TMS therapy : Optimizing Response in Depression

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Clinical TMS Society

www.clinicaltmssociety.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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Agenda

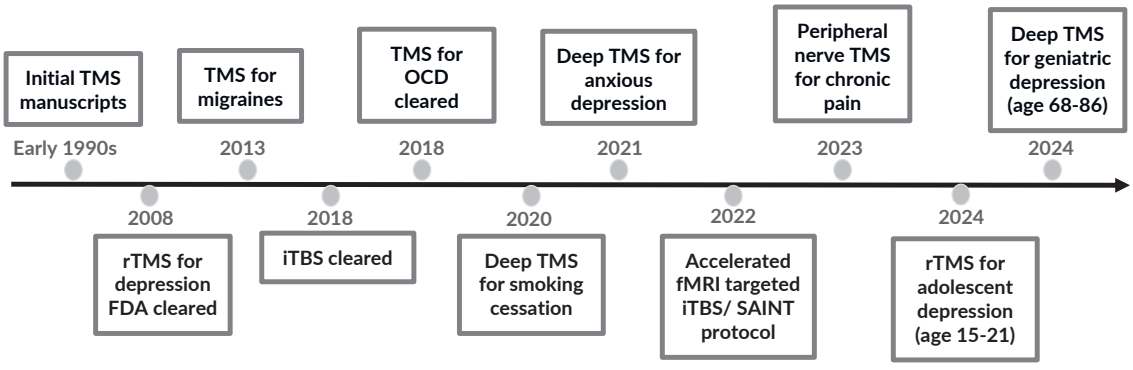
Quick review of some TMS basic science

Advances in TMS protocols for major depression

Unpack components of SAINT protocol

Explore role of accelerated TMS inpt/outpt

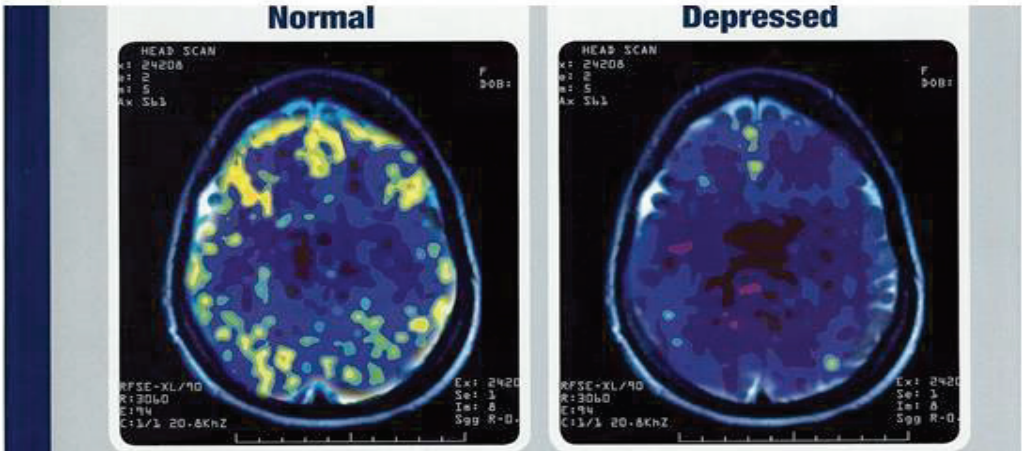
IT'S BEEN A BIG DECADE FOR THERAPEUTIC TMS



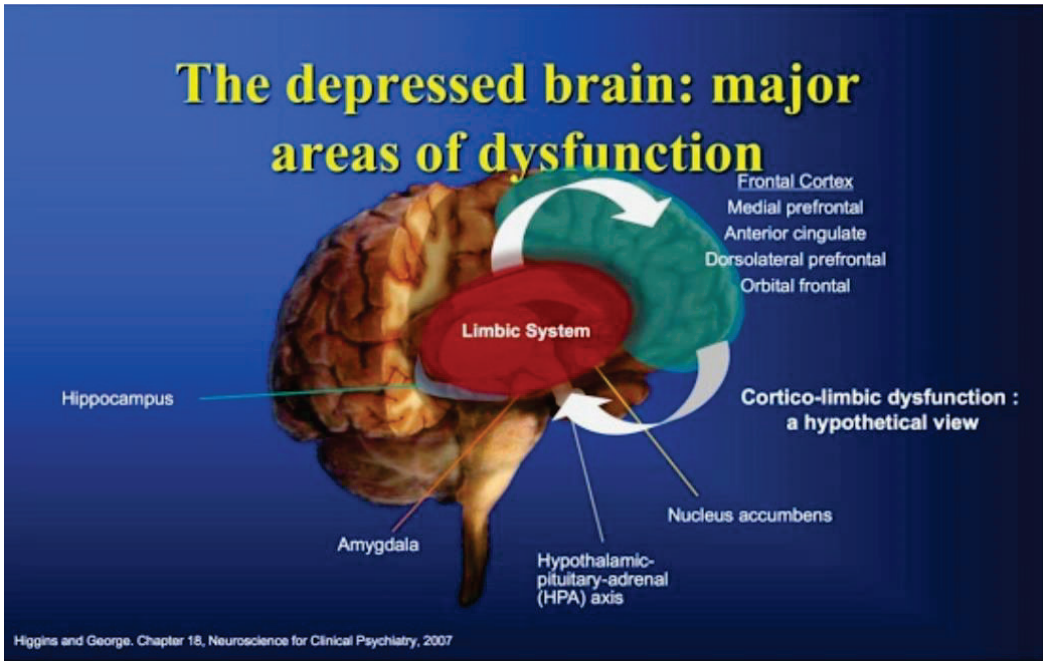
THE BIOLOGY OF DEPRESSION

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.

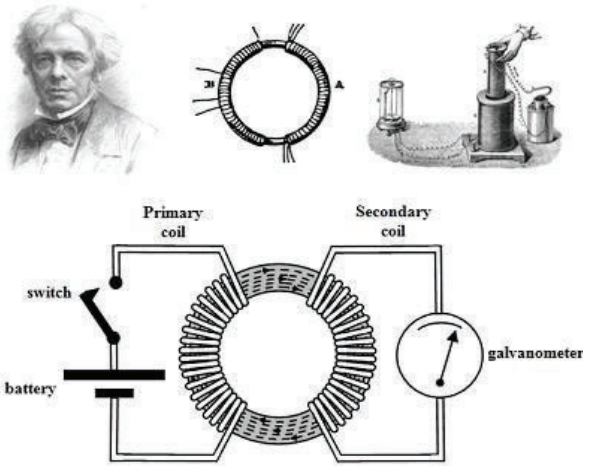


TRANSCRANIAL MAGNETIC STIMULATION: MECHANISM OF ACTION

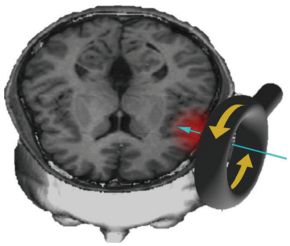
Science Behind TMS: 1831 Michael Faraday

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.

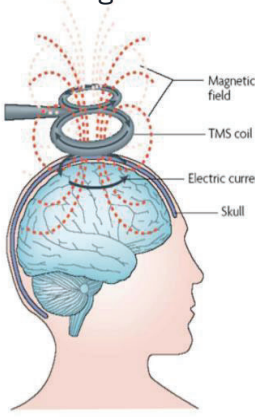
The rate of change (flux) of this magnetic field determines the induction of a secondary current in a nearby conductor that is placed in a perpendicular plane.

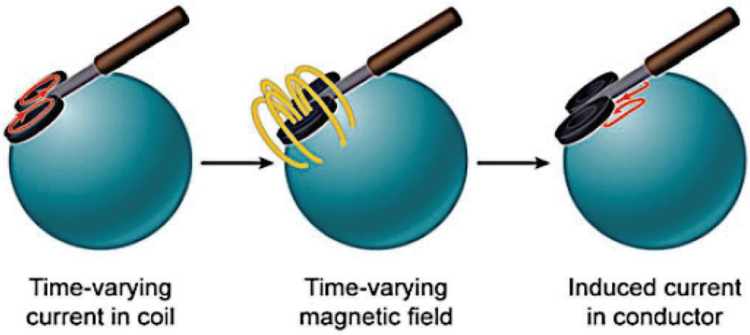


TMS Physics: Faraday's Law

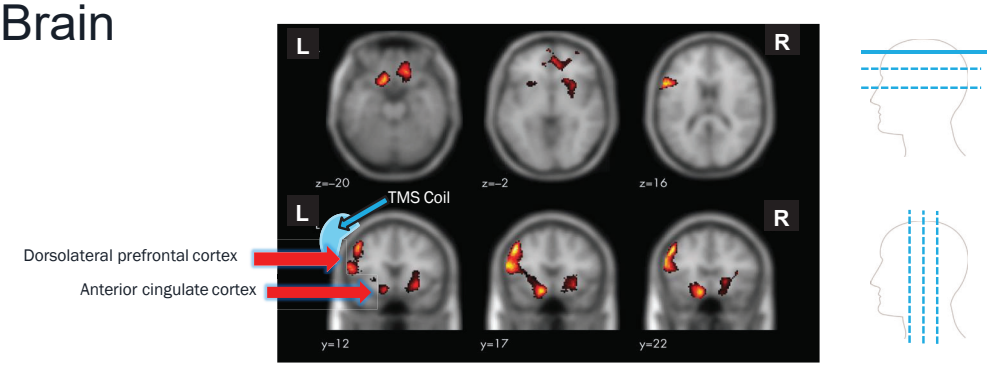


Magnetic Field Passes through Scalp and Skull Unimpeded
Cortical Neurons Act as Conductors, Like Copper Wire
Pulsed Magnetic Field Induces Current in Neurons





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

Biological & Behavioral Effects of TMS

Effects Seen After Chronic Exposure (Repeated TMS Applications):

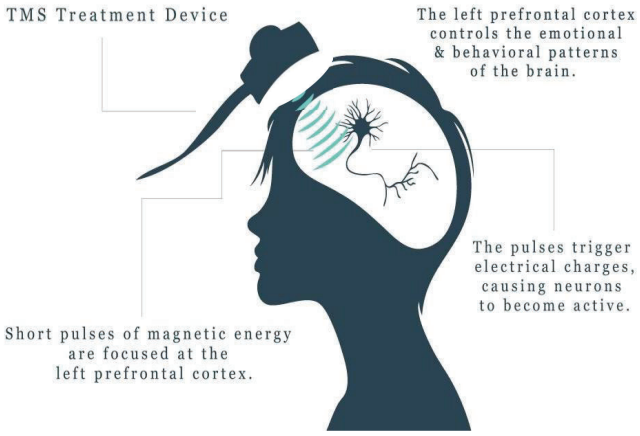
- Specific outcome is dependent upon stimulation parameters
- Alteration of monoamine concentrations
- Beta-receptor, serotonin-receptor modulation
- Evidence of induction of neurogenesis genes (eg, BDNF)
- Plasticity-like actions (ie, LTD/LTP-like effects)
- Local GABA, glutamate effects
- Stimulation 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.

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

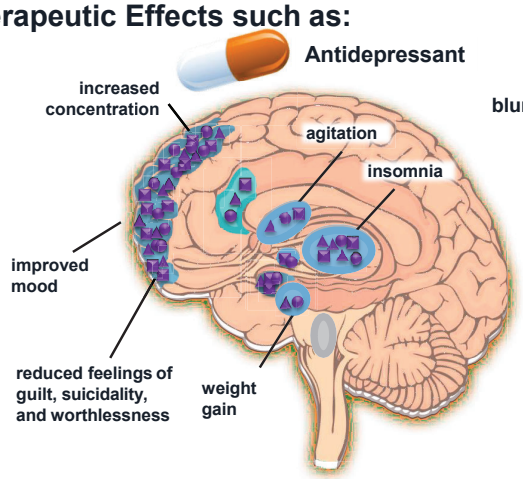
TMS: Contraindications

- 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)*

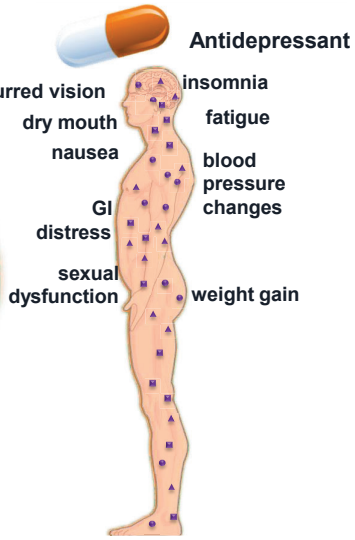
Hadley et al. J ECT 2010; Philip et al. Brain Stimulation. 2014; Schrader et al Clin Neurophysiol 2005

Monoaminergic Effects of Antidepressant Medications

Therapeutic Effects such as:



Side Effects such as:



Stahl SM. Cambridge University Press; 2008

TMS: is a Well-Tolerated Antidepressant

Most common adverse events with all Figure 8 Coil and Hesed 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

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

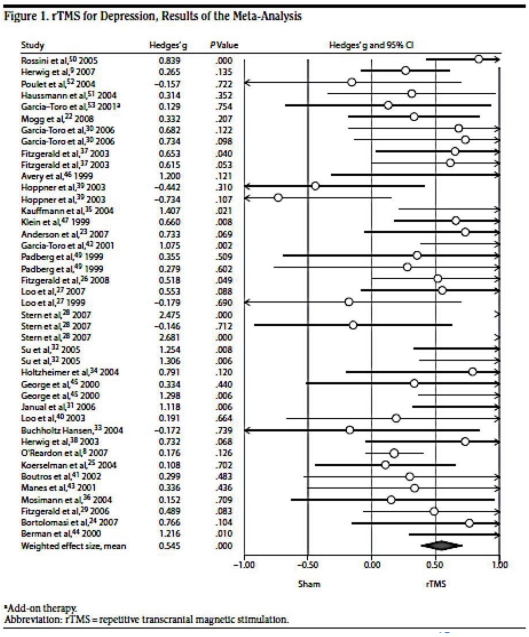
- Study reviewed 10 of 53 TMS studies involving both depressed and bipolar patients.
- *Early pooled data reported treatment emergent mania was 0.84% for active treatment group and 0.73% for sham group*
- *This difference was not statistically different*
- *The switch rate for unipolar patients was 0.34%*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

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

SCIENTIFIC EVIDENCE OF EFFICACY FOR TMS THERAPY

Evidence for Efficacy of TMS for MDD

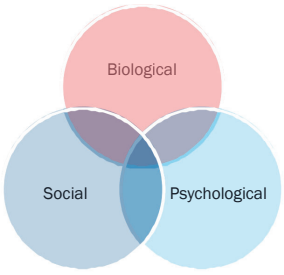
- 65 + clinical trials in adults
- Numerous meta-analyses
- Greater effects in more recent studies
  - Longer duration of treatment
  - Increase intensity
  - Increase pulse number
- Most recent
  - 65 RCTs , 2982 patients and found
  - TMS to be more effective than sham TMS
  - with a large effect size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



Dalhuisen et al., 2022 , McGirr et al., 2021 Pellet al ,2022

Why are Real World Results Better than Clinical Trial Results?

- Combination Strategies
  - *Well tolerated with many medications* [1]
- Psychotherapy [2]
- Engagement in Life
  - *Intensive Outpatient Program – Factors*
    - Routine
    - Interaction
    - Engaging with People who Care



[1]Rossi et al. J Neurol Neurosurg Psychiat 2007; [2] 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

Year Approved	Tx Type	Min / Tx	Tx Course
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 0f 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
- **MADRAS** was primary scale, remission <10, response 50% drop in score
- **78% remission rate** , 13% sham
- 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 pules 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

What is the Magic Ingredient to **SAINT**?

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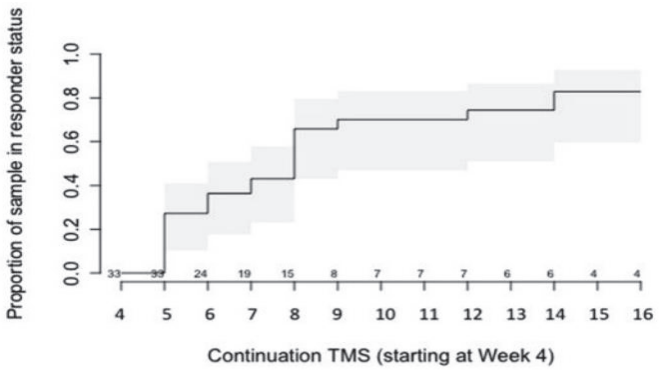
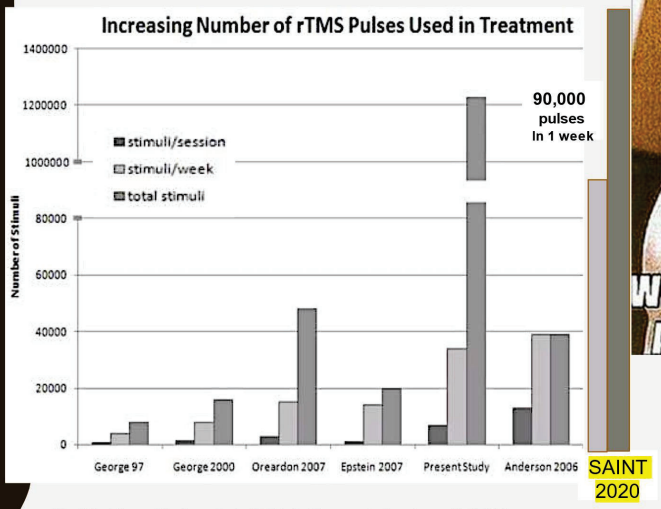
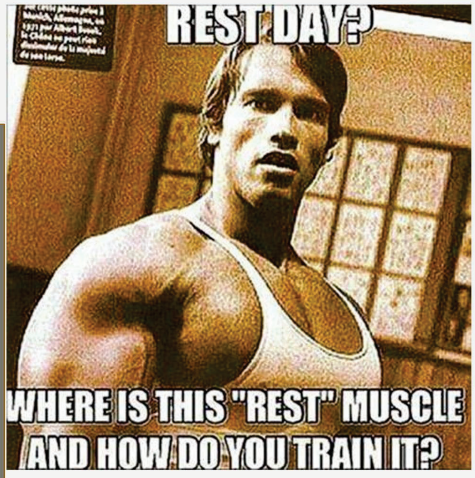
More treatments , better response



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**?

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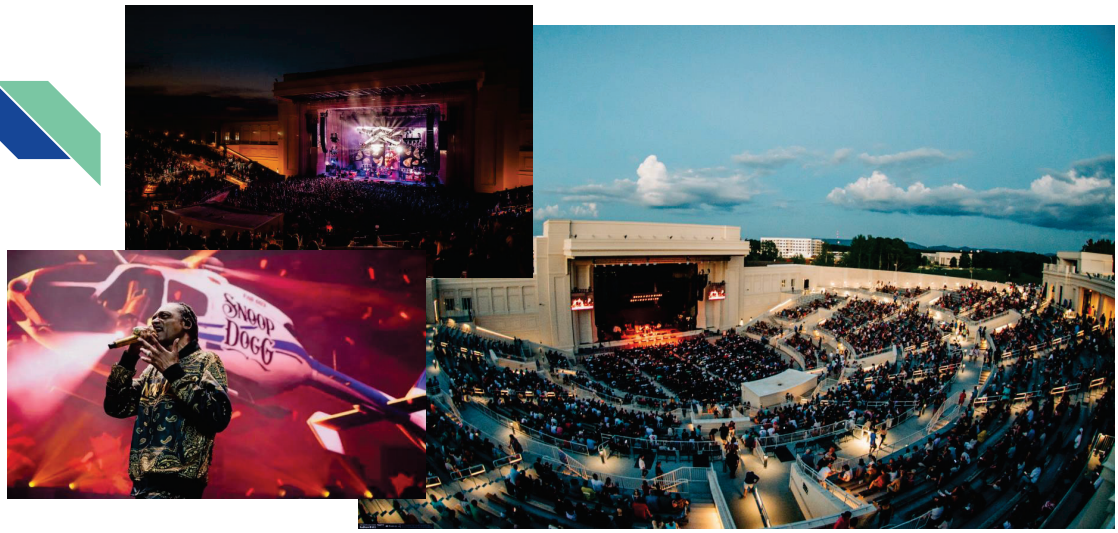
Patient Selection

- ❑ 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**?

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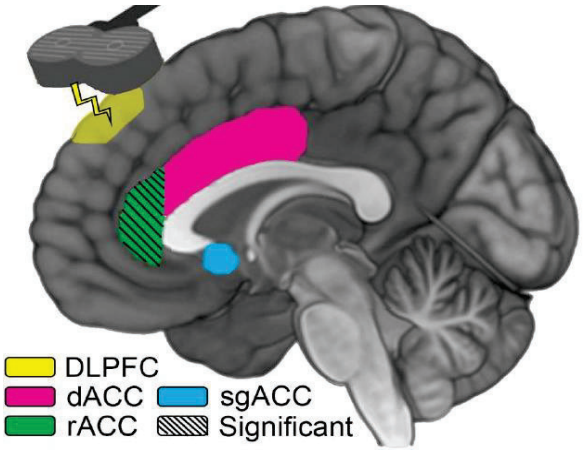
DLPFC and sgACC
"resting state fMRI "



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 !