Learning objectives

BASIC PRINCIPLES AND TERMINOLOGY OF TMS

TYPES OF STIMULATION, ADMINISTRATION AND SAFETY CONCERNS

TMS IN DEPRESSION & OFF LABEL USES

COMPARISON BETWEEN TMS AND ECT
Neuromodulation

Technology that acts directly upon on nerves.

The alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body
Methods of brain stimulation

Invasive
- DBS
- VNS
- EPIDURAL STIMULATION

Noninvasive
- ECT
- TMS
- tDCS
Continued...

**Methods of stimulus**
- Electric stimulation
- Magnetic stimulation

**Reaction of the Neurons**
- tDCS → spontaneous firing of neuron
- TMS → depolarization of neurons
- ECT → seizure
What is TMS

A noninvasive method of brain stimulation in which magnetic fields are used to induce electric currents in cerebral cortex, thereby depolarizing neurons.

It is sometimes called electrodeless electrical stimulation
History Of TMS

FARADAY - 1831 - Principals of Electromagnetic Inductions

In early 20th century - Unsuccessful attempts to use it stimulate nerves and brain

In 1985 - Anthony Barker and colleagues at University of Sheffield
Basic principal behind TMs

Consists of a conducting coil through which current is passed

Induces a brief magnetic field perpendicular to the plane of coil

Generates an electric current (Eddy current) in the brain- Depolarization of underlying the neurons
Acute effects (online) of TMS

- Phasic activation of neural circuit
- Observable motor response (e.g., twitch)
- Temporary disruption (e.g., speech arrest) or facilitation of ongoing process (e.g., speed reaction time)

Rossi et al 2012
Prolong (offline) effects

Neuroplasticity

Change in synaptic efficacy due to LTP or LTD

Induction of neurotrophin genes (BDNF)

Alteration in monoamines and salivary cortisol

Modulation of cortical excitability and functional connectivity

Rossi et al 2012
Few terms

Pulse: A single magnetic stimulation event

Burst: A combination of 3 pulses given at frequency of 50 Hz

Train: A series of pulses or bursts given together in a fixed pattern and repetitively
TMS theory of depression

Mayberg et al, 2010

Neuro-anatomy and physiology of Major depressive disorder

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

- Single pulse TMS
- Paired TMS
- Repetitive TMS

Rossi et al 2009
Repetitive

Conventional rTMS
- Low frequency < 1 Hz Inhibitory
- High frequency > 1 Hz Facilitatory 5, 10 & 20 Hz

Patterned rTMS
- Theta bursts 3 pulses are given at 50 Hz every 200 ms

Rossi et al 2009
Patterned rTMS

**THETA BURSTS**
- 3 pulses are given at 50 Hz every 200 ms

**TRAIN**
- Each train comprises of 10 bursts

Rossi et al 2009
Continued…

Rossi et al 2009
Types of coil

- Circular coil
- 8 figure coil (focal but not deep)
- H shape coil (deep but not focal)
Continued…

Figure-of-Eight Coil

Circular Coil

H-shape coil (Deep)

Kwasniewska et al, 2014
Do you have epilepsy or have you ever had a convulsion or a seizure?
Have you ever had a fainting spell or syncope? If yes, please describe on which occasion(s)?
Have you ever had a head trauma that was diagnosed as a concussion or was associated with loss of consciousness?
Do you have any hearing problems or ringing in your ears? (5) Do you have cochlear implants?
Are you pregnant or is there any chance that you might be?
Do you have metal in the brain, skull or elsewhere in your body (e.g., splinters, fragments, clips, etc.)? If so, specify the type of metal.
Do you have an implanted neurostimulator (e.g., DBS, epidural/subdural, VNS)?
Do you have a cardiac pacemaker or intracardiac lines?
Do you have a medication infusion device?
Are you taking any medications? (please list)
Did you ever undergo TMS in the past? If so, were there any problems.
Did you ever undergo MRI in the past? If so, were there any problems.

Rossi et al 2011
WHERE TO STIMULATE

Measurement based

• 5 cm rule
• 10-20 EEG (F3)

Neuronavigation
Continued…

STIMULATION POINT AND COIL ORIENTATION IN DEPRESSION TREATMENT

Tormos et al 2008 and 10-20 EEG
Continued...

Fitzgerald et al, 2009
TMS Mapping Protocol by neuronavigation

Woo-jin et al 2016
Neuronavigation

Neuronavigation software

Tracking device

TMS coil

Souza et al 2018
Determining motor threshold (MT)

MT representation of cortical excitability of motor cortex
Treatment dose based on the individual's cortical excitability

Changes in sleep medication, alcohol or drug use can alter cortical excitability

Gergory et al, 2014
Side effects

Seizures
Transient acute hypomania
Transient headache
Local pain in head, neck and teeth
Paresthesia
Transient hearing changes

Rossi et al, 2009
DEPRESSION TREATMENT OPTIONS

DNA & MOLECULAR

PSYCHOTHERAPY

BRAIN CIRCUIT
FDA Approved Protocol for depression

2008 multicenter randomized double blinded study for 18 months. TMS Device Neuronetic

Inclusion: 1-4 failed/not tolerated medications, HAMD 17 > 20

Exclusion: Comorbidity, BPD, psychosis, OCD, PTSD, ECT resistant, prior TMS, Seizures, medications affecting seizure threshold

Medication free during 6 weeks trial (Benza allowed)

30 sessions LDLPFC (5 cm M1), 10 Hz, 3000 pulses 120% MT

Taper treatment over 3 weeks and 6 months follow up

O'reardon et al 2008
Active vs Sham

O’reardon et al 2008
MADRS Response 23.9 % → 27.7%

MADRS Remission 14.2 % → 20.6%

O’reardon et al 2008
CGI-S Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Overall (N=307)</th>
<th>Low Treatment Resistance (N=140)</th>
<th>High Treatment Resistance (N=167)</th>
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</thead>
<tbody>
<tr>
<td>Response</td>
<td>58.0%</td>
<td>59.4%</td>
<td>56.8%</td>
</tr>
<tr>
<td>Remission</td>
<td>37.1%</td>
<td>39.9%</td>
<td>34.9%</td>
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</table>

OCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

PHQ-9 Outcomes

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<td>26.0%</td>
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</table>
IDS-SR Outcomes

<table>
<thead>
<tr>
<th>Category</th>
<th>Response</th>
<th>Remission</th>
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<tbody>
<tr>
<td>Overall (N=307)</td>
<td>41.5%</td>
<td>26.5%</td>
</tr>
<tr>
<td>Low Treatment Resistance (N=140)</td>
<td>41.4%</td>
<td>29.3%</td>
</tr>
<tr>
<td>High Treatment Resistance (N=167)</td>
<td>41.6%</td>
<td>24.1%</td>
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O'reardon et al 2008
Follow up trial by NIMH in 2010

Prospective, multisite, randomized, active sham-controlled

Used MRI for coil placement

Showed improved results from previous study

George et al, 2010
Real world study

339 patients with MDD

Concurrent use of medications

Response rate 41.5-58%

Remission rate 26.5-37.1%

Carpenter et al, 2012
<table>
<thead>
<tr>
<th></th>
<th>Procedure</th>
<th>Setting</th>
<th>Efficacy</th>
<th>Side effects</th>
<th>Cost</th>
<th>Site</th>
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</thead>
<tbody>
<tr>
<td>ECT</td>
<td>Anesthesia</td>
<td>Inpatient/outpatient</td>
<td>More</td>
<td>High</td>
<td>$2075/session</td>
<td>Non-Specific</td>
</tr>
<tr>
<td>TMS</td>
<td>No Anesthesia</td>
<td>Outpatient</td>
<td>Less</td>
<td>Low</td>
<td>$814/session</td>
<td>Specific</td>
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</table>
6 devices Cleared by FDA for depression

FDA cleared for MDD
• Neuronectics, magventure, magstim, neurosoft, nexstim, Brainsway (H1 coil)

For cleared for OCD
• Brainway (H7 coil)
N=181 with MDD
Taking psychotropic medications
All received 10 Hz rTMS to left DLPFC
Patient with inadequate response received 1 Hz in right DLPFC
Response rates at week 6 lower in benzodiazepine users versus non-users (16.4% vs. 35.5%, p = 0.008) higher in psychostimulant users versus non-users (39.2% vs. 22.0%, p = 0.02).

Amiee M Hunter, et al 2019
Space, time and context matters
196 patients received rTMS and PT for 10 sessions.

66% response rate, 56% reemission, and 60% remission at follow-up as measured by BDI.

Donse L, et al. 2019
Off label use

Level A (definite efficacy)
Level B (probable efficacy)
Level C (possible efficacy)
The analgesic effect

High-frequency (HF) rTMS of the primary motor cortex (M1) contralateral to the pain

The antidepressant effect

HF-rTMS of the left dorsolateral prefrontal cortex (DLPFC)

Lefaucheur et al, 2014
Level B (probable efficacy)

- The antidepressant effect
- Low-frequency (LF) rTMS of the right DLPFC
- The negative symptoms of schizophrenia
- HF-rTMS of the left DLPFC
- Chronic motor stroke
- LF-rTMS of contralesional M1

Lefaucheur et al, 2014
Level C (possible efficacy)

Tinnitus and auditory hallucinations

LF-rTMS of the left temporoparietal cortex

Lefaucheur et al, 2014
## Summary

TMS is technology that acts directly upon on nerves.

Protocol approved by FDA in 2008 after multicenter trial

Devices cleared for depression (rTMS) and OCD (deep TMS)

It can be used for patient who had failed 1-4 medications trials or no-compliance due to side effects

In open label trial, 1 in 2 patient had significant improvement and 1 in 3 had remission

Patient start seeing improvement in 2 weeks but most improvement in 4-6 weeks
In 6 months follow up study, patients received a single medications as maintenance, half had symptoms recurrence and required TMS re-treatment which resulted less then 10% relapse

It is not alternative for ECT

Can not be used for acute crises (e.g., psychosis and SI)

It is cost effective and better side effects profile

Insurance cover it for depression

It can be used with medications and therapy and has showed improved responses