

# TMS therapy : Optimizing Response in Depression

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Clinical TMS Society

[www.clinicaltmsociety.org](http://www.clinicaltmsociety.org)



Mission Statement:

The Clinical TMS Society is an international medical society dedicated to optimizing clinical practice, supporting research, and increasing access to high quality, evidence-based Transcranial Magnetic Stimulation.

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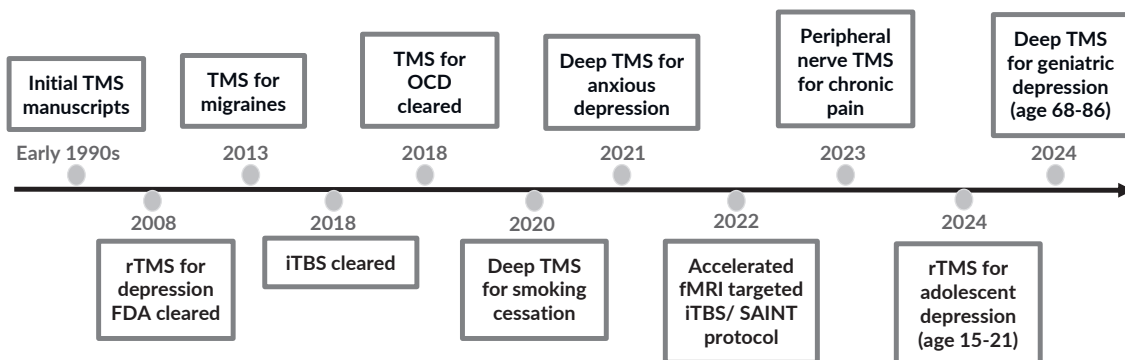
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## Agenda

- Quick review of some TMS basic science
- Advances in TMS protocols for major depression
- Unpack components of SAINT protocol
- Explore role of accelerated TMS inpt/outpt



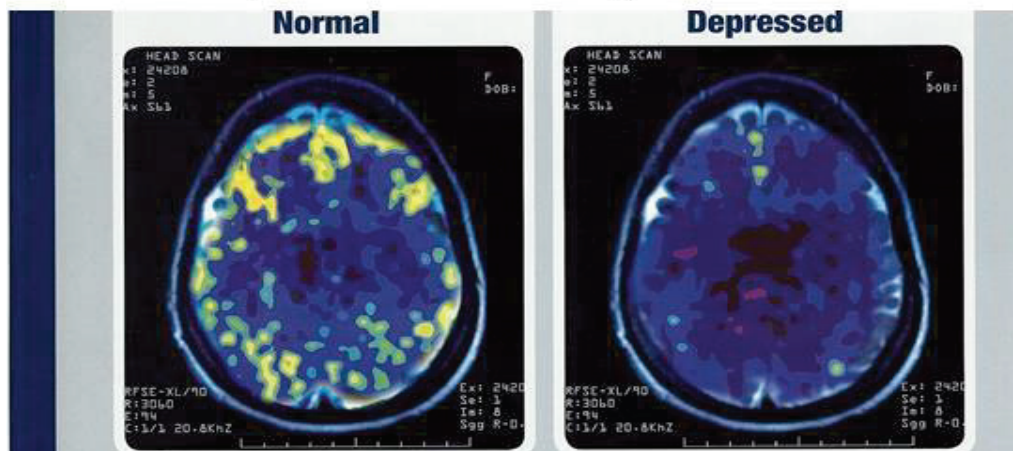
## IT'S BEEN A BIG DECADE FOR THERAPEUTIC TMS



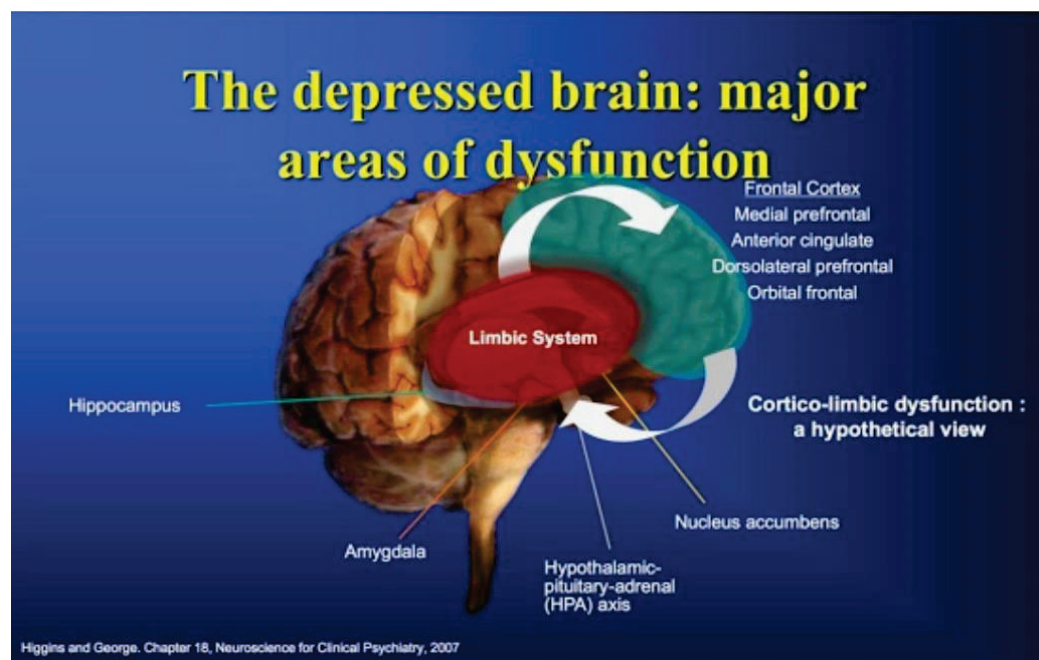
# THE BIOLOGY OF DEPRESSION

## Major Depression is a Brain Disease

In some patients the PFC was hypometabolic



Mark S. George, MD. Images acquired at the National Institute of Mental Health (NIMH, Bethesda, MD), 1994. 10

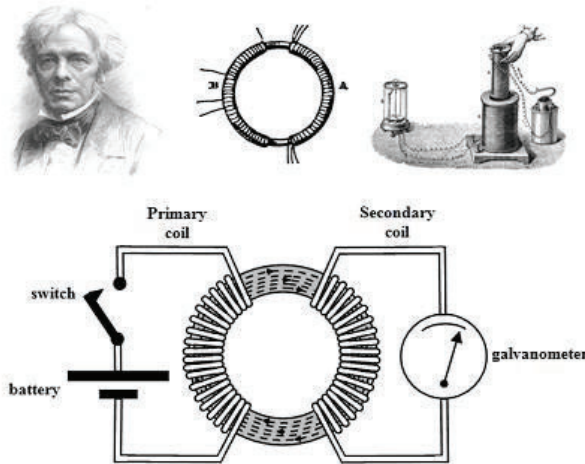


# TRANSCRANIAL MAGNETIC STIMULATION: MECHANISM OF ACTION

## Science Behind TMS: 1831 Michael Faraday

The physical principles of electromagnetism were discovered in 1831 by Michael Faraday, who observed that a pulse of electric current passing through wire coil generates a magnetic field.

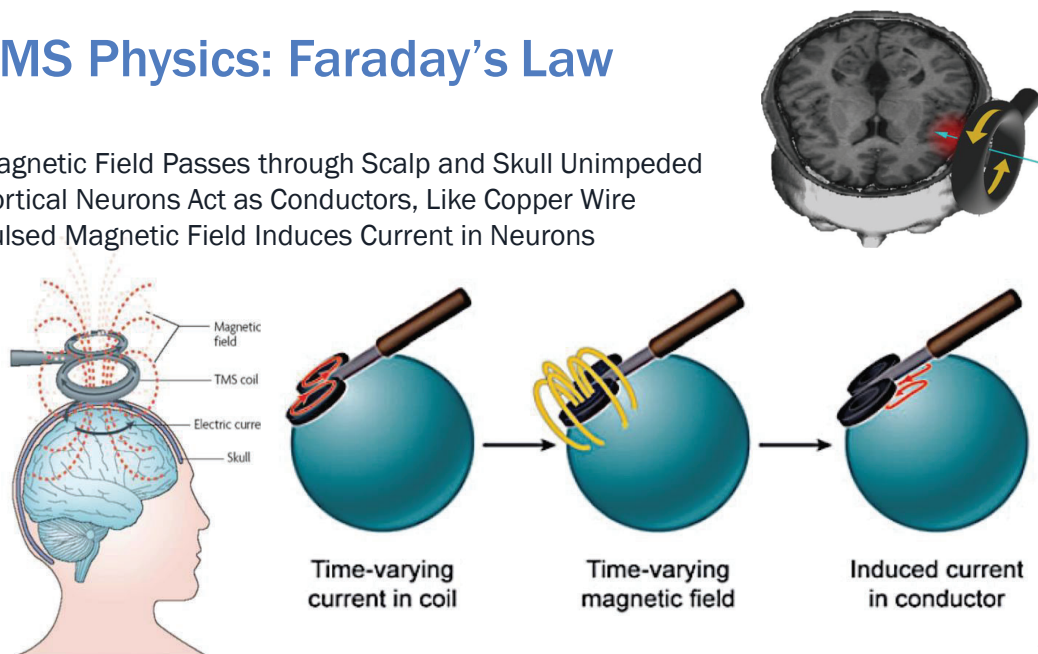
The rate of change (flux) of this magnetic field determines the induction of a secondary current in a nearby conductor that is placed in a perpendicular plane.



24

## TMS Physics: Faraday's Law

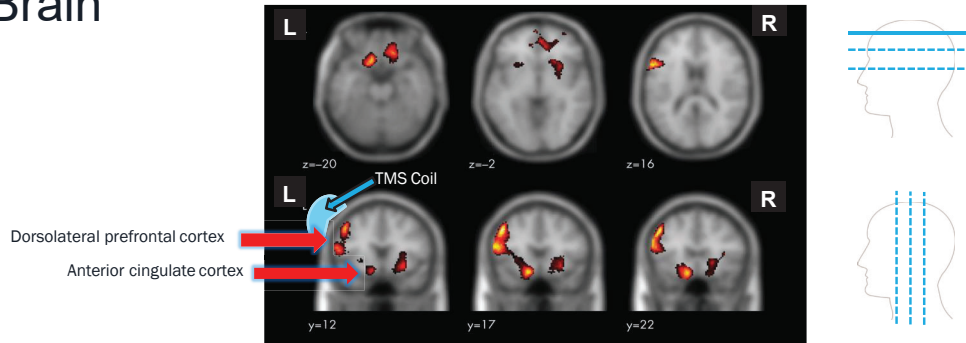
Magnetic Field Passes through Scalp and Skull Unimpeded  
Cortical Neurons Act as Conductors, Like Copper Wire  
Pulsed Magnetic Field Induces Current in Neurons



25



# Targeted Effects on Mood Circuits in the Brain



Activation of fronto-cingulate brain circuit following a course of TMS applied to the left dorsolateral prefrontal cortex in patients with Major Depression

Kito, *J Neuropsychiatry Clin Neurosci.* 2008

28

# Biological & Behavioral Effects of TMS

Effects Seen After Chronic Exposure (Repeated TMS Applications):

- Specific outcome is dependent upon stimulation parameters
- Alteration of monoamine concentrations
- Beta-receptor, serotonin-receptor modulation
- Evidence of induction of neurogenesis genes (eg, BDNF)
- Plasticity-like actions (ie, LTD/LTP-like effects)
- Local GABA, glutamate effects
- Stimulation of the dorsolateral prefrontal cortex (DLPFC) alters functional activity of the anterior cingulate (AC) and deeper limbic regions

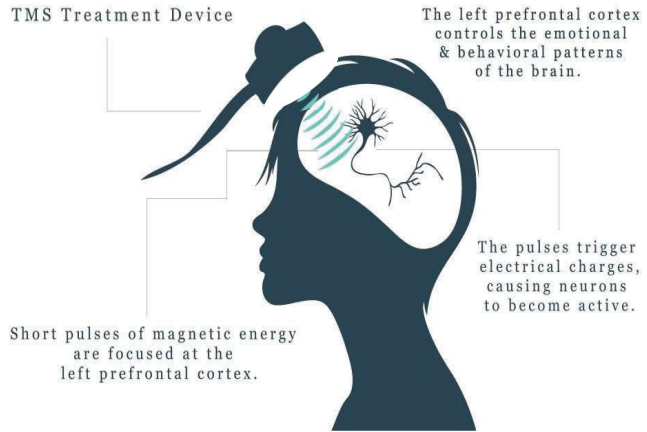
Lisanby SH, Belmaker RH. *Depress Anxiety.* 2000;12(3):178-187; Kim EJ et al. *Neurosci Lett.* 2006;405(1-2):79-83; Shajahan PM et al *Prog Neuropsychopharmacol Biol Psychiatry.* 2002;26(5):945-954; Teneback CC et al. *Neuropsychiatry Clin Neurosci.* 1999;11(4):426-435; Epstein CM et al. *Neurology.* 1990;40(4):666-670; George MS et al. *NeuroReport.* 1995;6(14):1853-1856.

30

**TRANSCRANIAL MAGNETIC  
STIMULATION:  
WHAT TO EXPECT FROM  
TREATMENT**

TMS Therapy Session

- Patient is awake and alert
- No anesthesia or sedation needed
- No negative effects on thinking and memory
- After treatment, patients can drive or return to work
- Some patients experience headache or mild to moderate pain or discomfort at or near the treatment area
- None of the side effects typical with antidepressant medications



NIMH Website Brain Stimulation

33

TMS: Contraindications

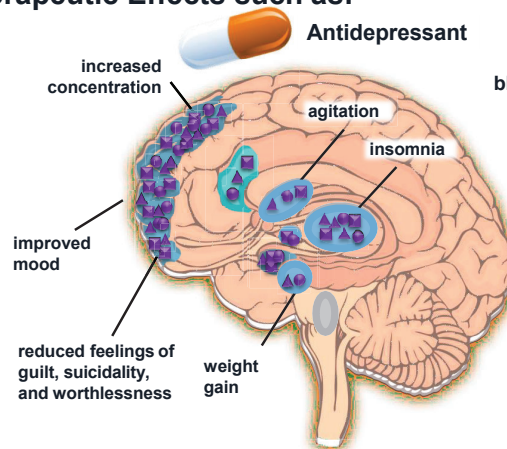
- Non-removable metallic objects in or around the head
  - *Conductive, ferromagnetic or other magnetic sensitive metals that are implanted or are non-removable within 30 cm of figure-8 treatment coil*
  - *Implanted electrodes/ stimulators*
  - *Deep Brain Stimulator*
  - *Aneurysm clips or coils*
  - *Cochlear implants*
  - *Intracranial Stents*
  - *Bullet or other metal fragments*
  - *Vagus Nerve Stimulators (per package insert vs. practical implementation)*

Hadley et al. J ECT 2010; Philip et al. Brain Stimulation. 2014; Schrader et al Clin Neurophysiol 2005

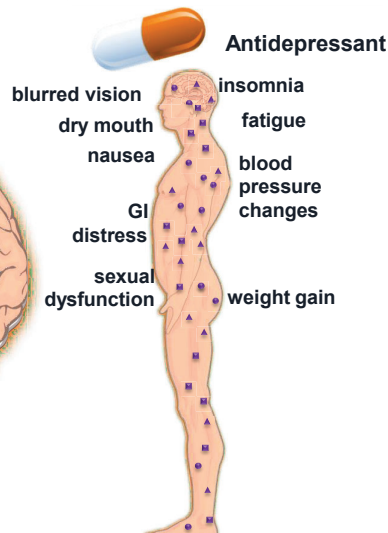
34

Monoaminergic Effects of Antidepressant Medications

Therapeutic Effects such as:



Side Effects such as:



Stahl SM. Cambridge University Press; 2008

14

## TMS: is a Well-Tolerated Antidepressant

Most common adverse events with all Figure 8 Coil and Hersed Coil with Incidence > 5%

### TMS Side Effects:

Scalp/Head Pain  
at Treatment Site  
and Headache

### No Systemic Side Effects:

Weight Gain	Nausea	Dry Mouth
Weight Loss	Nervousness/Anxiety	Sweating
Appetite changes	Sexual side effects	Tremor
Constipation	Impotence	Fatigue
Diarrhea	Weakness	Treatment Discontinuation symptoms

Reference: 510(k) applications for Neuronetics & Brainsway devices

35



## TMS effect on Cognitive Enhancement

Review of 41 peer reviewed articles published 2019  
10 open label studies and 31 RCT using sham coil  
( included studies on healthy volunteers )

### Positive effects :

Short term memory  
Working Memory  
Processing speed

Experimental Neurobiology Kim et al

## 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 G et al. International Journal of Neuropsychopharmacology 2008 (11) 119-130

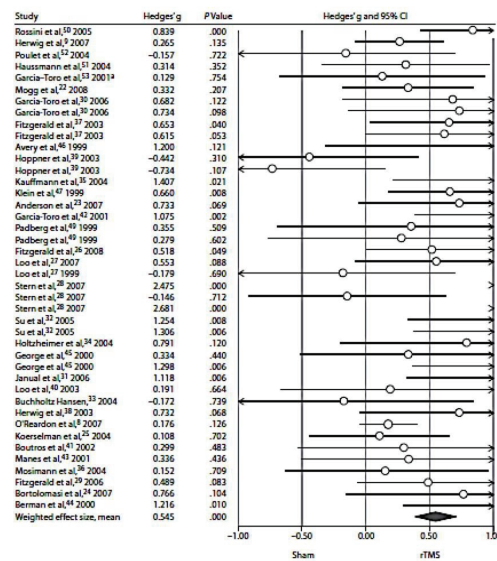
39

# SCIENTIFIC EVIDENCE OF EFFICACY FOR TMS THERAPY

## Evidence for Efficacy of TMS for MDD

- 65 + clinical trials in adults
- Numerous meta-analyses
- Greater effects in more recent studies
  - Longer duration of treatment
  - Increase intensity
  - Increase pulse number
- Most recent
  - 65 RCTs , 2982 patients and found TMS
  - TMS to be more effective than sham
  - with a large effect size = 0.79

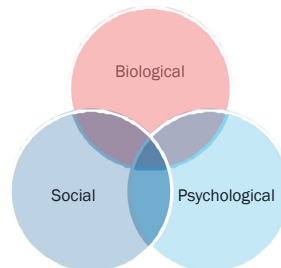
Figure 1. rTMS for Depression, Results of the Meta-Analysis



Dalhuisen et al., 2022 , McGirr et al., 2021 Pellet al ,2022 \*Add-on therapy. Abbreviation: rTMS= repetitive transcranial magnetic stimulation.

## Why are Real World Results Better than Clinical Trial Results?

- Combination Strategies
  - Well tolerated with many medications <sup>1</sup>
- Psychotherapy <sup>2</sup>
- Engagement in Life
  - Intensive Outpatient Program – Factors
    - Routine
    - Interaction
    - Engaging with People who Care



<sup>1</sup>Rossi et al. J Neurol Neurosurg Psychiat 2007; <sup>2</sup>Arns M et al Brain Stimulation 2012 Feb. 1-8.(3)313-319.





# Why are Real world results Better than Clinical Trials?

Medication impact :

**POS** : Amphetamines  
Cycloserine

**NEG**: Benzos  
Anticonvulsants  
Antipsychotics

Sleep pathology – sleep apnea, restless legs



## Evolution of FDA approved TMS protocols for major depression



### FDA Approved Protocol for Office Delivered TMS Therapy

<u>Year Approved</u>	<u>Tx Type</u>	<u>Min / Tx</u>	<u>Tx Course</u>
2008	10HZ	37.5 min	6-9 weeks
2017	10 HZ	19 min	6-9 weeks
2018	iTBS	3 min	6-9 weeks
2022	iTBS	9 min	* one week



# Theta Burst Stimulation (TBS)

- ❑ "Second generation TMS" a revolutionary form of brain stimulation developed out of research at University College London in early 2000s.
- ❑ Concept- finding a "resonating frequency" with other brain structures
- ❑ Early studies measuring *hypothalamic activation in rats* during exploratory behavior
- ❑ Rapid neuronal "bursts" in the hypothalamus were noted to be superimposed on a theta frequency ( 4-7 HZ)



## iTBS and rTMS

iTBS = 5 – 3 pulse bursts per second



rTMS = 10 pulses per second



## iTBS -Second generation TMS ?

3 minutes vs. 20-40 min treatment

**Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial.**

Daniel Blumberger et al., Lancet 2018

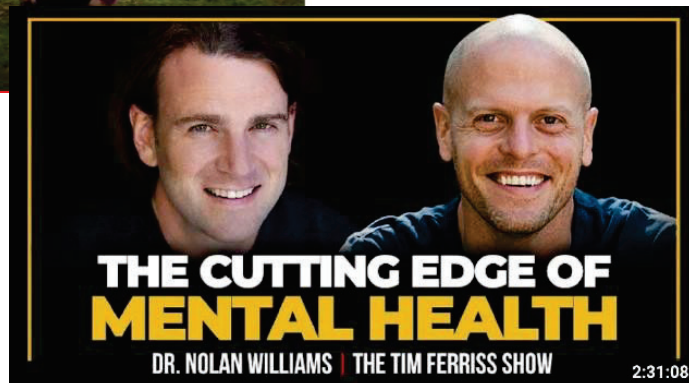
Comparing 3 minute , 600 pulse iTBS  
To standard 10 HZ 20-40 min treatment

"non – inferior " to standard 10 HZ 3000 pulse



## SAINT PROTOCOL (NOW SNT)

S TANFORD  
I NTELLIGENT  
A CCELERATED  
N EUROMODULATION  
T HERAPY



# SAINT – Three clinical trials

1. Nolan Williams 2018 5 Of 6 severely depressed and treatment resistant **remitted** , published in Brain Feb, 2018
2. Am Journal Psychiatry SAINT for TRD open label April , 2020 "ninety per cent remission" 19 of 21



## 3. Stanford Neuromodulation Therapy ( SNT):

A Double- Blind Randomized Controlled Trial  
Am J Psychiatry Feb 2022

- ❑ 29 patients total, mod - severe depression, treatment resistant
- ❑ **78% remission rate** , 13% sham
- ❑ **MADRAS** was primary scale, remission <10, response 50% drop in score
- ❑ Patient response at **2.6 days**



## FDA Approval of SNT

September 2022 "Breakthrough Device Designation" granted to Magnus Medical with proprietary algorithm using fMRI

Currently only eight centers nationwide



## SAINT protocol

Stanford Accelerated Intelligent Neuromodulation  
Treatment

- ❑ TBS 1800 pulses 9 min ( 3X of original FDA iTBS)
- ❑ Ten treatments/ day, 50 min rest between treatments
- ❑ Five days= 50 treatments = 90,000 pulses



## What is the Magic Ingredient to SAINT?

- A. TBS at 1800 pulses 90% MT
- B. Stacking treatments 10/day
- C. Patient Selection
- D. Personalized targeting- resting state fMRI



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# What is the optimal protocol for TMS therapy

iTBS at 1800 pulses may be superior to 600 pulses (original FDA approved dose)

□ studies on evoked potentials on human motor cortex 2014

90% MT may be optimal vs standard 120%

Nettekoven et al., Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system, Journal of Neuroscience. 2014 May

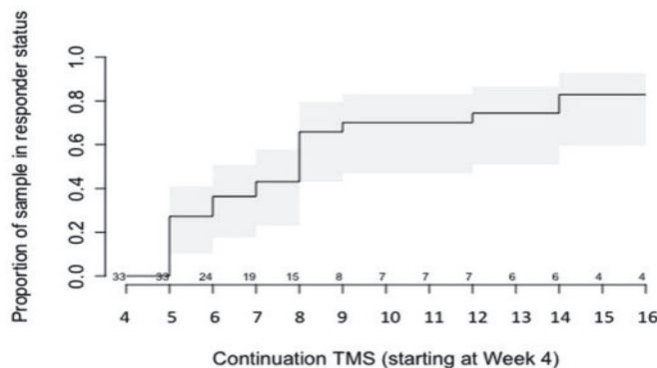


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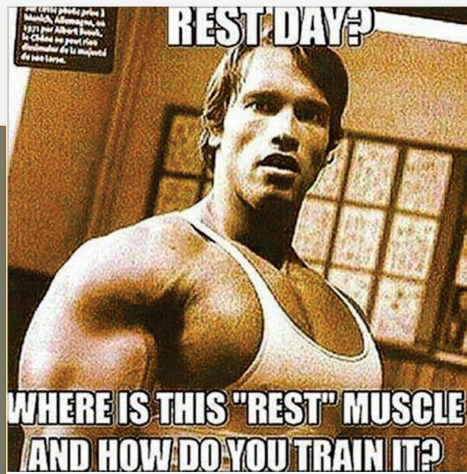
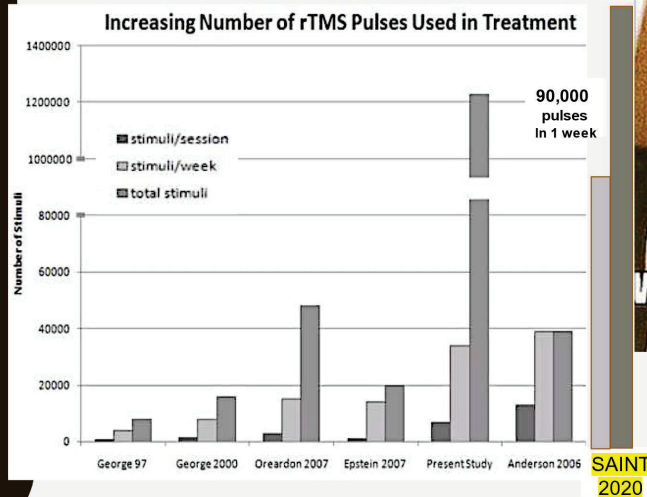


More treatments , better response



ACTIVE dTMS CONTINUATION PHASE: START AT WEEK 4  
2 sessions/week (12 weeks=24 sessions) Yip et al Brain Stim. 2017

# MORE REPS?!



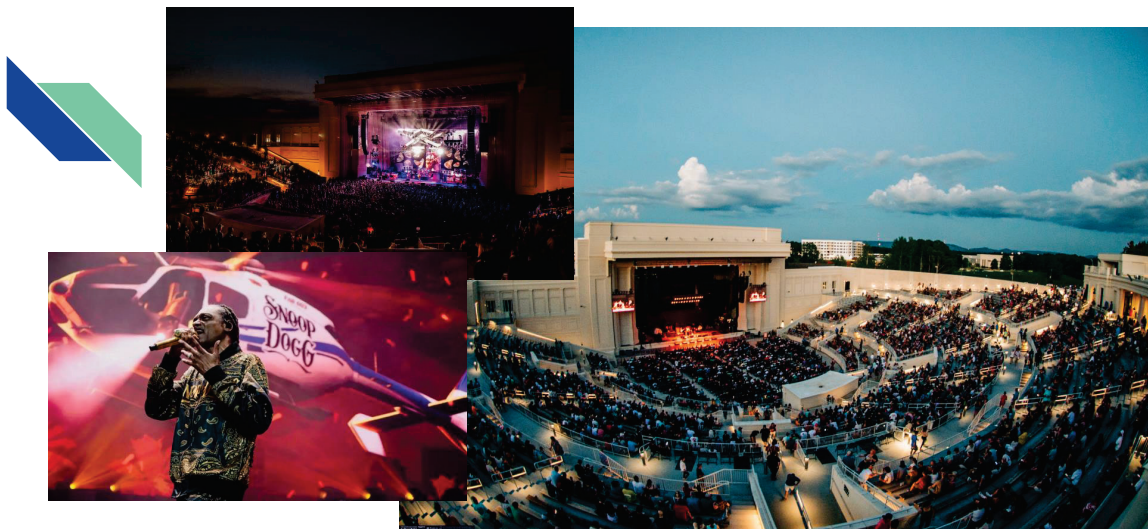
Modified from Hadley et al., 2011 (with permission from CTMSS)

## What is the Magic Ingredient to SAINT?

- A. TBS at 1800 pulses 90% MT
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- C. Patient Selection
- D. Personalized targeting- resting state fMRI

## Patient Selection

- No comorbid diagnosis- mod or severe depression only
- Sleeping at least 5 hr at night
- Age 22-80
- 13% on benzos , 3% on amphetamines
- Average duration of illness 26 years
- No change in antidepressant 4 weeks before tx or after



## Orion Ampitheatre- Our neighbor

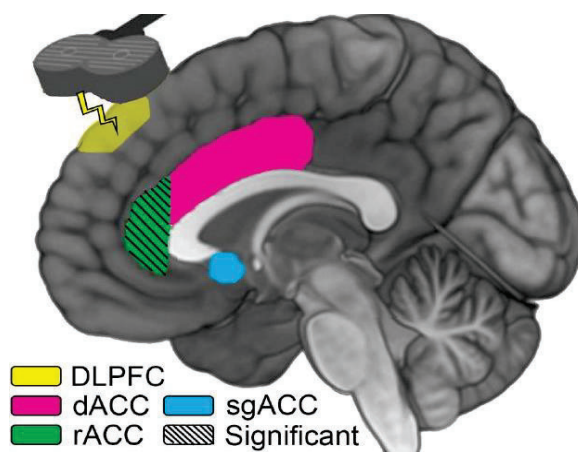


### What is the Magic Ingredient to SAINT?

- A. TBS at 1800 pulses 90% MT
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- D. **Personalized targeting- resting state fMRI**



DLPFC and sgACC  
"resting state fMRI "





## Personalized Targeting: Does it matter and How much?



### Shan Siddiqi MD

Grand Rounds presentation webinar  
August , 2024. Clinical TMS Society

Review of 6 studies comparing  
personalized MRI targeting vs clinical mapping

Harvard professor and director of psychiatric  
neuromodulation research for the **Center for Brain Circuit  
Therapeutics**. His research is focused on causal mapping of  
human brain function and dysfunction



### Dr. Siddiqi's conclusion:

“ Some studies show larger effect, some showed smaller effect representing about 10% of the variance in clinical outcome. In a proposed study, you would expect about 10% of the nonresponders would flip to responders utilizing personalized targeting. Individualization improves outcome by a little bit, but you can probably do fine without individualization if you don't have access to it.”



## Advantages of Accelerated TMS

- Quick onset of effect (2.3 days)
- Enhanced access/availability
- Possibly improved efficacy
- Facilitates quick advance an decision tree towards effective treatment



## Accelerated TMS: Unresolved Questions

- Risk of mania
- Risk of emergent anxiety
- Ideal number of treatments per day (6-10?)
- What are the most essential elements of SNT?
- Risk of seizures
- Durability compared with stand TMS



## Barriers to Accelerated TMS

- Lack of insurance coverage
- Resolving the role of personalized targeting
- Clinical staffing issues





**How could Accelerated TMS  
impact inpatient outcomes  
in patients with severe major  
depression?**



**Thank you for  
listening !**

