Transcranial Magnetic Stimulation - TMS

**Diagnostic Applications**

- Central Motor Conduction
- Cortical Output Mapping
- Cortical reactivity
- Intracortical E/I Balance
- Cortical Plasticity
- Metaplasticity
- Functional Connectivity
  - Cortico-cortical
  - Cortico-subcortical

**Therapeutic Applications**

- Medication Refractory Depression
  - Lancet 1995
  - FDA Approval, Neuronetics, 2008
- Parkinson’s Disease
  - Neurology 1994
  - MJFF Multicenter Study
- Pain
  - Neurolieve – Migraine
  - Cerephex – Fibromyalgia
- Neurorehabilitation
  - Nexstim – Stroke
- Epilepsy

...
Brain Behavior Relations

Genetic Defect → Environmental Factors → Acquired Insult

Pathology

Brain Adaptation/Compensation

Change in Cognitive Strategy

Pattern of Brain Activity

Behavior

Symptoms of Disease
TMS

• Focal Interference with Brain Activity
  – Adding causal information to brain imaging findings

• Modulation of a Specific Neural Network
  – Therapeutic potential in ‘circuit disorders’
rTMS: Lasting Modulation of Cortical Activity

Modulation Depends on Pattern of Stimulation

Sham TMS

1 Hz TMS

20 Hz TMS

rTMS: Modulation of a Neural Network

Modulation Depends on Neural Connectivity

FDA approved for the treatment of medication-resistant depression.

FDA approved for cortical brain mapping.
TMS Terminology

- **Single pulse TMS**
  - single stimulus every 5-10 sec

- **Paired pulse TMS**
  - Two stimuli separated by 1-20 msec
  - Same coil or different coils

- **Repetitive TMS (rTMS)**
  - trains of stimuli to one brain area
  - slow = low frequency
  - fast (high freq) > 1 Hz
  - Asynchronous trains (eg theta burst stimulation)
TMS: Central Conduction Time

Kobayashi et al Lancet Neuro
Motor Cortical Output Mapping
Comparing Noninvasive and Invasive Mapping

Nagib et al. *Neurosurg Clin* 2011
TMS: Paired-Pulse

Kobayashi et al. *Lancet Neurol.* 03

Diagram A: Conditioning TMS followed by Test TMS.

Diagram B: Test TMS followed by Conditioning TMS.

Graphs show the percentage of control size against interstimulus interval (ms).
Characterizing Neural Networks
TMS and EEG
Characterizing Neural Networks
TMS and fMRI
Measuring LTP/LTD in Humans

Cortical Reactivity → Cortical Plasticity → Cortical Reactivity

Theta Burst Stimulation (TBS)

cTBS

iTBS
Measuring LTP/LTD in Humans

Cortical Reactivity → Cortical Plasticity → Cortical Reactivity

Theta Burst Stimulation (TBS)

Graph showing EP amplitude as a proportion of baseline over time after TBS [min]:
- iTBS
- cTBS

LTP-like Plasticity
LTD-like Plasticity
FDA approved Treatment for Medication-Resistant Depression

Pascual-Leone et al *Lancet* 1996
Therapeutic Applications of rTMS

(1) Modulate cortical excitability (increase or decrease it) to normalize abnormal level of activity in the targeted brain region - Depression, Dystonia

(2) Suppress activity in the targeted brain region and induce paradoxical behavioral facilitations through distant effects - Neglect, Aphasia

(3) Induce distributed modulation of brain activity resulting in network-specific release of neurotransmitters and activity modulation - PD, Depression, Prefrontal function

(4) Induce release of neurochemical agents with generalized neuromodulatory effects - Epilepsy
rTMS in Dystonia

1 Hz rTMS to suppress cortical excitability

Siebner et al. 1999

Intracortical Inhibition
[% of TS alone]

Writing Pressure [N]

Patients Controls

Patients Controls

Before After Before After

Before After Before After
Interhemispheric inhibition and neglect

Transcallosal inhibitory connections may subserve rival networks between the two hemispheres, the dynamic balance of which permits normal redirection of attention. (Kinsbourne, 1977)
Interhemispheric inhibition and neglect

Two-lesion case studies

- Sprague (1966): Neglect from cortical lesion can be reversed by contralateral superior colliculus lesion.
- Vuilleumier et al. (1996): In humans with one lesion, a contralateral second lesion may attenuate neglect.
Therapeutic modulation of interhemispheric connections

Fregni & Pascual-Leone (2007)
Contralesional TMS attenuates neglect

- 5 subjects with neglect (3 right brain injury; 2 left brain injury)
- Stimulation over right and left parietal cortex
- 10 pulses of TMS at 25 Hz, synchronous with stimuli

Oliveri et al., 2001
Extended rTMS may lead to sustained improvement

Brighina et al., 2003

- 3 patients; right brain injury with neglect
- rTMS to left parietal cortex
  - 900 Pulses
  - 1 Hz (inhibitory)
  - Every other day x 2 weeks
- Improvement persisted 15 days after completing TMS
Extended rTMS may lead to sustained improvement

Song et al., 2009

- 14 Patients: 7 treatment, 7 control
- 0.5 Hz, 90% MT, 15 min, twice daily x 2 weeks
- Left P3 stimulated
- Testing 2 weeks prior, start of treatment, end of treatment, and two weeks later
- No control site, task, or sham
Extended rTMS may lead to sustained improvement

- Two chronic neglect patients
- Six rTMS sessions over two weeks
- 900 pulses to P5 per session
- 0.9 Hz, 95% MT
- Behavioral Inattention Test (BIT) administered at baseline, 2, 4, and 6 weeks.
Reduction of parietal hyperexcitability correlates with behavioral benefit

- Twin-coil TMS test of PPC-M1 influences.
- 12 RH patients with neglect, 10 without, 8 healthy controls
- MEP amplitude after conditioning pulse correlated with neglect severity

Koch et al., 2008
Reduction of parietal hyperexcitability correlates with behavioral benefit

- MEP amplitude in neglect patients reduced after 600 pulses of 1 Hz TMS (90% MT)
- Stimulation of right PPC also temporarily improved neglect symptoms of visual chimeric test (Sarri et al., 2006)

Koch et al., 2008
Therapeutic Applications of rTMS

• Increase or Decrease cortical excitability in the targeted brain region to normalize abnormal level of activity
• Decrease cortical excitability in the targeted brain region to release inhibition on distant area and achieve paradoxical functional facilitation
Modulation of Cortical Excitability

- Inter-individual variability
- Dependency on baseline cortical excitability

Maeda et al, 2000

rTMS condition

rTMS: 240 stimuli at 90% of motor threshold
Therapeutic Applications of rTMS

- Stimulate the release of neurotransmitters or other substances with neuromodulatory effects
Antiepileptic Property of the CSF after Exposure to rTMS

Flurothyl seizure model

Anschel, Holmes, Pascual-Leone 2002
Parkinson’s Disease

1994

R. J. Goldberg Foundation
NIH

MASTER-PD
5 yr Multicenter Study
Univ Florida • Cleveland Clinic
UCLA • Univ Toronto
Therapeutic Applications of rTMS

• Induce distributed modulation of brain activity resulting in network-specific release of neurotransmitters and activity modulation
Stimulation of prefrontal cortex
(human and animal studies showing release of dopamine after rTMS of prefrontal cortex)

Strafella, 2001; Keck, 2002
TMS in Parkinson’s Disease

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Fregni et al 2005
TMS in Parkinson’s Disease

Wu et al 2008
Depression in PD
TMS vs Fluoxetine

<table>
<thead>
<tr>
<th>Table 1 Descriptive characteristics of patient groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n = 21)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Male (n)</td>
</tr>
<tr>
<td>Female (n)</td>
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<tr>
<td>MMSE</td>
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</tbody>
</table>

**Depression features**
- HDRS: 25.6 (6.9) vs 25.6 (7.5), p = 0.775*
- BDI: 25.1 (7.7) vs 24.5 (8.8), p = 0.843*
- Major depression (n): 17 vs 16, p = 1.000‡
- Minor depression (n): 4 vs 5

**Motor threshold, mean**
- Initial (% output TMS): 57.0 (11.1) vs 54.8 (8.5), p = 0.774*

**Parkinsonian features**
- Age at onset (years): 58.8 (8.5) vs 57.5 (8.9), p = 0.621*
- Onset side
  - Right (n): 10 vs 7, p = 0.345†
  - Left (n): 11 vs 14
- UPDRS
  - Total: 34.6 (15.3) vs 38.1 (17.8), p = 0.505*
  - Freezing: 74.3 (18.3) vs 70.9 (21.4), p = 0.591*
- Hoehn and Yahr score
  - 1 (n): 21 vs 16, p = 0.697‡
  - 2 (n): 6 vs 5
  - 3 (n): 3 vs 2
  - 4 (n): 4 vs 5

**Drugs**
- Levodopa (n): 18/21 vs 16/21, p = 0.697‡
- Daily dose (mg): 472.2 (145.8) vs 546.9 (198.3), p = 0.217*

Values are mean [SD] or n where specified.
*Student’s t test for independent samples.
†Fisher’s exact test.
‡Fisher’s t test.
ADL, activities of daily living; BDI, Beck depression inventory; HDRS, Hamilton rating scale for depression; MMSE, mini-mental state examination; UPDRS, unified Parkinson disease rating scale.

Fregni et al
JNNP 2004
Depression in PD
TMS vs Fluoxetine

Fregni et al
JNNP 2004
Depression in PD
TMS vs Fluoxetine

Fregni et al JNNP 2004
**Depression in PD**

**TMS vs Fluoxetine**

*Table* Demographic and baseline clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>rTMS group</th>
<th>Fluoxetine group</th>
<th>p Value*</th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>13</td>
<td>13</td>
<td></td>
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<tr>
<td>Demographic data</td>
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<tr>
<td>Age, y</td>
<td>67.54 ± 6.83</td>
<td>65.04 ± 3.93</td>
<td>0.80</td>
</tr>
<tr>
<td>Men</td>
<td>8</td>
<td>8</td>
<td>0.999</td>
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<tr>
<td>Women</td>
<td>5</td>
<td>5</td>
<td></td>
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<tr>
<td>Parkinson features</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Duration of disease, y</td>
<td>7.08 ± 3.66</td>
<td>7.85 ± 4.94</td>
<td>0.65</td>
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<tr>
<td>ADL</td>
<td>76.92 ± 15.48</td>
<td>71.54 ± 23.04</td>
<td>0.84</td>
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<tr>
<td>Hoehn–Yahr</td>
<td>1.85 ± 0.90</td>
<td>1.92 ± 1.26</td>
<td>0.41</td>
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<tr>
<td>UPDRS</td>
<td>32.15 ± 12.21</td>
<td>37.23 ± 17.87</td>
<td>0.91</td>
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<tr>
<td>Psychiatric features</td>
<td></td>
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<td></td>
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<tr>
<td>BDI</td>
<td>25.92 ± 9.98</td>
<td>26.85 ± 8.12</td>
<td>0.80</td>
</tr>
<tr>
<td>HRSD</td>
<td>25.54 ± 6.57</td>
<td>27.46 ± 6.60</td>
<td>0.57</td>
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<tr>
<td>MMSE</td>
<td>25.77 ± 3.65</td>
<td>24.69 ± 4.17</td>
<td>0.53</td>
</tr>
</tbody>
</table>

* Using Student *t* test for continuous variables and Fisher exact test for categorical values. Note that the low score of baseline MMSE indicates the low level of education of these patients (patients with dementia were excluded from this study).
Depression in PD
TMS vs Fluoxetine

After rTMS

After Fluoxetine

Sagittal

Coronal

Sagittal

Coronal

Transverse

Transverse

Fregni et al Neurology 2006
NICE™
Non Invasive Cortical Enhancer
Neuronix ®

![Graph showing ADAS-Cog change over time for different treatments: NICE - Neuronix, ChEIs Drugs - average, Rivastigmine (6-12mg), Galantamine, Donepezil (5-10mg), Placebo.](image)
Identify Brain Target
Neuronavigation
Reliable Targeting of a Given Brain Region

Non-navigated

Neuronavigated
Neuronavigation: Enhanced Behavioral (Therapeutic) Effects
Current shunting by damaged tissue
Modeling Current Distribution in Subject’s Brain

Wagner et al.

IEEE 2005; Neuroimage 2006
Integrity of outputs?  
Network reorganization?

Normal  
Recovery from Stroke
Establish Integrity of Output

- **L FDI** (TMS of R affected M1)
- **R FDI** (TMS of L unaffected M1)

- 0.5 mV
- 20 ms

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DO NOT COPY

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Paired Pulse TMS Measures Hemispheric Interactions:
Patients after stroke have excessive interhemispheric inhibition
Promoting Stroke Recovery

Before After rTMS

Mansur et al. Neurology 2005

Khedr et al. Neurology 2005

Fregni et al. 2005 · Boggio et al. 2006, 2007
Hummel et al. 2005, 2006 · Schlaug et al. 2011
Modulation of Neural Networks as Therapeutic Strategy

Aphasia: Language Circuit - Rt. Pars Triangularis

Martin et al. 2005
Naeser et al. 2006, 07
Modulation of Neural Networks as Therapeutic Strategy

Aphasia: Language Circuit - Rt. Pars Triangularis

Before After rTMS
Modulation of Neural Networks as Therapeutic Strategy

Aphasia: Language Circuit - Rt. Pars Triangularis

After rTMS
Modulation of Neural Networks as Therapeutic Strategy

Aphasia: Language Circuit - Rt. Pars Triangularis

Pars Triangularis

Pars Opercularis

Martin et al. 2005
Naeser et al. 2006, 07
Therapeutic Applications of TMS

- Depression
- Autism
- Acute Mania
- Bipolar Disorder
- OCD
- PTSD
- Schizophrenia
- Auditory Hallucinoses
- Pain
  - Visceral pain
  - Neuropathic pain
  - Phantom pain
- Fibromyalgia
- Migraine
- PD
- Alzheimer’s Disease
- Focal dystonia
- Epilepsy
  - Myoclonic epilepsy
  - Focal status epilepticus
- Stuttering
- Tics
- Neurorehabilitation
  - Neglect
  - Aphasia
  - Hand weakness
- Addiction
  - Cocaine
  - Nicotine
  - Gambling
  - Food
Therapeutic Applications of TMS

- Depression
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  - Food

Fregni & Pascual-Leone
Nature Clinical Neurology 07

Proof of Principle ≠ Clinical Utility
DO NOT COPY
Clinical Trials Needed