Non-Invasive Brain Stimulation and Behavioral Therapy

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Limitations and advantages of restorative methods…?

Pharmacology
Brain Stimulation
Behavioral Intervention

How does repetitive behavior affect motor cortex?
Simple repetitive finger movements increase excitability

Motor map changes with skilled practice

How does NIBS affect motor cortex?

Di Lazzaro et al. (1998)

Periodicity ~ 1.5ms

I-waves

TMS

Emg instrument

SICF

Ziemann et al, 1998

“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
  - Intermittent
  - Theta-burst

- **Inhibitory**

**High-frequency (~10Hz)**

**Low-frequency (~1Hz)**

**Continuous**

**THETA BURST**

**Excitatory**

**Inhibitory**

**Long-term potentiation**

**Long-term depression**

**Clinical application - rTMS, Stroke Motor Recovery**

**IMPROVED CORTICOMOTOR OUTPUT FROM IPSI-LESIONAL M1 & IMPROVED MOTOR BEHAVIOUR**

**REFERENCES**

- Takesuechi et al, 2008
- Boggio et al, 2007
- Fregni et al, 2006
- Fregni et al, 2005
- Mansur et al, 2005
- Takesuechi et al, 2005
- Boggio, et al, 2006

- Yobartiran et al, 2009
- Malcom et al, 2007
- Hummel et al, 2007
- Talelli et al, 2007
- Kim et al, 2006
- Hummel et al, 2006
- Khedr et al., 2005
- Hummel et al, 2005

**Webster et al (2006)**

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

**Beth Israel Deaconess Medical Center**

**Harvard Medical School**
**How does combined intervention affect motor cortex?**

**Function Improvements**
- sRT/eRT
- Pinch force acceleration
- fingers/thumb AROM
- Movement accuracy
- Purdue Pegboard
- JTT

**TMS correlates**
- Resting MT
- Transcallosal Inhibition
- MEP Amplitude

**IMPROVED CORTICOMOTOR OUTPUT FROM IPSI-LESIONAL 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

*Lang et al (2004)*

**Is coupling NIBS with therapy good?**

- Motor Training = improvement in function ‘X’
- NIBS = improvement in function ‘X’
- Motor Training + NIBS = improvement in function 2X, X², or 0??

**If...**

**Motor Training**

**and...**

**NIBS**

**Motor systems example**

- If Motor Training and NIBS, does Motor Training + NIBS result in improvement?
Anodal tDCS combined with robotic motor training


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

Cor = 0.475, p<0.001

Increase in FM Post-Pre

Baseline FM Score

MEP > 0.05
MEP ≤ 0.05

Mean MEP amplitude

Post-tDCS Post-Robot Pre-tDCS

Pre-training Post-training

Group SICI Index
**Repertive Transcranial Magnetic Stimulation (rTMS)**

*Parameters:*
- 900 pulses
- 1 Hz rTMS (inhibitory) to M1 of non-lesioned hemisphere
- 110% of motor threshold for Extensor Digitorum Communis (m.EDC)

**Task Oriented Rehabilitation**

**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

**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

**Mean change UEFM points 6 mths**

**Experimental:** 8.2 ±7pts

**Control:** 8.5 ±8pts

\[ P = 0.87 \]
How does unaffected M1 excitability relate to hemiparesis?

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

Hot colour = maximum overlap for unaffected hemisphere hyper-excitibility

Courtesy A. Boes MD March 2017

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?
Evidence / Rationale


R hem 1 Hz rTMS + SL therapy improves language recovery and favors L hem language network activation.

rTMS plus speech therapy, inpatient stroke

Aiming tool: centering, rotation, tilting

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

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
TMS for Alzheimer’s disease—Neuronix Stimulation Sites

Brain Region | L IFG Broca | L STG Wernicke | R DLPFC | L DLPFC | R IPL | L IPL
--- | --- | --- | --- | --- | --- | ---
Cognitive Tasks | Stroop, simultaneity, differentiation, right/wrong sentences | Differentiation, words/pseudo words, associate pictures to statements | Action naming, word recall | Remember color/location of reorientation, word recall | Identify red/blue rectangles | Identity boxes R/C/TM in a cluster of boxes

Task examples

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*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


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Conceptual Guide for Timing of rTMS and Behavioral Therapy

**Concurrent**

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**Sequential**

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**rTMS & Psychotherapy in Major Depressive Disorder**

- Feasibility & clinical outcome of simultaneous rTMS + PT in MDD
- n=196 patients, major psychiatric MDD or dysthymia
- Treatment regimen: Min. 2-3 days per week; Max 2x per day, # of sessions varied

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TMS Intervention (20 Min)

- High, low, or both sequentially
  - High frequency (HF): 10 Hz left DLPFC, 110-120% RMT, 30 trains of 5 s duration, inter-train interval 30s, 1500 pulses per session
  - Low frequency (LF): 1 Hz right DLPFC, 110-120% RMT, 120 trains of 10 s duration, ITI 1s, 1200 pulses per session
  - LF + HF: Low frequency (1000 pulses per session) then HF protocol at full length

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Psychotherapy Intervention

- Primarily CBT, specific approach individualized on clinical needs of individual
- Duration: 45 minutes
- Decision to continue treatment were based on:
  1. Response to treatment
  2. Clinical evaluation of symptom severity
  3. Patient request

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Results

- Mean BDI scores significantly reduced after rTMS + PT (55.9% reduction)
- No differences in overall BDI score found between HF & LF protocol groups
- Remission rate of 56% (<37 monotherapy)
- Response rate of 66% (29-58 monotherapy)

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