MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Targeting brain circuits with non-invasive brain stimulation

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Instructor, Harvard Medical School

Outline

- rTMS for Depression
- rTMS for OCD
- Theta Burst Stimulation
- Accelerated Protocols
- Combining Therapies to Improve Outcomes
- Transcranial Direct Current Stimulation

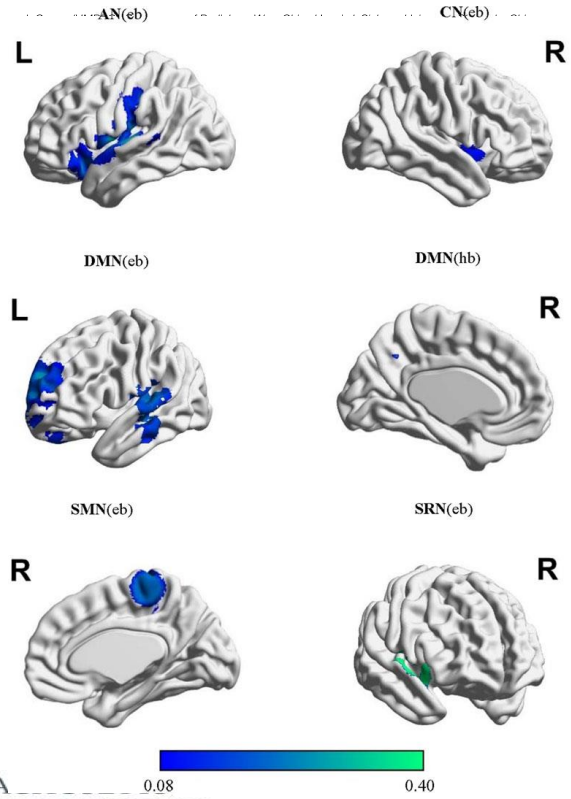
Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Psychiatric disorders are disorders of neural circuits

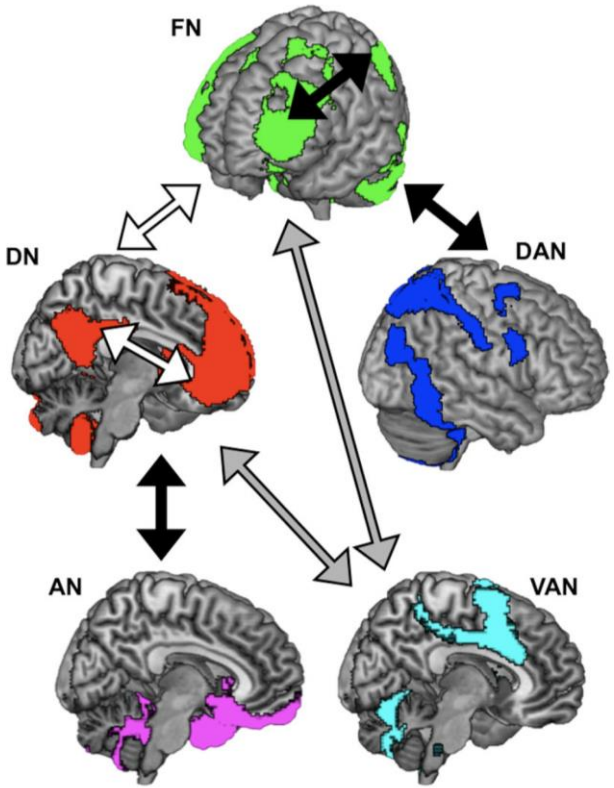
Dysconnectivity of Multiple Brain Networks in Schizophrenia: A Meta-Analysis of Resting-State Functional Connectivity

Siyi Li[1,2†], Na Hu[2†], Wenjing Zhang[1,2], Bo Tao[1,2], Jing Dai[3], Yao Gong[4], Youguo Tan[5], Duanfang Cai[5] and Su Lui[1,2]*



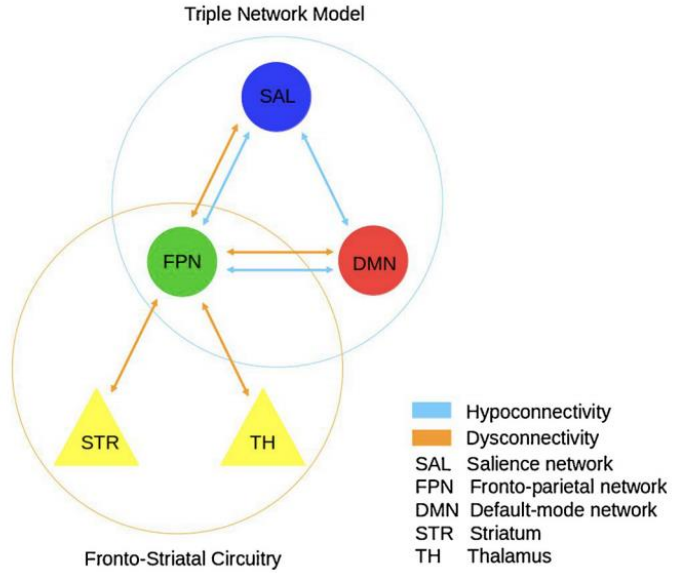
Large-scale network dysfunction in Major Depressive Disorder: Meta-analysis of resting-state functional connectivity

Roselinde H. Kaiser, Ph.D.[1,*], Jessica R. Andrews-Hanna, Ph.D.[2], Tor D. Wager, Ph.D.[2], and Diego A. Pizzagalli, Ph.D.[1]



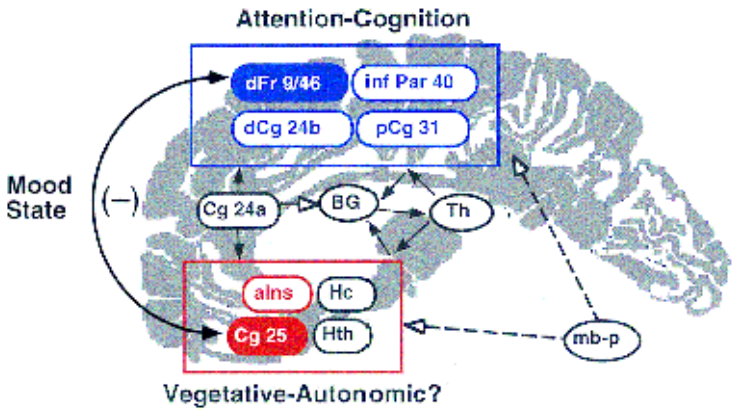
Frontoparietal areas link impairments of large-scale intrinsic brain networks with aberrant fronto-striatal interactions in OCD: a meta-analysis of resting-state functional connectivity

Deniz A. Gürsel[a,b,*,1], Mihai Avram[a,b,1], Christian Sorg[a,b,c], Felix Brandl[a,b,2], Kathrin Koch[a,b,2]



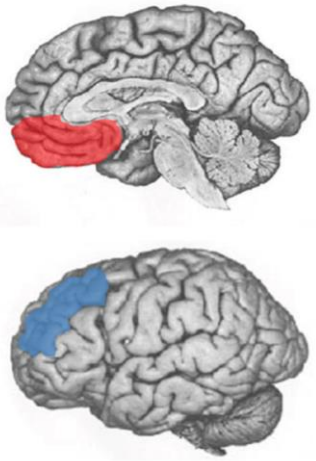
Circuit-based Interventions: need to know…

The circuit(s)



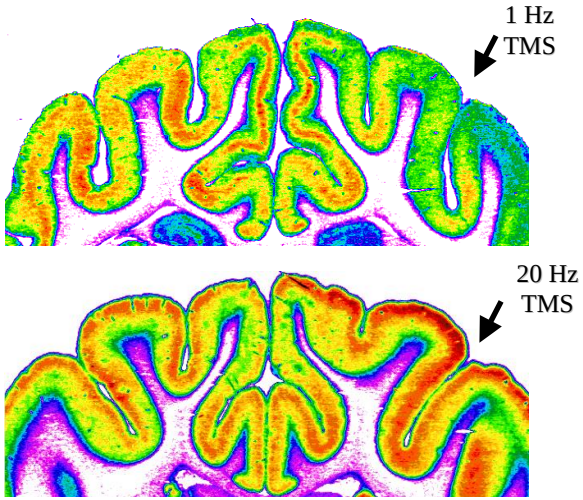
Mayberg et al., 2010

The target(s)



Koenigs et al. 2009

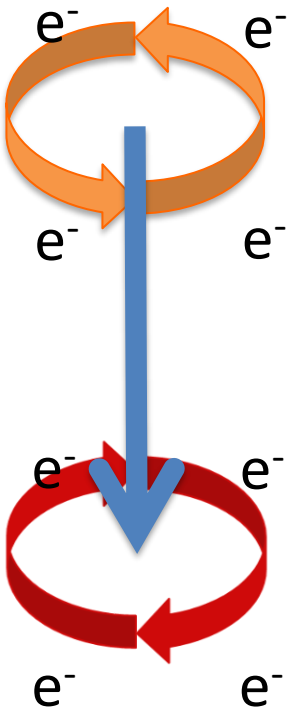
Direction of modulation



Valero Cabre et al., 2008

Transcranial Magnetic Stimulation

1831 Faraday's Electromagnetic Induction

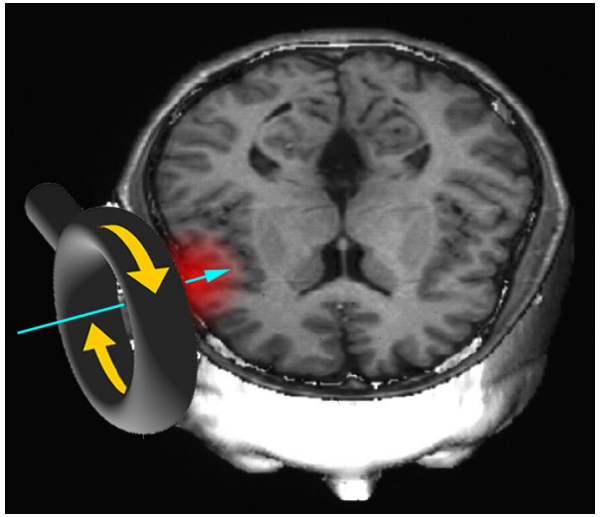


Primary Electric Current

Magnetic Field

Secondary Electric Current

Anthony Barker 1984



Transcranial Magnetic Stimulation

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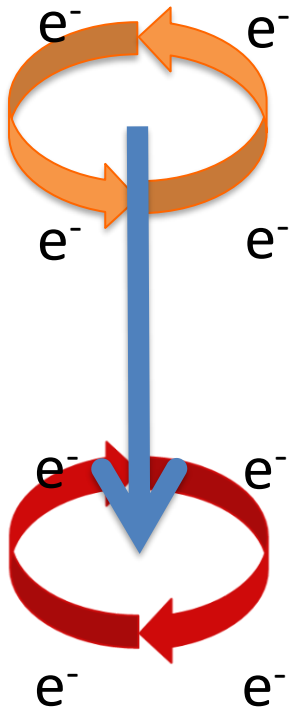

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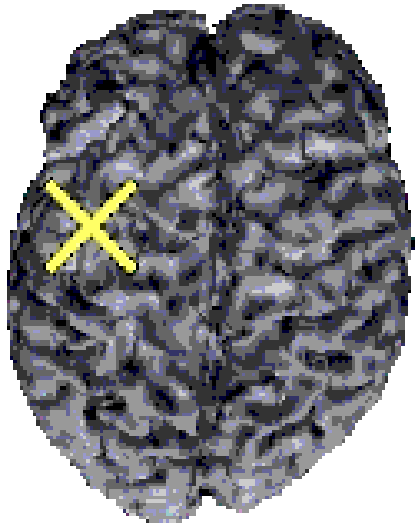
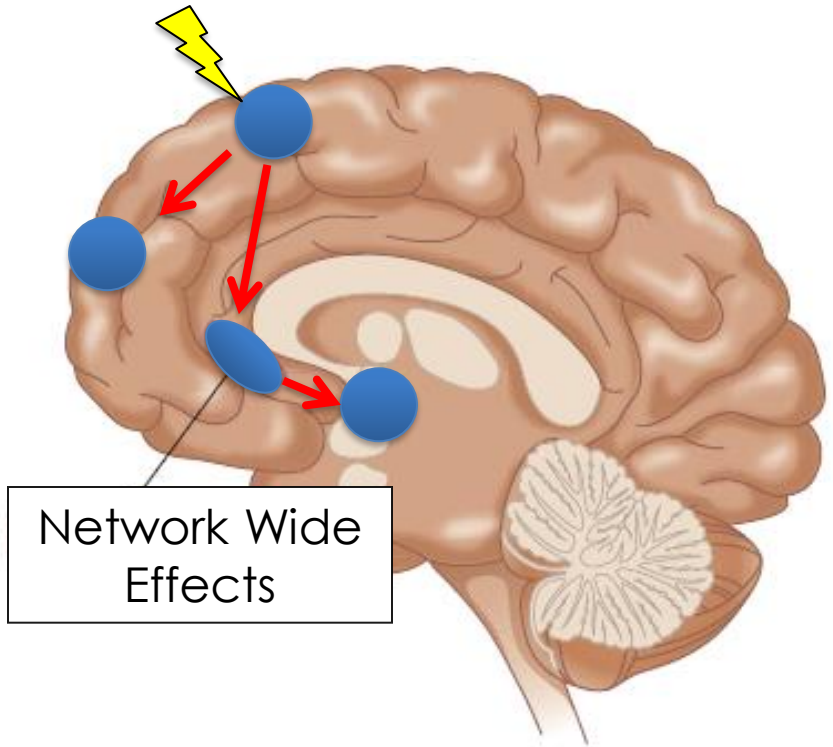


What is Transcranial Magnetic Stimulation (TMS)?

- Safe
- Noninvasive
- Nonconvulsive
- Neuromodulation therapy
  - Changes neural excitability and activity

TMS Theory

- Target treatment to a specific, affected region
- Changes spread to other regions
- Effects are network wide
- Repeated treatments lead to lasting effects

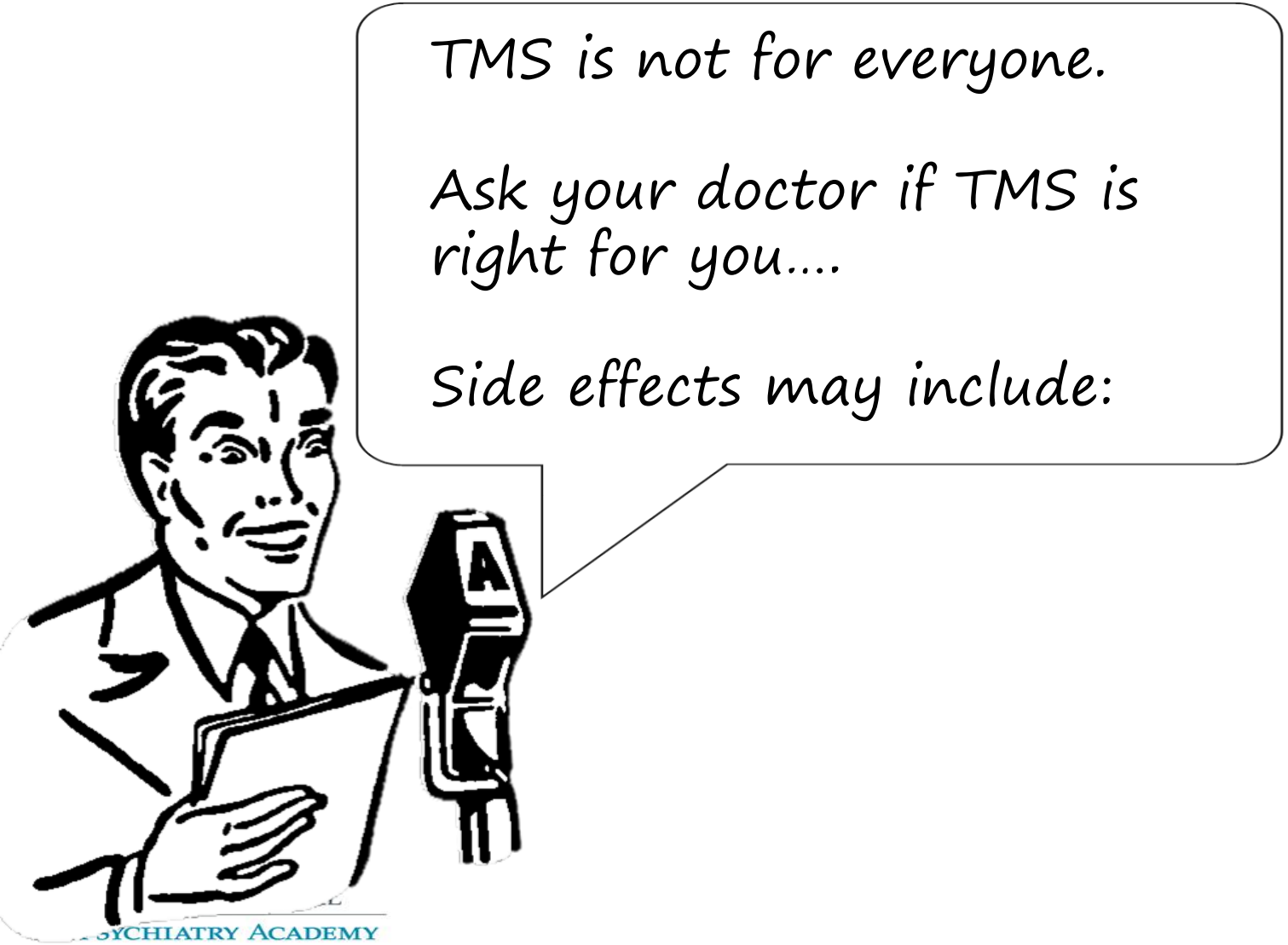


Liston 2014

TMS Parameters

1) Location (low tech vs. neuronavigation)
2) Focality & Depth (coil selection)
3) Frequency (up- or downregulate)
4) Intensity (relative to stimulator or subject)
5) Duration (number of pulses / sessions)

Potential Side Effects of TMS



- Headache
- Pain/Discomfort
- Nausea
- Syncope
- Psychiatric Symptoms
- Fatigue
- Hearing Loss
- Seizure

Rossi et al, 2009

TMS Safety

CONTRAINDCATION

- Cochlear Implant

EXERCISE CAUTION

- Pacing device
- Aneurysm clips
- History of Seizure
- Intracranial lesions

CONSIDER RISK

- Medications
- Age
- Hearing impairment
- Pregnancy

TMS – Basic Equipment

MagVenture © System

Brainsway © System

Treatment Logistics

- Remain **awake** during treatment
- No restrictions on activity
- Initial treatment course: five daily treatment per week (M-F) for 4-6 weeks
- Taper period: 1-3 treatments per week
- Daily treatment duration: 3 - 30 minutes
- A tapping sensation is experienced
- A clicking noise accompanies each electromagnetic pulse

Magventure ©

Current Therapeutic Uses

FDA Approved

- Unipolar Depression
- Obsessive Compulsive Disorder
- Migraine with Aura
- Smoking Cessation

Investigative

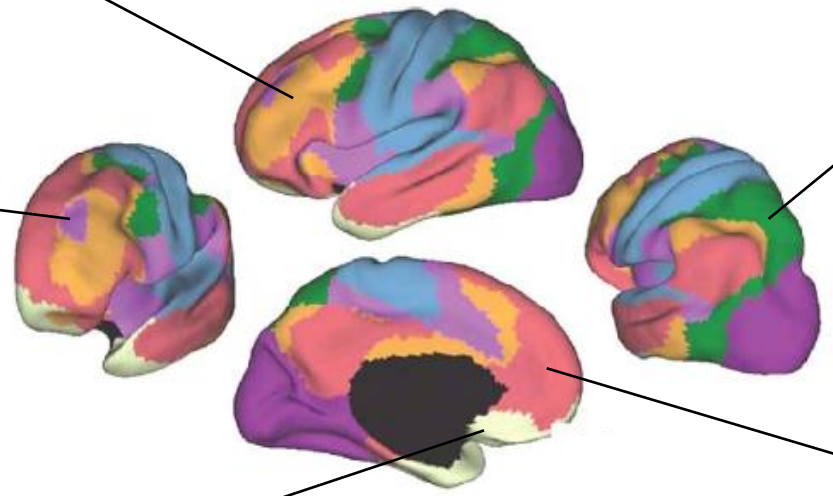
- Auditory Hallucinations
- Post Traumatic Stress Disorder
- Generalized Anxiety Disorder
- Tourette Syndrome
- Bipolar Depression
- Autism
- Neurorehabilitation
- Parkinson Disease
- Alzheimer Disease
- Epilepsy
- Focal Dystonia
- Chronic Pain

Neural Networks Associated with Depression

Fronto-Parietal Network
Executive Functioning
Associated with cognitive symptoms

Dorsal Attention Network
Attention toward environmental cues
Attention Bias

Ventral Attention Network
Attention toward individual goals
Inattention; Indecisiveness



Default Mode Network
Active when in quiet contemplation
Rumination

Limbic Network
Emotional Regulation
Depressed mood
Low Energy

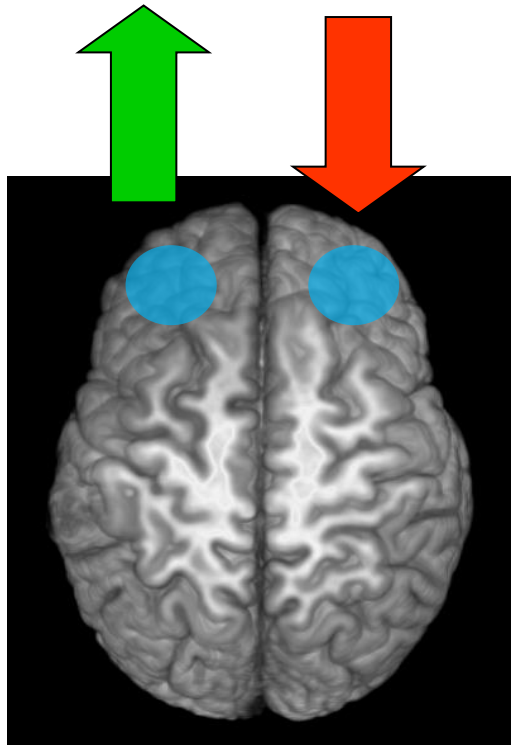
Kaiser et al 2015

Therapeutic applications: MDD

- Early PET data argued for an overall hypofrontality and metabolic asymmetry in the two frontal areas

Depression Rx Strategy:

Left DLPFC: High Frequency (5-20 Hz)



Right DLPFC: Low Frequency (1 Hz)

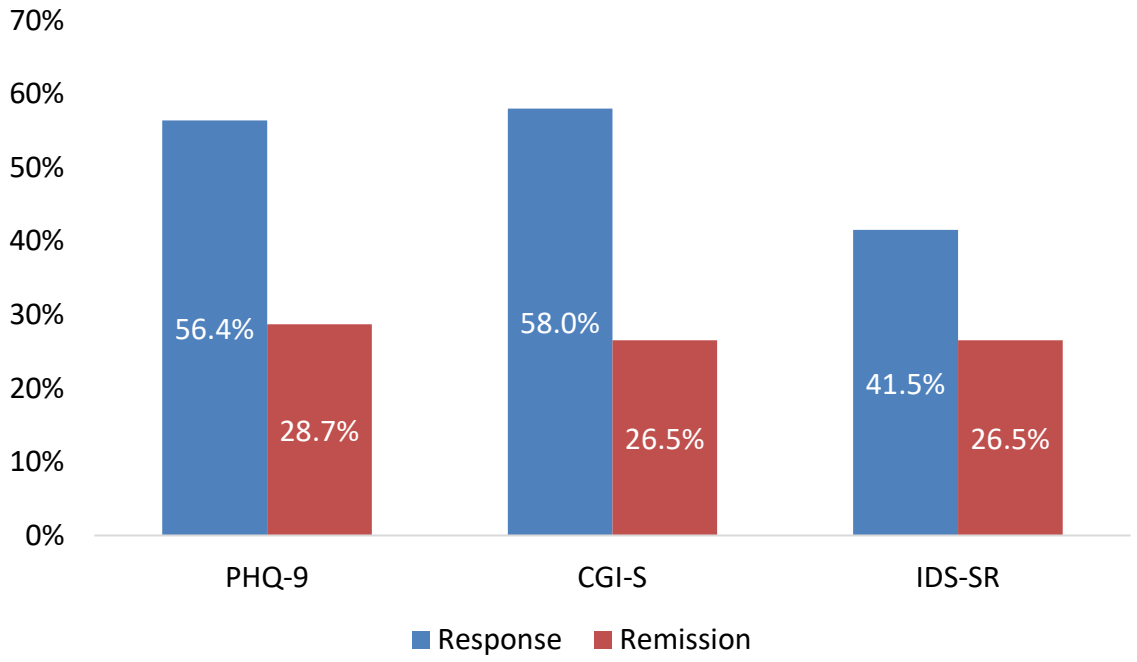
TMS Clinical Trials in MDD (make into a timeline)

- Multiple small single center trials since 1996
- Large multicenter trials in US leading to FDA approval in 2008 (O'Reardon et al., 2007)
- Follow up large NIMH trial confirms (George et al. 2010).
- Deep TMS (dTMS) system was granted FDA approval in 2013, after showing response rate of 38.4 % and remission rate of 32.6 % after 20 sessions.
- iTBS was FDA approved in 2018, after a non-inferiority study showed equivalent efficacy to 10 Hz stimulation protocol
- 7 companies have FDA-cleared devices for the treatment of MDD (6 Conventional rTMS systems and 1 dTMS system)

TMS in the Treatment of Depression

- **Conventional rTMS** was FDA approved for the treatment of unipolar depression in 2008

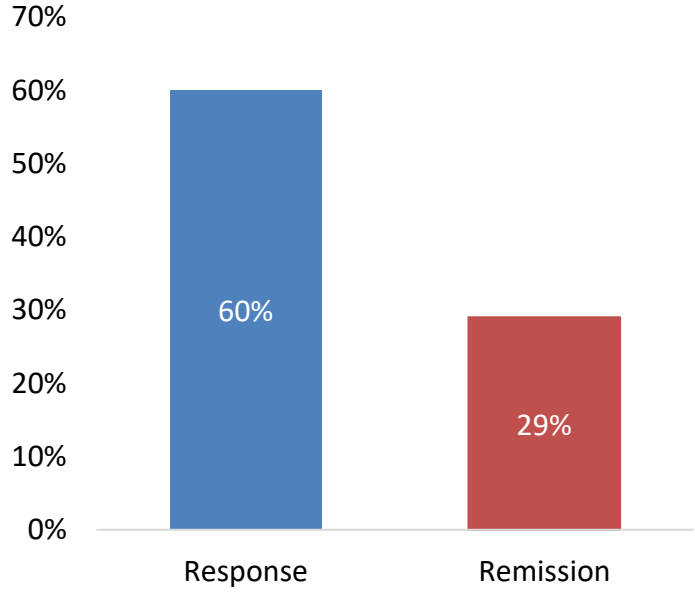
Open label study of 10 Hz rTMS using conventional TMS device



Carpenter et al. 2012

- The **H1 coil (deep TMS)** was FDA approved for treatment of depression in 2013

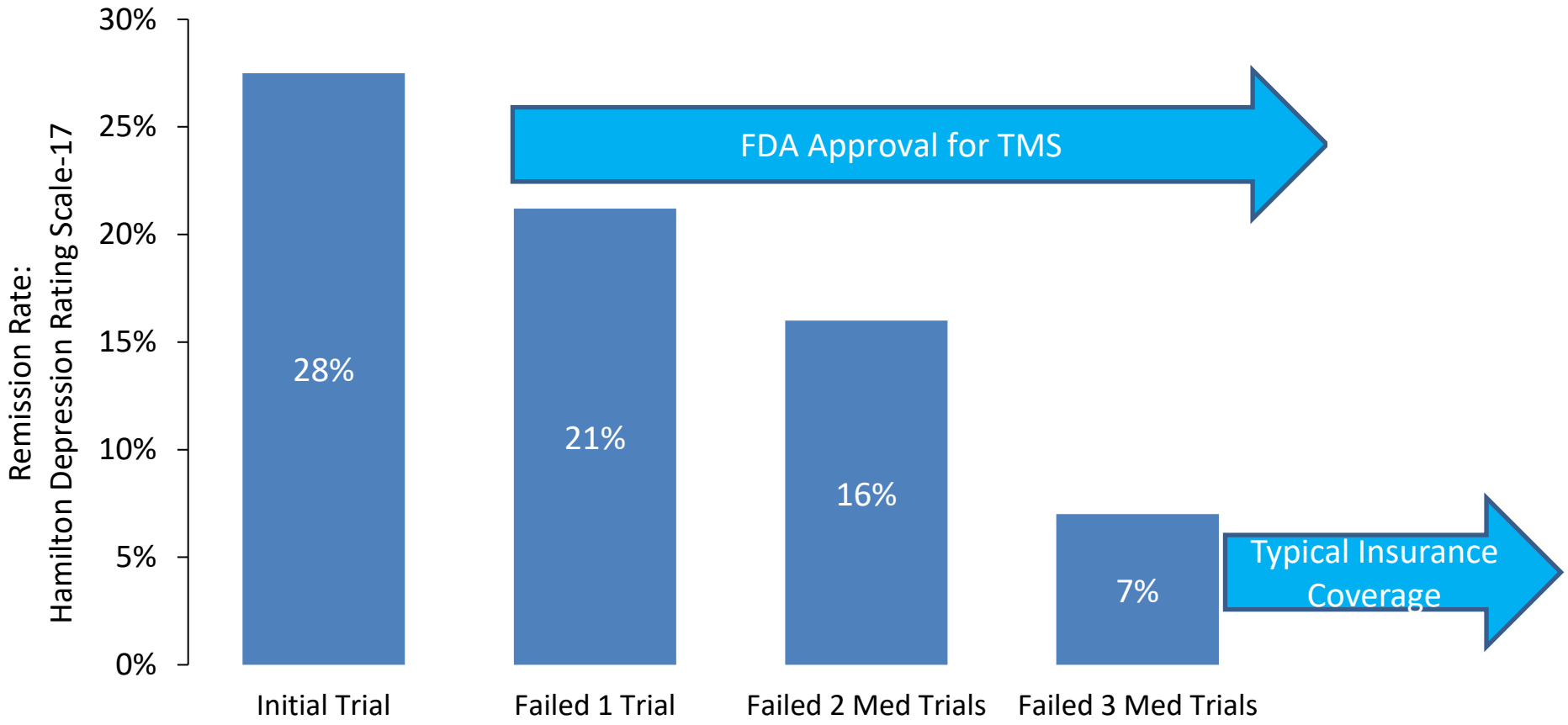
Meta-Analysis of 18 Hz rTMS using the H1 Coil



Kedzior et al, 2015

Why Consider TMS treatment for Depression?

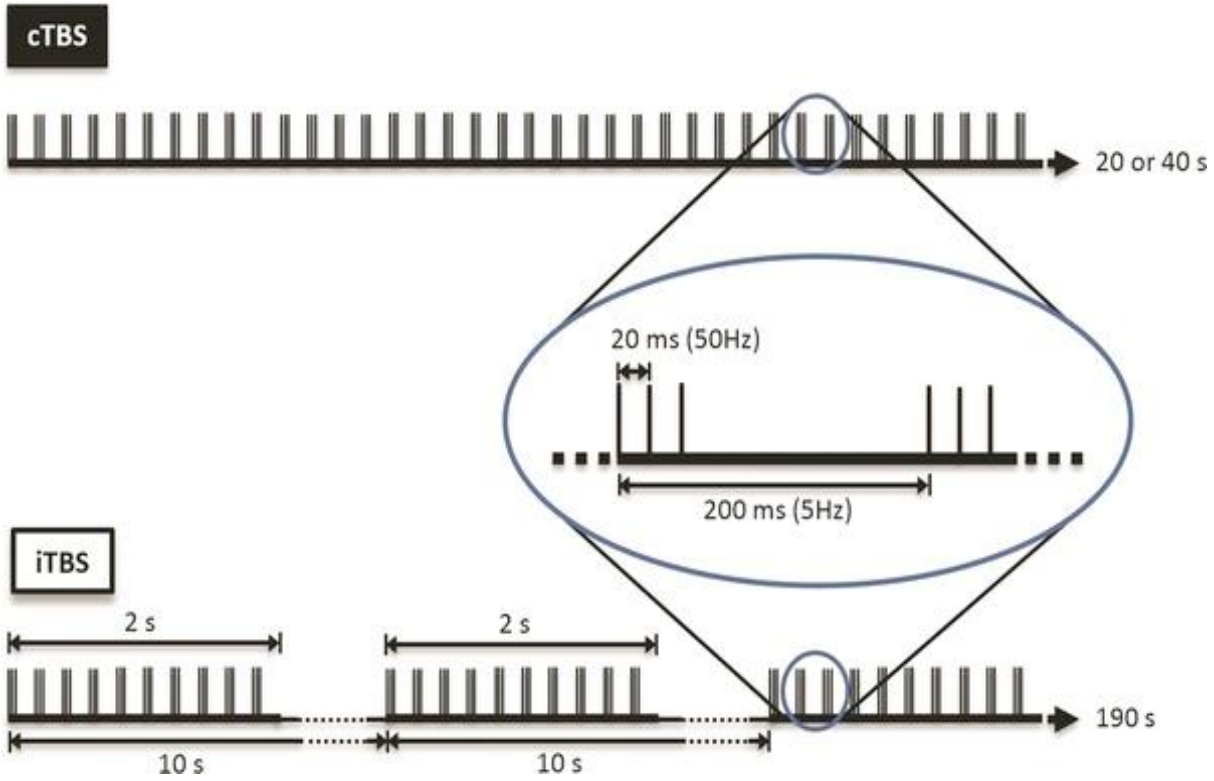
STAR*D Study: Depression Treatment Outcomes



Likelihood of achieving remission drops with each subsequent medication trial

Rush AJ et al. Am J Psych 163:1905-1917, 2006

Theta Burst Stimulation

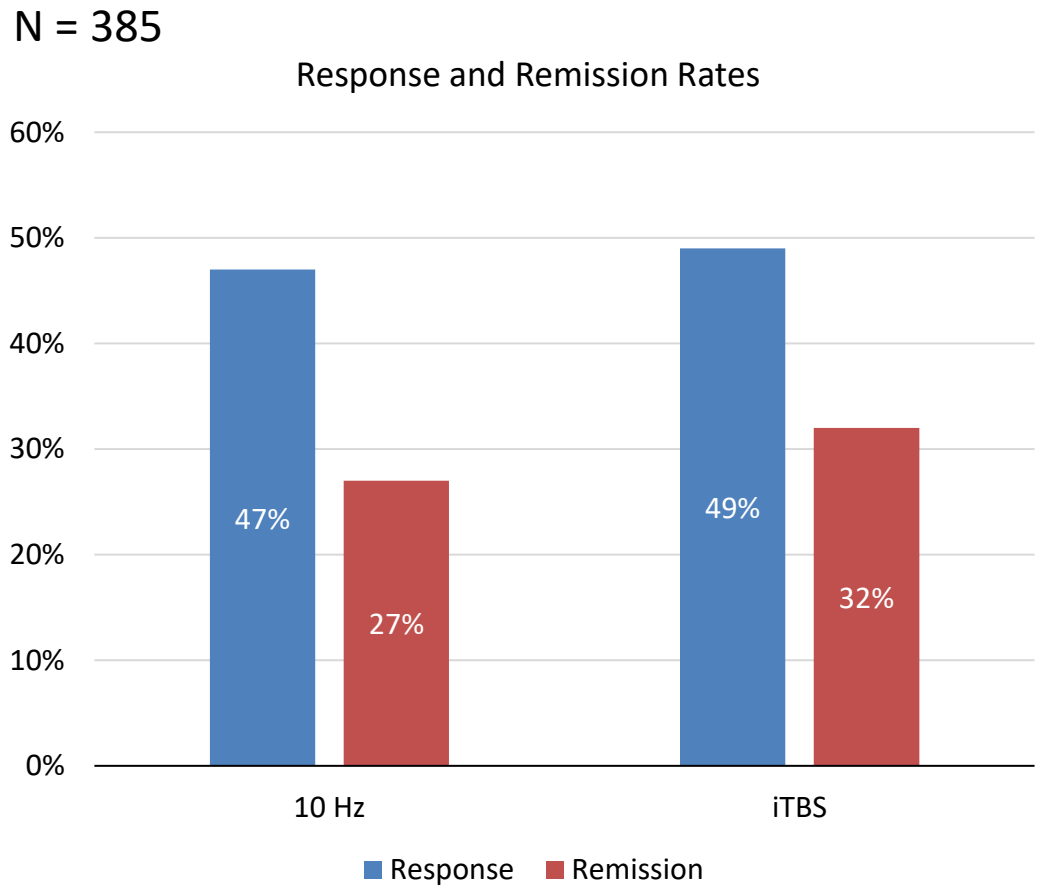


- Shorter duration
- May allow more sessions per day
- Longer-lasting physiological and cognitive effects are established in mechanistic studies

Standard 10 Hz vs iTBS

TBS is an FDA approved treatment protocol that takes ~3 minutes to administer!

Parameters	10 Hz	iTBS
Train Duration	4 seconds	2 seconds
Inter-Train Interval	26 seconds	8 seconds
Total Pulses	3000	600
Total Treatment Duration	**27 min 30 sec**	**3 min 9 sec**
Frequency	120% resting MT	120% resting MT

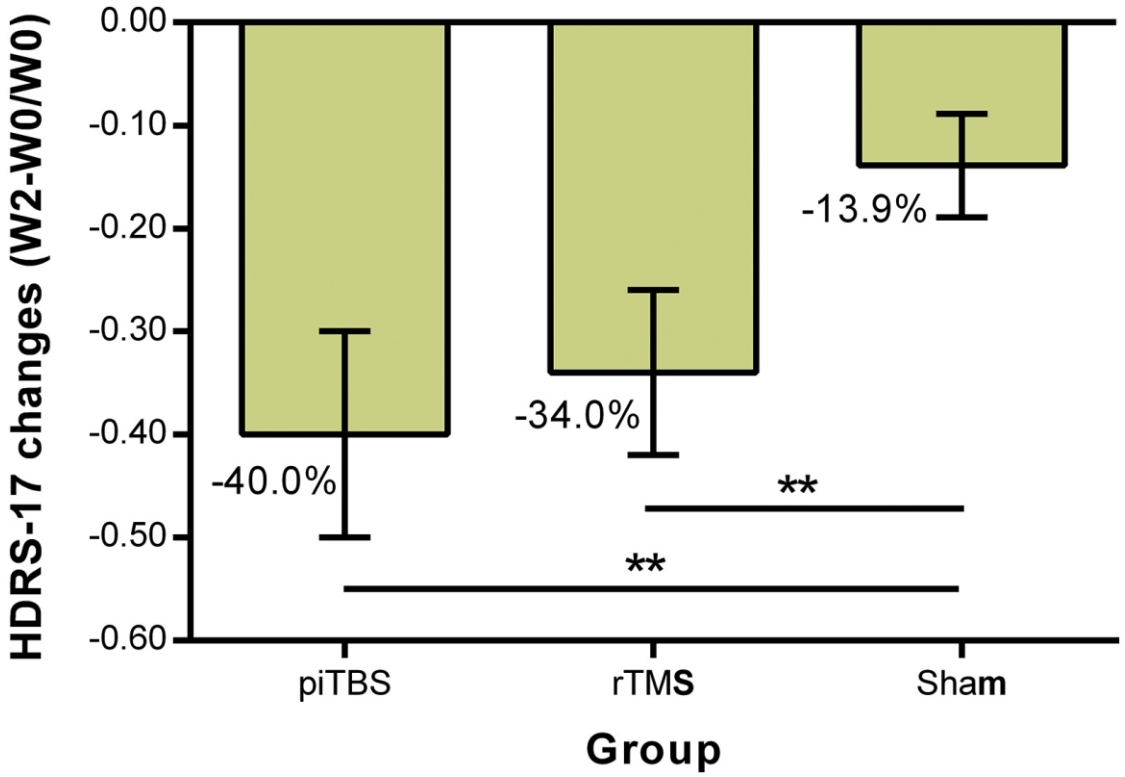


Adapted from Blumberger et al. 2018; *The Lancet*

Prolonged Theta Burst Stimulation

Increasing total number of iTBS pulses per treatment to 1800

Study suggested that 2 weeks of piTBS may be comparable to 4-6 weeks of standard iTBS or standard rTMS



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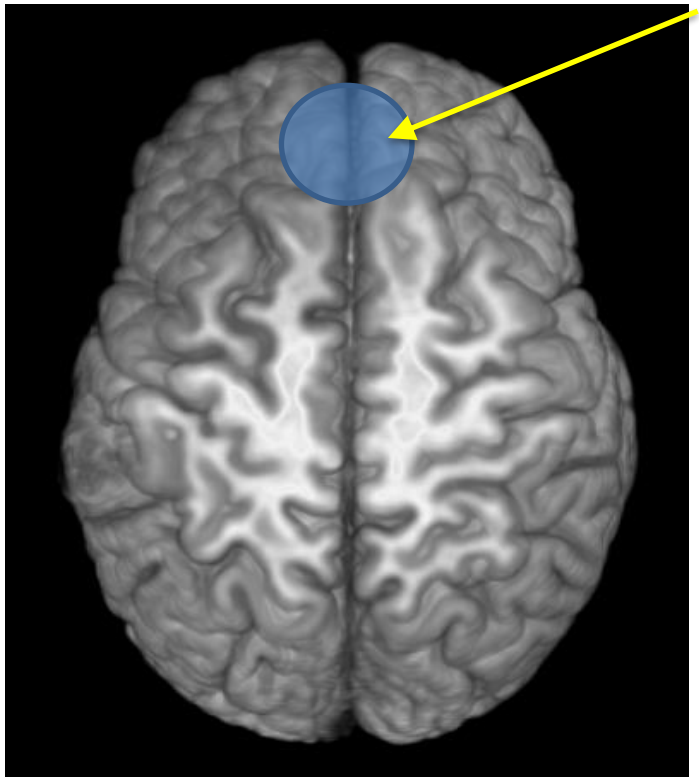
- Parkinson Disease
- Alzheimer Disease
- Epilepsy
- Focal Dystonia
- Chronic Pain

OCD Targets

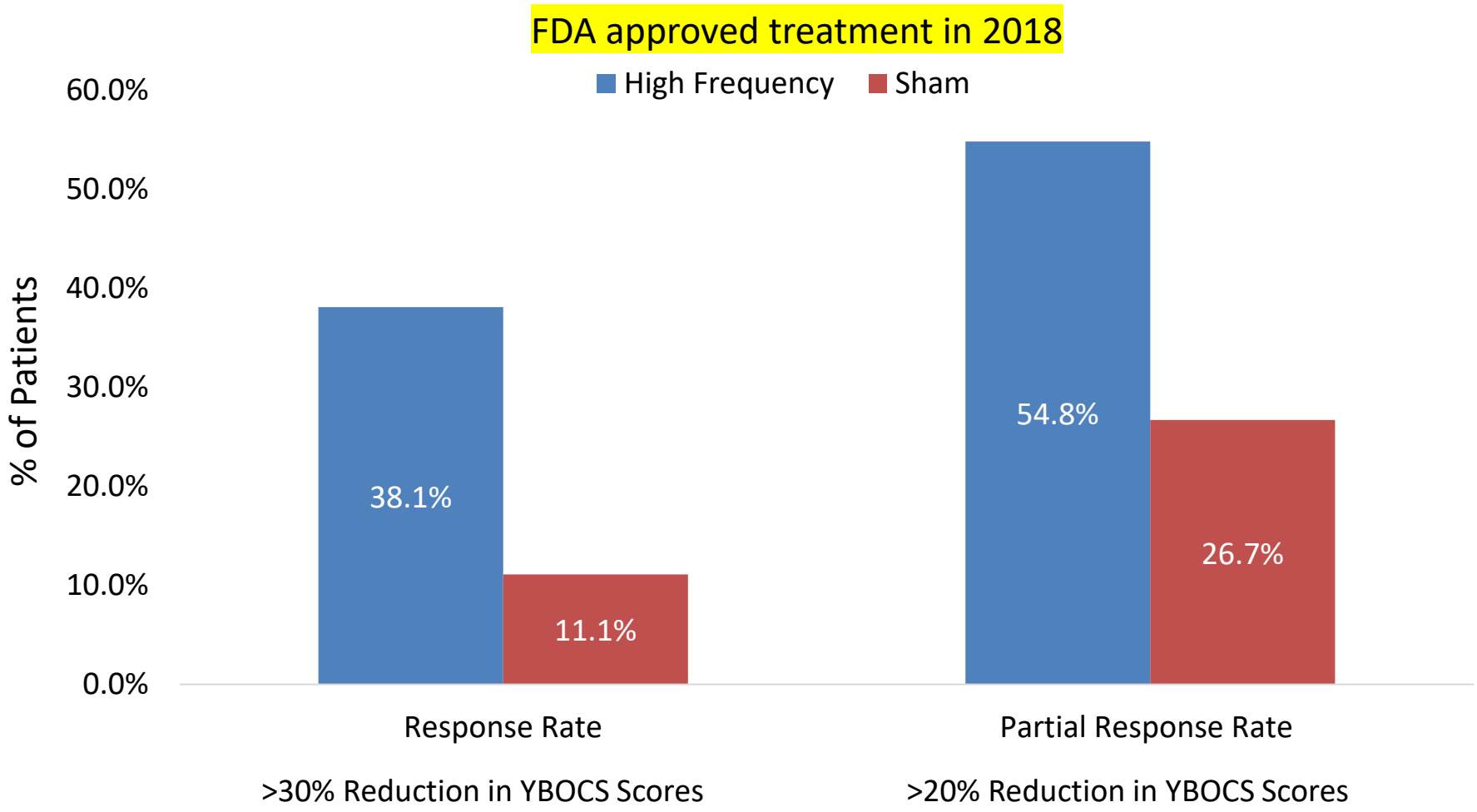
OCD has a well-defined neurologic basis:

- The Cortical – Striatal – Thalamic – Cortical pathway is a brain circuit that controls movement execution, habit formation, and reward.
- OCD is associated with hyperactivity of this pathway
- Poor thalamic gating may increase anterior cingulate cortex activity
- Medial prefrontal stimulation decreases anterior cingulate cortex activity



Medial prefrontal cortex/Anterior Cingulate Cortex

dTMS outcomes for OCD after 6 weeks of treatment



Parameters	
Coil	H7
Frequency	20 Hz
Train Duration	2 sec
Inter-Train Interval	20 sec
Total Pulses	2000
Intensity	100 % Ant. Tib RMT
Total Duration	18.3 minutes

Adapted from Carmi et al. 2019, AJP

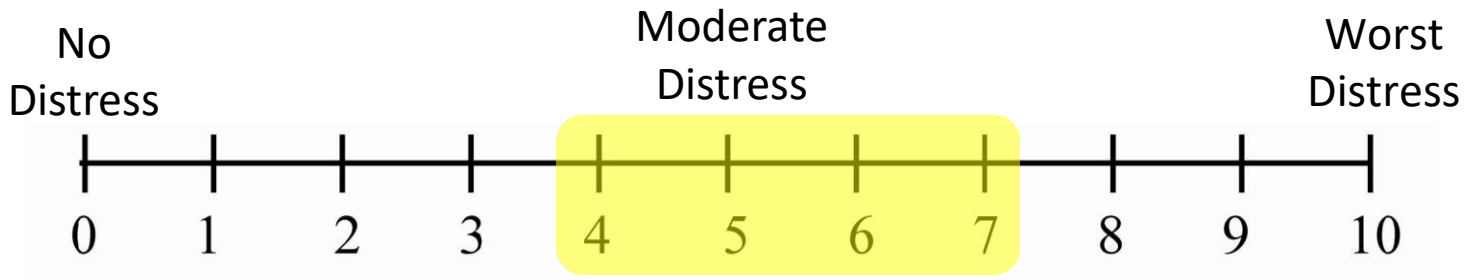
*MagVenture® received FDA approval for OCD treatment in 2020

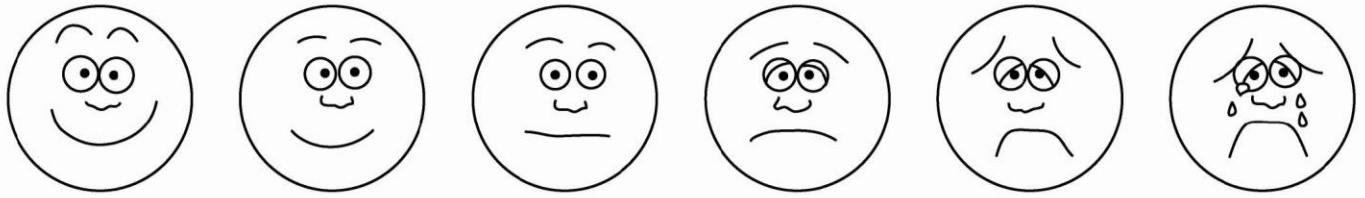
OCD Symptoms Must Be Provoked!

- Provocation consists of internal or external stimuli which will provoke or induce typical OCD symptoms and distress the subject – lasts up to 5 minutes

- The goal is to induce a moderate-to-major distress immediately before initiating TMS

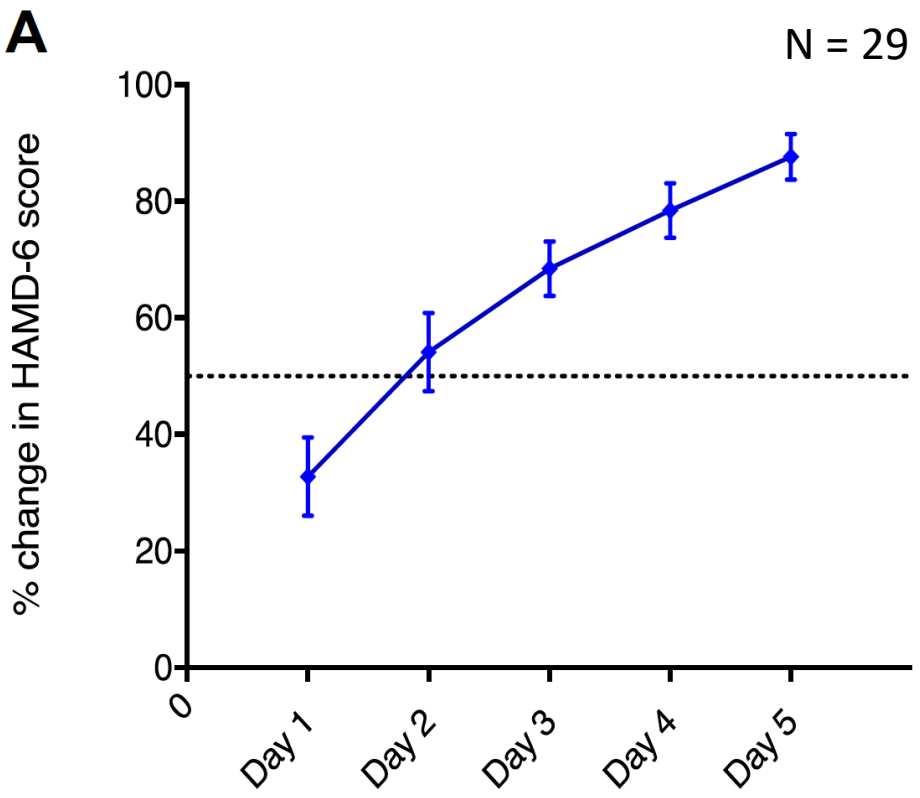
How much does the script/photo cause you distress right now?





Accelerated Protocols

Accelerated iTBS treatment of depression in an inpatient setting



- Each patient received 10 iTBS treatments per day
- Number of pulses delivered to in 1 day of treatment = standard treatment course.

HAMD-6

- Response Rate = 87.1%
- Remission Rate = 83.9%

MADRS

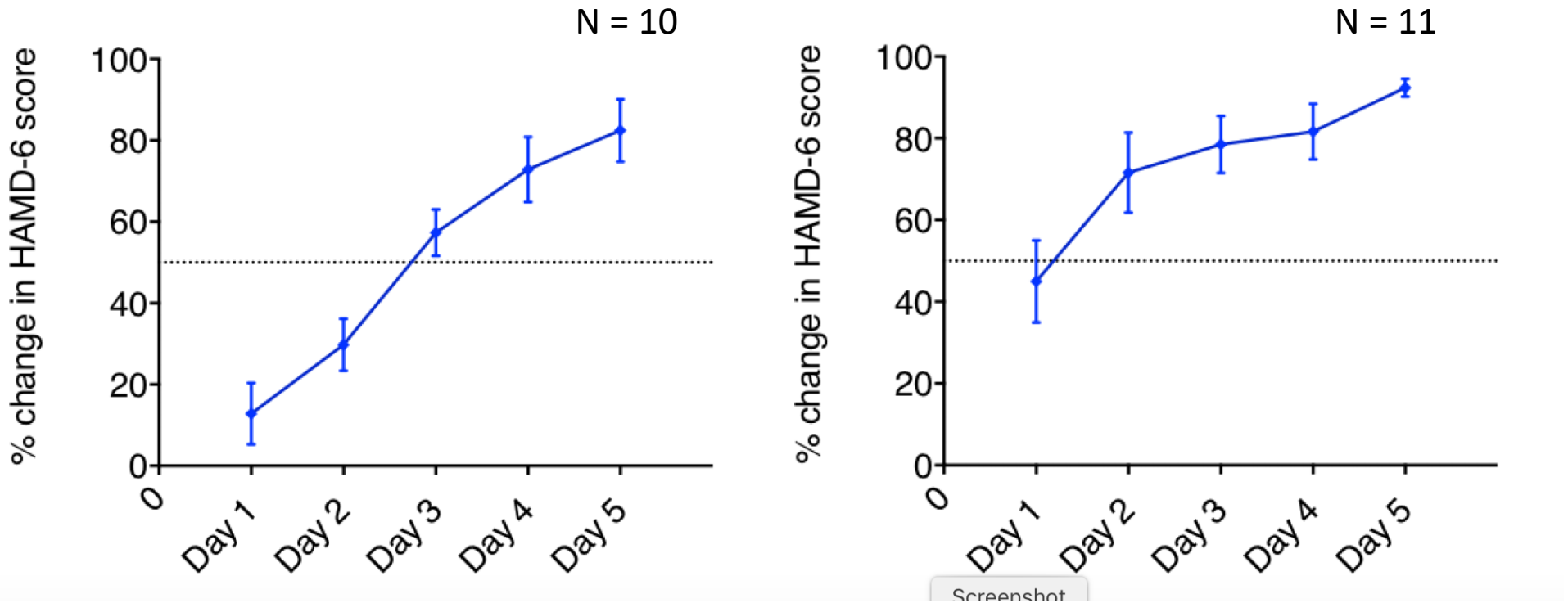
- Response Rate = 90.3%
- Remission Rate = 90.3%

Are safe and can shorten the duration of treatment!

Cole et al, 2019

MDD participants with previous TMS non-response

All Other TMS Participants

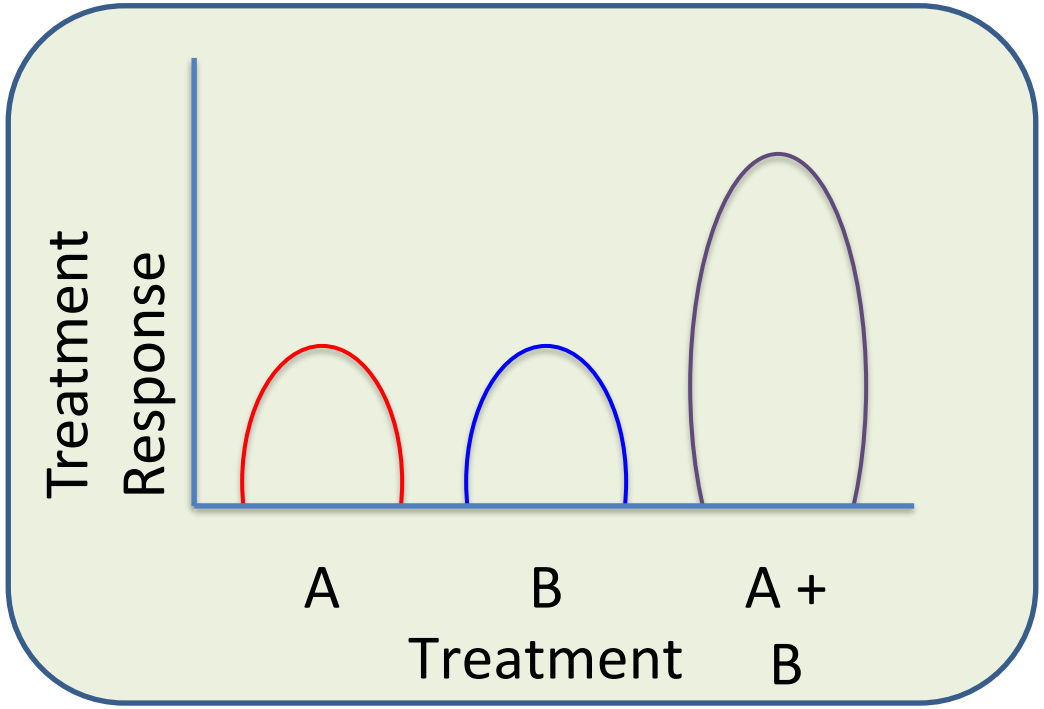


Patients with more treatment resistant depression may need more time to achieve response

Cole et al, 2019

Enhancing the effect of TMS?

State Dependence

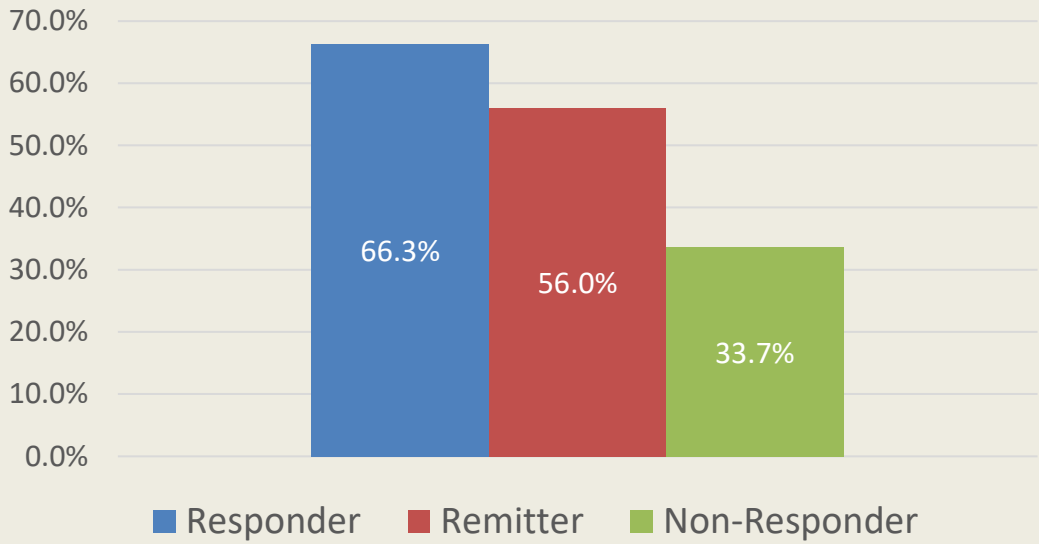


Idea: TMS + Second Therapy = Synergistic Effects

Activating a network with a task → Increases susceptibility of network to the changes introduced by TMS

State Effects: Simultaneous TMS + Therapy

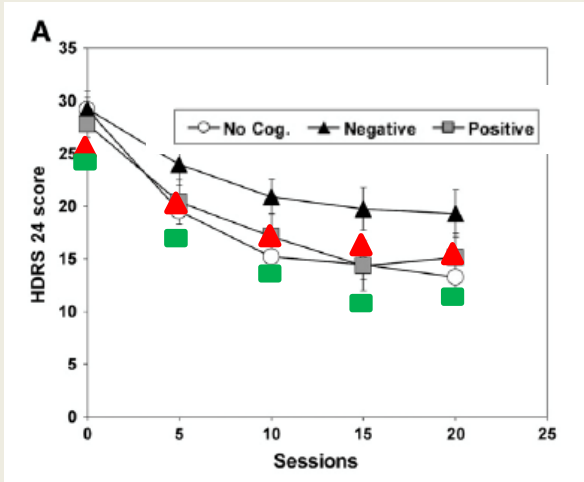
Donse et al. 2018



State Effects: Mood Alteration + TMS

Prior to dTMS for depression subjects randomized to:

- –Positive cognitive emotional reactivation
- –Negative cognitive emotional reactivation
- –None



Isserles et al, 2011

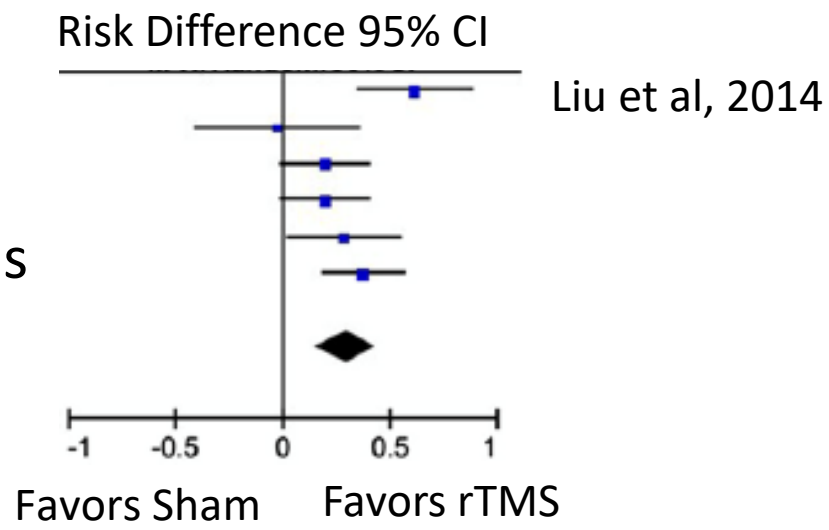
Medications

- Alter physiology:
  - Excitability → Affects Motor Threshold!
  - Plasticity → Affect Treatment Efficacy

Might continuing medication help the efficacy of treatment?

<u>Antidepressant + Active or Shame rTMS</u>

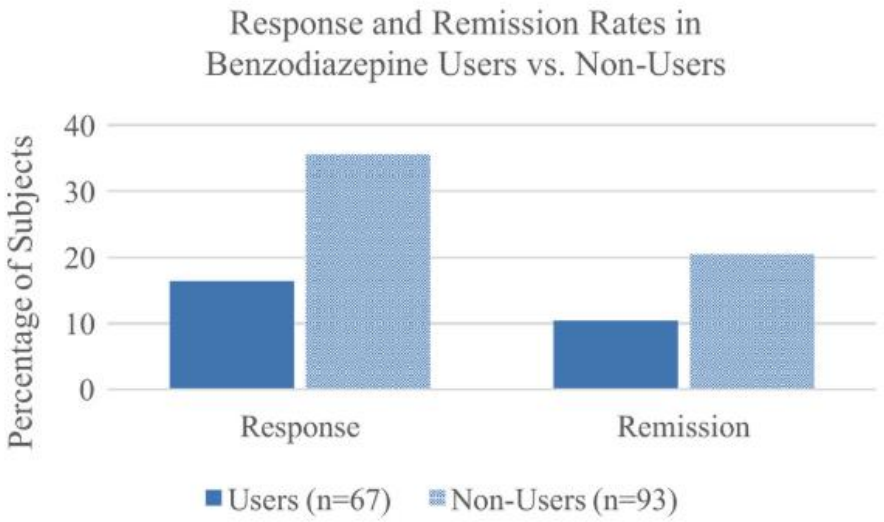
- –Augmentation with rTMS in treatment resistant depression is significantly superior to sham rTMS
- –OR: 5.12

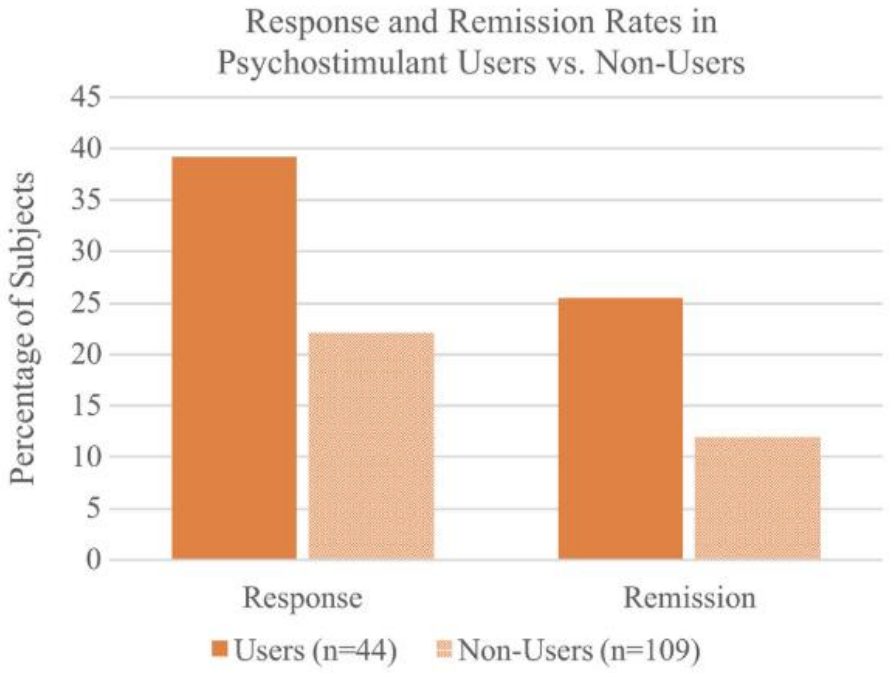


Liu et al, 2014

Augmentation of medication management with rTMS in treatment-resistant depression leads to significant symptom improvement

Medications Effects on Treatment Outcomes





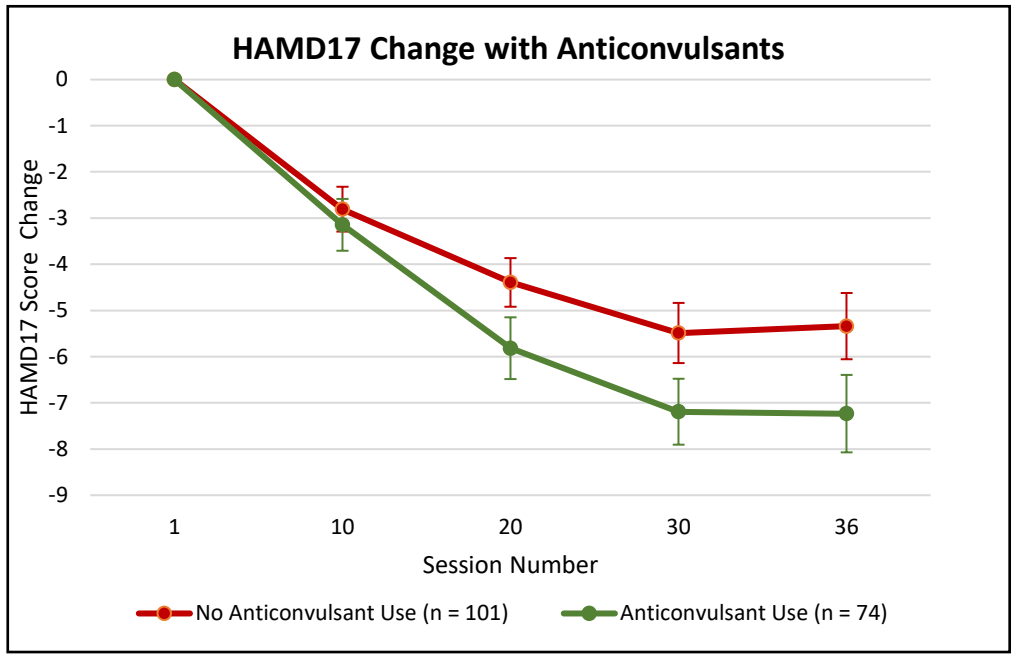
Medications May Impact Response

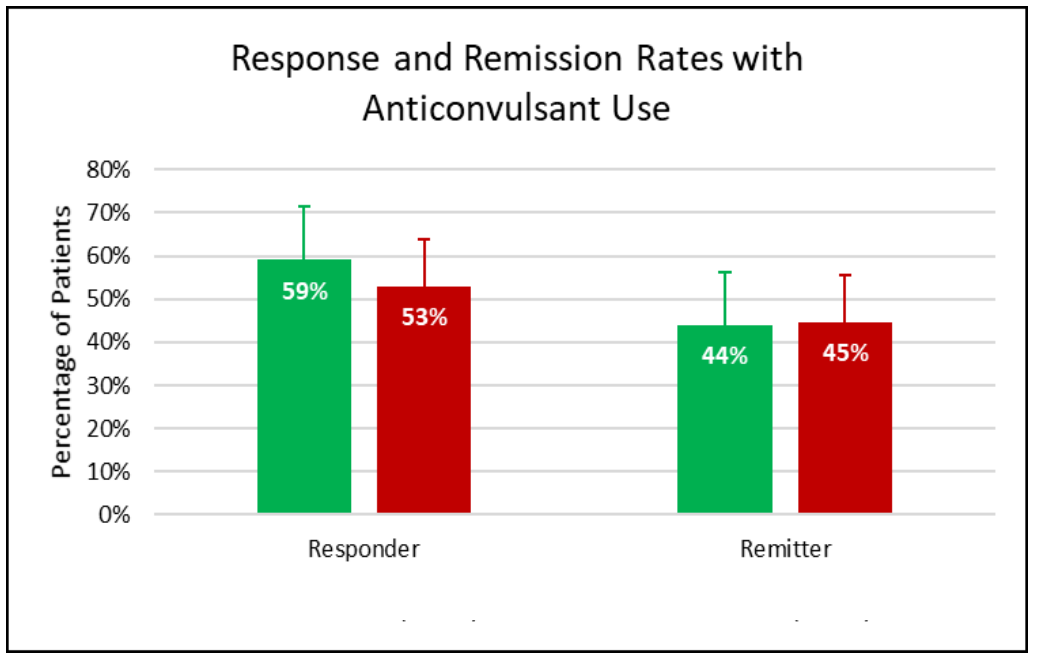
Hunter et al (2019) Brain and Behavior

Medication Effects on Treatment Outcome

Patients taking anticonvulsants had a *faster* rate of response than those not taking anticonvulsants.

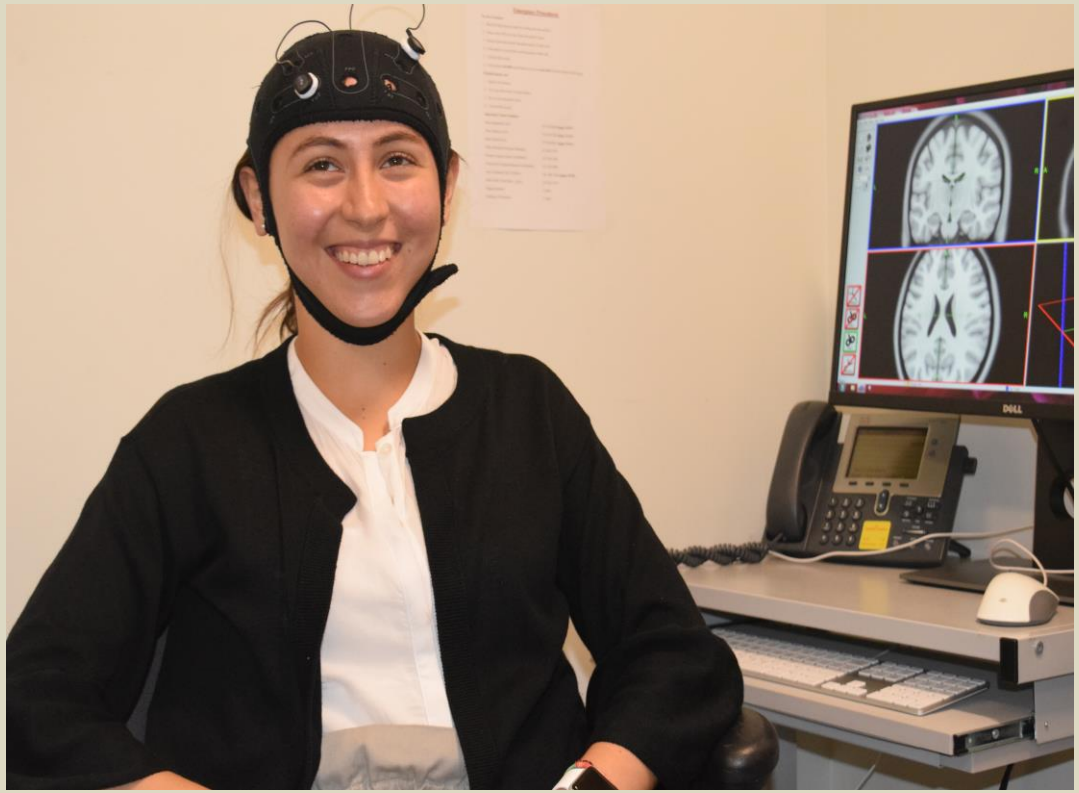
There was no significant difference between response and remission rates between those taking anticonvulsants and those not taking anticonvulsants.





Unpublished data from our clinic

Transcranial Direct Current Stimulation



- Continuous low amplitude electrical current is delivered to a specified cortical regions using scalp electrodes

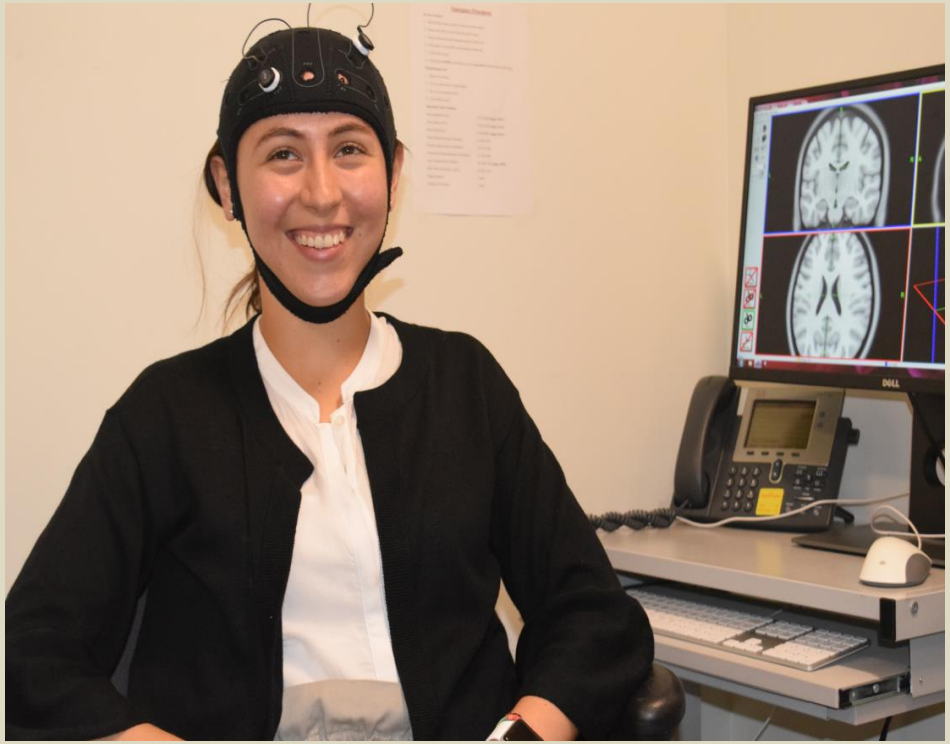
- Anodal Stimulation: Increases cortical excitability via depolarization of neuronal membrane potential
- Cathodal Stimulation: Decreases cortical excitability via hyperpolarization of neuronal membrane potential

- Repeated use may lead to neural plasticity

- Voltage: 2 mA over 30 minutes

- NOT FDA APROVED

Transcranial Direct Current Stimulation



Advantages:

- Easy to use
- Inexpensive
- Safe
- Potential for Home Use

A meta-analysis of 7 studies in Bipolar Depression

- Standardized Mean Difference after acute phase: 0.71
- Standardized Mean Difference after furthest endpoint from treatment: 1.97

May be good option for bipolar depression

Donde et al. 2017

Thank you for your attention!