

TRANSCRANIAL MAGNETIC STIMULATION: CLINICAL UPDATE FOR PSYCHIATRIC APPLICATIONS

ANNA MAZUR, PH.D.

OSU DEPT. OF PSYCHIATRY AND BEHAVIORAL SCIENCES



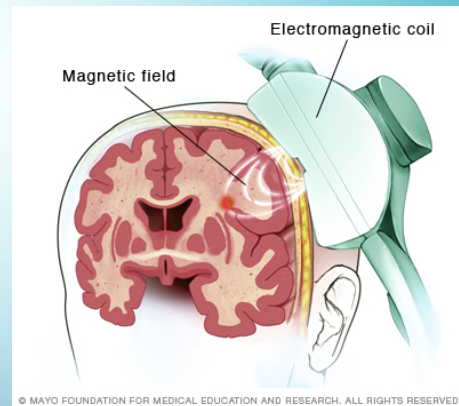
FINANCIAL DISCLOSURE

I have financial relationships to disclose:

- Employee of: Oklahoma State University
- Stockholder in: none
- Research support from: none
- Honoraria from: occasional academic talks

OUTLINE AND GOALS

1. Review of rTMS
2. Review of rTMS risks
3. FDA approved conditions
4. Efficacy of rTMS in Depression
5. Early Evidence:
 1. Depression
 2. Post Traumatic Stress Disorder (PTSD)
 3. Autism
 4. Obsessive-Compulsive Disorder (OCD)



WHAT IS REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS)?

- rTMS is a brain stimulation technique
- High intensity current (through a magnetic coil placed on the head) can produce a magnetic field that stimulates the brain tissue.
- rTMS uses an electromagnetic field to stimulate areas of the brain that are underactive or overactive, gradually returning them to healthy patterns of activity.
- Uses an electromagnetic field to non-invasively stimulate cortical neurons.
- rTMS uses powerful, focused magnetic field pulses that are applied using a magnetic coil placed against the scalp, over the target brain region.
- Produced at either Low Frequency or High Frequency
 - Low frequency TMS (<1 Hz) stimulation inhibits neurons and
 - High frequency TMS (>1 Hz) excites neurons that are targeted.
- When applied repeatedly, these pulses can strengthen or weaken the connections between neurons, known as synapses.
- The long-lasting changes in neural connections can achieve lasting changes in brain activity, reversing the abnormal patterns associated with depression or other conditions.

TYPES OF TMS TREATMENT

- TMS encompasses a wide spectrum of treatments.
- Aside from a single TMS stimulation, repetitive TMS, and deep TMS, strategies for using rTMS vary based on:
 - types of coils,
 - region of the brain stimulated (*i.e.*, left or right dorsolateral prefrontal cortex, or bilateral),
 - "dose" (*e.g.*, intensity, percent of resting motor threshold (% RMT)),
 - speed of pulses (*i.e.*, Hz, pulses per second),
 - pulse train duration,
 - inter-train interval,
 - trains per session,
 - total number of pulses
 - number of weekly sessions, duration (*i.e.*, 2 to 6 weeks), and total number of sessions.

EXAMPLES OF TMS DEVICES



EXAMPLES OF TMS DEVICES

- NeuroStar (Neuronetics, Inc.). Initially FDA approved in 2008
 - For patients who failed at least one antidepressant trial
 - The protocol reviewed by the FDA is 3,000 high-frequency (10 Hz) pulses administered to the left dorsolateral prefrontal cortex at 120% of motor threshold on a schedule of 5 sessions per week for 4–6 weeks (60,000 to 90,000 total pulses).
- MagVita (MagVenture)
- CloudTMS



PATIENT ELIGIBILITY

- The most common use of rTMS is for treating depression that has not responded to medications and psychotherapy.
 - If tried at least 1–2 different antidepressant medications without improvement,
 - or if unable to tolerate at least 2 different antidepressant medications
- In psychiatry, used most commonly for Major Depressive Disorder. Research has explored the following:
 - Depression in Bipolar Disorder,
 - PTSD
 - OCD
 - Addictions
 - Autism
 - Conversion disorder
 - and eating disorders

EXCLUSION CRITERIA

- Psychotic disorders (e.g., schizophrenia, hallucinations)
- Seizure disorders, since seizures may be a side effect
- Neurological conditions in general; History of moderate to severe TBI; stroke; or brain surgery
- Patients with any type of non-removable metal in their heads (with the exception of braces or dental fillings), should not receive rTMS. Failure to follow this rule could cause the object to heat up, move, or malfunction, and result in serious injury or death.
 - Aneurysm clips or coils
 - Stents in the neck or brain
 - Deep brain stimulators
 - Electrodes to monitor brain activity
 - Metallic implants in ears and eyes
 - Shrapnel or bullet fragments in or near the head
 - Facial tattoos with metallic or magnetic-sensitive ink
 - Other metal devices or objects implanted in or near the head

TREATMENTS

- Full course required
- Current recommendations suggest minimum 20–30 sessions, with tapers.
 - For example, 6 weeks of daily sessions + 1 week of 3 sessions, 1 week of 2 sessions, and 1 session during the final week
- Typically offered Monday to Friday during business hours



MOTOR THRESHOLD



- Prior to the first treatment
- The TMS physician measures the patient's motor threshold, by administering several brief pulses.
- The motor threshold is defined as the stimulator setting that moves the patient's thumb 50% of the time
- The motor threshold is the minimum amount of power necessary to make the patient's thumb twitch
- Helps to determine the amount of energy required to stimulate brain cells but minimize seizure risk

WHO ADMINISTERS rTMS

- rTMS is always prescribed by a physician.
- The initial motor threshold is always determined by a TMS physician.
- The treatment itself is administered by an experienced TMS technician under the supervision of the TMS physician.
- The TMS technician or physician will always be present to monitor the patient during the treatment. The patient can stop a treatment at any time by asking the staff m



WHAT HAPPENS DURING rTMS TREATMENT

- Comfortable chair
- Patient is awake
- No anesthesia or medications are needed
- rTMS technician places a coil on the patient head
- Patients are asked to avoid moving around so the coil stays in place
- When treatment starts, patients feel short bursts of stimulation on their scalp, followed by pauses. Some patients describe this experience as the feeling of static electricity on their nose, teeth, and forehead. This sensation is more pronounced during the first few sessions and then becomes less noticeable
- Patients sometimes wear earplugs during treatment for their comfort and hearing protection, as rTMS produces a loud clicking sound with each pulse, much like an MRI machine
- Each session lasts 15–40 minutes



AFTER EACH TREATMENT

- Patients return to normal functions
- No restrictions on driving or operating vehicle/machinery

SIDE EFFECTS

- rTMS has been in use since the early 1990s.
- So far no long-term risks have been shown.
- Most people experience only mild side effects. The most common side effect is scalp pain during treatment.
- The sensation is similar to static electricity and can be intense in the beginning.
 - Some patients take ibuprofen (Advil) or acetaminophen (Tylenol) 1 to 2 hours before treatment to reduce the pain. After the first few sessions, the nerves in the scalp adapt to the stimulation and patients do not experience much pain.
- There is also a small chance that rTMS could cause a seizure. Seizure occurs in about 1 out of every 10,000 people who receive rTMS.

rTMS AND MEDICATIONS

- Patients on antidepressants are allowed to continue medications during rTMS.
- Changes in medications and dosage are not advised during the treatment
- Patients should be stable on medications (i.e., take the medication for at least 4 weeks prior to treatment)

rTMS IN PSYCHIATRIC TREATMENT

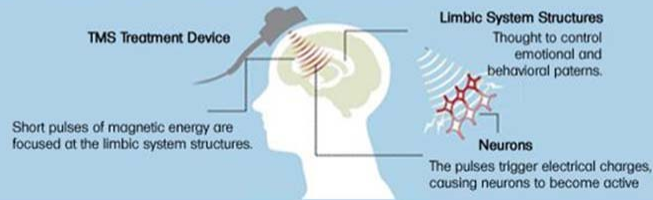
DEPRESSION

- Major depressive disorder is one of the most common mental disorders in the general and Veteran populations.
- In the general population, roughly 5 to 7% have had an episode of depression in the past 12 months and 13% have had an episode at some point in their life.
- Veterans: 11% to 17% of soldiers returning from Afghanistan or Iraq meet current criteria for depression.
- Among Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) Veterans entering VA health care from 2001 to 2010, 17% to 22% were diagnosed with depression
- The one- to two-thirds of MDD patients who do not respond to the first antidepressant prescribed, and the 15% to 33% who do not respond to multiple drugs are defined as having treatment-resistant depression (TRD).
- Whether the effectiveness of rTMS treatment differs by sex or in young (age 18–37 years) or older adults (age \geq 65 years) is unclear.

MECHANISM

Magnetic pulse to ease depression

A non-invasive procedure to help fight depression called transcranial magnetic stimulation, or TMS, uses a magnetic pulse to stimulate brain cells that control mood.



- Depression:
- rTMS works by directly stimulating areas of your brain involved in controlling emotions.
- These areas are thought to be less active in people with depression.
- The coil directs a series of magnetic pulses through your scalp and skull to the targeted area of the brain.
- With repeated treatments, the magnetic pulses change the activity of the brain cells (neurons), returning the brain to normal functioning

DEPRESSION AND TMS INTENSITY

Table 3: Trials comparing different LHF-DLPFC intensities

Author, Year Sample size	Intensity comparisons	Speed	Total pulses	Response	Remission	Adverse event withdrawals
Bakim 2012 ⁵⁶ N=35	110% vs 80% vs sham	20 HZ	24,000	73% vs 83% vs 17%	55% vs 25% vs 9%	NR
Rossini 2005 ⁵⁸ N=54	100% vs 80% vs sham	15 Hz	6,000	61% vs 28% vs 6.2%	NR	None
Padberg 2002 ⁵⁷ N=31	100% vs 90% vs sham	10 Hz	15,000	30% vs 20% vs 0	20% vs 10% vs 0	NR

Relationship not clear, response possibly better for higher intensity (Peterson, 2014)
Significant difference between rTMS and shamTMS

DEPRESSION AND FREQUENCY OF rTMS

Table 4: Trials comparing different LHF-DLPFC frequencies (Hz)

Author	Year	CC AD meds?	Hz comparison	Intensity (% RMT)	Total pulses	Response	Remission	Adverse event withdrawals
George	2000 ⁵⁹	N	20 vs 5 vs sham	100%	16,000	30% vs 60% vs 0	NR	0% vs 20% vs 0%
Su	2005 ⁶⁰	Y	20 vs 5 vs sham	100%	16,000	60% vs 60% vs 10%	50% vs 50% vs 0	NR
Fitzgerald ⁸	2006 ⁵⁸	Y	10 vs 5	100%	15,000	28% vs 6%; <i>P</i> =0.16	NR	NR
Stern	2007 ⁵⁴	N	10 vs 1 vs sham	110%	16,000	60% vs 0 vs 0	40% vs 0 vs 0	0% vs 50% vs 30%
Rosenberg	2002 ⁵⁰	Y	5 vs 1	90%	6,000	83% vs 67%	NR	1, group NR

Relationship not clear, due to methodological and sample differences across studies (Peter

DEPRESSION

- The American Psychiatric Association recommends Electro-convulsive Therapy (ECT) as a treatment of choice for patients with severe treatment-resistant MDD
- The recommendation was based on older meta-analyses of clinical trials which found remission rates of 70% to 90% for ECT and found that ECT was more effective than other therapies including rTMS.
- Although a 2014 meta-analysis confirmed these older findings about the superiority of ECT for severe or resistant depression overall
 - However, 23 findings from other recent meta-analyses that focused exclusively on TRD suggest there may be less of a difference between ECT and rTMS in response:
 - **Response Range for ECT: range, 20% to 64% vs Response Range for TMS: 20% to 58%**
 - **Remission Range for ECT: 15% to 53% vs Response Range for TMS: 9% to 43%**

Baeken et al. (2010), Borckardt (2013), Boggio (20

rTMS VS ELECTROCONVULSIVE THERAPY (ECT) IN DEPRESSION

- Both are considered effective for treatment-resistant depression
- For those who have not responded to medication, or who have not been able to tolerate the side effects of medication
- Some patients are uncomfortable with undergoing ECT
- Unlike ECT, rTMS has no known side effects on memory, attention, concentration, or intellectual function.
- rTMS does not require anesthesia or sedation, so people undergoing treatment can usually continue with their daily activities immediately after treatment.



POSTTRAUMATIC STRESS DISORDER (PTSD)

- The National Co-morbidity Survey (NCS) reported a lifetime prevalence rate of 7.8% for PTSD in a national sample (Kessler et al., 2005, 1995).
- In veterans
 - The National Vietnam Veterans Readjustment study reported PTSD in 31% of males and 27% of females (n = 3016) (Kulka et al., 1990).
 - PTSD from deployments to Iraq and Afghanistan = 23% (Fulton et al., 2015).
- Causes significant functional impairment (Rodriguez et al., 2012; Shea et al., 2010).

MECHANISM OF ACTION

- **LOW FREQUENCY:**
 - This abnormal increase in the activation of the right prefrontal cortex may be the cause of PTSD symptoms related to hyperarousal and anxiety (Simmons et al., 2004).
 - 1 (Low Frequency) Hz stimulation applied over the prefrontal cortex produces an inhibitory effect, including reduction of the hyperarousal response to threatening stimuli
 - Low Frequency rTMS applied to the right dorsolateral prefrontal cortex (DLPFC) decreases cortical excitability and improves hyperarousal symptoms (Osuch et al., 2009; Tillman et al., 2011).
- **HIGH FREQUENCY**
 - High Frequency rTMS (5 Hz, 10 Hz or 20 Hz) also significantly alleviated core PTSD symptoms, such as re-experiencing and avoidance (Bie and Wang, 2011; Cohen et al., 2004; Isserles et al., 2013).
 - Explanation of the effects of High Frequency rTMS possibly activates the hypoactivated medial prefrontal cortex (mPFC), which is one part of PTSD patients' impaired stress-induced fear circuitry (Shin and Handwerker, 2009)
- Thus High Frequency and Low Frequency rTMS have both achieved some success in treating PTSD

AMYGDALA REGULATION

- PTSD patients also show increased amygdala response when engaged in PTSD-related script-driven imagery and when shown fearful stimuli
- This suggests dysfunctional amygdala activation.
- Importantly, rTMS administered to right dorsolateral prefrontal cortex (rDLPFC) has been shown to decrease amygdala activation to threatening stimuli (Baeken et al., 2010).

OVERALL IMPROVEMENT IN PTSD USING rTMS

In meta-analysis, active rTMS is significantly superior to placebo
(Hedges' $g=0.75$; 95% CI = 0.06–1.42)

(Trevizol,

Table 1 - Overview of demographics and stimulation parameters

Article	Sham group		Active group		TMS parameters				
	n	Age	n	Age	TMS Site	F (Hz)	No. of Sessions	PPS	MT (%)
Boggio et al. ⁶	10	45.9	10	47.1	L-DLPFC	20	10	1600	80
Boggio et al. ⁶	10	45.9	10	40.7	R-DLPFC	20	10	1600	80
Watts et al. ¹¹	10	57.8	10	54	R-DLPFC	1	10	400	90
Isserles et al. ^{8*}	9	40.4	8	40.5	Bilateral	20	12	1680	120
Isserles et al. ^{8*}	9	40.4	9	49	Bilateral	20	12	1680	120
Cohen et al. ⁷	6	42.8	8	40.8	R-DLPFC	1	10	100	80
Cohen et al. ⁷	6	42.8	10	41.8	R-DLPFC	10	10	400	80
Osuch et al. ⁹	9	41.4	9	41.4	R-DLPFC	1	20	1800	100

* Deep transcranial magnetic stimulation.

F = frequency; L-DLPFC = left dorsolateral prefrontal cortex; MT = motor threshold; PPS = pulses per session; R-DLPFC = right dorsolateral prefrontal cortex; TMS = transcranial magnetic stimulation.

Trends
in Psychology and Neuroscience

Brief Communication

Transcranial magnetic stimulation for posttraumatic stress disorder: an updated systematic review and meta-analysis

Estimulação magnética transcraniana para transtorno de estresse pós-traumático: revisão sistemática de literatura e metanálise

Alisson Paulino Trevizol,¹ Mirna Duarte Barros,¹ Paula Oliveira Silva,¹ Elizabeth Osuch,² Quirino Cordeiro,¹ Pedro Shiozawa¹

COMORBID DEPRESSION AND PTSD

- Studies conducted with the newest rTMS technology report a significant baseline-to-endpoint improvement in PTSD and depression.
- A recent study conducted with individuals with comorbid PTSD & depression showed that after 30 to 36 sessions of rTMS:
 - 50% of patients demonstrated at least 50% improvement in depressive symptoms
 - 40% demonstrated at least 50% improvement in PTSD symptoms (Philip, 2016).

AUTISM

- There are a small number of studies examining the therapeutic effects of rTMS in ASD;
- Applied low-frequency stimulation to left DLPFC and reported a reduction in repetitive behaviors, although this research did not involve a "sham" or "placebo" control condition.
- Recent sham-controlled study with 28 adult individuals with autism (fluid language), were randomized into deep rTMS or ShamTMS for 2 weeks.
 - rTMS involved bilateral prefrontal cortex
 - Participants in the active condition showed a reduction in self-reported social relating symptoms from pre-treatment to one month follow-up, and a significant reduction in social relating symptoms (relative to sham participants) for both post-treatment assessments.
 - Sham condition did not show improvements (Enticott et al., (2014)
- In another study, 45 children with ASD were treated with rTMS and neuro-bio-feedback, and showed significant improvements in behavioral and daily function. However, poor study design and a lack of sham treatment limits the applicability of the findings (Sokhadze, et al., 2014)

OBSESSIVE COMPULSIVE DISORDER

- Haghghi et al., 2015 published findings from a larger sham-controlled study:
 - 21 patients with treatment-resistant OCD assigned to 4 weeks of shamTMS or rTMS
 - Symptom reduction in patients with OCD
 - Full or partial response was observed in rTMS condition and not sham
- Meta analysis of previous studies suggests that among 18 randomized sham controlled studies:
 - rTMS is modestly effective in reducing symptoms
 - Low frequency TMS is more effective than high frequency TMS
 - Best results when rTMS is applied to the supplementary motor area
 - Results observed over time
 - Symptom reduction was greater at 12 weeks follow up than 4 weeks follow up.

CONCLUSIONS

- Effective for treatment resistant conditions
- Effective for depression and PTSD
- Effects long lasting
- Other conditions still under research
- Not perfect
- Mechanism of action poorly understood

REFERENCES

- Abraham G, O'Brien S. Repetitive transcranial magnetic stimulation for PTSD: a maintenance treatment. *Canadian Journal of Psychiatry*. 2002;47(4):386.
- Baeken C., De Raedt, R., Van Schuerbeek, P., Vanderhasselt, M-A., De Raedt, D., Derom, A., Luyckaert, R., 2010. Right prefrontal HF-rTMS attenuates right amygdala processing of negatively valenced emotional stimuli. *NeuroImage*. Brain Res. 214, 450-455.
- Baeken C, De Raedt R, Vanderhasselt M-A, et al. A "hypersensitive" hypothalamic-pituitary-adrenal system could be indicative for a negative clinical high-frequency repetitive transcranial magnetic stimulation outcome in melancholic depressed patients. *Brain Stimul*. Jan 2010;3(1):54-57.
- Boggio PS, Fregni F, Berman F, et al. Effect of repetitive TMS and fluoxetine on cognitive function in patients with Parkinson's disease and concurrent depression. *Mov Disord*. Sep 2005;20(9):1178-1184.
- Borckardt JJ, Nahas ZH, Teal J, et al. The painfulness of active, but not sham, transcranial magnetic stimulation decreases rapidly over time: Results from the double-blind phase of the OPT-TMS trial. *Brain Stimul*. 2013;6(6):925-928.
- Fulton, J.J., Calhoun, P.S., Wagner, H.R., Schry, A.R., Hair, L.P., Feeling, N., Elbogen, E., Beckham, J.C., 2015. The prevalence of posttraumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans: a meta-analysis. *J. Anxiety Disord*. 31, 98-107. Hallett M. Transcranial magnetic stimulation: a primer. *Neuron*. 2007;55(2):187-199.
- Kessler, R.C., Sonnega, A., Bromet, E., Hughes, M., Nelson, C.B., 1995. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch. Gen. Psychiatry* 52, 1048-1060.
- Kessler, R.C., Chiu, W.T., Demler, O., Merikangas, K.R., Walters, E.E., 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry* 62, 617-627.
- Kulka, R.A., Schlenger, W.E., Fairbank, J.A., Hough, R.L., Jordan, B.K., Marmar, C.R., Weiss, D.S., 1990. Trauma and the Vietnam War Generation: Report of Findings from the National Vietnam Veterans Readjustment Study. Brunner/Mazel Psychosocial Stress Series, No. 18. Brunner/Mazel, Philadelphia, PA.
- Rodriguez, P., Holowka, D.W., Marx, B.P., 2012. Assessment of posttraumatic stress disorder-related functional impairment: a review. *J. Rehabil. Res. Dev*. 49, 649-665.
- Trevizol, A. P., et al. (2016). "Transcranial magnetic stimulation for posttraumatic stress disorder: an updated systematic review and meta-analysis." *Trends Psychiatry Psychother* 38(1): 50-55.
-