

Recovery from traumatic brain injury and...magnets?!?!

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Case

- BL 36 yo male sustained polytrauma from blast injury in Afghanistan 15 years ago
 - Severe TBI w/SDH s/p craniectomy
 - LOC 7 week
- Extensive rehabilitation Polytrauma Centers of care
- Right sided weakness with tone, communication impairment, sensory impairment, pain, cognitive impairments

Case

- Rehab included Polytrauma Transitional Rehabilitation Program
- Community integration
 - Can perform most ADLs, cannot manage finances
 - Part time job with significant oversight, well ordered setting
- Chronic headache, attention deficits, significant depression, aphasia
- Significant other read about repetitive magnetic stimulation helping with depression...

Can the magnetic thing
help my loved one?

Objectives

- Participants will become familiar with rTMS and basic history of neuromodulation and uses
- Participants will be familiar with common and uncommon issues after TBI
- Participants will learn current experimental applications of rTMS with individuals recovering from TBI
- Participants will learn new avenues of research being conducted with rTMS

Neuromodulation

- “alteration of nerve activity through targeted delivery of a stimulus to modulate abnormal neural pathway behavior caused by the disease process”
- Invasive or non-invasive
- Physical or chemical

The History of Neuromodulation in Medicine

- Electroconvulsive Therapy
 - AKA “Shock Therapy”
- Before electricity, there was chemicals...
 - Antagonism between schizophrenia and epilepsy
 - Meduna: “...if I can stimulate epileptic seizure in schizophrenics then these...will alter the chemical and humoral processes in the body in a way..that the abatement of the disease will be made physiologically possible”
 - Use a chemical to induce convulsion to treat the schizophrenia
 - Treated 100 patients, more than half recovered or significantly improved

The History of Neuromodulation in Medicine

- Chemical seizure induction unpredictable
- Italian researcher Ugo Cerletti witnessed chemical seizure
 - Experience in electricity with animals and epilepsy
- April 11, 1938, electroconvulsive therapy trialed on patient Enrico X
- 13 total treatments, discharged from psychiatric hospital

And more history...

- More effective for affective disorders
 - Prior to SSRI's for depression
- Anti-suicide effect
- Used more in pharmaco-resistant patients
- Safe

Wait...so how does it actually work??

- Theoretical mechanism of action of what the electrically induced seizure actually does
 - Neurotransmitters
 - Inflammatory
 - Blood brain barrier disruption
 - Gene expression
 - Neuroplasticity
- Reality → not quite sure

Is all Neuromodulation there to cause seizures then?

- NOPE!
- Over last 2 decades non-invasive brain stimulation techniques have been pursued and evaluated.
 - Stimulate or inhibit targeted parts of brain
 - Transcranial direct current stimulation (tDCS) and repetitive Transcranial Magnetic Stimulation (rTMS)
 - Neither intended to induce seizures

So lets focus on rTMS...

1800
1830s
1885
1990s
2000s
2003
2008
2015
2020

Transcranial magnetic stimulation initially used in mid-1980s, however, not able to put into clinical practice until 2008

1800s Scientists first discovered that our nerve cells carry electrical activity

1830 Michael Faraday discovered that a changing magnetic field can generate an electrical current (known as magnetic induction)

1885 The first modern rTMS device was developed by Anthony Barker in Sheffield, England

1990-2000 Used to study the function of different brain areas and causes of neurological and psychiatric illness and as a therapeutic tool

2003 Canada approved the use of rTMS therapy for depression

2008 The FDA in the United States gave its approval for rTMS to be used for treatment-resistant depression

2015 NICE in the UK approved the use of rTMS for treatment resistant depression

2020 the FDA approved rTMS treatment for OCD in the United States

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6114591/figure/fig1/>

How does it work

- Pulsed electric current into coil creates magnetic field at focal point of coil
- Coil on scalp, pulse passes through skull to brain
- Repetitive pulses → induce long term changes

- Increase or decrease cortical excitability

- **NO SEIZURES!!!!!!!!!!!!**

Targets

- Dorsolateral prefrontal cortex (dlPFC)
 - Left dlPFC and depression

- Decrease activity on the left, increase the right

Dorsolateral prefrontal cortex

<https://www.quora.com/Neuroanatomy-What-are-the-primary-functions-of-the-dorsolateral-prefrontal-cortex>

More of the connections

- Anterior Cingulate Cortex
 - Limbic system

The corticolimbic system

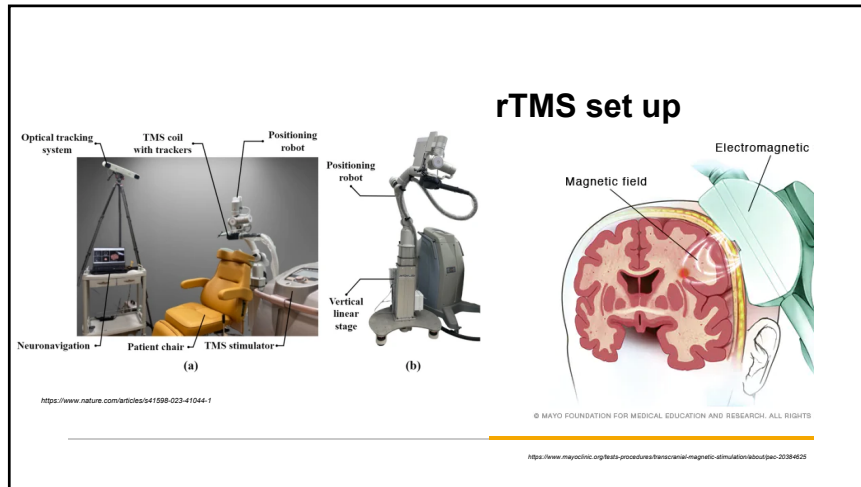
Anterior cingulate cortex: Affect, selective attention and social interactions

Dorsolateral prefrontal cortex: Motivation/executive function

Amygdala: Emotional stress and learning

Hippocampus: Learning and memory

https://commons.wikimedia.org/wiki/File:The_corticolimbic_system_including_the_left_dorsolateral_prefrontal_cortex_and_anterior_cingulate_cortex_%28Benes_2010%29.png



The variables

- Stimulation flexibility
 - Pulse frequency, intensity, temporal patterns
- Focality flexibility
 - Any location, focal or diffuse
 - Dependent of coil used
- Supra threshold to sub threshold

What to expect

- First appointment is "Mapping" process
 - Sit in recliner, given earplugs
 - Electromagnetic coil on head
 - Coil moved around
 - Find contralateral twitch
 - Find the motor threshold → Treatment dose
- Following appointments coil to treatment position and then pulse
 - rTMS usually 20 minutes

What is it used for now?

- rTMS approved by FDA for treatment of:
 1. Major Depressive Disorder in pharmacological non-responders
 2. Migraine with Aura
 3. Obsessive-Compulsive Disorder
 4. Nicotine Use Disorder

The unwanted effects...

Common Side Effects

- Scalp discomfort
- Headache
- Tingling, spasm or twitching of facial muscles
- Lightheadedness

Uncommon Side Effects

- Seizures
- Mania
- Hearing loss

Who gets ruled out of treatment

Definitive → metal implants

Stents
 Aneurysm clips/coils
 Implanted stimulators
 Implanted vagus nerve or deep brain stimulators
 Implanted electrical devices
 Electrodes for monitoring brain activity
 Cochlear implants
 Bullet fragments
 Magnetic implants

Possible rule out

Epilepsy
 Drug/alcohol use disorder
 Bipolar disorder
History of CVA, brain tumor or TBI
 Frequent severe headaches
 ? Other medical conditions

Great, so you're telling me that folks with injuries to their brains can't do this...so why are we having this talk again?!?!?!?



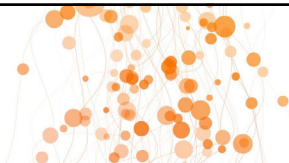
Lets talk TBI



So what might your more chronic common issues be with TBI...?

- **Post-traumatic Seizures/Epilepsy**
- Post-traumatic Headache
- Paroxysmal Autonomic Instability and Dystonia
- Post-Traumatic Hydrocephalus
- Cranial Nerve Injuries
 - CN 1, CN 7, CN 8
- Agitation
 - Aggression, akathisia, disinhibition, emotional lability
- Heterotopic Ossification
- Post-traumatic Hypertension
- Sleep disturbance/Insomnia
- Fatigue
- DVT
- Urinary Incontinence
- Neuro-endocrine Disorders
 - DI, hypothyroid, hypogonadism
- Hyponatremia
 - SIADH/CSW
- Cognitive Dysfunction
 - Attention, executive functioning, recall of new memory, self monitoring
 - Visuospatial impairment, communication impairment
- Arousal and attention
- **Mood**
- Substance abuse

Researchers quickly saw the link with depression, TBI and potential for rTMS...



Depression and suicidal ideation

- For depression, case studies and small clinical trials
- 3 case studies
 - Significant reduction via Depression Rating Scale
- 3 clinical trials
 - 2 compared rTMS with sham
 - Did not follow long term
- Suicidality study – inconclusive...but not specific to TBI

Tinnitus

- 53 yo severe tinnitus after TBI
 - Low frequency rTMS to left auditory cortex
 - 10 sessions – 3 months improvement
 - Reduced loudness tinnitus
- 63 yo musical hallucinosis
 - Low frequency rTMS by temporal lesion
 - PET information
 - Decreased severity musical hallucinations

Dizziness

- Post traumatic chronic dizziness
 - Case study rTMS in 61 yo
 - Significant improvement dizziness
- Delayed response treatment
- Only 10 sessions

Visuo-spatial/Neglect

- 20 yo with severe TBI and hemi-spatial neglect
 - Theta burst stimulation left posterior parietal cortex
 - Significant improvement Behavioral Inattention Test
- Patient with TBI and Central visual oscillopsia
 - Low frequency rTMS to bilateral visual cortex
 - Decreased large amplitude oscillations

Disorder of Consciousness

- One case study
 - Improved VS to MCS at week 15, reverted by week 30
- Multipatient studies with DOC
 - Most showed no changes in CRS-S or therapeutic benefits
 - One time treatments
 - Did NOT distinguish between TBI vs ABI vs CVA with DOC
 - No consistency with any protocols
- Nothing shown to really investigate further
- Seizure risks

Cognitive

- A few case studies
 - 26 yo after severe TBI with LOC and DAI
 - Large improvements executive functioning, behavior
 - 67 yo severe TBI with DAI
 - Improved MMSE
- 2 case studies no changes
 - Methodology issue with MoCA
- Cognitive impairment → WIDE variety of issues

Aphasia

- Most studies in CVA patients
- 29 yo female severe TBI in a cross over study
 - Post rTMS → increase Western Aphasia Battery vs. neuro-cog training alone
- Cross over design
- No details regarding neuro-cog training program

Pain/Headache



Headache clinical trials

4 session rTMS left DIPFC decreased intensity, frequency, duration mTBI headaches
No correction for mood based symptoms



Central pain clinical trials

10 sessions high frequency rTMS primary cortex, less self reported pain
• No additional follow up

OK, so what does this all mean and can we use rTMS to help our patient???

So what does this all mean?

- Appears to have potential for efficacious therapeutic intervention to treat symptoms after TBI
 - Depression, dizziness, aphasia, neglect, headache
- And minimal serious side effects
- A lot of flexibility on where and how to apply rTMS
- However...

So what does this all mean?

- Small sample sizes
 - Mostly case reports, very little data to report
- No study consistency or protocol
 - Unclear time frame since TBI
 - No control for medication interventions
 - Location of treatment, time and type of rTMS treatment inconsistent – no firm treatment parameters
- Cannot generalize the results

Where do we go from here?

- The Obstacle is the Way
 - Initiate more homogeneous studies looking at specific issues post-TBI
 - Set protocols, controlling for times since injury, medications
 - Monitor longevity and time-course of rTMS effects
 - Develop comprehensive safety guidelines
 - Coil selection, location, method and placement
 - Motor thresholds
 - Number, time course, duration and treatment parameters

Ongoing studies currently?

- Randomized Controlled Trial (RCT) aiming at assessing the efficacy of a novel rehabilitation protocol, based on repetitive transcranial magnetic stimulation (rTMS) in combination with a conventional cognitive treatment (CCT). The protocol will be statistically compared to the same CCT administered without the rTMS in a sample of traumatic brain injury patients (age between 18 and 80 years) with left hemispatial neglect.
 - In Italy
- This study will assess the combined effectiveness of repetitive transcranial magnetic stimulation and telehealth based therapy in helping manage mild traumatic brain injury related headaches. The investigators hypothesize that active rTMS combined with telehealth therapy will provide marked reduction in MTBI related headaches and symptoms in comparison to their placebo counterparts.
 - San Diego, CA

But for today...

- To answer the original question if rTMS can help our patient for today, no.
- But there remains hope for potential innovations in the future



Questions?

References

- Galimberti A, Tik M, Pellmarino G, Schuler AI. Effectiveness of rTMS and tDCS treatment for chronic TBI symptoms: A systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2024 Jan 10;128:110863. doi: 10.1016/j.pnpb.2023.110863. Epub 2023 Sep 12. PMID: 37709126.
- Pink AE, Williams C, Alderman N, Stoffels M. The use of repetitive transcranial magnetic stimulation (rTMS) following traumatic brain injury (TBI): A scoping review. *Neuropsychol Rehabil*. 2021 Apr;31(3):479-505. doi: 10.1080/09602011.2019.1706595. Epub 2019 Dec 27. PMID: 31880207.
- Oberman LM, Eslev S, Philto NS, Siddiqui SH, Adamson MM, Brody DL. Use of Repetitive Transcranial Magnetic Stimulation in the Treatment of Neuropsychiatric and Neurocognitive Symptoms Associated With Concussion in Military Populations. *J Head Trauma Rehabil*. 2020 Nov/Dec;35(6):388-400. doi: 10.1097/HTR.0000000000000628. PMID: 33165152. PMCID: PMC7664843.
- Dhallwal SK, Meek BP, Modirrousta MM. Non-Invasive Brain Stimulation for the Treatment of Symptoms Following Traumatic Brain Injury. *Front Psychiatry*. 2015 Aug 26;6:119. doi: 10.3389/fpsy.2015.00119. PMID: 26379560; PMCID: PMC4549551.
- <https://www.mayoclinic.org/tests-procedures/transcranial-magnetic-stimulation/about/pec-20384625>
- Garsden G, Bennett CS. Electroconvulsive therapy: 80 years old and still going strong. *World J Psychiatry*. 2019 Jan 4;9(1):1-6. doi: 10.5498/wjpv.9.1.1. PMID: 30631748. PMCID: PMC6323937.
- Cuccurullo, SF, editor. *Physical Medicine and Rehabilitation Board Review*. 2nd Edition. 2010. Traumatic Brain Injury: 49-94.
- <https://clinicaltrials.gov/study/NCT04573413>
- <https://clinicaltrials.ucsd.edu/trial/NCT05176392>