Potential Neurological Applications of Transcranial Magnetic Stimulation

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Overview of Talk

- Diagnosis / Prognosis
  - Presurgical Motor & Language Mapping
  - Motor outcome after stroke

- Therapeutics across neurologic indications
  - Migraine (FDA-Cleared)
  - Neuropathic Pain
  - Stroke (Motor, Aphasia, Neglect)
  - Alzheimer's Disease
  - Epilepsy
  - Tinnitus
  - Parkinson's Disease

Noninvasive Brain Stimulation (e.g. rTMS or tDCS)

- Diagnostic Applications
  - TMS
  - Characterization of underlying neurobiology
  - Physiologic Biomarker
  - Predictor of Treatment

- Therapeutic Applications
  - TMS & tDCS
  - Stimulation alone or in combination with other interventions

Neuronix
Neuronetics
Brainsway
Magstim
FDA cleared for the treatment of medication-resistant depression.
FDA cleared for cortical brain mapping
Motor / Language Mapping

- FDA approval of Nexstim NBS device for:
  - Mapping of the primary motor cortex
  - Localization of cortical areas that do NOT contain essential speech function
  - For pre-procedural planning

Motor Cortical Output Mapping

Comparing Noninvasive and Invasive Mapping

- Comparing nTMS to Direct Cortical Stimulation (DCS):
  - Mean distance between nTMS & DCS hotspots was 7.83 +/- 1.18 mm for APB (95% CI 5.36 to 10.36 cm)
  - nTMS and DCS hotspots were in same gyrus for all patients

Motor mapping

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  - nTMS and DCS hotspots were in same gyrus for all patients
nTMS vs fMRI

- Several studies have evaluated accuracy of motor mapping with nTMS vs fMRI (with DCS as gold standard)
  - Forster 2011, Neurosurgery: 10 pts, mean distance to DCS hotspot 10.5 +/- 5.7 mm for nTMS vs 15.0 +/- 7.6 mm for fMRI
  - Mangraviti 2013, Neurol Sci: 7 patients, mean distance to DCS hotspot 8.5 +/- 4.6 mm for nTMS vs 12.9 +/- 5.7 mm for fMRI

Coburger 2013, Neurosurg Rev: 30 patients; all 30 completed nTMS, whereas only 23 completed fMRI. Authors binned results into 4 levels, where 1 is most accurate, 4 is least accurate

Motor mapping w/ nTMS improves outcome?

- Krieg 2014 Neurosurgery: Compared outcomes in 100 consecutive patients bw 2010-2013 vs 100 historical controls without nTMS from immediately prior period
  - All patients underwent intraoperative MEP monitoring as well
  - Craniotomy size significantly smaller in nTMS group
  - 12 pts in nTMS group improved, vs only 1 in control group
  - Residual tumor in 22% of nTMS group vs 42% of controls

Language mapping

- Picht 2013, Neurosurgery: Evaluated nTMS and DCS responses during language mapping in 20 patients with tumors close to left-sided language areas

| Table 1. Sensitivity, Specificity, Positive/Negative Predictive Values for All Brain Regions in All Patients |
|---------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Chiasm (left) | 0.00 | 0.10 | 0.10 | 8.00 | 0.10 |
| Chiasm (right) | 0.00 | 0.10 | 0.10 | 8.00 | 0.10 |
| Sensitivity | 0.10 | 0.10 | 0.10 | 8.00 | 0.10 |
| Specificity | 0.10 | 0.10 | 0.10 | 8.00 | 0.10 |
| Positive predictive value | 0.10 | 0.10 | 0.10 | 8.00 | 0.10 |
| Negative predictive value | 0.10 | 0.10 | 0.10 | 8.00 | 0.10 |

Language mapping ...

- A subsequent study (Tarapore 2013, NeuroImage) also demonstrated high negative predictive value, with improved specificity
MEPs predict functional recovery after stroke

The PREP algorithm predicts potential for upper limb recovery after stroke

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  - Alzheimer’s Disease
  - Epilepsy
  - Tinnitus
  - Parkinson’s disease

Therapeutic effects?

- rTMS has been studied as a therapeutic modality in different neurologic conditions including
  - Epilepsy
  - Migraine prevention
  - Motor rehabilitation after stroke
  - Cognitive rehabilitation in post-stroke aphasia, post-stroke neglect and Alzheimer’s Disease
  - Movement Disorders (primarily Parkinson’s)
  - Chronic Pain
  - Tinnitus
- However, FDA indication has not been yet obtained for any of these (multi-center trials currently underway in several disease conditions)
Principles for successful intervention with TMS/tDCS

- Known brain region or network
- Known goal to enhance or decrease activity of that network
- Target can be engaged by stimulation intervention

Key References

- Handbook of Clinical Neurology
  - Volume 116, Pages 2-763, 2013, Edited by Andres Lozano and Mark Hallett
  - Overview of Deep Brain Stimulation and Noninvasive Brain Stimulation across spectrum of neurologic diseases
- Lefaucheur et al, Clinical Neurophysiology 2014
  - Recent evidence-based review/guidelines on therapeutic use of rTMS in neurologic and psychiatric diseases

Blinding in TMS studies is difficult

- TMS produces
  - An auditory clicking sound w/ bone conduction
  - A tapping sensation (trigeminal afferents)
  - Contraction of the temporalis and frontalis muscles
- Particularly problematic in trials in which “real” stimulation is used to determine motor threshold for titration of stimulation intensity → crossover trials compromised, parallel-group studies are needed!
- Recently, placebo coils that can be preprogrammed and that use electrical stimulation to produce scalp sensations have become commercially available
As a result, study quality is often poor

- Primarily due to lack of allocation concealment and inadequate blinding of participants (e.g., coil tilted away as sham stimulation group). Random sequence generation also often not specified in reports

**Transcranial Magnetic Stimulation**
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**Abortive therapy migraine**
- FDA approval for the SpringTMS single-pulse portable TMS system obtained for abortive therapy of migraine with aura
  - 2 pulses of TMS administered approximately 30s apart to occipital region

**Efficacy in acute migraine**
- Randomized 201 patients with migraine with aura, 1-8 episodes per month, aura for at least 30% of episodes
  - 201 randomized, 164 had migraines and treated
  - Higher pain-free response rates after 2 hours (39% in verum vs 22% in sham), sustained at 24 and 48 hours

**Migraine (chronic treatment)**
- A total of 4 studies evaluating efficacy of rTMS for prophylactic treatment of migraine
  - In largest (class III) study of 95 patients, 10 Hz stimulation to L M1 resulted in more than 50% reduction in headache frequency in 79% of patients receiving real TMS, vs only 33.3% of pts receiving sham (Misra 2013 J Neurol)
  - Small studies evaluated HF stimulation of LDPFC with mixed results; LF stimulation of vertex with no benefit.
Chronic pain

- Trials have attempted to normalize dysregulated corticothalamic pain networks in conditions as diverse as post-stroke pain, complex regional pain syndrome, fibromyalgia, chronic neuropathic pain, visceral pain, and post-operative pain
- Largest crossover study in 60 patients showed rTMS reduced pain by 22% on a VAS scale (vs 8% in sham).
- Studies suggest improvement from HF but not LF stimulation, targeting of M1 but not other regions.
- Beneficial response to rTMS may correlate with subsequent positive outcome of implanted epidural stimulator over M1

Motor Rehab after stroke

- High-frequency ("excitatory") stimulation of ipsilesional hemisphere
- Low-frequency ("inhibitory") stimulation of contralesional motor cortex

All pain trials

Lefaucheur 2014 Clin Neurophys

Most studies show a beneficial effect

Hsu 2012 Stroke

Mean effect size of 0.55 in one recent meta-analysis
Open questions

• Does benefit actually exist?
  – Multi-center study of “inhibitory” contralesional navigated rTMS currently underway (NICHE trial)
• Optimal type of stimulation
  – High-frequency ipsilesional vs low-frequency contralesional vs both?
  – Acute, subacute or chronic?
• Combining brain stimulation with physical therapy beneficial? Timing?
• Current multi-center RCT underway

Effects of parameters?

<table>
<thead>
<tr>
<th>SUPPLEMENTAL TABLES</th>
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<tbody>
<tr>
<td>Summary of the subgroup mean effect sizes</td>
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<tr>
<td>Effect size</td>
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<tr>
<td>Subgrouped by frequency</td>
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<tr>
<td>Low</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Subgrouped by post stroke duration</td>
</tr>
<tr>
<td>Acute</td>
</tr>
<tr>
<td>Subacute</td>
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<td>Subgrouped by lesion site</td>
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<td>Non-specified</td>
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<tr>
<td>Subcortical</td>
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</table>

Hsu 2012, Stroke

Repetitive 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

Collaborative process between therapist and patient
**rTMS for aphasia**

- Trials have focused on primarily the right hemispheric analog of Broca’s area (pars triangularis).
  - MRI neuronavigation is critical! Stimulation of nearby pars opercularis has no benefit, and leads to worsening on some measures (Naeser 2011 Brain & Lang).
- Beneficial effects on naming and language only seen in trials with MRI-neuronavigation, but absent in 2/3 trials with stimulation based on scalp/EEG coordinates.

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**Visuospatial neglect**

- Studies again based on framework of pathophysiologic interhemispheric balance.
- Most studies to date have applied continuous theta burst stimulation to the contralesional left posterior parietal cortex.

**Improvement in neglect and ADLs**

- cTBS to left PPC improved detection of left-sided targets and activities of daily living in one class III trial (Cazzoli 2012 Brain).
- Benefits sustained at least two weeks in another class III trial (Koch 2012 Neurology).
Alzheimer’s Disease

A 65 year old man has a 1/4 probability of developing dementia
A 65 year old woman has a 1/3 probability of developing dementia

Process onset 15-20 years before Sx

World Population Under 5 vs Over 65

Note: Estimates and ranges are based on the mean, minimum, and maximum age-specific incidence rates shown in Table 1.
Hypoplasticity in Alzheimer’s Disease

Modulation: Intermittent Theta-Burst Stimulation (iTBS) (600 pulses over 192 seconds)

After iTBS

Motor evoked potential (MEP)

Baseline

Setup:
TMS applied to left primary motor cortex
Electromyography (EMG) recorded from right first dorsal interosseous (FDI) muscle

NEURONIX Treatment

Concurrent Stimulation with Cognitive Training

Daily Session Overview

Daily sessions: Monday through Friday, consisting of stimulation and cognitive remediation to 4 target regions.

NeuroAD combines computerized cognitive training with navigated TMS
TMS: 20 trains of 2 sec, 10 Hz per region per day at 120% MTx intensity

TMS coil
Technician stand
Computer TMS Treatment chair

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6#

PLEASE DO NOT COPY
Brain Region

- L IFG: left inferior frontal gyrus
- L STG: left superior temporal gyrus
- R DLPFC: right dorsolateral prefrontal cortex
- L DLPFC: left dorsolateral prefrontal cortex
- R IPL: right inferior parietal lobule
- L IPL: left inferior parietal lobule

Cognitive Tasks

- Sentence similarities, differentiate right/wrong sentences
- Differentiate words/pseudo words, assign pictures to categories
- Action naming, word recall
- Remember color/location of rectangular word recall
- Identify red/blue rectangles
- Identify letters B/E/UI in a cluster of letters

Task examples

- Sentence similarities: [example sentence]
- Differentiate words/pseudo words: [example sentence]
- Action naming: [example action]
- Remember color/location of rectangular word recall: [example recall]
- Identify red/blue rectangles: [example identification]
- Identify letters B/E/UI in a cluster of letters: [example identification]

Neuronix Stimulation Sites

- Real treatment (n=10)
- Sham treatment (n=6)
- Real/Sham Treatment (n=5)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mean ± SD</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Real</td>
<td>69 ± 10</td>
<td>0.892</td>
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<tr>
<td>Sham</td>
<td>70 ± 7</td>
<td>0.512</td>
</tr>
<tr>
<td>Real/Sham</td>
<td>68 ± 6</td>
<td>0.802</td>
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<table>
<thead>
<tr>
<th>Education (years)</th>
<th>Mean ± SD</th>
<th>p Value</th>
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<td>Real</td>
<td>16 ± 4</td>
<td>0.544</td>
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<tr>
<td>Sham</td>
<td>17 ± 3</td>
<td>0.111</td>
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<tr>
<td>Real/Sham</td>
<td>15 ± 4</td>
<td>0.512</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>MMSE</th>
<th>Mean ± SD</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Real</td>
<td>22 ± 2</td>
<td>0.353</td>
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<tr>
<td>Sham</td>
<td>21 ± 2</td>
<td>0.015</td>
</tr>
<tr>
<td>Real/Sham</td>
<td>21 ± 2</td>
<td>0.591</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>n</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Real</td>
<td>7 Female, 3 Male</td>
<td>0.211</td>
</tr>
<tr>
<td>Sham</td>
<td>2 Female, 4 Male</td>
<td>0.056</td>
</tr>
<tr>
<td>Real/Sham</td>
<td>3 Female, 2 Male</td>
<td>0.512</td>
</tr>
</tbody>
</table>

Alzheimer's Disease
Cognitive Improvement Related to Modulation of Plasticity

BIDMC Neuronix Pilot

Increased Brain Connectivity Following NeuroAD

Before NeuroAD After NeuroAD difference (post-pre)
Results of Initial NeuroAD trials

**Disease Burden**

* presymptomatic disease modifying
* symptomatic

**CURE**

**M.C.I.**

**A.D.**

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**TMS for Epilepsy**

- Trials have assessed the utility of rTMS in medication-refractory epilepsy (~1/3 of patients)
  - Typically apply low-frequency rTMS to the epileptic focus or applied to the vertex (regardless of location of epileptic focus)

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### Focal TMS to Epileptic focus

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Target</th>
<th>Pulses/session</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theodore, et al</td>
<td>24</td>
<td>3 frontal, 1 parietal, 10 mesiotemporal, 10 lateral temporal</td>
<td>1hz, 900 pulses, 14 sessions</td>
<td>No significant reduction</td>
</tr>
<tr>
<td>Fregni, et al</td>
<td>21</td>
<td>17 partial, 4 diffuse/multifoc</td>
<td>1hz, 1000 pulses, 5 days</td>
<td>Up to 72% reduction in sz.</td>
</tr>
<tr>
<td>Sun, et al, 2012</td>
<td>60</td>
<td>21 frontal, 3 mesiotemporal, 26 parietal, 3 lateral temp, 7 occipital</td>
<td>0.5hz, 1500 pulses, 14 sessions</td>
<td>80% reduction in sz. frequency</td>
</tr>
</tbody>
</table>

### Non focal TMS to Vertex

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Target</th>
<th>Pulses/session</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tergau, et al, 2003</td>
<td>17</td>
<td>Vertex</td>
<td>0.33hz-1hz, 1000 pulses</td>
<td>30% reduc only after 0.33 hz</td>
</tr>
<tr>
<td>Cantello, et al, 2007</td>
<td>43</td>
<td>Vertex</td>
<td>0.3hz, 1000 pulses</td>
<td>No signific. reduction</td>
</tr>
</tbody>
</table>
Efficacy of Targeted TMS for Epilepsy

- Decrease in seizure frequency greater than is typically seen in pharmacologic trials
- But beneficial effects only seen when rTMS is targeted specifically to the seizure focus on the neocortical surface
- Multi-center trials needed to confirm findings!

The Lesson from Tinnitus...

- Known neural target that is hyperactive
- Target can be reached with TMS
- Yet...Trials to date have been negative
- Possible reasons:
  - Limbic involvement, like central pain?
  - Bilateral treatments necessary?

TMS and tDCS for Neurological indications

What about tinnitus?

The Lesson from Tinnitus...

- Known neural target that is hyperactive
- Target can be reached with TMS
- Yet...Trials to date have been negative
- Possible reasons:
  - Limbic involvement, like central pain?
  - Bilateral treatments necessary?

Model for therapy

- Expertise in brain stimulation
- Expertise in the disorder
- Team-based approach
- Clinician-based approach

Clinical Standards Committee of Clinical TMS Society
Conclusions

- Currently, TMS is FDA approved for motor / language mapping, and for abortive treatment of migraine.
- Early studies suggest that TMS metrics may have an important role as diagnostic and prognostic biomarkers in a number of disease states.
- rTMS shows promise as a therapeutic modality in a number of disease states, although well-designed multi-center parallel-group randomized trials are necessary.