We have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this presentation.

Objectives

• Upon completion of this course, attendees will be able to:
  - Compare and contrast the indication for Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS).
  - Compare and contrast the difference between neuromodulation and neurostimulation in the context of Transcranial Magnetic Stimulation.
  - Describe the mechanism of action and physical application of TMS and tDCS for patients with neurologic disease.
  - Discuss the therapeutic application of TMS and tDCS and its efficacy in neurologic physical therapy.
  - Identify limitations of the current evidence and implications for future research of TMS and tDCS in neurologic physical therapy.

The beginning of non-invasive brain stimulation...

• Direct stimulation dates back to AD 47 when records of physicians using electrical currents to treat headaches were found.
• In the 1960s, researchers began investigation of noninvasive direct current stimulation applied directly to exposed cortices of animals.

Where did the idea of TMS arise?

• In 1985, Barker and colleagues sought to find a new way of using electrical currents to stimulate the brain.
• Direct stimulation was too painful, but the magnetic current has less resistance and requires less intensity making it nearly painless.
• They applied what is known as Faraday’s Law of electromagnetic induction.
What is TMS?

- A technique that allows noninvasive magnetic stimulation to stimulate underlying brain tissue to increase or decrease cortical excitability.
- A high current pulse generator produces a discharge current and a wire coil is used to deliver the magnetic field over the scalp.
- This magnetic field creates an electrical field sufficient to depolarize superficial axons thus activating neural networks.

How does TMS work?

- Faraday’s Law of Electromagnetic induction: Magnetic current is used to create an electric current that flows through a targeted area and causes neuronal depolarization.
- Axonal excitation occurs when the gradient of the applied electric field is largest with respect to the direction of the axon.

Is TMS safe?

Possible Safety Concerns:
- Heat, forces and magnetization, induced voltages
- Epilepsy, implanted devices such as aneurysm clips, pregnancy, severe or recent heart disease, deep brain electrodes, a brain lesion, concurrent use with drugs that lower the seizure threshold, sleep deprivation, alcohol use

Precautions:
- Cochlear implants, internal pulse generators, medication pumps, metallic content close the coiling wires

Possible side effects of TMS:

Transcranial Magnetic Stimulation Types of application and Dosage

What dosage of Transcranial Magnetic Stimulation is applied?

- The dosage depends on orientation of the coil, type of coil, distance between coil, the magnetic pulse waveform, the intensity, frequency, and pattern of stimulation
- Dosage is typically described as a measure of the percentage of resting motor threshold (RMT).

RMT - the minimum stimulation intensity required to evoke a motor evoked potential (MEP).
TMS: Types of Application

1. Single Pulse
   - can be applied to synchronously depolarize neurons such as eliciting muscle contraction

2. Paired Pulse
   - explores the effect of the first TMS pulse on the response elicited by a second pulsed application

3. Repetitive Pulse
   - applied to modulate cortical excitability beyond the duration of the pulse application

Repetitive TMS (rTMS)

- Higher intensities have excitatory effect by synchronously firing neurons (long term potentiation, LTP)
- Lower intensities stimulate inhibitory interneurons in the motor cortex and result in inhibition (long term depression, LTD)

Theta Burst: Recently developed form of rTMS designed to mimic the naturally occurring pulse pattern theta rhythm of the hippocampus

Interrupted theta burst = LTD
Continuous theta burst = LTD

TMS: Location of application

- Primary Motor Cortex
  - M1
  - Dorsolateral prefrontal cortex (DLPFC)
  - Supplementary motor area (SMA)

- Image guided TMS
  - fMRI
  - PET

TMS: Image Guided

TMS: What populations is it used for?

- Stroke
- Movement Disorders
- Parkinson’s Disease, Cerebellar Ataxia, Huntington’s Disease
- Various Psychiatric disorders
- Depression, Anxiety, Schizophrenia
- Brain Injury
- Minimally conscious state
- Spinal Cord Injury
- Multiple Sclerosis
- Pain

Transcranial Magnetic Stimulation
Therapeutic Applications
TMS: What is it used for?

**Neurostimulation**
- Brain mapping
- Measure of change
- Assesses the corticospinal tracts
  
**Neuromodulation**
- Long term potentiation
- Long term depression
  
**Neuroplasticity**

Transcranial Magnetic Stimulation
Understanding the role of TMS in neurostimulation

TMS: Neurostimulation

- Corticospinal integrity
- Prognosis
- Diagnosis
- Brain Mapping

TMS: Corticospinal integrity

TMS: Prognostic in the Stroke Population

- TMS used at early stage after ACA stroke appears to have predictive value for the recovery of lower limb motor function and ambulation.
- MEPs can be predictive of motor recovery after stroke
  - Those that an MEP can be elicited in the paretic limb early after stroke have significantly better clinical outcomes then those without MEPs at early stage
TMS: Brain mapping

- TMS determines the electrical excitability of tissue by measuring the muscle response to stimulation
- Can provide two dimensional maps of the brain surface
- Gives information on volume, focality, and the size of represented area

Brain mapping and Incomplete Spinal Cord Injury

- Control vs. incomplete SCI
- Cortical representation of weaker muscle areas are smaller and areas represented by stronger muscles are bigger
- Reduction in map size is directly related to motor impairment
- Decreased cortical representation of the LEs in chronic SCI

TMS and Diagnosis

- TMS can give information to assist differential diagnosis
  - Parkinson’s Disease vs. Parkinsonism syndrome
    - Corticospinal evaluation may help in the differential diagnosis between idiopathic Parkinson disease, in which central conduction time (CCT) is normal, and other parkinsonisms, in which the corticospinal tract can be involved
  - Motor paralysis vs. psychogenic paralysis
    - The presence of normal MEPs in the paretic arm is of clinical value to detect psychogenic paralysis

Transcranial Magnetic Stimulation

Understanding the role of TMS in neuromodulation

TMS: Neuromodulation

- Application to facilitate LTP or LTD
- Applying TMS with concepts we know about neuroplasticity for therapeutic application
- Can be combined with rehabilitation interventions to improve function

What do we know about neuroplasticity?

- “Use it or lose it”
- “Use it and improve it”
- Specificity matters
- Intensity matters
- Time matters
- Salience matters
- Repetition matters
TMS and Stroke
Therapeutic applications and research

Cortical Reorganization after stroke

- After a stroke there is increased activity in the unaffected hemisphere and decreased activity in the affected hemisphere.
- To function normally we need a balance between hemispheres.

Why is understanding this concept important?

- Post stroke motor recovery relies on cortical reorganization of the ipsilesional and contralesional hemispheres through disinhibition of the intact motor cortex via transcallosal fibers.
- Contralateral hemisphere exerts its inhibitory tone on the ischemic hypoactive hemisphere.
- Studies have shown that increased activity in the contralesional hemisphere results in worse recovery and outcomes after stroke.

TMS and stroke

- Preliminary studies have shown promising results using rTMS for improved motor performance after stroke.
- Researchers have explored different variables applying TMS in stroke: including location of stimulation (ipsilateral [affected] vs. contralateral [unaffected hemisphere]), chronic vs. acute, in combination with other therapeutic techniques, and different patterns of stimulation.
- Both low-frequency and high-frequency rTMS applied to the unaffected and the affected hemisphere respectively can aid motor recovery in patients with stroke.

Stroke: Ipsilateral TMS (stimulation to the affected hemisphere)

- High frequency rTMS has shown a positive long term effect on motor recovery in patients with acute and subacute stroke (not seen in chronic stroke).
- Better results seen in local area of stimulation.
- Outcome measures at the activity level don't show significant differences between sham and TMS groups.

Daily Repetitive Transcranial Magnetic Stimulation for Post-stroke Upper Limb Pareis in the Subacute Period
Hosomi et al. 2016

Results: rTMS group demonstrated better and faster motor recovery of hand function (area of stimulation) at the impairment level but not in outcome measures at the activity and participation level (FIM).

Stoke: Ipsilateral TMS (stimulation to the affected hemisphere)
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Stroke: Ipsilateral TMS (stimulation to the affected hemisphere)
- High frequency rTMS has shown a positive long term effect on motor recovery in patients with acute and subacute stroke (not seen in chronic stroke).
- Better results seen in local area of stimulation.
- Outcome measures at the activity level don't show significant differences between sham and TMS groups.
Stroke: Contralateral TMS (stimulation to the unaffected hemisphere)

- The effect of TMS was more effective in improving ADLs’s and motor function with protocols using low frequency rTMS over the unaffected hemisphere
- More of a positive effect in the chronic stroke population (> 6 months)


Low-frequency rTMS promotes use-dependent motor plasticity in chronic stroke

Avenanti et al. 2012

- Does timing with physical therapy matter?
- Results suggest that rTMS prior to physical therapy intervention promotes use-dependent plasticity

TMS and Stroke: Why does research vary so much between subjects?

- Corticospinal tract integrity
- BDNF genotype
- lesion location

TMS and Stroke: improving research results

- Corticospinal integrity (MEPs) and BDNF genotype have been shown to significantly influence the response to high-frequency rTMS of patients with stroke
- CST functional integrity more strongly influences the response to high frequency rTMS compared with stroke lesion type

TMS and Parkinson’s Disease

Therapeutic applications and research
Parkinson’s Pathophysiology review

- Progressive loss of dopaminergic neurons in Parkinson’s Disease results in functional disruption within the cortico-basal ganglia-thalamo-cortical motor circuit
- This includes excessive inhibition of the thalamocortical projection to cortical targets including M1, SMA, and DLPCA

TMS and Parkinson’s: What does the Research tell us?

- Stimulation locations: M1, SMA or DLPCA or both M1 and DLPCA
- Motor symptoms: bradykinesia, tremor, levodopa induced dyskinesias
- Amount: High intensity > low intensity
- Timing: “On” versus “off” medication time

Research limitations

- Small sample size
- Varied parameters and dosing
- Limited studies
- Number of variables
- Difficulty with “sham”
- Long term follow up

TMS Conclusion and Clinical Implications

- TMS is a diverse tool that provides many different clinical uses
- TMS has been shown to increase cortical activity via inhibition and excitation that has resulted in functional improvement in certain patients with neurologic conditions
- More studies are needed with larger sample size and more consistent parameters

Transcranial Direct Current Stimulation (tDCS)
Amanda M Hyslop, PT, DPT
History of cranial e-stim

- **1867**: Hitzig pioneered a constant current stimulator on the skull of his patients with depression.
- **1870**: Hitzig and Fritsch found that e-stim of various cortical areas produced distinct contralateral limb responses in a dog.
- **1926**: Bishop and Erlanger studied the effects of anodal and cathodal stimulation of motor neurons in vitro.
- **1962**: Biederman demonstrated that low amplitude currents (0.1-0.5µA) could produce neuronal excitability shifts in rat cortex.
- **1964**: Lippold and Redfern used direct currents of 50-500µA with the target electrode above the eyebrow and the reference electrode on the leg of depressed patients.
- **2000**: Nitsche and Paulus showed that cathodal stimulation reduced the size of Motor-evoked potentials (MEPs), while anodal stimulation increased MEPs in humans.

Basics of tDCS

- **Definition**: Transcranial direct current stimulation provides a subthreshold [electrical] stimulus that modulates the likelihood neurons will fire by hyperpolarizing or depolarizing the brain tissue, without direct neuronal depolarization.
- **Anodal**: Increase excitability through depolarization
- **Cathodal**: Decrease excitability through hyperpolarization

Mechanism of tDCS

Effects are attributed to persistent, bidirectional modification of postsynaptic connections, similar to long term potentiation (LTP) and long term depression (LTD).

Application of tDCS

FIGURE 3: Publications on tDCS and motor recovery - number of publications on tDCS and motor recovery 2000-2016.
Electrode Application: 10-20 System

Electrode Positioning and Montage in tDCS

Electrode Montage

1. Unilateral
   - Monopolar
   - Bipolar
   - Multiple monopolar
2. Bilateral
   - Bipolar-balanced
   - Bipolar-nonbalanced
   - Multiple-monopolar
3. Midline
   - Monopolar
   - Bipolar-balanced
   - Bipolar-nonbalanced
4. Dual Channel
   - Bipolar
   - Midline double-monopolar
   - Bilateral double-monopolar

Safety

- Do NOT use TENS or NMES units to deliver tDCS.
- Do NOT use [TENS or NMES] gel electrodes.
- Generally, current intensity should be maintained between 0.5 and 2.0 mA.

Relative contraindications: epilepsy, implanted defibrillators/pacemakers/deep brain stimulators, or medical implants in the head.

Side effects: tingling/itching under electrodes, headache, fatigue

tDCS Research in Neurologic Populations

- Stroke
- Parkinson’s Disease
- Multiple Sclerosis

tDCS and Stroke
Interhemispheric Inhibition Hypothesis

- Spontaneous recovery following stroke is often attributed to neuroplasticity in both the perilesional area and the contralateral hemisphere.
  - **Regeneration**: involves axonal and dendritic sprouting, new synapse formation
  - **Reorganization**: involves remapping of the lesion area representations onto nonlesion cortex (perilesion cortex or contralateral hemisphere)

**tDCS Stroke studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome Measures</th>
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<tbody>
<tr>
<td>No Difference</td>
<td>No Difference</td>
</tr>
<tr>
<td>Improved Upper Limb Function (2 of 3 outcome measures)</td>
<td>Improved Motor Performance &amp; ADLs</td>
</tr>
<tr>
<td>No difference in Walking Tests</td>
<td>Improved QOL, no difference in Motor Performance</td>
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<tr>
<td>Improved Motor Performance (2 of 3 outcome measures)</td>
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**tDCS and Parkinson’s Disease (PD)**

**Basal Ganglia-Thalamocortical Network**
tDCS for Motor Symptoms in PD

- Lefaucher et al. (2016)
  + Improved 10MWT & Bradykinesia
  - No change in UPDRS, Reaction Time
  + Improved Gait, Freezing, and Motor Performance
  - Sustained improvement in Gait & Motor Performance

Articles

Number and type of patients (protocol design) | Stimulation electrode location | Stimulation intensity, session duration, total number of sessions (protocol duration, follow-up)
--- | --- | ---
Lefaucher et al. (2016) | 9 patients | Anode: M1 (first dorsal interosseous) | 1 mA, 20 min, 1 session
Meesen et al. (2014) | 21 patients | Anode: M1 (front) | 1 mA, 20 min, 1 session

Factors influencing tDCS efficacy

- Stimulation parameters
  + Stimulation duration
  • Polarity
  • Current density/intensity
  • Timing of stimulation and use of a concurrent task
- Brain state of the patient

Conclusion

1. tDCS is a safe and inexpensive, but not yet FDA approved for physical therapy.
2. tDCS falls within the scope of physical therapy practice and can be used to promote adaptive neuroplasticity.
3. tDCS as a complementary intervention to improve motor recovery in neurologic populations shows promise, but further research is needed.

Comparison

<table>
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<tr>
<th>TMS</th>
<th>tDCS</th>
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<tr>
<td>• Induces high intensities of short-lasting electromagnetic currents</td>
<td>• Bi-directionally modulates neuron firing activity through subthreshold alterations of resting membrane potentials</td>
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<tr>
<td>• Generates supra-threshold activation of neurons</td>
<td>• Does not generate action potentials in neurons</td>
</tr>
<tr>
<td>• Able to produce long-lasting excitatory or inhibitory plastic changes in neural systems</td>
<td>• Able to produce long-lasting excitatory or inhibitory plastic changes in neural systems</td>
</tr>
<tr>
<td>• Concurrent application with physical therapy can be difficult</td>
<td>• Concurrent application with physical therapy is easy</td>
</tr>
</tbody>
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Comparison