TMS: An Update with Practical Implications for the Clinician

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TMS Background and Treatment-Resistant Depression

Main Brain Stimulation Techniques
(partial listing)

- ECT
- FEAST
- rTMS
- Brainsway, Magstim, Neuronetics, Neurelave, Neosdm, Neosync
- DBS – Parkinson’s disease
- RET
- Epidual cortical stimulation
- VNS – Epilepsy and Depression
- MST
- TENS
- CES
- EPI-fMRI
- Transcranial pulsed ultrasound

FDA Approved

- Not FDA Approved

Impact of Persistent Depression

- The impact on health resource use is profound
  - Excess health care visits are for medical evaluation of untreated depression symptoms (eg, chest pain, backache, chronic pain)
  - Excess utilization of healthcare resources overall
  - Increases are evident on both direct and indirect costs

- 30% of depressed patients attempt suicide
  - Nearly half of these complete (> 19,000 suicides/year in the United States)

Major Depression is a Leading Health Risk in the Workplace Setting

Cost Impact of Depression on Associated Illnesses

<table>
<thead>
<tr>
<th>Condition</th>
<th>Annual Medical Costs per Patient without Depression (USD$)</th>
<th>Annual Medical Costs per Patient with Depression (USD$)</th>
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</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>2.56</td>
<td>6.74</td>
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<tr>
<td>Allergic rhinitis</td>
<td>3.27</td>
<td>8.46</td>
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<td>Asthma</td>
<td>3.73</td>
<td>10.56</td>
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<td>Migraine</td>
<td>3.82</td>
<td>15.47</td>
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<td>Back pain</td>
<td>11.61</td>
<td>33.25</td>
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<td>Diabetes</td>
<td>13.06</td>
<td>27.16</td>
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<tr>
<td>Hypertension</td>
<td>13.38</td>
<td>27.16</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>62.40</td>
<td>110.94</td>
</tr>
</tbody>
</table>

FTE = full time equivalent.

STAR*D Study Demonstrates That Current Treatments Have Limited Effectiveness

STAR*D = Sequenced Treatment Alternatives to Relieve Depression; HAM-D = Hamilton Rating Scale for Depression.


Likelihood of Discontinuing Treatment Increases with Each New Medication Attempt

Systemic Drug Side Effects

- Weight Gain
- Constipation
- Headache/Migraine
- Diarrhea
- Abnormal Sphincter Function
- Drowsiness
- Insomnia
- Increased Appetite
- Decreased Libido
- Tremor
- Nervous Anxiety
- Treatment Discontinuation


Relapse during Long-Term Follow-Up

STAR*D Study Results

The higher the level of treatment resistance prior to remission, the faster the relapse in long-term follow-up.

- Level 1 (non-resistant)
- Level 2 (1 prior Tx failure)
- Level 3 (2 prior Tx failures)
- Level 4 (3 prior Tx failures)


MDD

In MDD, some areas of the brain are hypoactive and others are hyperactive.

TMS

- Application of electromagnetic induction described by Michael Faraday in 1839
  - Faraday’s Law: a time-varying magnetic field induces an electric current that runs perpendicular to the time-varying motion of the magnetic field
- Clinical application: pulsed magnetic fields can induce electrical currents in brain tissues and neurons


How Do ECT and TMS Differ?

ECT

- Direction of induced current: Radial
- Current reaches deep structures: Yes
- Anesthesia required: Yes
- Seizure induced: Yes

TMS

- Direction of induced current: Tangential
- Current reaches deep structures: No
- Anesthesia required: No
- Seizure induced: No

**Key Take-Aways**
- ECT and rTMS vastly differ
- High Frequency rTMS (> 1 Hz) enhances cortical excitability

**Mechanism of Action for TMS**

**Faraday’s Law**

Michael Faraday (1797–1867)

Cortex  TMS Coil

\[ E = -d\Phi/dt \]

“The induced electromotive force in any closed circuit is equal to the time rate of change of the magnetic flux through the circuit”

**The Forgotten Half of the Truth**

Electricity is the Currency of the Brain

All of synaptic pharmacology simply serves to transmit electrical signals to the next neuron

**The Brain is an Electrochemical Organ**

**TMS Mechanism of Effect**

**Acute effects of pulsed magnetic fields in the brain:**
- Induction of localized electric current
- Depolarization of neurons in superficial cerebral cortex
- Alteration in cerebral blood flow and metabolic activity; neurotransmitter release
- Distant action on connected circuits


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**TMS Increases Neurogenesis in Hippocampal Dentate Gyrus**


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**Treating the Brain as an Electrochemical Target**

- Brain activity can be altered:
  - Chemically (eg, via drugs)
  - Electrically (eg, via TMS)

- Drug action is anatomically diffuse and systemic
- TMS is focused, non-invasive and non-systemic


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**How Can TMS Affect the Brain?**

- Physical property of TMS
  - Pain, noise, placebo
- Electrical fields effects – most likely mechanism
- Magnetic field effects (not electrical)?
  - Highly unlikely but not impossible
- Change in blood brain barrier?
  - Possible – checking with diffusion scanning – assume effects are due to neuronal (glial) excitation and cascade of effects thereafter
- Clinical effects might be neurohormonally mediated (eg, TSH, prefrontal)
- Short-term effects (eg, speech arrest) are likely circuit mediated

TSH = thyroid stimulating hormone.

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**Biological Effects of TMS**

**Acute Effects**
- Induces electric current
- Depolarizes neurons in superficial cortex
- Leads to local and trans-synaptic changes in brain activity

Example
- Left prefrontal TMS
- 22 depressed individuals
- Activation demonstrated at site of stimulation and also at synaptically connected cortical and subcortical regions


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**Biological Changes with rTMS in Human Studies**

- rTMS produces changes in PFC and paralimbic blood flow with DLPFC stimulation
- Increased output of TSH in association with acute mood change in depression
- Normalization of the DST with rTMS

PFC = prefrontal cortex; DLPFC = dorsolateral PFC; DST = dexamethasone suppression test.
Biological Effects of TMS (continued)

- Chronic Effects
  - Specific outcome is dependent upon stimulation parameters
  - Alteration of monoamine concentrations
  - β-receptor, serotonin-receptor modulation
  - Induction of neurogenesis genes (e.g., BDNF)
  - Plasticity, LTD/LTP effects
  - Local GABA, glutamate effects
  - Stimulation of the DLPFC alters functional activity of the anterior cingulate and deeper limbic regions

How Does TMS Correct the Neurophysiologic Defect in MDD?

- The brain is a distributed network system whose connections are maintained by rhythmic oscillations. Alpha rhythms are responsible for regulating functional connectivity over long distances in the brain
- In MDD, the brain is locked into a state marked by highly resonant low-frequency rhythmic oscillations
  - Normal oscillations: synchronous and asynchronous rhythm
  - Oscillations in MDD: monotonous synchrony
- Goal of TMS is to reset cortical and thalamocortical oscillators, leading to increased variability in network formation
- Successful treatment is marked by increased variability in oscillatory activity

Prefrontal TMS Effects Limbic Blood Flow

Pooled effects of 1 Hz prefrontal TMS in 5 healthy adults, 120% MT, BOLD fMRI, P < .001, cluster P < .05 for display

TMS Affects β-adrenergic and Serotonergic Transmission in Animal Models

Chronic rTMS modulates β-adrenergic receptors in cortex

TMS Affects β-adrenergic and Serotonergic Transmission in Animal Models (continued)

Chronic rTMS (15 Hz, 3.5 s, 10 d, 7 cm coil) reduced 5-HT₃ receptors in cortex

Prefrontal TMS Induces Dopamine Release in Ipsilateral Caudate

15 10 pulse 1s trains @10 Hz, total 450
Declining Amygdala and Prefrontal Activity with Worsening Depression

Could we wake this up with TMS?

Cortical Governance over Limbic Activity

Clinical Safety and Tolerability Considerations

- What's common, what's not...
- No evidence of cognitive sequelae
- Common adverse events
  - Self-limited headache after treatment (~1 in 4)
  - Cutaneous discomfort during stimulation (~1 in 6)
  - Pain during stimulation (~3–5%)
- Risk of seizure
  - 9 cases reported in the world literature with rTMS
  - Self-limited
  - No reported sequelae or progression to seizure disorder
  - No additional cases since inception of 1998 guidelines

Key Take-Aways

- Synaptic pharmacology serves to transmit electrical signals to the next neuron; in clinical practice, rTMS uses pulsed magnetic fields to induce electrical current in brain tissue and neurons
- One goal of rTMS is to reset cortical and thalamocortical oscillators, leading to increased flexibility in network formations
- rTMS modulates monoamines, glutamate, GABA, as well as intracellular plasticity cascades

Initial TMS Antidepressant Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Freq</th>
<th>MT %</th>
<th>Pulsed %</th>
<th># Sess</th>
<th>Total Pulses</th>
<th>% Change</th>
<th>HDSR</th>
<th>ES</th>
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<tr>
<td>Hoflich et al, 1993</td>
<td>2</td>
<td>3</td>
<td>105-130</td>
<td>250</td>
<td>10</td>
<td>2500</td>
<td>10.3</td>
<td>0.71</td>
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<td>Kolbinger et al, 1995</td>
<td>15</td>
<td>25</td>
<td>90</td>
<td>290</td>
<td>5</td>
<td>1250</td>
<td>15</td>
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<td>George et al, 1995</td>
<td>6</td>
<td>20</td>
<td>80</td>
<td>900</td>
<td>5</td>
<td>4000</td>
<td>26</td>
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<td>Pascual-Leone, 1996</td>
<td>17</td>
<td>10</td>
<td>90</td>
<td>2000</td>
<td>5</td>
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<td>Epstein et al, 1998</td>
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<td>110</td>
<td>250</td>
<td>5</td>
<td>1250</td>
<td>52</td>
<td>1.12</td>
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<tr>
<td>Figiel et al, 1998</td>
<td>56</td>
<td>10</td>
<td>110</td>
<td>500</td>
<td>5</td>
<td>2500</td>
<td>44.4</td>
<td>1.78</td>
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</table>

1,2 = randomized, controlled; remainder of studies were open.
Comparative Analysis of Effect Size: TMS Therapy vs Medications


Meta-Analysis of Left DLPFC rTMS

- Included 12 controlled trials (n = 230)
- Mean effect size 0.53 (CI 0.24-0.82)
- Comparable effect to antidepressants
- Would need—at a minimum—20 negative studies to override this result

Cochrane Meta-Analysis

- Included 14 RCTs of rTMS but critiqued the small sample size of rTMS studies generally (Median n = 19, range 6–40 participants) if Klein et al is excluded
- Found benefit for rTMS of the left DLPFC at 2 weeks and for right DLPFC at 1 Hz but...
- Concluded—“there is no strong evidence for benefit from using transcranial magnetic stimulation to treat depression”

Learning to Optimize TMS or Why Cochrane is Definitely Not the Last Word

- RCT of bilateral TMS in TRD
- Sequential slow TMS on the R and fast TMS on the L
- 6-week trial, daily TMS added on to existing medications, N = 50
- Response rate of 44% and remission of 36% observed on MADRS, 52% and 40% respectively on HAM-D-17
- Significantly greater response to active than sham stimulation at 2 weeks and across the full duration of the study
- Better results than citalopram over 12-weeks in the STAR*D outcomes in the same issue of AJP (47% and 30% on MADRS)

Summary of TMS Acute Unipolar Depression Trials

- 3 large prospective RCTs support TMS for treating acute moderately TRD
- Remission rates from 15% to 30% in the double-blind phase, and ≥ 30% in open-label
- Safe, tolerable, but inefficient
- Good clinical adoption
  - 500 Neuronetics machines sold in United States alone
  - App 12 remitters/day in United States alone
- Durability appears good: 90% retention of response at 12 months

Clinical Benefit Varies by Prior Treatment Failure in STAR*D and TMS Therapy

Comparison of Monotherapy Outcomes: Pharmacotherapy vs TMS Therapy

<table>
<thead>
<tr>
<th>Treatment Resistance</th>
<th>TMS Therapy Outcome</th>
<th>Pharmacotherapy Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>No or Limited Prior Rx</td>
<td>27.5%</td>
<td>21.2%</td>
</tr>
<tr>
<td>1 Prior Failure</td>
<td>16.2%</td>
<td>17.7%</td>
</tr>
<tr>
<td>2 Prior Failures</td>
<td>6.9%</td>
<td>8.2%</td>
</tr>
<tr>
<td>3 Prior Failures</td>
<td>6.9%</td>
<td>8.2%</td>
</tr>
</tbody>
</table>


TMS Therapy Demonstrates a Clear Separation between Active and Sham Treatment

RCT Key Outcome Measure – MADRS Change Score

> 3 x Reduction in Depressive Symptoms at Week 4

LOCF analysis of intent-to-treat population

Independent Study Reinforces Efficacy for TMS

Daily Left Prefrontal Transcranial Magnetic Stimulation Therapy for Major Depressive Disorder

- NIMH-sponsored Optimization of TMS (OPT-TMS) Study
  - Independent of industry
  - Rigorous RCT; active sham-controlled (1:1 randomization), duration- adaptive design with 3 weeks of daily weekday treatment (fixed-dose phase) followed by continued blinded treatment for up to another 3 weeks in improvers
  - 190 patients treated at 4 premier academic sites
- Primary outcome measure: Percent Remission at 3 weeks
  - 4 x greater likelihood of achieving remission with active treatment vs sham treatment


NIMH Multi-Site OPT-TMS Study with Active Sham Control

N = 190; Odds ratio is 4.2
P < .015

Remission


Consistent Response and Remission Rates across a Broad Range of Treatment Resistance

1 in 2 Patients Respond, 1 in 3 Patients Achieve Remission

Naturalistic, Open Label Treatment Utilization and Outcomes Study

Patient reported outcomes (PHQ-9) were consistent with physician-rated outcomes

LOCF analysis of intent-to-treat population. CGI-S outcomes in acute phase.
PHQ-9 > 3-item Patient Health Questionnaire.

TMS Therapy is Cost Effective When Compared to Antidepressant Medication Use-As-Usual

Model Assumptions for Comparison of Treatments over One Year of Care:

TMS Therapy
- TMS: Total utilization, 60 sessions/yr
- Reimbursement Cost Assumption: US $300/treatment
- Follow Up: Medication – monotherapy maintenance
- Lost time to attend TMS treatment sessions included in the model

Antidepressant Medication Management As-Usual
- Efficacy as described in STAR*D study outcomes (Levels 2 and 3)
- Costs for Medications (avg. wholesale price, including generic)
- Includes cost of physician visits for medication management

TMS Represents a Cost Saving over Treatment-As-Usual

- TMS represents a cost savings per patient per year compared to current standard of care:
  - US $1123
    - Without productivity and work loss costs included in the model (Payer Perspective)
  - US $7621
    - With productivity and work loss costs included in the model (Employer Perspective)

Annual Estimated Cost Savings with TMS as a Covered Benefit for a Mid-Sized Payer

Annual Cost Savings in Millions ($)

TMS Therapy in the Care Continuum

Change in HAM-D Measured Weekly

Response and Remission Rates for dTMS and Sham Groups at the End of Week 5 and Week 16

Antidepressant Effect of dTMS in Relation to the Number of Failed Pharmacotherapy Trials
Percentage of Patients Achieving Response or Remission for 0%, 0% to 30%, and > 30% of the Total Time in the Study of dTMS and Sham Groups


Mean HAM-D-17 Scores for the 80% rTMS, 110% rTMS, and Sham Groups at Timepoints throughout the Study


Mean MADRS Scores for the 80% rTMS, 110% rTMS, and Sham Groups at Timepoints throughout the Study


TMS Therapy Modulates Discrete Deep Brain Regions


TMS Modulates EEG Gamma Frequency in Distributed Brain Regions


Long-Term Treatment Outcomes of TMS in Naturalistic Setting


• 257 patients with medication-resistant unipolar depression received TMS and followed post-treatment for 52 weeks
• At the end of acute treatment 120 patients met criteria for either response or remission. Of those, 75 (62.5%) met response criteria throughout the follow-up period
• Of the entire cohort, 93 patients (36.2%) received reintroduction of TMS at some point during the 52-week follow up. Average number of TMS days was 16.2 days
Need for Maintenance rTMS

✓ In principle, the best way to maintain benefit would be rTMS sessions
✓ Options include transition back to ADM or rTMS sessions at reduced frequency
✓ Maintenance ECT may be a model in this regard
✓ Very small amount of data with maintenance rTMS

ADM = antidepressant medication.

No Efficacy/Effectiveness Gap

• 307 real-world US patients, on medication, 58% response, 37% remission, average 28 sessions
• 100 patients, U Penn practice model, 50% response, 25% remission


Failure!

Despite 2 decades of research
• We still largely use the initial approximations (marginally refined)
• We have not achieved the same remission rates as ECT
• We do not understand the LD50 or upper safety limit of dose
• We do not understand, fully, the translational neurobiology (neural mechanisms) of how TMS acts to get patients undepressed


TMS and Postoperative Pain

RCT, 20 Gastric Bypass Patients, L DLPFC, 20 minutes, 10 Hz, 100% rMT


One rTMS Session Cuts Cumulative Morphine Use by 40%


TMS Anti-Suicide Study

• High dose, 3-day adjunctive TMS study on inpatients admitted for suicidal ideation
• Randomized, sham-controlled
• N = 45, 2 sites – Ralph H. Johnson VA Medical Center, Walter Reed National Military Medical Center
• 2 years
• 18,000 stimuli/day, 54,000 total

Active TMS Significantly Reduced Suicidal Ideation

Beck Suicide Scale

Future Applications

<table>
<thead>
<tr>
<th>Psychiatry</th>
<th>Neurology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>Stroke rehab</td>
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<tr>
<td>Bipolar depression</td>
<td>Chronic pain</td>
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<tr>
<td>PTSD</td>
<td>Trigeminal neuralgia</td>
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<tr>
<td>OCD</td>
<td>Headache</td>
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Preliminary human data suggest the potential application of TMS in these conditions

PTSD = posttraumatic stress disorder; OCD = obsessive-compulsive disorder; ADHD = attention-deficit/hyperactivity disorder.


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<td>ADHD</td>
<td>Tinnitus</td>
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<td>Parkinson’s disease</td>
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</table>

Future Applications

• Stroke rehab
• Chronic pain
• Trigeminal neuralgia
• Headache
• ADHD
• Tinnitus
• Epilepsy
• Parkinson’s disease


Future Applications

Future Applications

Key Take-Aways

• Early rTMS trials were flawed in that they were inconsistent in the frequency and number of treatments given
• More recent studies have shown that rTMS is equal to, if not superior to pharmacotherapy for TRD
• A very recent study has demonstrated that high dose, 3-day adjunctive rTMS reduces suicidal ideation

Further Reading


Further Reading

Further Reading

Practical Discussion & Conclusions #1

1. Which patients are most likely to benefit from TMS in clinical practice?
   – Per FDA guidelines, adults patients who have failed 1 antidepressant medication at or above the minimal effective dose and duration in the current episode
   – Patients must be free of seizure disorders and metallic implants on or near the head (Examples include cochlear implants, electrodes/stimulators, aneurysm clips and coils, bullet fragments, jewelry, and hair barrettes)
   – On the market and what makes them different? What about the economic differences and what about reimbursement?

Practical Discussion & Conclusions #1 (Continued)

– Per insurance guidelines, adults patients with moderate or severe MDD diagnosis who have failed 2 antidepressants and 2 medication augmentation therapies (TRD)
– Patients must be free of seizure disorders and metallic implants on or near the head (Examples include cochlear implants, electrodes/stimulators, aneurysm clips and coils, bullet fragments, jewelry, and hair barrettes)
Practical Discussion & Conclusions #2

2. Should I start my own TMS practice?
   - A good estimate of startup cost for equipment and space requirements ranges between $100,000 to $150,000
   - Additional monies for staff cost must be considered as well (TMS coordinator, TMS treater, billing specialist)
   - Insurance coverage varies state to state, as do reimbursement rates
   - Medicare is the only carrier that covers nationally

Practical Discussion & Conclusions #3

3. What are the approved rTMS devices and how do I find them?
   - NeuroStar TMS Therapy – www.neurostar.com or call 1-877-600-7555
   - Brainsway – www.brainsway.com/us or call 1-844-386-7001