Non-Invasive Brain Stimulation and Behavioral Therapy

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Orthopedic conditions
Cancer
Cognitive impairments
Pain
Drug abuse
Sensorimotor disorders
Psychiatric disorders
Brain damage
Pediatrics
Speech/language
Eating disorders
Brain damage
Speech/language
Cancer

Listings for “TMS”
Source: www.clinicaltrials.gov

rTMS combined with behavioral therapy?

Plasticity
Adaptive
Maladaptive

Limitations and advantages of restorative methods....?
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?

TMS Demonstration
Physiology of TMS

"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

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(Hebb, 1932, p.13).

Donald Hebb

Rate-dependent TMS protocols

- Excitatory
  - Repetitive
  - Intermittent
  - Continuous
  - High-frequency ~10Hz
  - Low-frequency ~1Hz
  - THETA BURST


D Edwards

PLEASE DO NOT COPY
**Experimental Procedure**

How does combined intervention affect motor cortex?

**Alteration of cortical excitability before repetitive synaptic activity**

- **1mA 10mins tDCS**
- **rTMS at 3Hz 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

**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

**Improvement in Corticomotor Output**
- IMPROVED CORTICOMOTOR OUTPUT FROM IPSI-LESIONAL M1 & IMPROVED MOTOR BEHAVIOUR

**References**

- Takeuchi, et al., 2008
- Boggio et al., 2007
- Fregni et al., 2006
- Fregni et al., 2005
- Mansur et al., 2005
- Talelli et al., 2007
- Malcom et al., 2007
- Hummel et al., 2007
- Kim et al., 2006
- Khedr et al., 2005
- Hummel et al., 2005
- Yozbatiran et al., 2009

**Composite**

- Functional Improvements
- TMS correlates
- IMPROVED CORTICOMOTOR OUTPUT FROM IPSI-LESIONAL M1 & IMPROVED MOTOR BEHAVIOUR

**Webster et al. (2006)**
- Berenson-Allen Center for Noninvasive Brain Stimulation
- Beth Israel Deaconess Medical Center
- Harvard Medical School

**Clinical applications**
- Stroke Motor Recovery

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Is coupling NIBS with therapy good?

Motor systems example

If…

**Motor Training** = improvement in function ‘X’

and…

**NIBS** = improvement in function ‘X’

does…

**Motor Training** + **NIBS** = improvement in function 2X, X², or 0??

Anodal tDCS combined with robotic motor training

Anodal tDCS combined with robotic motor training

Robotics for assessment of performance kinematics

Pre - training
Post - training

Upper limb robotics at Burke-Cornell, New York

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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<td>&gt;60 min</td>
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<td>no change</td>
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<td>voluntary (finger abduct’n) *</td>
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<td>rTBS</td>
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<td>&gt;20 min</td>
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<td>enhanced inhibition</td>
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</table>

*N presumed excitation

Inhibitory
Excitatory

Prelim data for Nexstim NICHE Trial

Repetitive Transcranial Magnetic Stimulation (rTMS)

Nexstim NICHE Trial 2014-16

Clinicaltrials.gov # NCT02089464
PI: Richard Harvey RIC

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**

- 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**

Clinicaltrials.gov # NCT02089464

International Stroke Conference Feb 2017 Announcement

Mean change across both groups (n ~150): UEFM was 8.2 points

*no difference between sham and real groups


**Active coil**

**Sham Coil**

How does unaffected M1 excitability relate to hemiparesis?

**Figure 4. Sample data for patient with cor3cal/subcor3cal'stroke' (A) axial'T1'MRI'with'leE'cor3cal/subcor3cal'stroke'and'(B) stroke'lesion'mask'employed'for'quan3ta3ve'analysis'of'infarc3on'volume''(C)'Topographic'maps'of'TMS'motor'evoked'poten3als'for'APB'and/or'EDC'hand'muscles'of'unaffected'hemisphere'(right)'and'(D)'affected'hemisphere'(leE).''Gray'is'no'response.''

CA

DB

Mike Fox MD PhD
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Aaron Boes MD PhD
BIDMC/IGH/UIOWA

Amy Kuceyeski, Ph.D.
Radiology and Neuroscience,
Weill Cornell
VLSM in 3-12month Post-Stroke (hemiparesis)

Hot colour = maximum overlap for unaffected hemisphere hyper-excitability

n=103

Berenson-Allen Center for Noninvasive Brain Stimulation
Beth Israel Deaconess Medical Center
Harvard Medical School

Other cortical areas?

Webster et al (2006)

Post-stroke aphasia?

How is the network disrupted?

Is NIBS useful?

Can it be effectively combined with SL therapy?


No evidence for tDCS as useful adjunct some merit in cathodal stimulation?


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

Evidence / Rationale


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

Repetitive transmagnetic stimulation (rTMS)

Patient set up

Parameters:
• 900 pulses
• 1 Hz rTMS (inhibitory) to pars triangularis of non-lesioned hemisphere
• Motor threshold determination with First dorsal interosseus muscle
• Real – 80% RMT
• Sham – 10% RMT

Subject 1

Electrical field display

Aiming tool: centering, rotation, tilting

CIHR: MOP-286185
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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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
rTMS & Psychotherapy in Major Depressive Disorder


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

TMS Intervention (20 Min)
- High, low, or both sequentially
- High frequency (HF): 10 Hz left DLPFC, 110-120% RMT, 3 trains of 5 s duration, inter-train interval 30s, 1500 pulses per session
- Low frequency (LF): 1 Hz right DLPFC, 110-120% MT, 120 trains of 10 s duration, ITI 1s, 1200 pulses per session
- HF + LF: Low frequency (1000 pulses per session) then HF protocol at full length

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

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)

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