EPFL

TMS: Transcranial Magnetic Stimulation

Curing depression with magnets!

Anas SIDI MOHAMED
Roberto GOELZER

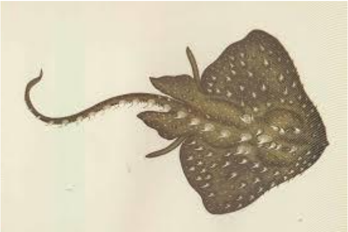
https://psychedenver.com/tms-therapy/

BIOENG-310
Midterm
presentation

Outline

- History and motivation of brain stimulation techniques
  - ECT, tDCS, TMS
- Main experiments
  - Anthony Barker first TMS device testing
- Clinical applications
  - Seizures prevention with low frequency rTMS stimulation
  - Depression symptom reduction with high frequency rTMS stimulation
  - Other applications
- Conclusion

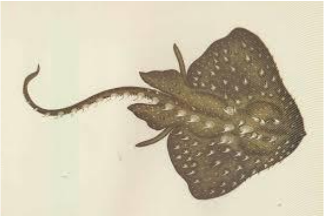
History of brain stimulation techniques (1)



- Romans found **electric rays** soothe headaches when applied on the scalp.
  - ➢ mentioned in "*Compositiones medicamentorum*" 46 AD [1]
  - ➢ electric rays were used until 18th century (for seizures, depression) [2]
- G. Aldini (1804) found electrical stimulation on open cortex provoked grimaces → paved way for much research on brain stimulation (19th + 20th) [2]
  - ➢ 2 goals: a) for mapping brain regions | b) for therapeutic purposes
  - ➢ research done mostly on animals/cadavers, later on humans
- Cerletti & Bini (1938) developed **ECT** (**E**lectro**C**onvulsive **T**herapy) to replace previous attempts to induce seizures (e.g. metrazol to cure schizophrenia) [3]
  - ➢ Goal: **induce seizures** using electrodes on scalp of anesthetized patients
  - ➢ stronger AC currents (120V) compared to other DC stimulation methods
  - ➢ ended up being cheaper, safer, and also more effective for depression!

[1] Debru A. (2006) : The power of torpedo fish as a pathological model to the understanding of nervous transmission in antiquity
[2] V. A. SIroni (2011) : Origin and Evolution in Deep Brain Stimulation
[3] Gazdag & Ungvari (2019). Electroconvulsive therapy: 80 years old and still going strong. World journal of psychiatry

History of brain stimulation techniques (2)



- Stigma & backlash against ECT in 1950-70s led to multiple improvements: [4]
  - ➢ standardization of anesthetics & muscle relaxants (e.g. curare)
    - were not always used! → could lead to bone fractures during convulsions
  - ➢ safer stimulation techniques developed for ECT
    - brief DC pulses / unilateral electrode placement
  - ➢ 1978: redefinition of consent by APA (→informed consent required for ECT)
- Further research led to invention of other **n**on **i**nvasive **b**rain **s**timulation (NIBS) methods: like TMS, tDCS → no need for general anesthesia, less side-effects

Recap of brain stimulation techniques:

- ➢ **tDCS**: weaker *sustained* DC currents, more versatile than ECT [5]
- ➢ **ECT**: seizure-inducing electric shocks, effective 2nd line treatment for depression
- ➢ **TMS**: using magnets to induce currents in localized brain regions [5]

[4] Leiknes et al. (2012) : Contemporary use and practice of electroconvulsive therapy worldwide
[5] Dayan et al. (2013) : Noninvasive brain stimulation: from physiology to network dynamics and back

The emergence of Transcranial Magnetic Stimulation (TMS)

- ECT are not perfect, need to burst lots of current (~800mA), only to have a small portion go through the scalp into the brain
- Anthony Barker(1985) and his team developed the first device to overcome ECT disadvantages
    - device generates magnetic field
    - electric field crosses scalp and skull very effectively

- First experience consisted of stimulating the cortex motor area.
    - After TMS pulse, patients member of the opposite side would move slightly
    - End-plate Potential (EPP) could be measured

[6] Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex.

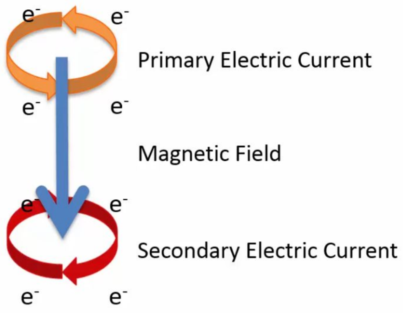
How TMS works & affects the brain

- TMS coil
  - current goes through coil to generate magnetic field
  - placed on the zone to stimulate
- electrical field goes up to 6 cm in the brain and stimulates superficial brain areas (cortical)

- electrical field induces current in the brain
  - outside neuron environment is mostly positive
  - positive ions movement induce electrical current
  - electrical make the outside of the neuron more negative
  - it **reduces membrane potential** (depolarization) and neurons fire
- all neurons in targeted brain area fire and activity propagates in the brain

- Faraday's law of induction:
  - magnetic field variation induces electrical field
  - as brain is conductive, it serves as secondary electric current

1831 Faraday’s Electromagnetic Induction

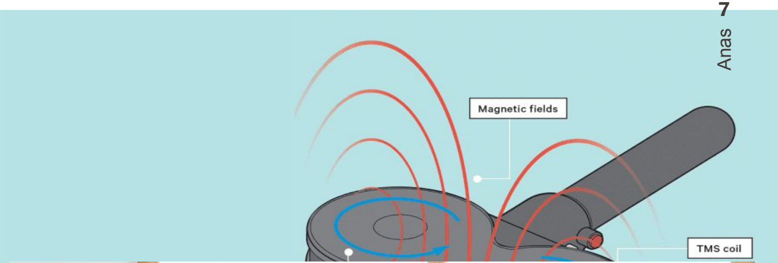


TMS therapy

- Treatment
  - 5 sessions a week for 1.5-2.5 months
  - 20-40 mn session
  - 300-500$ a session
  - FDA approved for depression

- Secondary effects
  - very few
  - headache

https://www.youtube.com/watch?v=fkkyqFS_XPg&t=456s



https://www.americastms.com/blog/transcranial-magnetic-stimulation-tms-to-treat-symptoms-of-depression/

Psychiatry Associates of Kansas City, https://pakconline.com/what-is-tms-therapy/

Epilepsy treatment with TMS

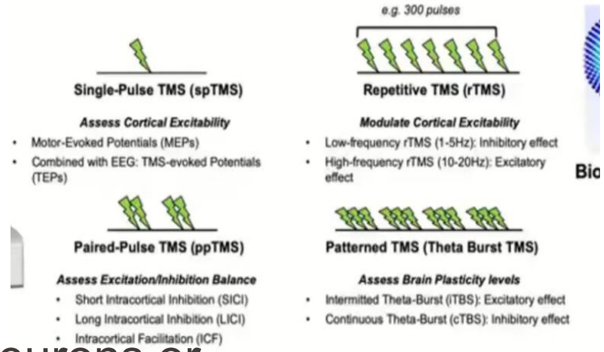
- Epilepsy is due to cortical hyperexcitability
  - epilepsy seizures preceded interectical spikes
  - spikes are spontaneously generated by the synchronous discharges of a group of neurons in a region referred to as the epileptic focus
  - spikes could be initiated by death of intermediate inhibitory neurons, axons growth after brain injury leading hyperactivity
  - activity can spread through the brain and initiates general body seizures

- A study showed that rTMS can reduce by 54.9% interectical spikes [7], reducing seizures up to 23% less
  - rTMS at low frequency applied to epileptic focus (3000 pulses session, 5 time a week for 8 month)
  - lead to long term epileptic depression in epileptic focus

[7] Joo et al. (2007). Antiepileptic effects of low-frequency repetitive transcranial magnetic stimulation by different stimulation durations and locations. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology

rTMS

- rTMS applied over long period of time leads to LDP or LTP
  - depends of rTMS pulse frequency
  - studies show that low frequency rTMS stimulation leads to LDP[6]
  - high frequency (2-5hz) rTMS leads to LTP[6]
  - low frequency (<1hz) rTMS leads to LDP



- depending of frequencies, it targets inhibitory neurons or excitatory neurons
  - with law frequencies, each pulse arrives during inhibitory phase, which stimulates inhibitory neurons
  - with high frequencies, each pulse arrives during excitatory phase, , which stimulates excitatory neurons

https://pmc.ncbi.nlm.nih.gov/articles/PMC8092469/#:~:text=excitatory%20and%20inhibitory%20processes%20may,depression%20when%20each%20incoming%20pulse

Treating depression with TMS

- high frequency stimulation of left prefrontal Cortex, 10hz
  - Increased activity in this area (LTP)
  - reduction of depressive symptoms up to 30% after course of treatment

- how it may affect brain:
  - prefrontal cortex stimulation stimulates dopaminergic neurons
  - more dopamine liberated in the brain due to increased activity

[8] Padberg et al. (2002). Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology
[9] Pogarell et al. (2006). Striatal dopamine release after prefrontal repetitive transcranial magnetic stimulation in major depression: preliminary results of a dynamic [123I] IBZM SPECT study. Journal of psychiatric research

Other applications of TMS

Many new and interesting avenues of research:

- NIBS for **t**raumatic **b**rain **i**njury (TBI) [11]
  - ➢ rTMS can reduce some long term symptoms of TBI
    - depression, dizziness, central pain, and visual neglect [10]
  - ➢ more research is needed to set more repeatable guidelines
    - large variety of TMS protocols and inter-individual differences [10]

- Studying neuronal dynamics with TMS (and tDCS) [5]
  - ➢ applying TMS and measuring shortly after (a few ms) changes in intra- & inter-microcircuit dynamics
  - ➢ using rTMS to perturb certain frequency bands in the brain (theta, alpha, beta, gamma)
  - ➢ pairing TMS (on M1) with fMRI to show connected regions with more blood flow

More research is needed, there are many parameters to tune and many more discoveries to be made!

[5] Dayan et al. (2013) : Noninvasive brain stimulation: from physiology to network dynamics and back
[10] Pink et al. (2021). The use of repetitive transcranial magnetic stimulation (rTMS) following traumatic brain injury (TBI): A scoping review.
[11] Demirtas-Tatlidede et al. (2012). Noninvasive brain stimulation in traumatic brain injury. The Journal of head trauma rehabilitation

Conclusion

- TMS uses magnets to induce currents in localized brain regions
- TMS has therapeutic effects for many conditions:
  - epilepsy, smoking cessation, TBI, OCD and more
- TMS has promising avenues of research in brain network dynamics

- Other stimulation techniques (ECT, tDCS) are also used today for treatment-resistant depression, each with their own mechanisms of action

Bibliography

[1] Debru A. (2006). The power of torpedo fish as a pathological model to the understanding of nervous transmission in Antiquity. Comptes rendus biologies, 329(5-6), 298–302. https://doi.org/10.1016/j.crvi.2006.03.001

[2] Sironi V. A. (2011). Origin and evolution of deep brain stimulation. Frontiers in integrative neuroscience, 5, 42. https://doi.org/10.3389/fnint.2011.00042

[3] Gazdag, G., & Ungvari, G. S. (2019). Electroconvulsive therapy: 80 years old and still going strong. World journal of psychiatry, 9(1), 1.

[4] Leiknes, K. A., Jarosh-von Schweder, L., & Høie, B. (2012). Contemporary use and practice of electroconvulsive therapy worldwide. Brain and behavior, 2(3), 283–344. https://doi.org/10.1002/brb3.37

[5] Dayan, E., Censor, N., Buch, E. R., Sandrini, M., & Cohen, L. G. (2013). Noninvasive brain stimulation: from physiology to network dynamics and back. Nature Neuroscience, 16(7), 838–844. https://doi.org/10.1038/nn.3422

[6] Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. Lancet (London, England), 1(8437), 1106–1107. https://doi.org/10.1016/s0140-6736(85)92413-4

[7] Joo, E. Y., Han, S. J., Chung, S. H., Cho, J. W., Seo, D. W., & Hong, S. B. (2007). Antiepileptic effects of low-frequency repetitive transcranial magnetic stimulation by different stimulation durations and locations. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 118(3), 702–708. https://doi.org/10.1016/j.clinph.2006.11.008

[8] Padberg, F., Zwanzger, P., Keck, M. E., Kathmann, N., Mikhaiel, P., Ella, R., Rupprecht, P., Thoma, H., Hampel, H., Toschi, N., & Möller, H. J. (2002). Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 27(4), 638–645. https://doi.org/10.1016/S0893-133X(02)00338-X

[9] Pogarell, O., Koch, W., Pöpperl, G., Tatsch, K., Jakob, F., Zwanzger, P., Mulert, C., Rupprecht, R., Möller, H. J., Hegerl, U., & Padberg, F. (2006). Striatal dopamine release after prefrontal repetitive transcranial magnetic stimulation in major depression: preliminary results of a dynamic [123I] IBZM SPECT study. Journal of psychiatric research, 40(4), 307–314. https://doi.org/10.1016/j.jpsychires.2005.09.001

[10] Pink, A. E., Williams, C., Alderman, N., & Stoffels, M. (2021). The use of repetitive transcranial magnetic stimulation (rTMS) following traumatic brain injury (TBI): A scoping review. Neuropsychological rehabilitation, 31(3), 479–505. https://doi.org/10.1080/09602011.2019.1706585

[11] Demirtas-Tatlidede, A., Vahabzadeh-Hagh, A. M., Bernabeu, M., Tormos, J. M., & Pascual-Leone, A. (2012). Noninvasive brain stimulation in traumatic brain injury. The Journal of head trauma rehabilitation, 27(4), 274–292. https://doi.org/10.1097/HTR.0b013e318217df55