Clinical application of repetitive transcranial magnetic stimulation

6th Annual Adult Mental Health Update: Strategies for Primary Care

DATE: March 11.2022

PRESENTED BY: Brandon Cornejo MD, PhD, Assistant Professor, Department of Psychiatry

Disclosures

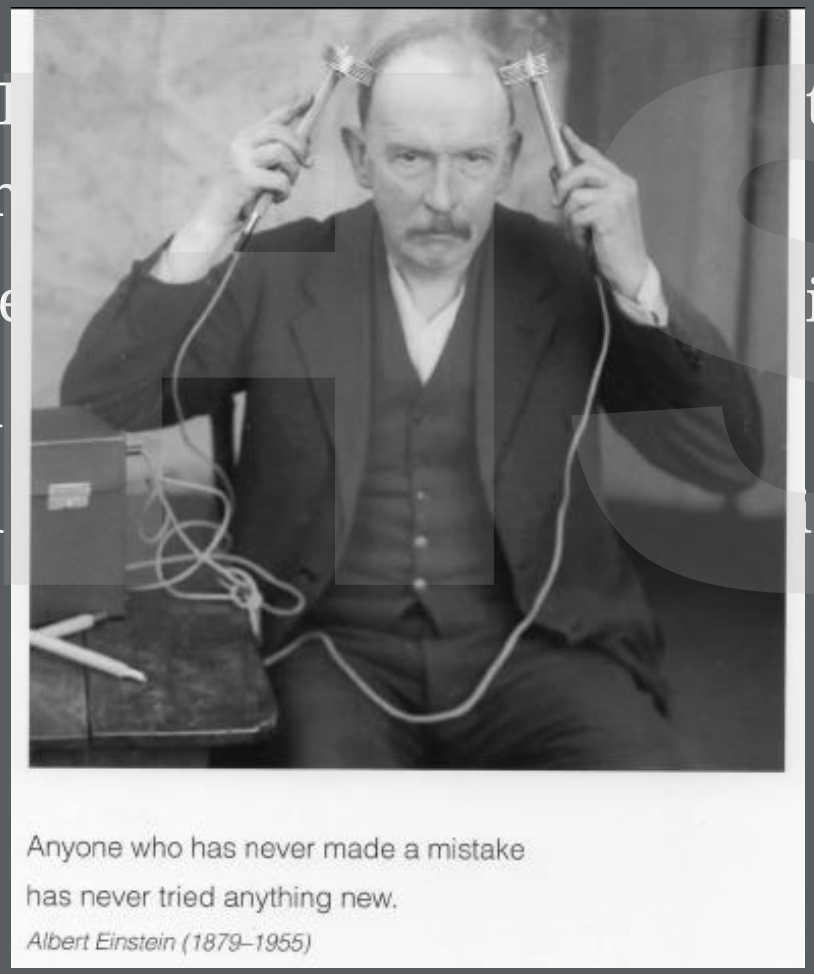
- Brandon J Cornejo MD, PhD
  - Greenbrook TMS: private practice clinician providing dTMS for treatment of MDD, OCD
  - Clinical TMS Society Research Committee – slides are guided by the CTMSS educational slide deck without influence from industry or monies exchanged

Educational Objectives

- Describe the various forms of transmagnetic stimulation (TMS)
- Briefly understand how TMS may alter cortical excitability and the mechanisms that may be responsible for these changes
- Understand the clinical application of TMS in psychiatric disorders, such as depression and OCD, including benefits, risks and side effects
- Be able to explain how to identify a potential candidate for rTMS and how to access these resources in the community.

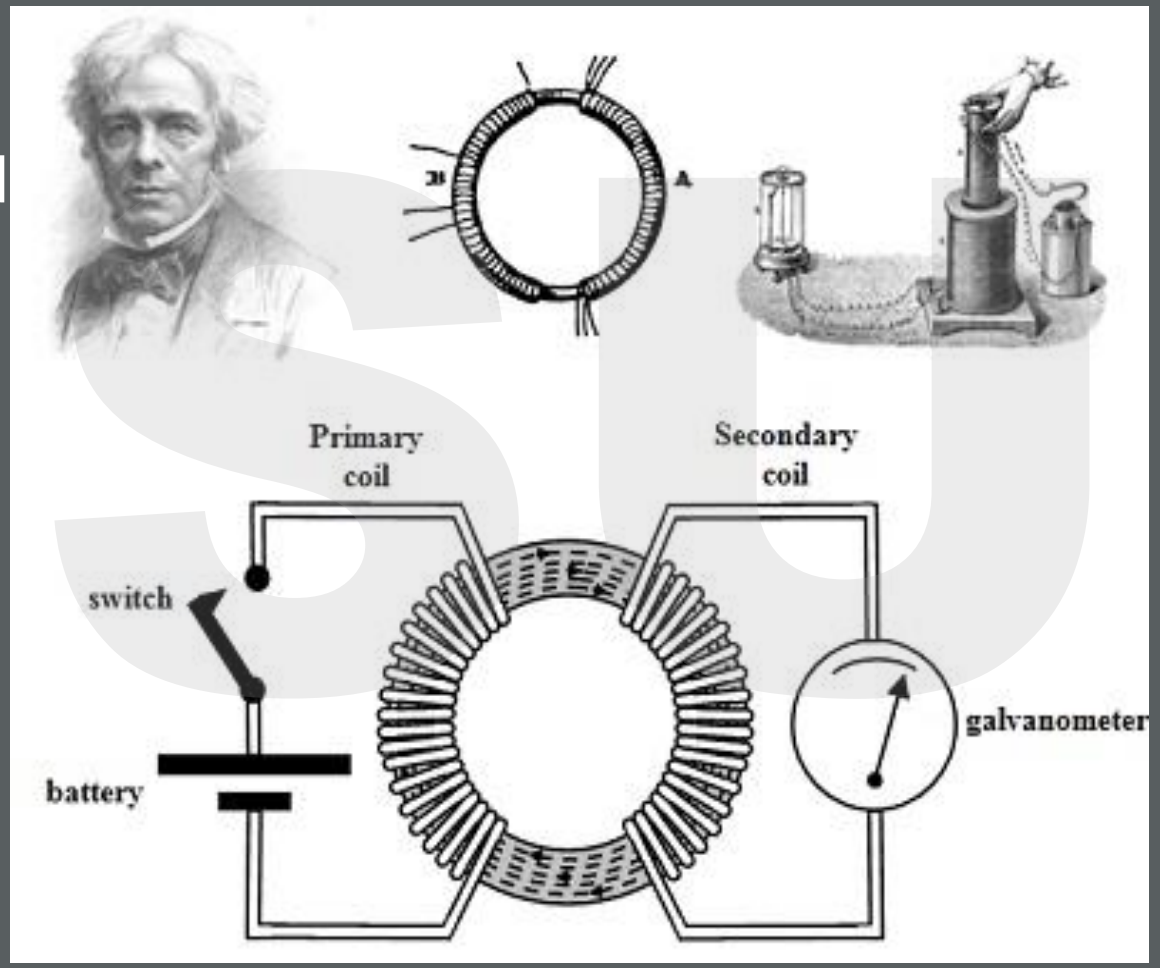
What is transcranial magnetic stimulation (TMS)?

- Clinically, T tment for depression, OCD and sr
- This is a me in through intact scalp
- Produces a as an MRI very briefly
- Induces an in



Transcranial Magnetic Stimulation – The History

- Physical principles of electromagnetism were discovered in 1831 by Michael Faraday
- A pulse of electrical current generates a magnetic field
- The rate of change (flux) induces a secondary current that is perpendicular



Electromagnetic Induction

Mike Polson, 1982
University of Sheffield

Using magnetic field to stimulate peripheral nerves and induce muscle activity (EMG) in hand

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Birth of Transcranial Magnetic Stimulation (TMS)

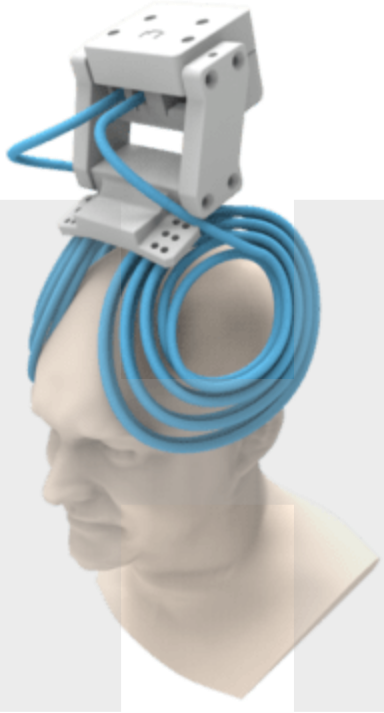
Reza Jalinous, Ian Freeston, Tony Barker
University of Sheffield, 1985

What is transcranial magnetic stimulation (TMS)?

Transcranial Magnetic Stimulation – The History

- 2008 : TMS first given FDA clearance for the treatment of MDD
- 2013-2018: 6 more devices approved
- 2018: Theta-burst stimulation approved
- Late 2018: TMS approved for treatment of refractory OCD
- 2021: TMS approval for smoking cessation

H1-Coil
for Major Depressive Disorder (MDD)



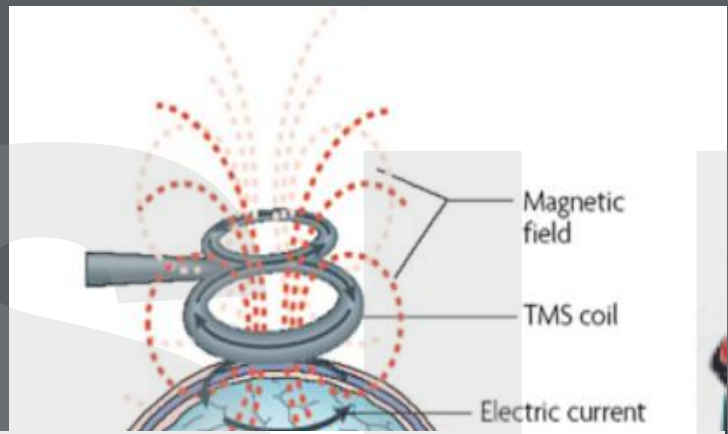
H7-Coil
for Obsessive-Compulsive Disorder (OCD)

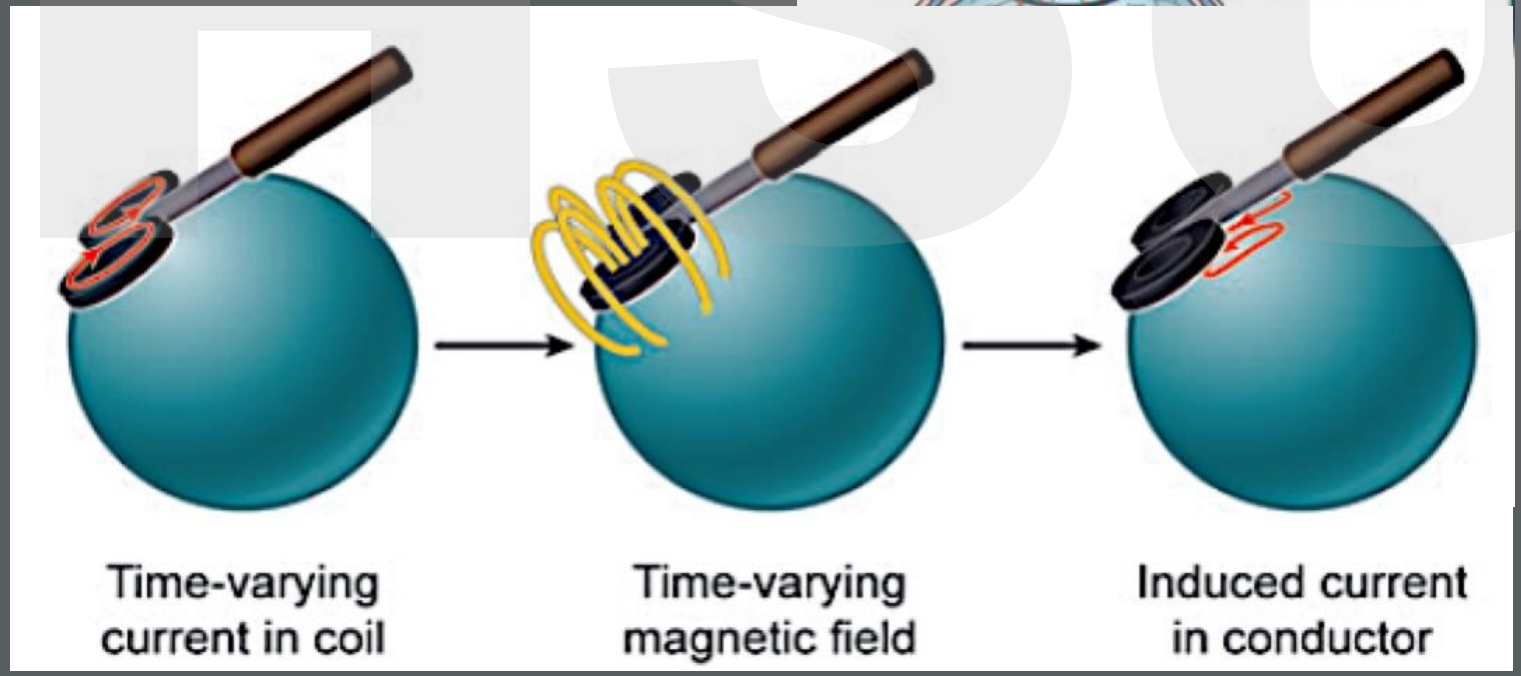
H4-Coil
for Smoking Cessation

Traditional TMS Coil
for Major Depressive Disorder (MDD)

rTMS – Potential mechanisms of action

- A pulsed magnetic field is passed through the scalp and skull
- Magnetic field passed through cortical neurons
- Cortical neurons then act as a conductor resulting in an induced current

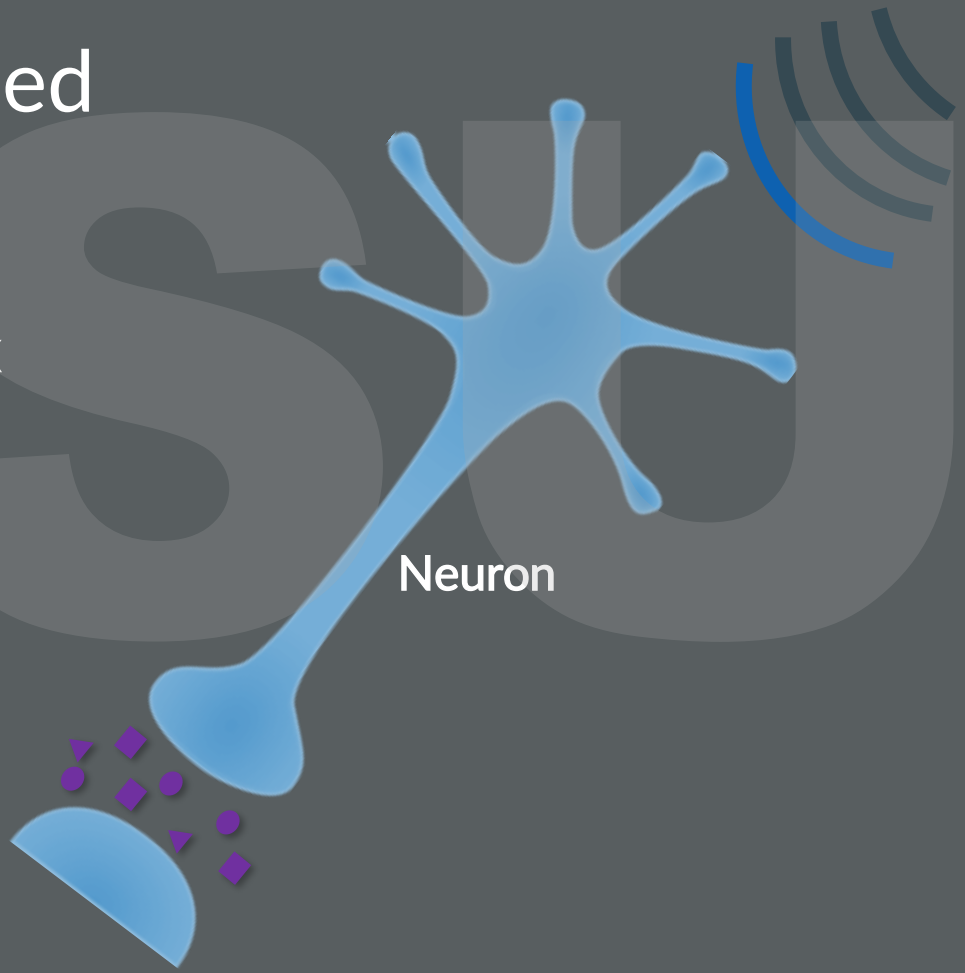




TMS Directly Depolarizes Cortical Neurons to Produce an Action Potential

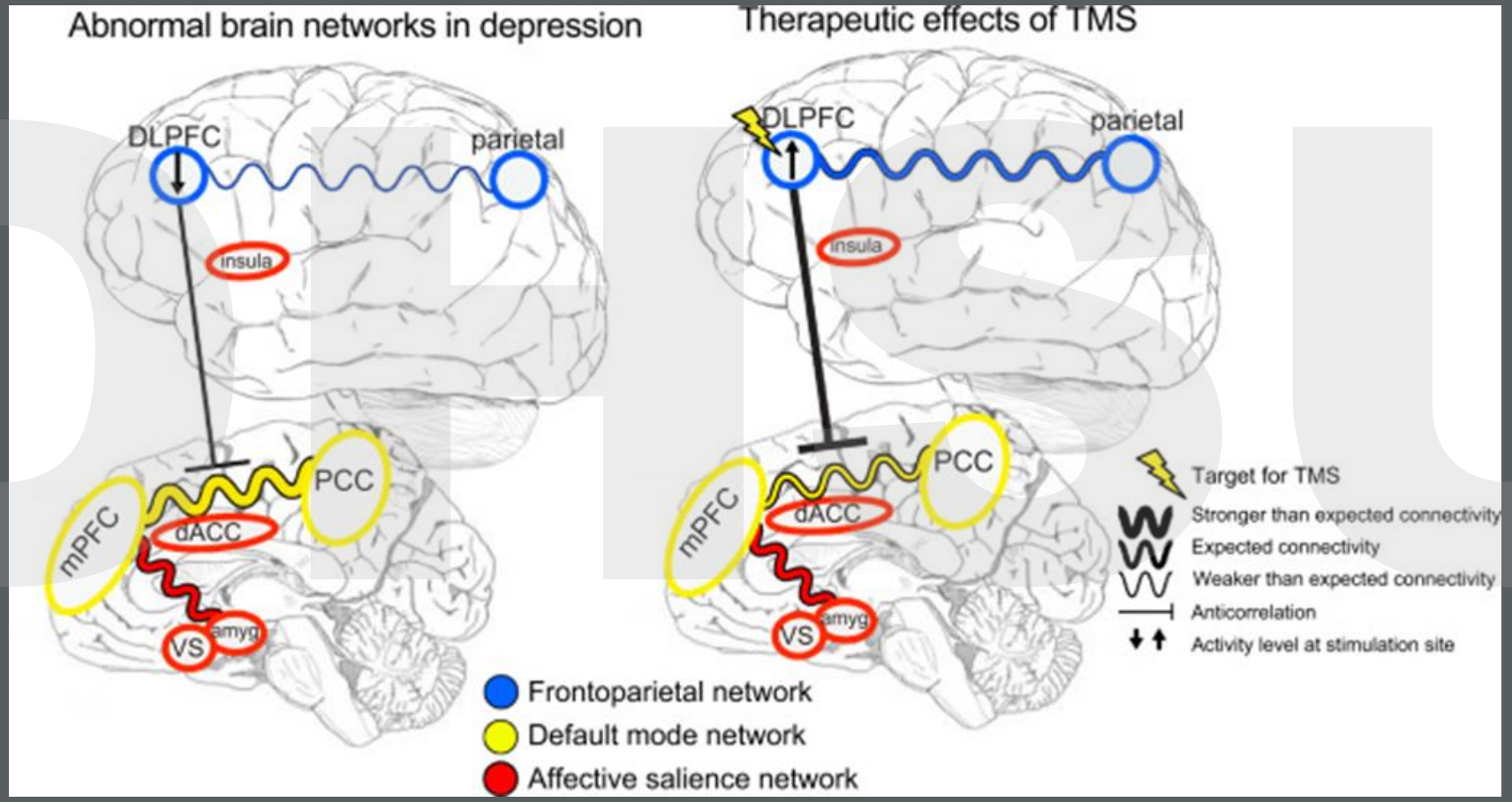
Sequence of effects of TMS pulsed magnetic fields:

- Pulsed magnetic fields induce a local electrical current in the superficial cortex
- Depolarizes neurons (change in charge differential across the membrane)
- Elicits an action potential (neuron fires)
- release of chemical neurotransmitters at synapse
- Propagation of signal to other brain regions and structures



Post A, Keck ME. (2001) *J Psychiatric Research*

rTMS – Potential mechanisms of action in depression



Fisher et. al. *Biological Psychiatry: CNNI*. 2016; 1; 3. 262-270

Biological and Behavioral Effects of TMS

Effects Seen After Chronic Exposure (Repeated TMS Applications):

- Outcome dependent upon stimulation parameters
- Changes in blood flow and metabolism at stimulation site
- Alteration of monoamine concentrations
- Beta-receptor, serotonin-receptor modulation
- Local GABA & glutamate effects
- Effects on thyroid hormones and HPA axis
- Evidence of neurogenesis gene induction (eg, BDNF upregulation)
- Plasticity-like actions (i.e, Long Term Depression/Long Term Potentiation-like effects)
- Increase in grey matter volume and hippocampal volume
- Changes in connectivity/activity of neural circuitry (eg, DLPFC-anterior cingulate cortex)

Lisanby SH, Belmaker RH. (2000) *Depress Anxiety*
Kim et al. (2006) *Neurosci Lett*
Shajahan et al (2002) *Prog Neuropsychopharmacol*
Teneback et al. (1999) *Neuropsychiatry Clin Neurosci*;
Epstein et al. (1990) *Neurology*;
George et al. (1995) *NeuroReport*;
Czeh et al. (2002) *Biol Psychiatry*

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Why rTMS?

From: magstim.com

Current Treatment for Depression

Medications (chemical neuromodulation)

- SSRIs, SNRIs, TCAs, MAOIs, lithium and other augmentation agents

Psychotherapy (behavioral neuromodulation)

- CBT, DBT, ACT, Psychodynamic Therapy, Interpersonal Therapy, & Group Therapy

Neurostimulation ('electrical' neuromodulation)

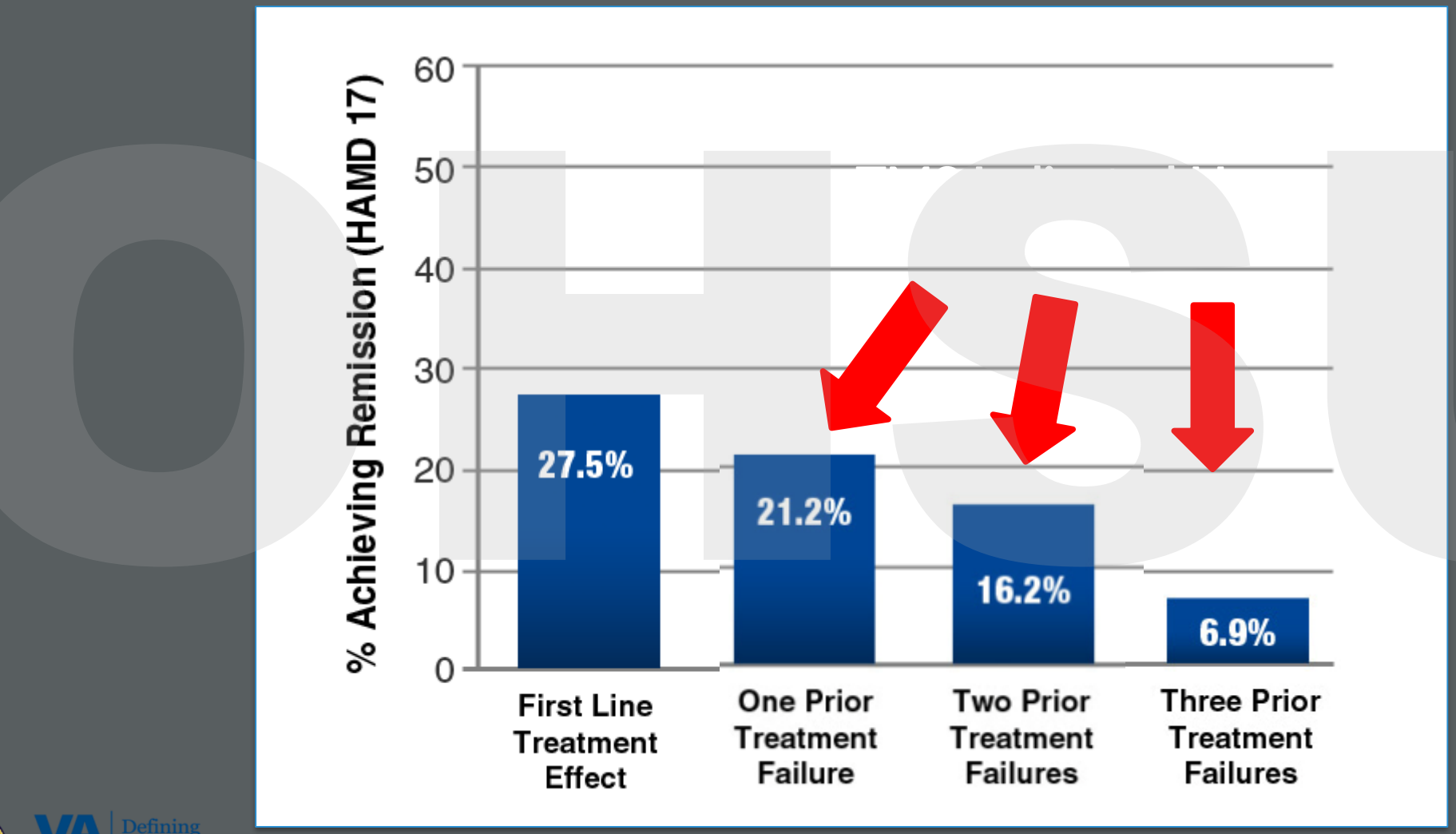
- ECT (Electroconvulsive Therapy), VNS (Vagal Nerve Stimulation); DBS (Deep Brain Stimulation), rTMS (repetitive Transcranial Magnetic Stimulation)

Antidepressant Medications

- Individual antidepressants get patients to remission about a third of the time.[1,2]
- A recent meta-analysis shows that antidepressants have only a modest effect size of approximately 0.3[3]
- With medication combinations and the development of pharmacogenomic testing we are likely improving these outcomes
- Unfortunately, many patients still do not respond to medications or do not tolerate the side effects associated with the medications

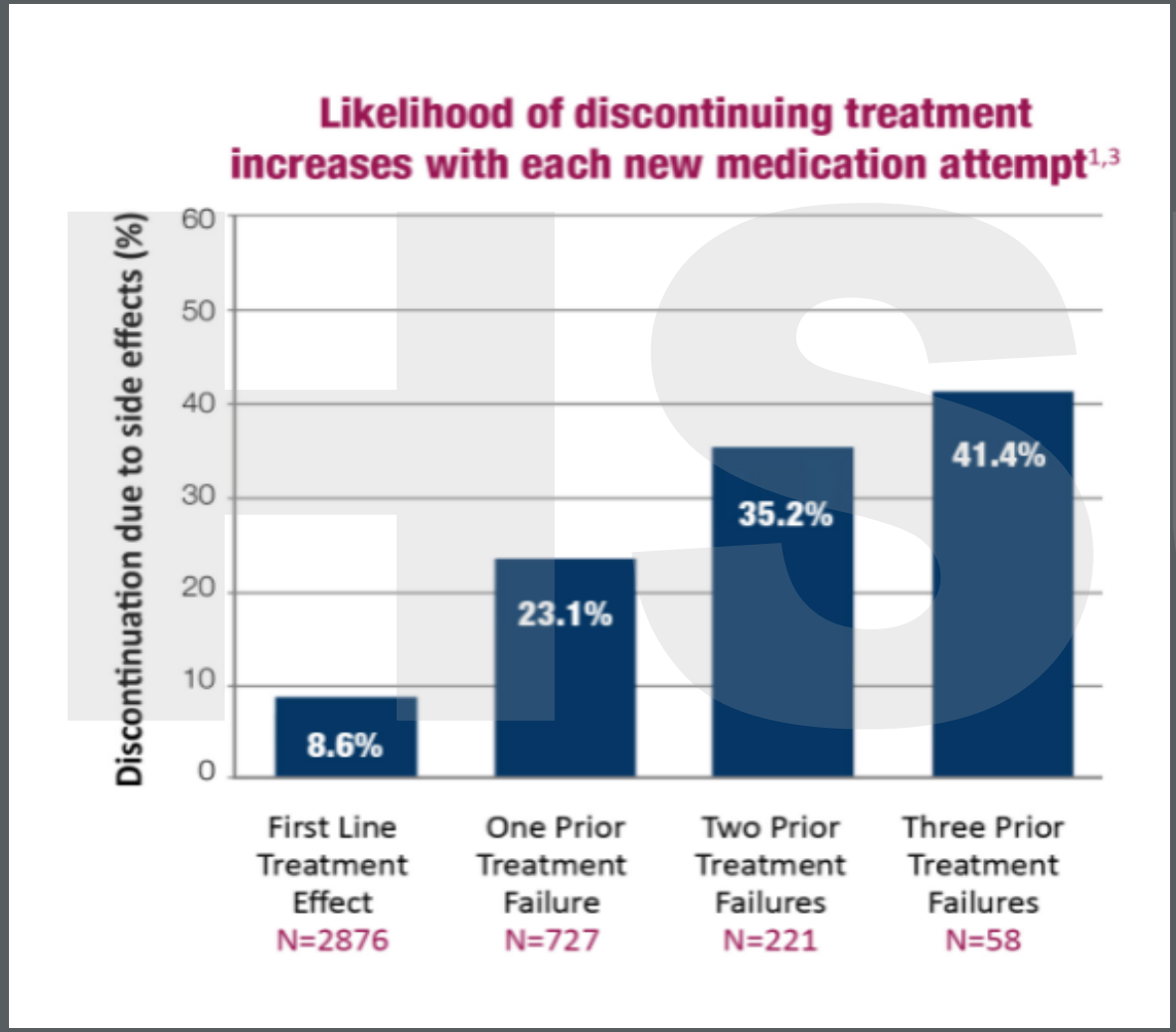
[1]Trivedi et al. (2006) *Am J Psychiatry*
[2]Fava et al. (2006) *Am J Psychiatry*
[3]Cipriani et al. (2018) *Lancet*

STAR*D Study Demonstrates Decreasing Remission With Each Treatment Failure



Trivedi et al. (2006) *Am J Psychiatry*
Fava et al. (2006) *Am J Psychiatry*

STAR*D Discontinuation rates further support the need for other treatment options



Trivedi et al. (2006) *Am J Psychiatry*
Fava et al. (2006) *Am J Psychiatry*

Advantages of TMS Over Other Treatments

- Unlike medications, TMS does not cause systemic side effects
- Unlike medications, which are prone to errors and non-adherence, TMS is an observed procedure during which proper administration is supervised
- Unlike ECT, TMS is an office-based procedure that requires no sedation, anesthesia, hospitalization or recovery time
- Unlike ECT, there are no known cognitive side effects with TMS
- Unlike VNS, TMS is non-invasive
- TMS has proven to be effective in treatment resistant depression (TRD) for patients who have not responded to several medication trials[1,2]

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[1] Carpenter et al. (2012) *Depress Anxiety*
[2] Connolly et al. (2012) *J Clin Psych*

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rTMS versus ECT

- TMS is not a replacement for ECT, but is a significantly less invasive treatment modality, and should likely be used earlier in course of depression care
- ECT is still considered best for MDD with psychotic features, acute suicidality, or catatonia
- Some patients who fail to respond to ECT respond to TMS, and vice versa[1]
- Head-to-head trials comparing ECT and TMS are not possible due to the challenge of creating double sham designs

[1] Sackeim, H. (2016) *Brain Stimulation*

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rTMS – Candidates

rTMS Therapy is FDA cleared for:

- Treatment of MDD in adult patients who have failed to receive satisfactory improvement from prior antidepressant medications at or above the minimal effective dose and duration in the current episode[1]
- Treatment of OCD with dTMS that has not responded to other modalities of treatment[2]
- Brainsway dTMS cleared for smoking cessation[3]

[1]McIntyre R et al. J Clinical Psychiatry June 2017 78:6, 703-713;
[2] Press Release from FDA August 17, 2018;
[3]Zangen A et al, World Psychiatry 20:1-8 (2021)

rTMS – Candidates

Best Practices:

- In recurrent episode of depression, inadequately treated OCD
- Multiple medication attempts, yet still symptomatic
- Prescribed a complex drug regimen
- Experience frequent side effects from medication

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rTMS – Contraindications

- Only absolute contraindication is non-removable metallic objects in or around the head
- Conductive, ferromagnetic or other magnetic sensitive metals that are implanted or are non-removable within 30 cm treatment coil

[1] Hadley et al. J ECT 2010
[2]Philip et al. Brain Stimulation. 2014
[3]Schrader et al Clin Neurophysiol 2005

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rTMS – Contraindications

- Concerns
  - Implanted electrodes/ stimulators
  - Deep Brain Stimulator
  - Aneurysm clips or coils
  - Cochlear implants
  - Intracranial Stents
  - Vagus Nerve Stimulators (per package insert vs. practical implementation)[1, 2, 3]

[1] Hadley et al. J ECT 2010
[2] Philip et al. Brain Stimulation. 2014
[3] Schrader et al Clin Neurophysiol 2005

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rTMS side effects – most common adverse events with all coils (< 5% incidence)

- Application site discomfort/pain
- Headache
- Referred (eye, tooth, jaw) discomfort/pain
- Insomnia
- Anxiety

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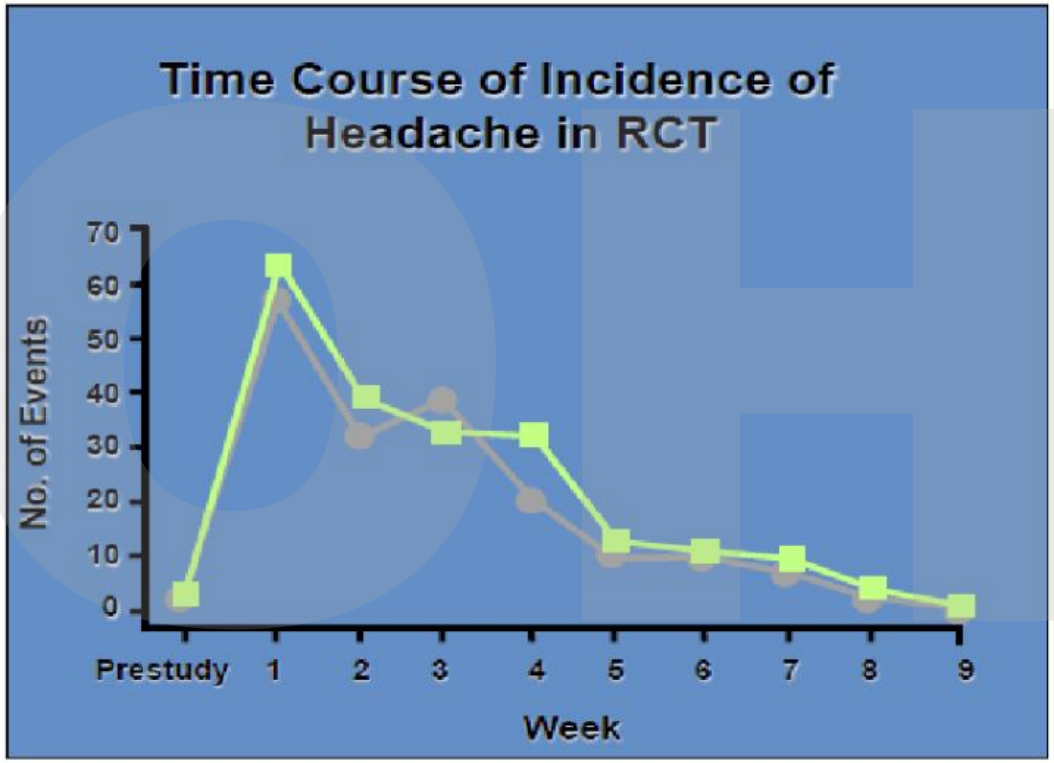
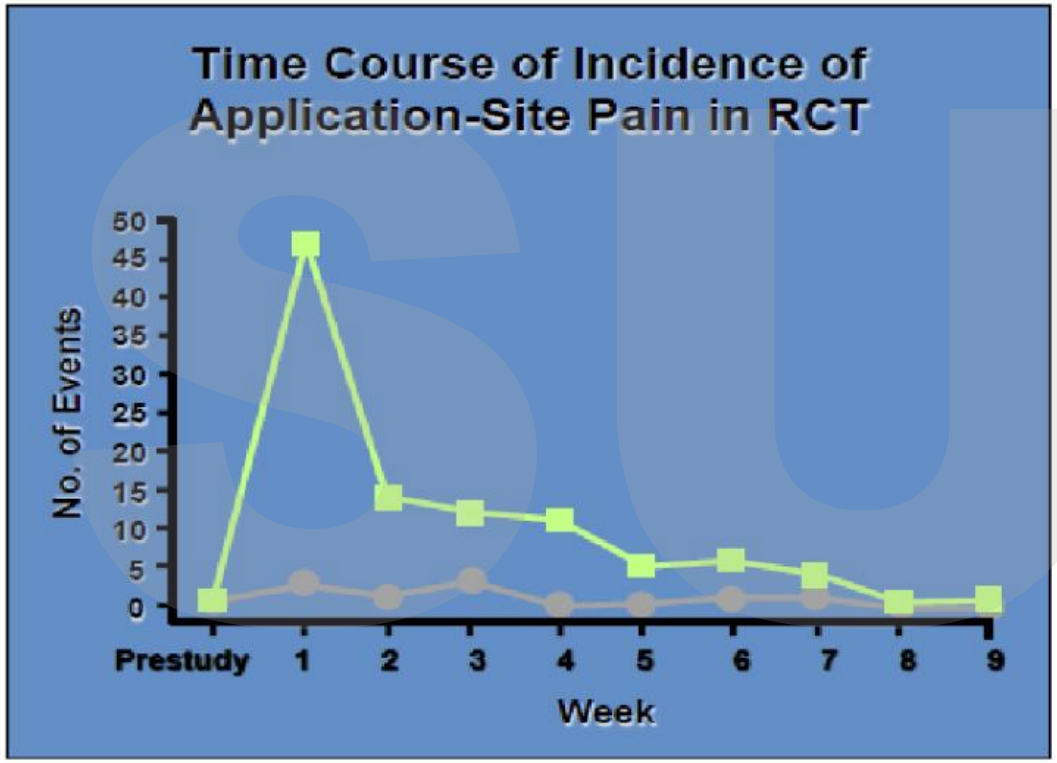
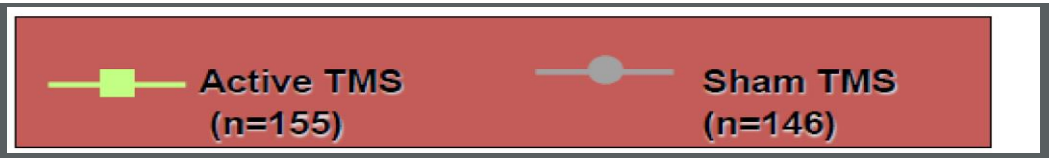
rTMS side effects – most common adverse events with all coils (< 5% incidence)







Janicak et al. (2008) *J Clin Psychiatry*

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Rare, but Serious Adverse Events That Have Been Studied

Treatment Emergent Mania

- Study reviewed 10 of 53 TMS studies involving both depressed and bipolar patients.
  - Early pooled data reported treatment emergent mania was 0.84% for active treatment group and 0.73% for sham group
  - This difference was not statistically different
  - The switch rate for unipolar patients was 0.34%
  - The switch rate for bipolar patients was 3.1%

Xia et al. (2008) *International Journal of Neuropsychopharmacology*

Emergence of Suicidal Ideation: Multicenter Study

- Treatment emergent disease exacerbation

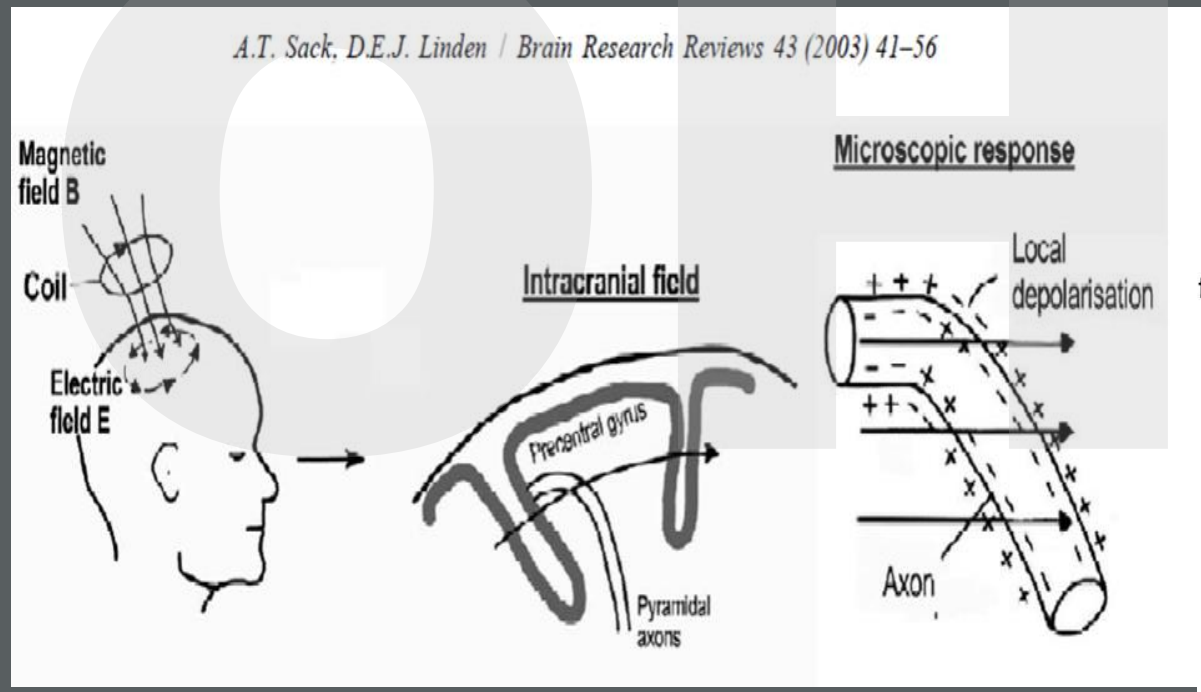
  Population with increased severity of clinical condition

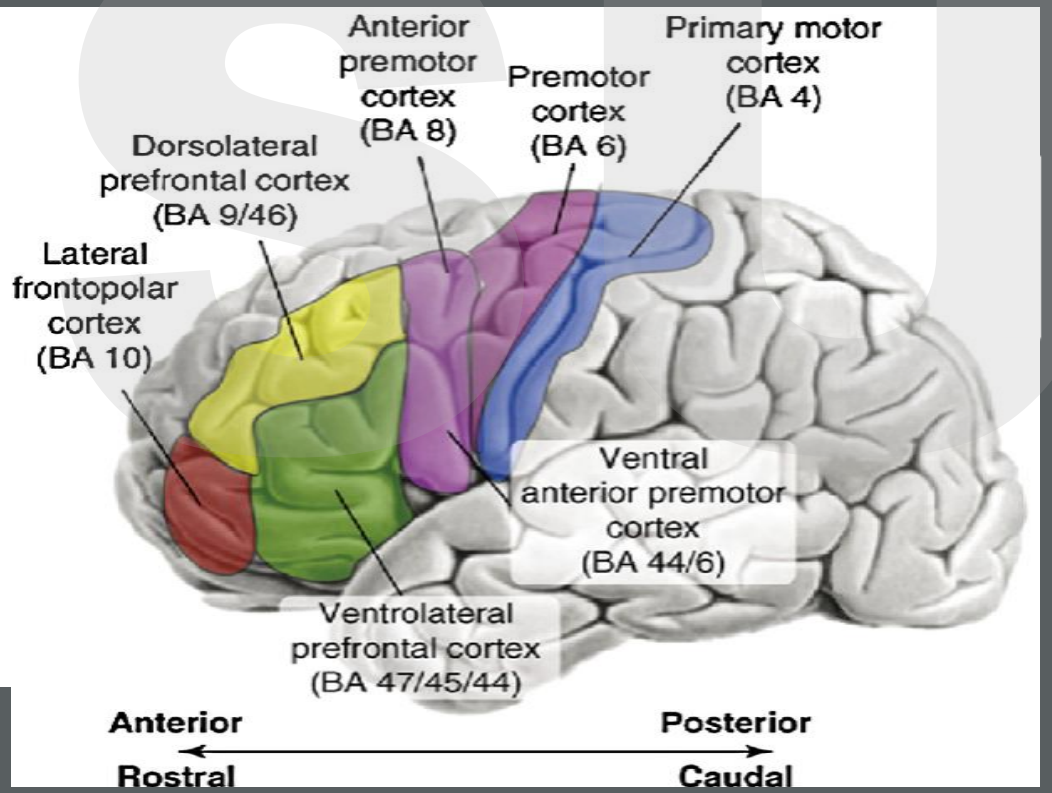
  Most commonly reported event
- 1.9% with sham; 0.6% active TMS
- One non-lethal overdose in sham treatment group

Janicak et al. (2008) *J Clinical Psychiatry*

TMS and Seizures

- Seizure is the most serious side effect associated with TMS The risk of seizures is < 0.1% per treatment course.





Dumontheil. (2014) *Developmental Cognitive Neuroscience*

TMS and Seizures

- Most cases associated with TMS were prior to the publication of the TMS safety guidelines in 1998 [1]
- In a multi-site survey of active TMS labs and clinics from 2012-16, TMS delivered within published guidelines to individuals without risk factors appears to cause fewer than 1 seizure per 60,000 sessions[2]
- The risk is less than or comparable to risk of seizure associated with antidepressant medications [3]
- All reported TMS induced seizures have occurred during treatment session, been self limited, had no sequelae, and no progression to a seizure disorder

[1] Wassermann. (1998) *Electroencephalography and Clinical Neurophysiology*
[2] Lerner et al. (2019) *Clinical Neurophysiology*
[3] George et al. (2013) *Curr Opin Psychiatry*

Hearing Loss

- Small Proportion of adult humans have experienced transient increases in auditory thresholds[1]
- Permanent threshold shift in a single patient who did not wear ear plugs and was stimulated with H1 coil [2]
- Majority of studies which hearing protection was used report no changes in hearing after TMS[3]
- Recommendations: Patients, visitors and TMS Technicians are required to use earplugs that meet a minimum standard of 30dB of protection

[1]Loo et al. (2001) *Biol Psychiatry*;
[2]Zangen et al. (2005) *Clin Neurophysiol*;
[3]Folmer et al. (2006) *Acta Otolaryngol*;
Rossi et al. (2007) *J Neurol Neurosurg Psychiatry*
Janicak et al. (2008) *J Clin Psychiatry*

Clinical application of TMS

From: magstim.com

Applications of TMS

Box 4 | **Conditions treated with rTMS**

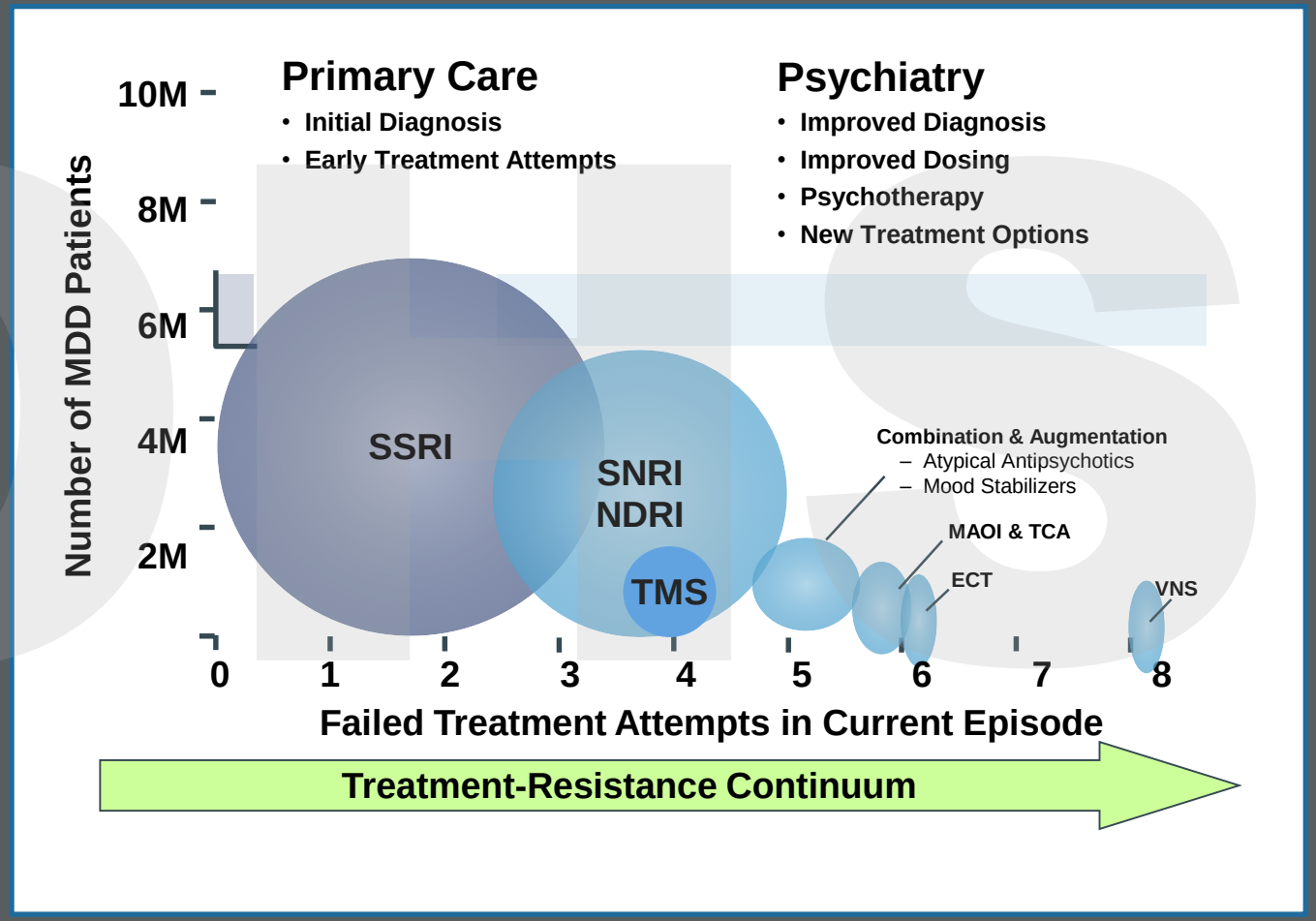
Below is a list of some of the conditions in which repetitive transcranial magnetic stimulation has been used with reported success, with references to examples of such work.

Stroke[54,60–63]
Parkinson's disease[64,65]
Depression[37,38,41]
Dystonia[66–68]
Tinnitus[48,49]
Neurogenic pain[69,70]
Epilepsy[71–74]
Amyotrophic lateral sclerosis[75]
Schizophrenia[46,47]
Addiction[76,77]
Obsessive-compulsive disorder[78,79]
Tourette's syndrome[80]
Memory dysfunction[81]

Ridding et. al. *Nature Reviews Neuroscience*. 2007 (8) 559-567

Depression treatment

rTMS – Clinical application for MDD



Evidence supporting the use of rTMS in MDD

Four large-scale studies (sample sizes > 100), 3 studies patients off medications and 1 study patients on medications concurrently

- Two large multicenter industry supported trials that lead to FDA approval for two devices[1,2]
- NIH-funded study[3] with dosage parameters similar to those in the industry-sponsored study but with sham design enhancements
- European study of the augmentation effects of TMS when used in combination with pharmacotherapy[4]
- Naturalistic study suggests 1 in 2 pts respond and 1 in 3 achieve remission [5]

[1]O'Reardon et al. (2008) *Biological Psychiatry*
[2]Levkovitz et al. (2015) *World Psychiatry*
[3]George et al. (2010) *Archives of General Psychiatry*
[4]Herwig et al. (2007) *British Journal Psychiatry*
[5]Carpenter et al. (2012) *Depression and Anxiety*

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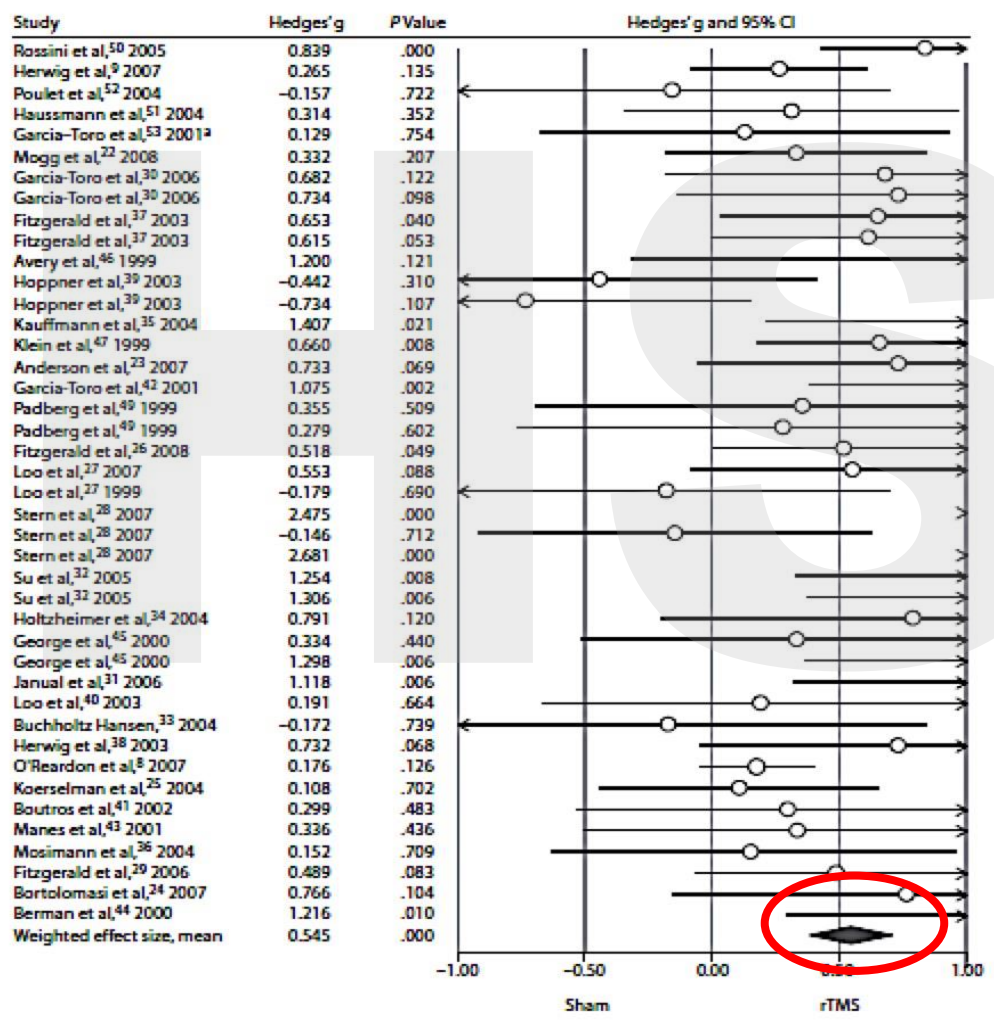
Evidence supporting the use of rTMS in MDD

Figure 1. rTMS for Depression, Results of the Meta-Analysis



[a]Add-on therapy.
Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

Slotema et al. (2010) *J Clin Psychiatry*

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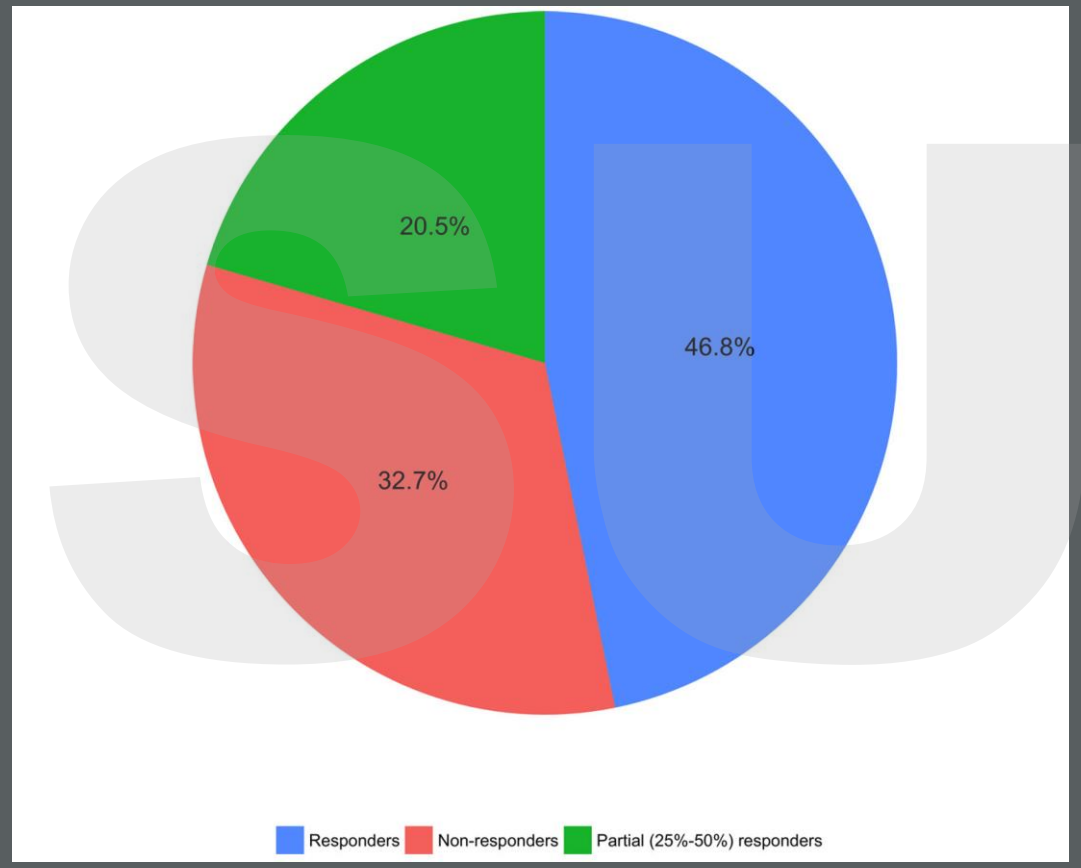
Evidence supporting the use of rTMS in MDD

- rTMS may have a 60% response rate
- Reality is more nuanced



Fitzgerald et. al. *Depression Anxiety*, 2016.33. 746-753

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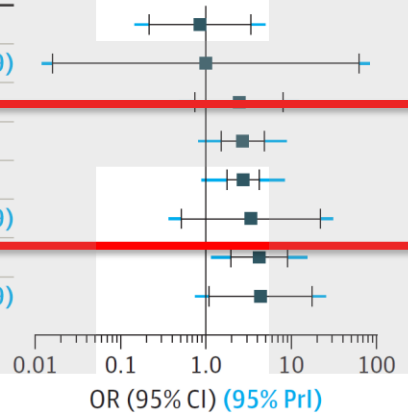
Evidence supporting the use of rTMS in MDD

Figure 3. Forest Plot Showing the Network Relative Odds Ratios (ORs) With Their 95% CIs and Predictive Intervals (PrI)

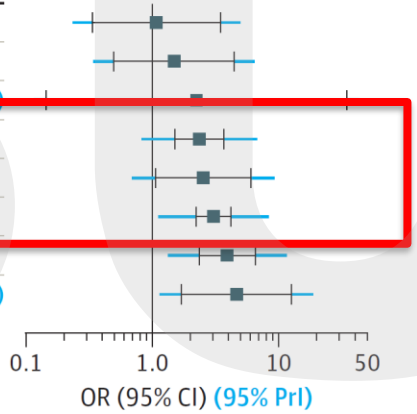
A Remission

Active Device	OR (95% CI) (95% PrI)
sTMS	0.85 (0.22-3.35) (0.15-4.94)
aTMS	1.00 (0.02-62.31) (0.01-83.19)
dTMS	2.45 (0.74-8.07) (0.49-12.28)
LF-rTMS	2.70 (1.51-4.82) (0.82-8.89)
HF-rTMS	2.73 (1.78-4.20) (0.89-8.40)
TBS	3.37 (0.52-22.05) (0.37-30.69)
Bilateral rTMS	4.22 (1.96-9.05) (1.15-15.47)
pTMS	4.37 (1.10-17.47) (0.74-25.69)



B Response

Active Device	OR (95% CI) (95% PrI)
sTMS	1.08 (0.34-3.49) (0.24-4.98)
dTMS	1.49 (0.50-4.47) (0.34-6.48)
aTMS	2.25 (0.14-35.03) (0.12-42.39)
LF-rTMS	2.37 (1.52-3.68) (0.83-6.78)
TBS	2.54 (1.07-6.05) (0.70-9.32)
HF-rTMS	3.07 (2.24-4.21) (1.12-8.37)
Bilateral rTMS	3.96 (2.37-6.60) (1.34-11.70)
pTMS	4.66 (1.70-12.77) (1.15-18.91)



aTMS indicates accelerated TMS; dTMS, "deep" (H-coil) TMS; HF, high frequency; LF, low frequency; pTMS, priming TMS; sTMS, synchronized TMS; TBS, θ-burst stimulation.

Brunoni et. al. *JAMA Psychiatry*, 2016.74:(8). 559-567

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Obsessive Compulsive Disorder

Evidence supporting the use of rTMS in OCD

- Many (40-60%) patients do not show clinically meaningful response to an SSRI, with only a third showing response after switching to another SSRI***
- Other treatment strategies, including augmentation with medication (antipsychotics) and Cognitive Behavioral Therapies like DBT, ERP and ACT, may help, but many patients remain symptomatic and impaired***
- Same limitations with medication side effects as those reviewed with the treatment of depression
- Psychosurgery comes with risk of severe complications

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OCD treatment

Right Prefrontal Repetitive Transcranial Magnetic Stimulation in Obsessive-Compulsive Disorder: A Double-Blind, Placebo-Controlled Study

Pino Alonso, M.D.
Jesús Pujol, M.D., Ph.D.
Narcís Cardoner, M.D.
Luisa Benlloch, M.D.
Joan Deus, Ph.D.
José M. Menchón, M.D., Ph.D.
Antoni Capdevila, M.D., Ph.D.
Julio Vallejo, M.D., Ph.D.

Objective: The efficacy of repetitive transcranial magnetic stimulation (rTMS) of the right prefrontal cortex for patients with obsessive-compulsive disorder (OCD) was studied under double-blind, placebo-controlled conditions.

Method: Patients were randomly assigned to 18 sessions of real (N=10) or sham (N=8) rTMS. Treatments lasted 20 minutes, and the frequency was 1 Hz for both conditions, but the intensity was 110% of motor threshold for real rTMS and 20% for the sham condition.

Results: No significant changes in OCD were detected in either group after treatment. Two patients who received real rTMS, with checking compulsions, and one receiving sham treatment, with sexual/religious obsessions, were considered responders.

Conclusions: Low-frequency rTMS of the right prefrontal cortex failed to produce significant improvement of OCD and was not significantly different from sham treatment. Further studies are indicated to assess the efficacy of rTMS in OCD and to clarify the optimal stimulation characteristics.

(Am J Psychiatry 2001; 158:1143–1145)

Alonso et. al. *AJP*. 2001 158: 1143-1145.

OCD treatment

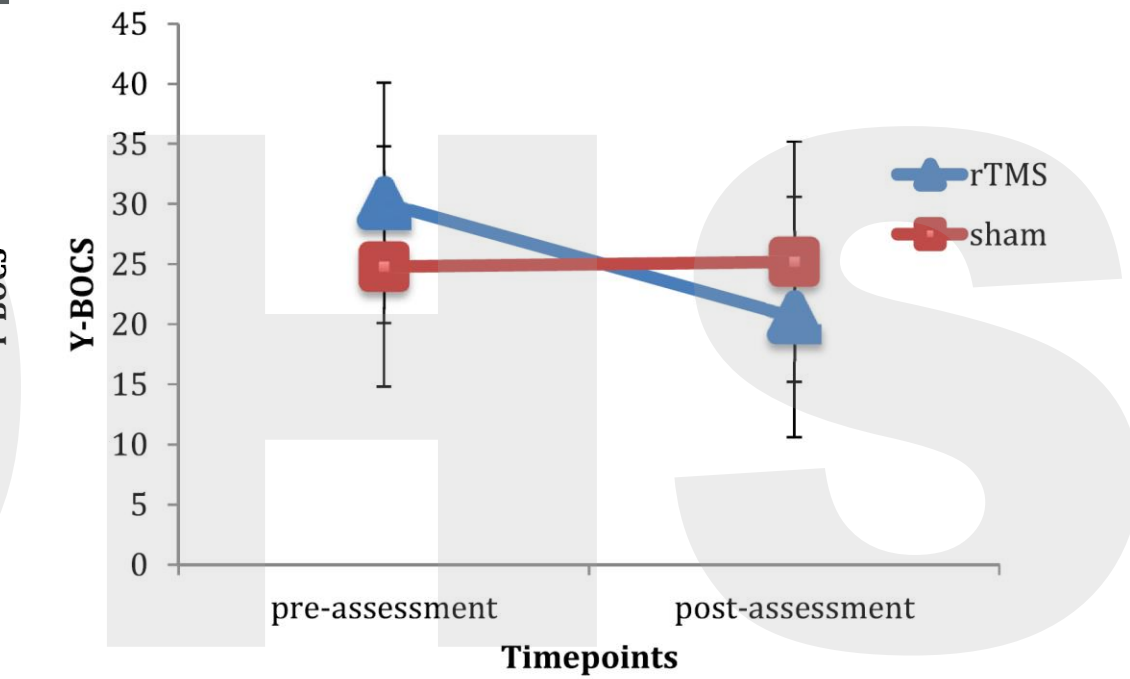
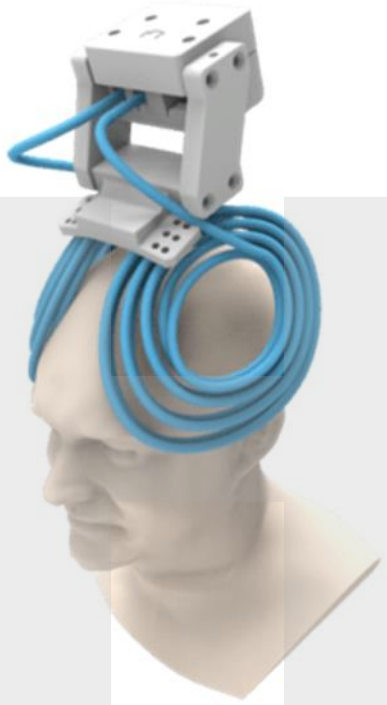


Fig. 2. Y-BOCS values decreased significantly over time in the rTMS condition, but not in the sham condition.

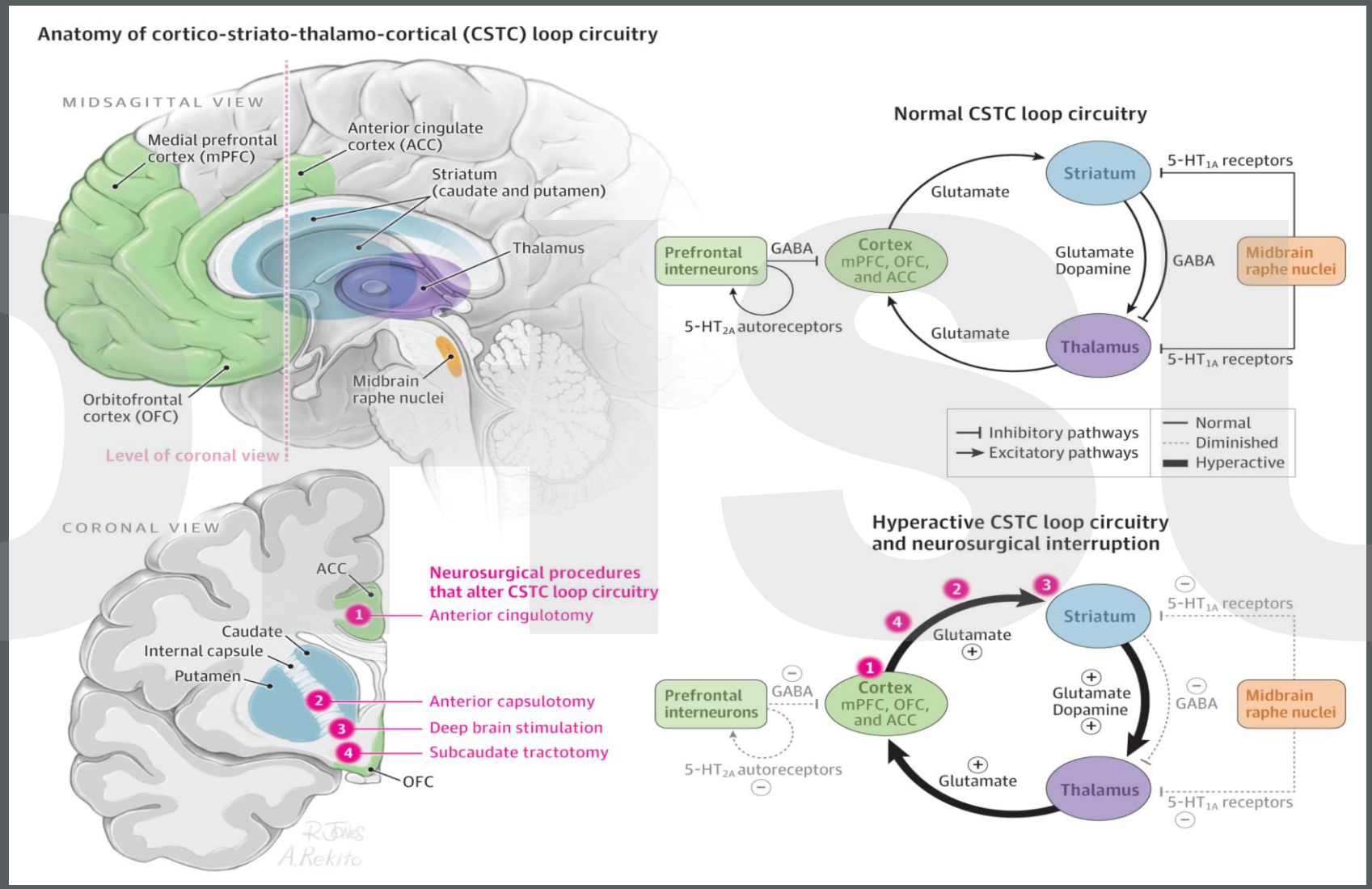
Haghgigi et. al. *J Psychiatr Res.* 2015 Sep;68:238-44.

OCD treatment



H7-Coil
for Obsessive-Compulsive Disorder (OCD)

Evidence supporting the use of rTMS in OCD



Dougherty et al. (2018) *JAMA Psychiatry*

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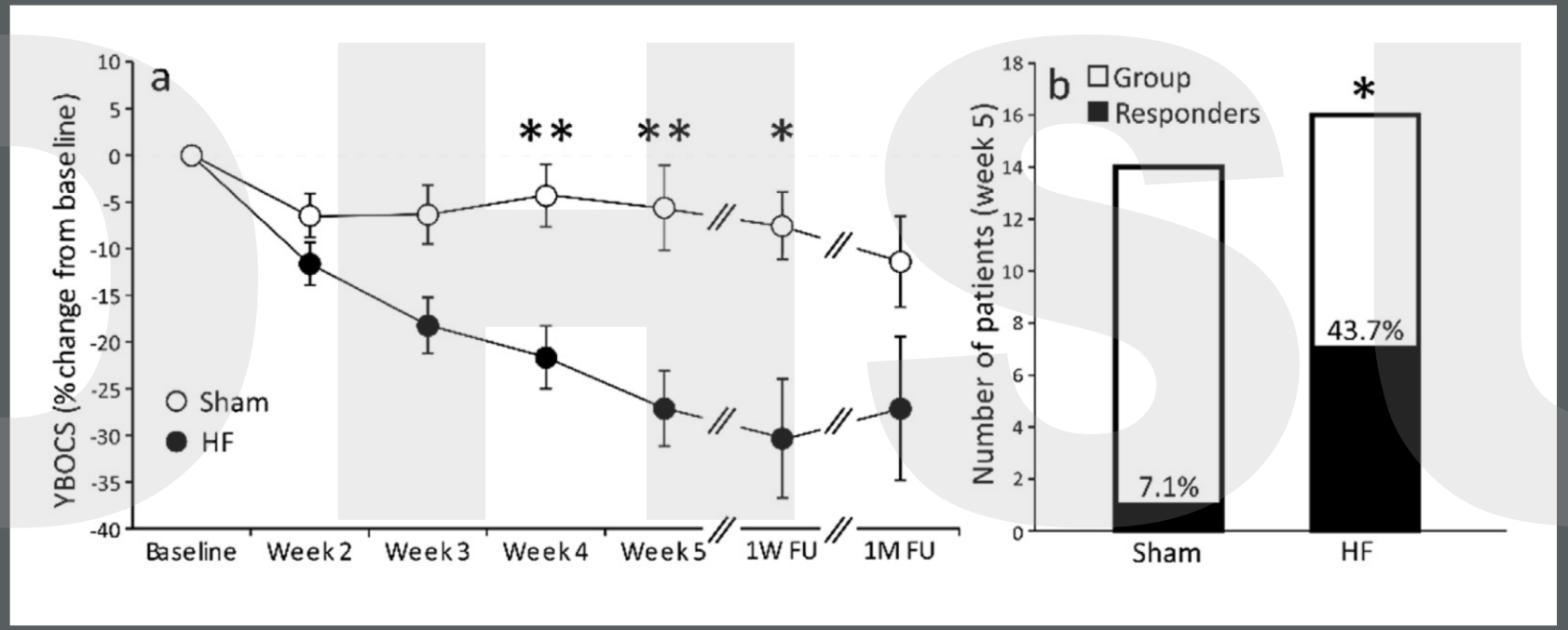
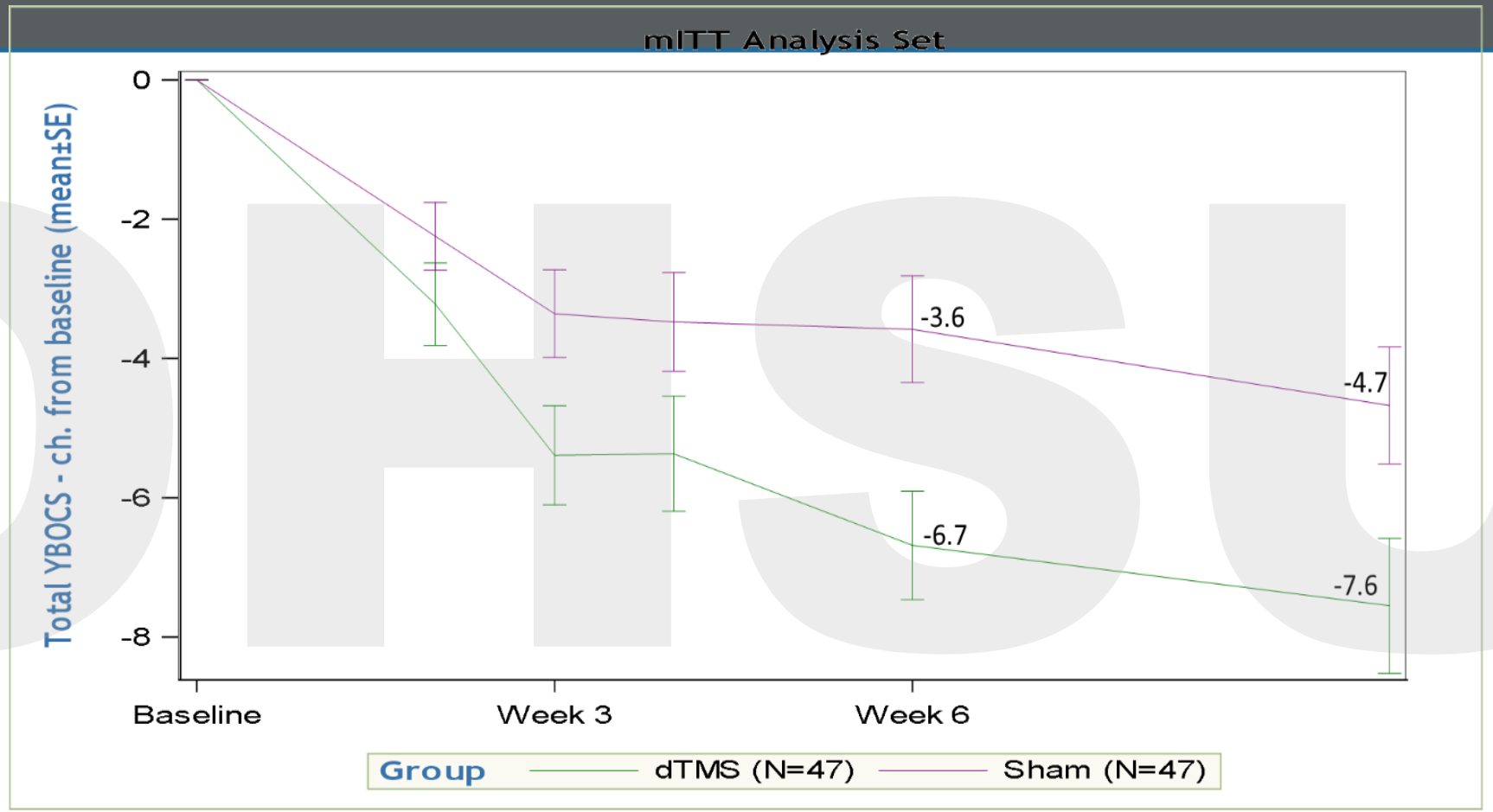
OCD treatment



Carmi et. al. *Brain Stim.* 2018 11, 158-165.

Evidence supporting the use of rTMS in OCD



YBOCS adjusted mean change difference from baseline to week 6: p=0.0157

Carmi et al. (2019) American Journal of Psychiatry

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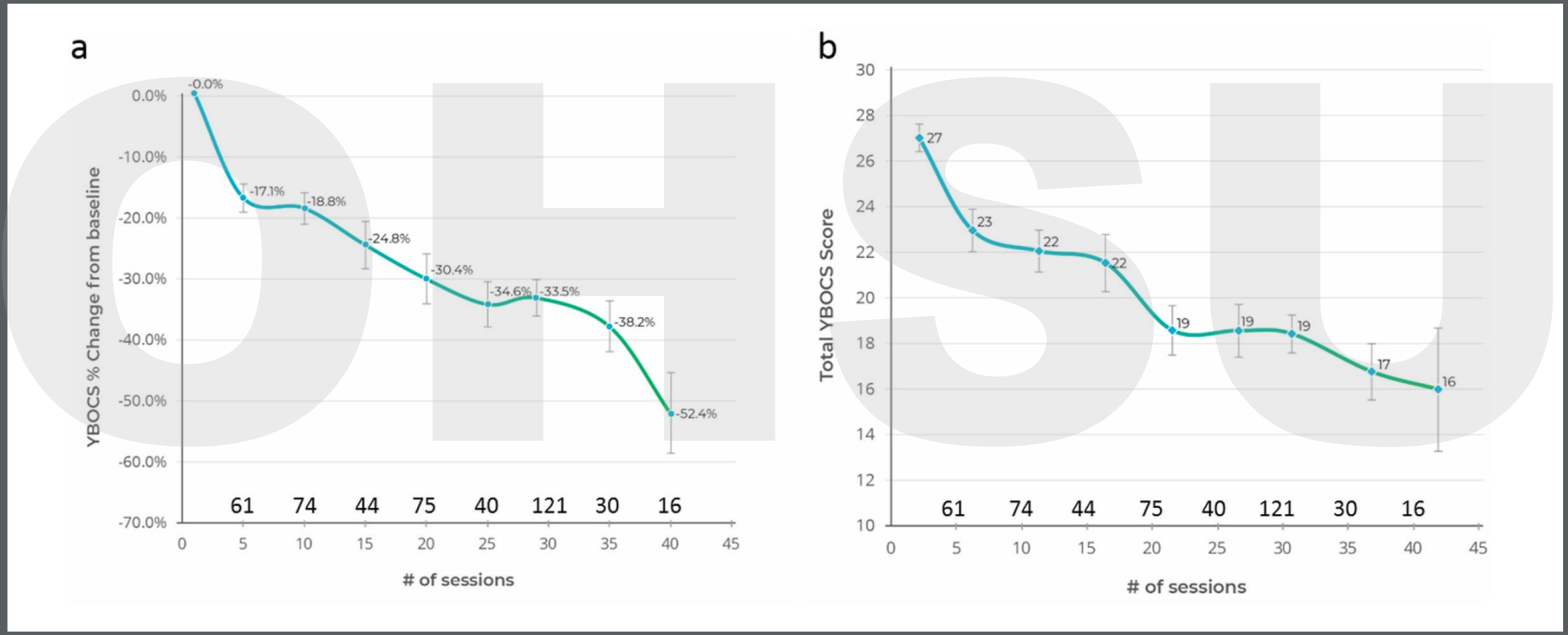
Evidence supporting the use of rTMS in OCD



Roth et al. (2021) Journal of Psychiatric Research

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Smoking Cessation

H4-Coil
for Smoking
Cessation

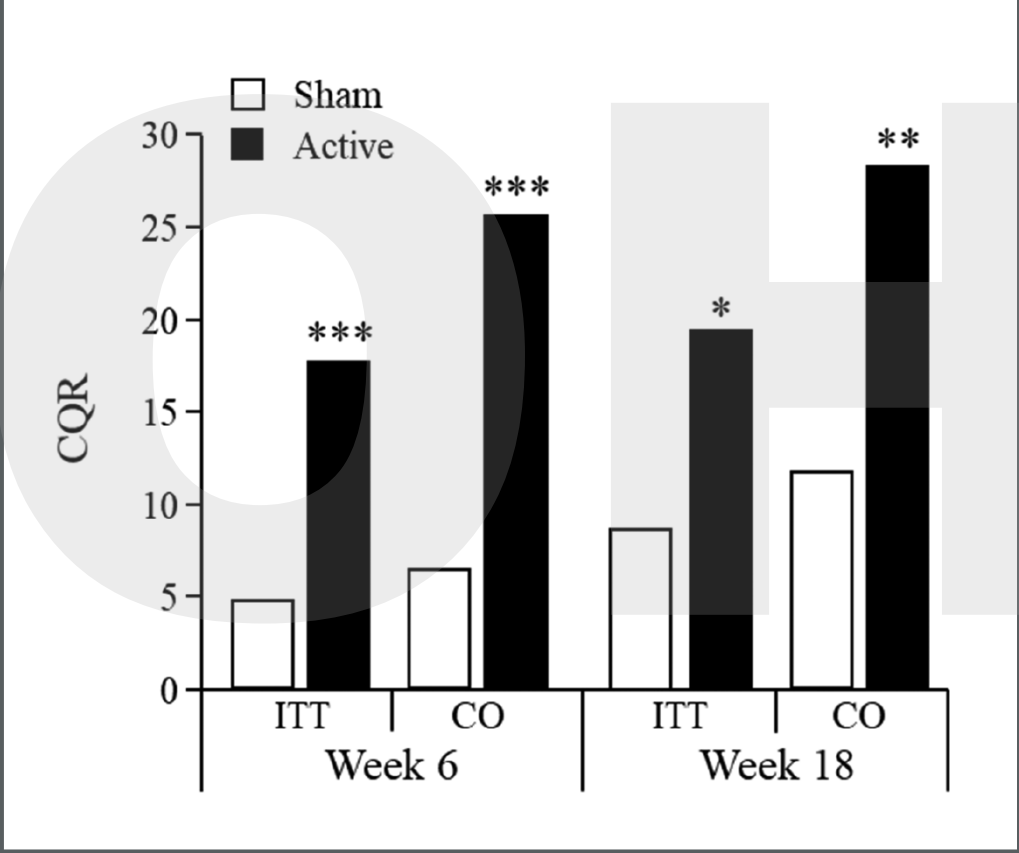
Smoking Cessation

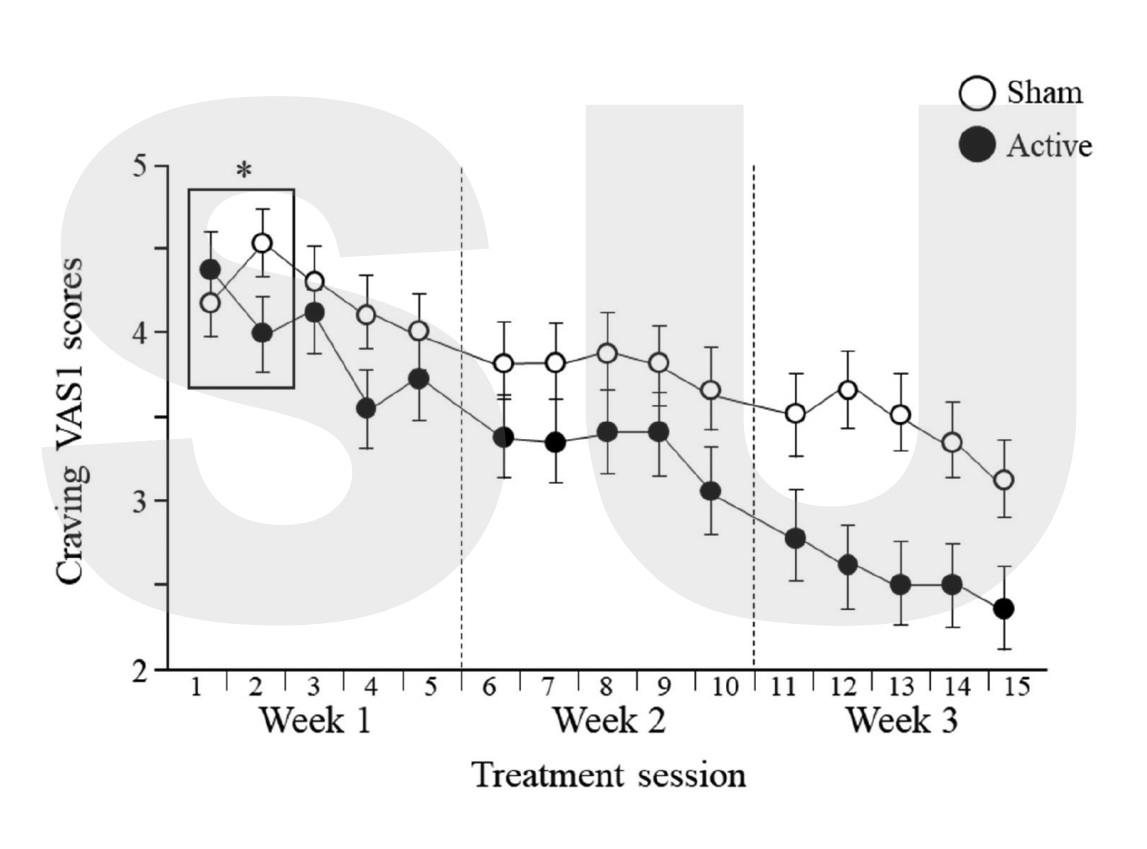
Repetitive transcranial magnetic stimulation for smoking cessation: a pivotal multicenter double-blind randomized controlled trial

Abraham Zangen[1], Hagar Moshe[1], Diana Martinez[2], Noam Barnea-Ygael[1], Tanya Vapnik[3], Alexander Bystritsky[3], Walter Duffy[4], Doron Toder[1,5], Leah Casuto[6], Moran Lipkinsky Grosz[7], Edward V. Nunes[2], Herbert Ward[8], Aron Tendler[9], David Feifel[10], Oscar Morales[11], Yiftach Roth[1], Dan V. Iosifescu[12], Jaron Winston[13], Theodore Wirecki[14], Ahava Stein[15], Frederic Deutsch[16], Xingbao Li[17], Mark S. George[17,18]

Zangen et. al. *World Psych* 2021 20, 1-8.

Smoking Cessation





Zangen et. al. *World Psych* 2021 20, 1-8.

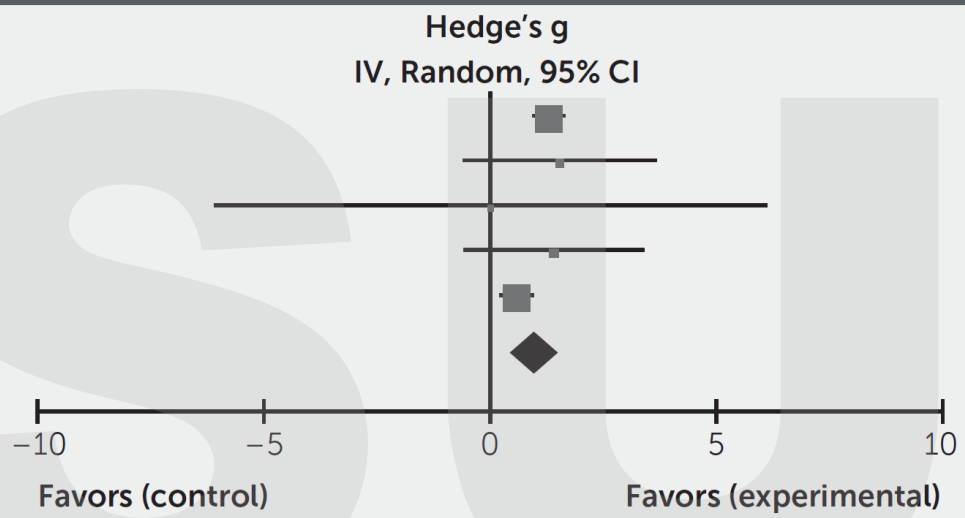
Smoking Cessation

Study or Subgroup	Hedge's g	SE	Weight	Hedge's g IV, Random, 95% CI
Amiaz 2009 (1)	1.538	1.0934	5.2%	1.54 (−0.61, 3.68)
Amiaz 2009 (2)	1.297	0.1872	44.4%	1.30 (0.93, 1.66)
Dinur-Klein L 2014 (3)	0.009	3.1194	0.7%	0.01 (−6.10, 6.12)
Li 2013	1.408	1.0163	5.9%	1.41 (−0.58, 3.40)
Pripfl 2014	0.586	0.1918	43.9%	0.59 (0.21, 0.96)
Total (95% CI)			**100.0%**	**1.00 (0.48, 1.51)**

Heterogeneity: $Tau^2=0.12$; $Chi^2=7.61$, df=4 (P=0.11); $I^2=47\%$

Test for overall effect: Z=3.82 (P=0.0001)

Footnotes
(1) VAS
(2) sTCQ
(3) High frequency rTMS



Maiti et. al. J Neuropsychiatry Clin Neurosci. 2016 Oct 6:appineuropsych16040065.

Summary

- rTMS is a form of neuromodulation that targets components of the central executive network and reduces input from networks associated with depression.
- rTMS is an effective approach for treatment resistant depression with minimal side effects
- Candidates may have failed two or more medications, have no risk factors for seizures and no ferromagnetic devices in their chest, neck or head.
- TMS can also be used to treat OCD and smoking cessation, but the data is not nearly robust

Thank You

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