Transcranial Stimulation to Enhance Neuroplasticity after Brain Injury

LISA POTTS, PHD
Overview

- Neuroplasticity
- Types of brain stimulation
- Transcranial stimulation research
- How transcranial stimulation techniques alter neural activity
- Implementation considerations
FIGURE 4: Generated comparison to demonstrate the evolution of topics over three selected time periods. The weight of the links is a representation of the quantity of publications.
Neuroplasticity

- Ability of nervous system to change
  - Development
  - Learning
  - LTP
  - Recovery from injury
  - Activity dependency

- Factors that can influence plasticity
  - Aerobic exercise
  - Sleep
  - Visualization / imagery
  - Meditation
  - Practice
    - Task specificity
    - Repetition
  - Stimulation of neural structures
Types of Brain Stimulation

- Non-invasive (NBS)
  - TUS
  - TMS
  - tRNS
  - tACS
  - tDCS
Non-Invasive (Transcranial) Stimulation Techniques

- Transcranial magnetic stimulation (TMS)
- Transcranial ultrasound stimulation (TUS) uses sound waves to alter neural activity, but the mechanisms are not fully understood. It may influence neuronal excitability by altering activity of ion channels.
  - Improved 2-point discrimination in median nerve with LIFU (Legon et al 2014 Nature Neuroscience)
- Transcranial direct current stimulation (tDCS)
- Transcranial alternating current stimulation (tACS)
- Transcranial random noise stimulation (tRNS)
- Low frequency pulsed electromagnetic fields (IFPEF)
Underlying Principles of & Considerations for NBS Efficacy

- Interhemispheric connectivity & transcallosal inhibition
- Baseline state & individual differences
- Site & extent of neural injury
- Non-linear frequency & temporal dependency
- Other protocol considerations
  - Stimulation sites
  - Electrode / stimulator positioning
- Multimodal affects
  - Blood flow
  - Ion channel
  - Neurotransmitter regulation
  - Gene expression
- Outcome measures
  - EEG
  - MRI
  - MEP
  - Functional
- Contraindications & Adverse effects
Interhemispheric Connectivity & Transcallosal Activity

Kim 2019
Transcranial magnetic stimulation (TMS)

- Magnetic coils used to stimulate or inhibit specific areas of the brain
- Generates electrical field parallel to brain
- Spike timing dependent plasticity
Types of TMS

- **Single pulse**
  - Depolarizes a specific area triggering a response

- **Paired pulse**
  - 2 stimuli separate by several ms
  - Used to determine interhemispheric connectivity and state of cortical excitability

- **Theta Burst Stimulation (TBS)**
  - High frequency / low intensity stim
  - Intermittent
  - Continuous
  - Improved UE function in chronic stroke when combined with therapy (Chen et al. 2019)

- **rTMS**
  - Most commonly used for therapy
  - Short intervals of high or low frequency stimulation
  - Modulates gene expression & neurotransmitter release
  - Low frequency may act via different mechanism

![Brain diagram with TMS stimuli]
REVIEW ARTICLE

Current evidence on transcranial magnetic stimulation and its potential usefulness in post-stroke neurorehabilitation: Opening new doors to the treatment of cerebrovascular disease☆

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Utility of rTMS for Motor Recovery After Stroke (Ruiz et al. 2017)

- rTMS + task oriented training stimulates NMDA and inhibits GABA → increase MEP amplitude
- HF-rTMS to lesioned hemisphere + neurorehab → improved UE function (not with CIMT)
- Inhibitory stimulation to unaffected hemisphere + motor rehab → improved motor performance
- LF-rTMS to intact hemisphere > lesioned
- Theta burst stimulation (TBS) effects depend on stimulation protocol → may be more effective to stimulate the somatosensory cortex
Potential Utility of rTMS to Enhance Recovery After Stroke (Ruiz et al. 2017)

rTMS shown to improve:
- language impairment
- swallowing function
- hemispatial neglect
- mood
Clinical Study

Effects of 20 Hz Repetitive Transcranial Magnetic Stimulation on Disorders of Consciousness: A Resting-State Electroencephalography Study

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Received 16 November 2017; Accepted 14 December 2017; Published 25 March 2018
He et al. 2018: rTMS and EEG changes in disorders of consciousness

- N=6 brain injured patients recovering from coma
- rTMS or sham over left M1 x 5 days
- CRS-R scores
- EEG activity
- 2 patients showed improved CRS-R scores, 1 associated with changes in EEG activity
Modulation of long-term potentiation-like cortical plasticity in the healthy brain with low frequency-pulsed electromagnetic fields

Enrico Premi, Alberto Benussi, Antonio La Gatta, Stefano Visconti, Angelo Costa, Nicola Gilberti, Valentina Cantoni, Alessandro Padovani, Barbara Borroni and Mauro Magoni
Low frequency-pulsed electromagnetic fields (LF-PEMFs) → no action potential, but may act via synaptic and ion channel modulation

N=10 healthy participants

LF-PEMF to left M1 at 7Hz for 15 minutes
  - One session with stimulation
  - One session with sham stimulation (~16 days apart)

TMS used to elicit MEP
  - Pre-stim
  - Post-stim (0, 15, 30 minutes)
Results & Conclusions from Premi et al. 2019: Modulation of LTP-like plasticity with LF-PEMFs

- LF-PEMF stimulation increased MEP > 60% in healthy adults
- Effect lasted at least 30 minutes after stimulation
- TMS did not produce significant change in MEP
- LF-PEMF stim is a possible new technique for neuromodulation
Considerations for TMS Use

- **Adverse Effects:**
  - mild, transient headache or neck pain.

- **Contraindications:**
  - Pregnancy
  - <2 yo
  - Drug-resistant epilepsy
  - Electrical or metal implants

- **Advantages**
  - Not impeded by the skull
  - safe
Transcranial Electrical Stimulation (TES) Techniques

- Use electrodes to deliver electric current to the brain
  - Alternating current (tACS) → oscillating electrical currents alter neural excitability.
  - Random noise (tRNS)
  - Direct current (tDCS)
Types of TES

- Alternating current (tACS) → oscillating electrical currents alter neural excitability.
- Random noise (tRNS)
- Direct current (tDCS)
Transcranial Random Noise Stimulation (tRNS)

- More recent type of alternating current
- Electric current applied in a random frequency window
Behavioral/Cognitive

Boosting Learning Efficacy with Noninvasive Brain Stimulation in Intact and Brain-Damaged Humans

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Herpich et al. 2019: Enhancing visual perceptual learning in normal adults

- 45 healthy adults with normal vision in 5 groups:
  - tRNS of visual cortex
  - a-tDCS of visual cortex
  - Sham control
  - No-stim control
  - Active control (tRNS to parietal cortex)
- Stimulation during training
- Asked to discriminate direction of visual stimulus
- Measured normalized direction range (NDR) response
- Repeated for 10 days
tRNS group showed improvement in perceptual learning

Effect persisted 6 months post-training
Herpich et al. 2019: Enhancing visual recovery in cortically blind patients

- 11 patients:
  - tRNS of visual cortex
  - Sham control
  - No-stim control
  - Stimulation during training
  - Asked to discriminate direction of visual stimulus
  - Measured normalized direction range (NDR)
  - Repeated for 10 days
Conclusions from Heprich et al.

- tRNS can affect visual learning in healthy and brain injured adults
- Effects persist beyond time of stimulation
- tRNS offers a new way to potentially enhance recovery of visual deficit and do so in a shorter time frame than visual training alone
Transcranial Direct Current Stimulation (tDCS)

- Direct electrical current
- Anodal - increases excitability
- Cathodal - decreases excitability
Mechanisms of tDCS

- Can influence activity of neural networks
  - Does not directly elicit action potentials
  - Alters neuronal excitability possibly by influencing membrane potential
  - Mechanisms not well understood
  - Effects may be due to alterations in GABA & Glutamate neurotransmission
Randomized controlled trial of home-based 4-week tDCS in chronic minimally conscious state

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b Centre Hospitalier Neurologique William Lennox, Saint-Luc University Clinics, Université Catholique de Louvain, Belgium
c Neuromodulation Center, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA
Martens et al. 2018: At Home tDCS in Patients in a Minimally Conscious State

- N=37 patients, >3 months post brain injury
- 20min / day x 4 weeks active or sham a-tDCS of left dlPFC
- Coma Recovery Scale-Revised (CRS-R)
Results and Conclusions from Martens et al. 2018

- Active stimulation group showed improvement in CRS-R scores after 4 weeks of stimulation
- Effect did not persist
- 6 patients showed a new sign of consciousness
- No serious adverse events associated with stimulation
- Challenges to long term studies in this patient population
Clinical Study

Transcranial Direct Current Stimulation (tDCS) in Unilateral Cerebral Palsy: A Pilot Study of Motor Effect

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Inguaggiato et al. 2019: Effect of tDCS on UE function in Unilateral Cerebral Palsy (UCP)

- Cross-over, double blind pilot study
- N = 8 CP patients
- 2 stimulation sessions over damaged M1
  - Sham stimulation, anodal tDCS (a-tDCS) (n=5)
  - a-tDCS, sham (n=3)

Outcome measures:
- Hand dexterity (Box & Block Test)
- Hand Grip strength (HGS)
- Safety measures
  - BP, HR
  - Safety questionnaire
Inguaggiato et al. 2019: Effect of tDCS on UE function in Unilateral Cerebral Palsy (UCP)

- a-tDCS of ipsilesional motor cortex → improvement in BBT, not HGS,
- Effect was sustained for at least 24 hrs
Conclusions from Inguaggiato et al. 2019

- a-tDCS is capable of improving hand function in unilateral cerebral palsy
- Functional improvement is maintained beyond initial stimulation
- a-tDCS is safe for use in the adolescent population (check ok to say this)
A review of transcranial electrical stimulation methods in stroke rehabilitation

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<table>
<thead>
<tr>
<th>Articles</th>
<th>Type of subjects</th>
<th>Size and electrode material</th>
<th>Maximum current</th>
<th>Electrode montage</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hummel et al. (2005)</td>
<td>Single ischemic cerebral infarct</td>
<td>Gel-sponge electrodes (TransQE) in saline-soaked solution, 25 cm²</td>
<td>1 mA, 20 min</td>
<td>A: hand knob area of M1</td>
<td>Improvement in hand function that lasted even after stimulation stopped</td>
</tr>
<tr>
<td>Hummel et al. (2006)</td>
<td>Sub-cortical ischemic cerebral infarct</td>
<td>Gel sponge electrodes, 25 cm²</td>
<td>1 mA, 20 min</td>
<td>A: ipsilesional M1</td>
<td>Improvement in pinch force with tDCS</td>
</tr>
<tr>
<td>Boggio et al. (2007)</td>
<td>Sub-cortical stroke</td>
<td>35 cm²</td>
<td>1 mA, 20 min</td>
<td>A: ipsilesional M1</td>
<td>Improvement after cathodal tDCS of non-lesional hemisphere and anodal tDCS of lesional hemisphere</td>
</tr>
<tr>
<td>Lindenberg et al. (2010)</td>
<td>Chronic stroke patients</td>
<td>Saline-soaked surface gel sponge electrodes, 16.3 cm²</td>
<td>1.5 mA, 30 min</td>
<td>A: ipsilesional motor cortex</td>
<td>Improvement in motor function</td>
</tr>
<tr>
<td>Ang et al. (2015)</td>
<td>Sub-cortical stroke patients</td>
<td>Saline-soaked sponge electrodes (na) for upper-extremity</td>
<td>1 mA, 20 min</td>
<td>A: over ipsilesional M1</td>
<td>No improvement in motor imagery after the application of tDCS</td>
</tr>
<tr>
<td>Fleming et al. (2017)</td>
<td>Mono-hemispheric stroke</td>
<td>Carbon electrodes encased in 20 cm² saline-soaked sponge</td>
<td>1 mA, 20 min</td>
<td>1. A: ipsilesional M1</td>
<td>Improvement during anodal or cathodal tDCS but not bihemispheric</td>
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<td>2. A: contralesional M1</td>
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<td>3. A: ipsilesional supra-orbital ridge</td>
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<td>C: contralesional M1</td>
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</table>

tDCS=Transcranial direct current stimulation; EEG=Electroencephalography
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<tr>
<td>Celnik et al. (2009)</td>
<td>Peripheral nerve stimulation</td>
<td>Unilateral ischemic stroke</td>
<td>Sponge electrode (Amrex) 3” x 3”</td>
<td>1 mA, 20 min</td>
<td>A: ipsilesional M1 over APB</td>
<td>Improved results with PNS + tDCS rather than either PNS or tDCS alone or neither.</td>
</tr>
<tr>
<td>Bolognini et al. (2011)</td>
<td>Constraint-induced movement therapy</td>
<td>Hemiparesis</td>
<td>Saline-soaked sponge electrodes, 35 cm²</td>
<td>2 mA, 40 min</td>
<td>A: ipsilesional M1</td>
<td>Increased gain in motor function.</td>
</tr>
<tr>
<td>Takeuchi et al. (2012)</td>
<td>Repetitive transcranial magnetic stimulation</td>
<td>Sub-cortical stroke</td>
<td>Gel sponge electrodes (IGOGEL, IOMED), 35 cm²</td>
<td>1 mA, 20 min</td>
<td>A: ipsilesional M1 over FDI</td>
<td>No effect of either tDCS or TMS in motor tasks.</td>
</tr>
<tr>
<td>Sattler et al. (2015)</td>
<td>Radial nerve stimulation</td>
<td>Unilateral ischemic stroke</td>
<td>Saline-soaked sponge electrodes, 35 cm²</td>
<td>1.2 mA, 13 min</td>
<td>A: ipsilesional M1 over extensor carpi radialis</td>
<td>Improvement in motor control but unable to characterize the effect of radial nerve stimulation</td>
</tr>
<tr>
<td>Cho et al. (2015)</td>
<td>Mirror therapy</td>
<td>Chronic hemiplegic stroke</td>
<td>Sponge electrode (Phoresor II) IOMED 7x5 cm²</td>
<td>2 mA, 20 min</td>
<td>A: ipsilesional M1</td>
<td>Significant increase in grip strength in comparison with control group.</td>
</tr>
<tr>
<td>Satow et al. (2016)</td>
<td>Neuromuscular electrical stimulation</td>
<td>Complete hemiparesis (single subject)</td>
<td>Saline-soaked sponge electrodes, 35 cm²</td>
<td>2 mA, 20 min</td>
<td>A: foot area of sensorimotor cortex</td>
<td>Gait improvement was seen after cathodal stimulation.</td>
</tr>
<tr>
<td>Straudi et al. (2016)</td>
<td>Robotics</td>
<td>Ischemic or hemorrhagic stroke</td>
<td>Saline-soaked sponge electrodes, 35 cm²</td>
<td>1 mA, 30 min</td>
<td>A: ipsilesional M1</td>
<td>Improvement noted only in subcortical stroke and in the chronic stage.</td>
</tr>
<tr>
<td>Andrade et al. (2017)</td>
<td>Constraint-induced movement therapy</td>
<td>Unilateral sub-acute stroke</td>
<td>Saline-soaked sponge electrodes, A=16 cm²</td>
<td>0.7 mA</td>
<td>A: ipsilesional M1</td>
<td>Significant motor improvement with combination therapy.</td>
</tr>
</tbody>
</table>

tDCS=Transcranial direct current stimulation, PNS=Peripheral nerve stimulation, rtMST=Transcranial magnetic stimulation
Cerebral Hemodynamics after Transcranial Direct Current Stimulation (tDCS) in Patients with Consequences of Traumatic Brain Injury

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²Department of Neurosurgery, University of New Mexico School of Medicine, 1 University of New Mexico, MSC 10 5615 Neurosurgery, Albuquerque, NM 87131, USA
Trofimov et al. 2018: tDCS improves cerebral blood flow in TBI patients

- N=20 post-traumatic encephalopathy patients
- Perfusion computed tomography (PCT) measured before and after a-tDCS of left M1
- tDCS reduced hypoperfusion

Fig.1. Comparison of CBF levels before 1) and after HD-tDCS 2). The white arrow shows a decrease of hypoperfusion zone in the left thalamus.
Clinical Study

Different Brain Connectivity between Responders and Nonresponders to Dual-Mode Noninvasive Brain Stimulation over Bilateral Primary Motor Cortices in Stroke Patients

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3Department of Global Prestige Radiological Science, Dongseo University, 47 Jurye-ro, Sasang-gu, Busan 47011, Republic of Korea
Lee et al. 2019: Different brain connectivity between responders & non-responders to bilateral NBS

- N=21 subacute stroke patients, 12 age-matched controls
- Contralesional LF-rTMS + ipsilesional a-tDCS 20 min / day x 10 days
- Fugl-Meyer Assessment (FMA) motor & resting state fMRI before & 2 mos after stimulation
- Grouped as responder (n=12) or non-responder (n=9) based on functional change after stimulation (< or > 10, respectively)
Results & Conclusions from Lee et al. 2019

- Responders showed contralesional dominance before stimulation.
- It is important to consider individual differences in network connectivity as a potential influencing factor for NBS efficacy.

Figure 2: Changes in M1 intrahemispheric connectivity (a) ipsilesional, (b) contralesional, (c) laterality index. The laterality index of the M1 intrahemispheric connectivity was significantly lower in the responder group than in the healthy control group. The laterality index in the responder group significantly increased after stimulation (*p < 0.05).
Modulating Regional Motor Cortical Excitability with Noninvasive Brain Stimulation Results in Neurochemical Changes in Bilateral Motor Cortices

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Bachtia et al. 2018: tDCS induced neurochemical changes in motor cortex

- N=12 healthy adults
- Sham, anodal, or cathodal tDCS to left M1 for 10 minutes
- MRS measures of GABA and glutamate
Bachtiar et al. 2018: MRS Results
Anodal $\rightarrow$ decreased GABA in BOTH hemispheres
Cathodal $\rightarrow$ decreased GABA only in UNSTIMULATED hemisphere
Bilateral M1 $\rightarrow$ decreased GABA only on the cathode-stimulated side
Changes in GABA lasted at least 30 minutes
No changes in glutamate with any stimulation
For CATHODAL stimulation only, greater white matter integrity in the corpus callosum → greater decrease in contralateral GABA
Conclusions from Bachtiar et al. 2018

- tDCS can elicit changes in GABA in the unstimulated hemisphere
- Bilateral stimulation is not summative of individual anode and cathode stimulation
- Callosal integrity may influence the efficacy of cathodal tDCS
- Implications for protocol development
Considerations for TES Use

- **Adverse Effects:**
  - Potential for skin irritation

- **Contraindications:**
  - Pregnancy
  - <2 yo
  - Drug-resistant epilepsy ???
  - Electrical or metal implants

- **Advantages**
  - Cost-effective vs. TMS
  - Alters excitability vs. directly exciting target
  - May cause artifact in outcome measures such as EEG
Implementation Considerations

- TMS device cost
- tDCS device cost
- tDCS provider
- Neuroelectrics workshop and info
- Neuromodec transcranial workshops and conferences

Pricing & Finance

TMS practice pricing & costs breakdown

TMS device price

The cost of the complete TMS system with laptop is $49,995.

Fees

1. Shipping & Handling is $1,699 anywhere in the lower 48 States.
2. Installation & Training is $599 and includes 10 hours of live online training which includes a TMS certificate of completion - (Onsite training can be purchased for an additional $3500).

The total cost of the machine, delivery, installation and training is $52,293 + tax (if applicable).
Conclusions & Considerations for Utilizing Transcranial Stimulation

- Capable of enhancing neuroplasticity via a variety of mechanisms likely involving neurotransmitter regulation
- May improve functional recovery following stroke, brain injury and other neurological conditions.
  - Note the efficacy of stimulating contralesional motor cortex
- Alter cortical excitability thereby acting as a primer for rehabilitation therapy
- Offer a variety of protocol options to tailor stimulation according to your clients needs
  - Note attention must be paid to electrode configurations and other stimulation parameters, which can alter the effect of stimulation
- Compatible with various imaging techniques
- Relatively safe to implement and offer the option for in home treatment
References

- Lee et al. Different brain connectivity between responders and nonresponders to dual-mode noninvasive brain stimulation over bilateral primary motor cortices in stroke patients. 2019. Neural Plasticity.
- Carey et al. Finding the intersection of neuroplasticity, stroke recovery, and learning: Scope and contributions to stroke rehabilitation. 2019 Neural Plasticity.
Thank You!