Richard Harvey RIC

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**Preliminary data for Nexstim NICHE Trial**

Repetitive Transcranial Magnetic Stimulation (rTMS)

- Aiming tool: centering, rotation, titling
- Electrical field display
- Parameters:
  - 900 pulses
  - 1 Hz rTMS (inhibitory) to M1 of non-lesioned hemisphere
  - 110% of motor threshold for Extensor Digitorum Communis (m.EDC)

**Patient set up**

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**Repetitive Transcranial Magnetic Stimulation (rTMS)**

**Patient Goals:**
- Cut food with knife & fork
- Cook
- Reach for items above shoulder height
- Fasten clothing (buttons, zippers, laces)
- Hold grandchild
- Hold tools in affected hand
- Driving
- Golf

**Collaborative process between therapist and patient**

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**Nexstim NICHE Trial 2014-16**

**Improvement ≥ 5 UEFM points 6 mths post (Primary)**

**Experimental group:**
- 67% (95% CI, 58%–75%) n=117

**Control Group:**
- 65% (95% CI, 52%–76%) n=52

**P** = 0.76

**Mean change UEFM points 6 mths**

**Experimental:** 8.2 ±7pts

**Control:** 8.5 ±8pts

**P** = 0.87

Harvey et al, 2018 Stroke
How does unaffected M1 excitability relate to hemiparesis?

VLSM in 3-12 month Post-Stroke (hemiparesis)

Hot colour = maximum overlap for unaffected hemisphere hyper-excitability

n=103

Webster et al (2006)

Transcranial Magnetic Stimulation as a Complementary Treatment for Aphasia

Other cortical areas?

How is the network disrupted?

Is NIBS useful?

Can it be effectively combined with SL therapy?

R hem1 Hz rTMS + SL therapy improves language recovery and favors L hem language network activation.

Parameters:
- 900 pulses
- 1 Hz rTMS (inhibitory) to pars triangularis of non-lesioned hemisphere
- Motor threshold determination with First dorsal interosseus muscle
- Real - 90% RMT
- Sham – 10% RMT

**Patient set up**

**Parameters:**
- 600 pulses
- 1 Hz rTMS (inhibitory) to pars triangularis of non-lesioned hemisphere
- Motor threshold determination with First dorsal interosseus muscle
- Real - 90% RMT
- Sham – 10% RMT

**Distribution of Literature**

- rTMS & Speech 23%
- TMS & Cognitive training 4%
- rTMS & Motor 73%

**rTMS combined with behavioral therapy?**

**TMS for Alzheimer’s disease - Neuronix**

- Combines TMS to enhance plasticity with cognitive exercises
- TMS to a brain network followed by cognitive tasks that activate that network
- Daily sessions lasting 1 hour for 6 weeks

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**Subject 1**

**Berenson-Allen Center for Noninvasive Brain Stimulation**

**Beth Israel Deaconess Medical Center**

**Harvard Medical School**

**NICETM Neuronix Ltd.**

**NICETM System Neuronix Ltd., Israel**

**Sereen N Brown Center for Noninvasive Brain Stimulation**

**Beth Israel Deaconess Medical Center**

**Harvard Medical School**

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**BEM**

**Brain stimulation parameters**

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<thead>
<tr>
<th>Brain Region</th>
<th>Left IFG</th>
<th>Left STG</th>
<th>R DLPFC</th>
<th>L DLPFC</th>
<th>R IPL</th>
<th>L IPL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Task</td>
<td>Sentence similarities, differentiates right/wrong sentences</td>
<td>Differentiates words/pseudo words, associates pictures to situations</td>
<td>Action naming, word recall</td>
<td>Remember color/location of rectangle, word recall</td>
<td>Identify red/white rectangles</td>
<td>Identify letters in a cluster of letters</td>
</tr>
</tbody>
</table>

Abbreviations: L IFG: left inferior frontal gyrus; L STG: left superior temporal gyrus; R and L DLPFC: right and left dorsolateral prefrontal cortex; R and L IPL: right and left inferior parietal lobule.

Results of Initial NeuroAD trials

- Neuronix has completed a phase III trial of TMS + Cognitive therapy in mild-moderate AD
- Prospective, double-blind trial of 130 patients
- Initial results presented at meetings showing efficacy in the mild AD patients but not in overall group

Donse et al. (2018)

Conceptual Guide for Timing of rTMS and Behavioral Therapy

<table>
<thead>
<tr>
<th>Concurrent</th>
<th>rTMS</th>
</tr>
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<tbody>
<tr>
<td>BT</td>
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<table>
<thead>
<tr>
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<td>BT</td>
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</table>

<table>
<thead>
<tr>
<th>Sequential</th>
<th>rTMS</th>
<th>BT</th>
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<tbody>
<tr>
<td>rTMS</td>
<td>BT</td>
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Donse et al. (2018)
Conclusions

- Brain state influences the response to neuromodulation
- Homeostatic mechanisms may oppose further enhancement when interventions are combined
- Combined neuromodulation & behavioral therapy can be effective
- The optimal circumstances require further investigation