An Introduction to Transcranial Magnetic Stimulation: Beyond Depression

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The Clinical TMS Society (CTMSS)

- **CTMSS is an international professional association of about 1000 clinicians, researchers, technicians, students and industry partners dedicated to:**
  - ***Optimizing the clinical practice of TMS***
  - ***Awareness of TMS***
  - ***Accessibility of TMS***

This slide deck was originally conceived, produced, and edited by the Outreach Committee of the Clinical TMS Society.

The society's board of directors originally approved slide decks for educating other clinicians in September 2017.

Since that time, the slide decks have evolved and been edited.

Learning Objectives

At the end of this educational activity, the learner will

- Know FDA cleared psychiatric indications for TMS
- Understand the basic neurobiology of OCD and addictions as related to the potential mechanism of TMS
- Review the data supporting the use of TMS for OCD, smoking cessation, depression with anxious features, and SAINT
- Identify the potential risks of TMS
- Understand patient appropriateness for TMS based on demographics, diagnosis, and treatment history

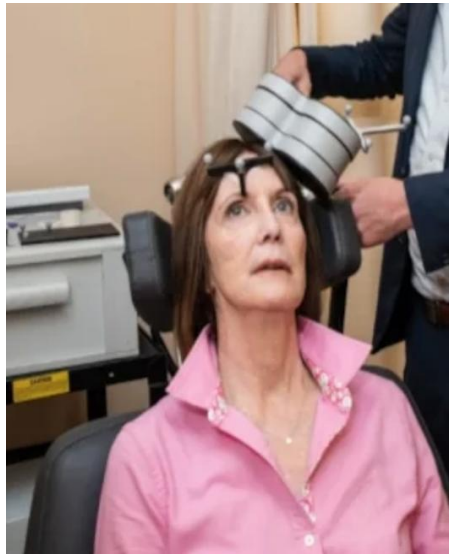
TMS:
FDA-Cleared Indications Other Than MDD

TMS Therapy is FDA-Cleared for:

- MDD in adult patients who have failed to receive satisfactory improvement from one prior antidepressant medication
- Refractory MDD with the SAINT neuromodulation system (accelerated protocol and personalized neuro-navigation)
- Anxious depression
- Treatment refractory OCD
- As an aid in short-term smoking cessation
- Acute and preventative treatment of migraine (single pulse device)

Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT)

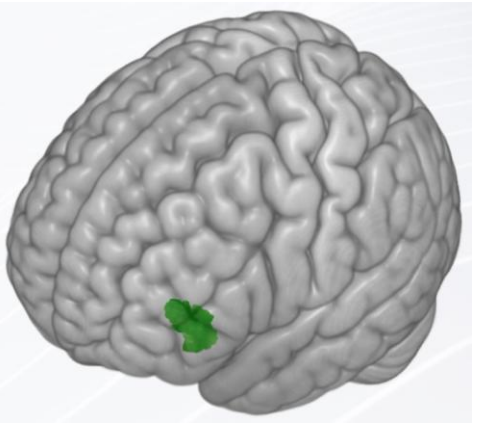
SAINT: Neuromodulation System I



- TMS system developed with the idea that iTBS protocol for depression might be improved through
  1. Multiple sessions per day at optimally spaced intervals
  2. A higher overall pulse dose of stimulation
  3. Precision functional targeting of the left dorsolateral prefrontal cortex (DLPFC) to subgenual anterior cingulate cortex (sgACC) circuit.

- FDA-cleared for the treatment of major depressive disorder (MDD) in adults who failed to achieve satisfactory improvement from prior antidepressant medication in the current episode

SAINT:
Neuromodulation System II



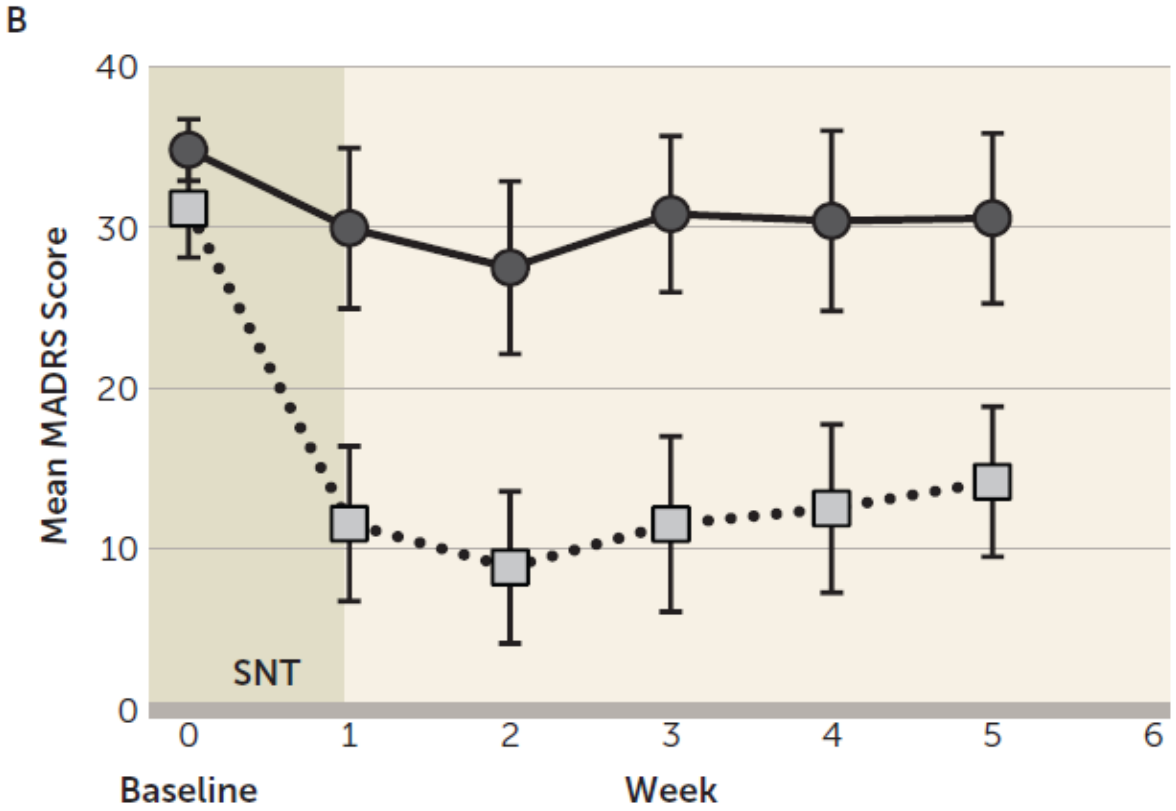
- RCT of 29 participants with moderate to severe MDD:
  (14 active in group; 15 in sham group)

- Resting-state fMRI individually targeted the region of the L-DLPFC most functionally anticorrelated with the sACC

- 50 iTBS sessions delivered 10 times daily over 5 consecutive days:
  (1,800 pulses per session; 50-minute intersession interval;
  90% resting MT (adjusted for cortical depth)

SAINT: Neuromodulation System III

- Mean percent reduction from baseline in MADRS score 4 weeks later:
  - 52.5% in the active group
  - 11.1% in the sham group
- Large, long-term durability studies are not yet available



TMS:
Anxious Depression

Anxious Depression: Treatment Challenges

- Anxiety is a frequent co-morbid symptom of MDD and is recognized in the DSM 5-TR with an anxious specifier[1]
- Anxious depressed patients are often older, unemployed, less educated, more severely depressed, and have suicidal ideation before and after adjustment for severity of depression[3]

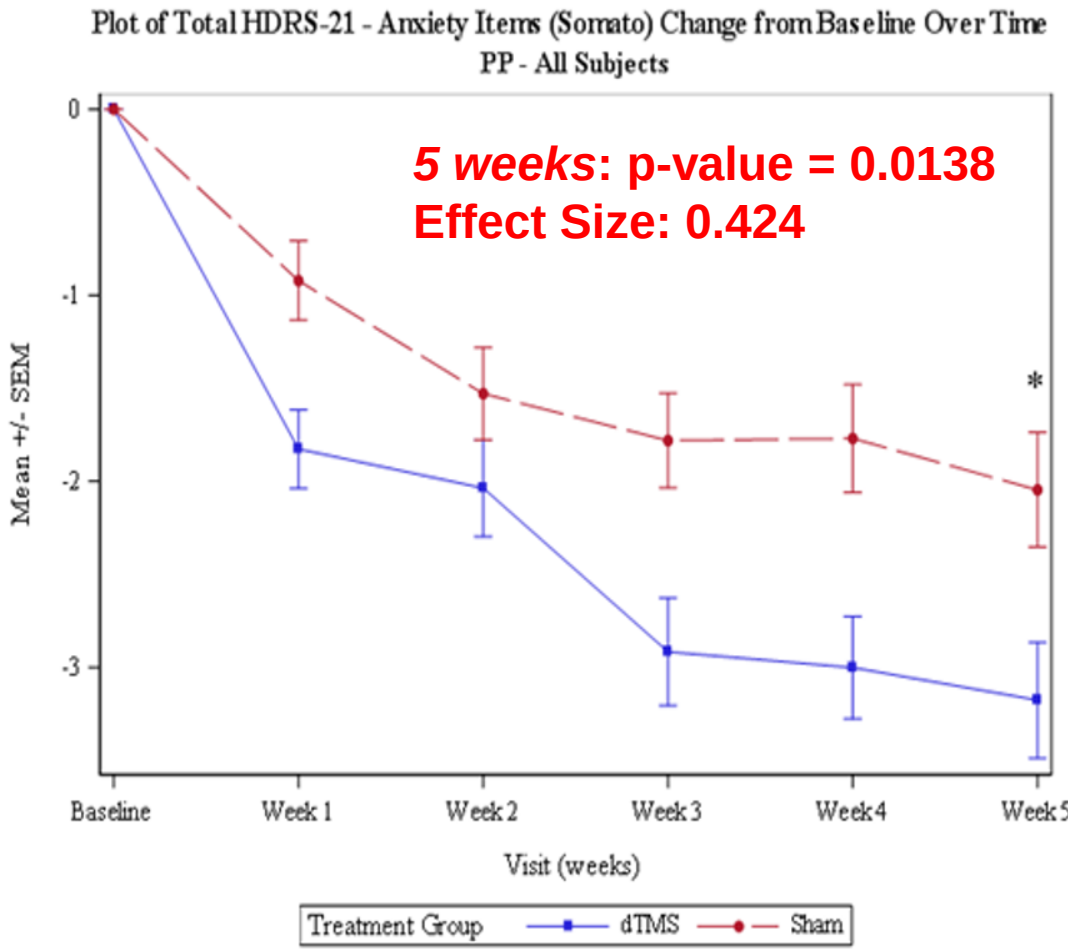
[1]DSM 5-TR, [2]Fava et al. 2000,[3]Fava et al. 2004

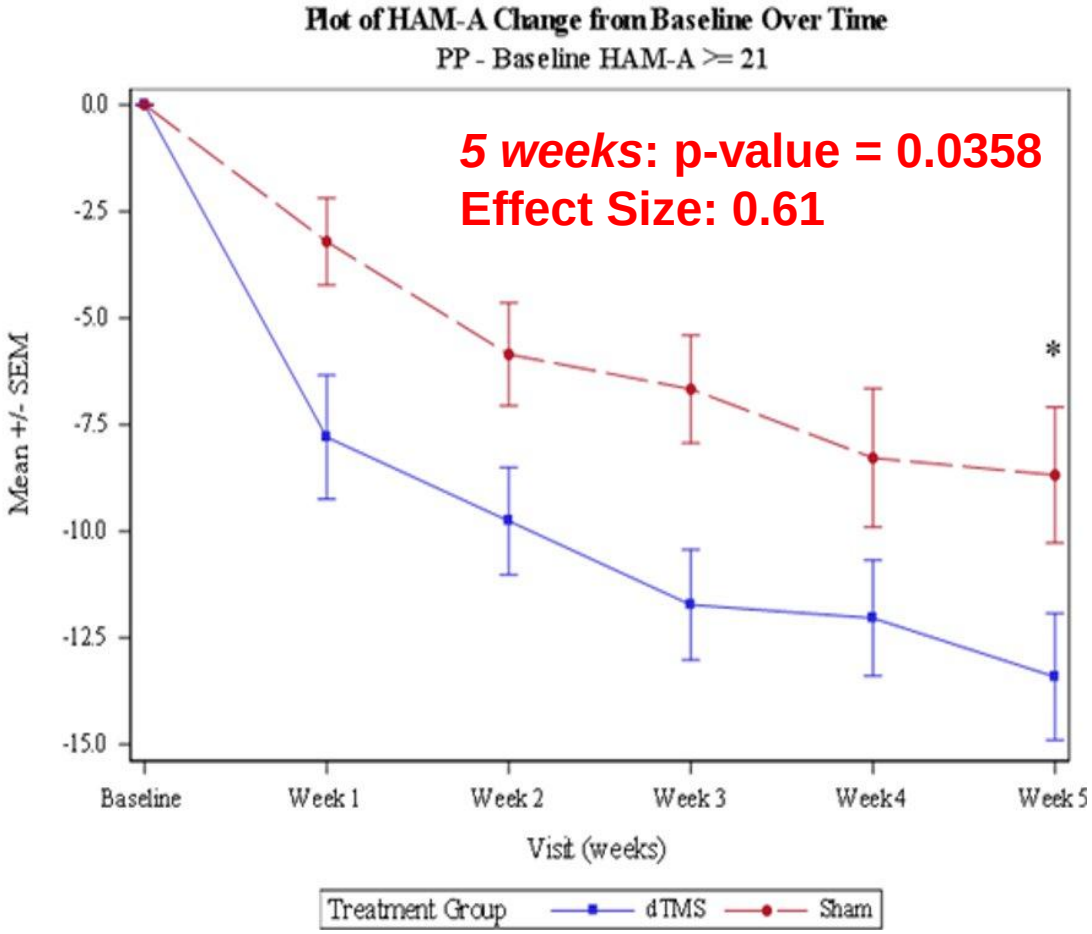
Anxious Depression: Supporting Evidence for FDA-Clearance

- Post-hoc analysis of a double-blind, sham-controlled study in treatment-resistant MDD
- Looked at changes in the HDRS Anxio-Somatic item and Hamilton Anxiety Scale total score at weeks 5 and 16
- Protocol:
  - HF (18 Hz), 120% MT, dTMS H-Coil targeting L DLPFC versus a sham procedure
  - 4 weeks of 5 treatments per week for 20 sessions, then 12 weeks of 2 treatments per week
  - Total weeks of treatment = 16 ; Total sessions = 44

[1] CTMSS communication with Brainsway CMO A. Tendler; [2] Levkovitz Y, et al. 2015

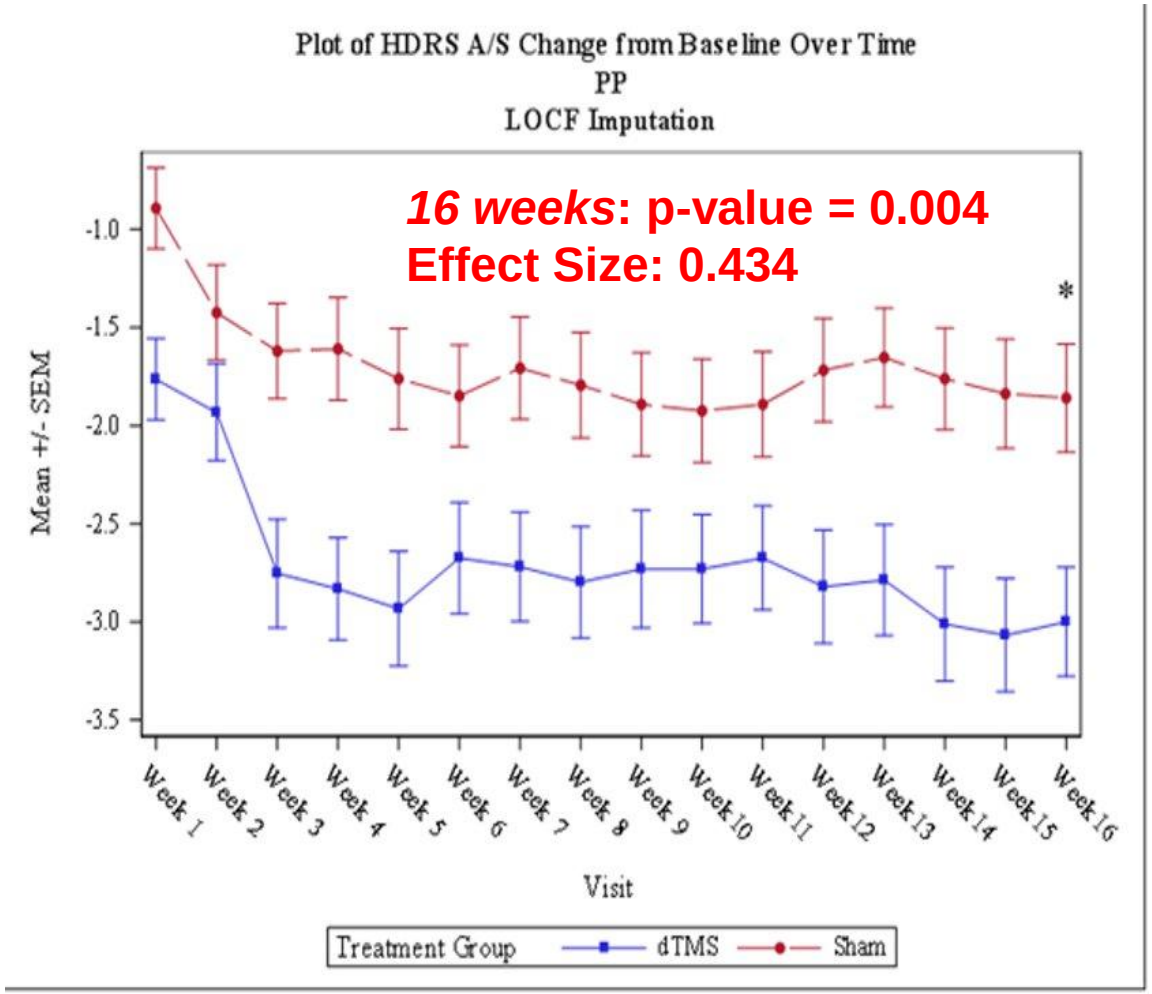
Anxious Depression:
Supporting Evidence for FDA-Clearance I

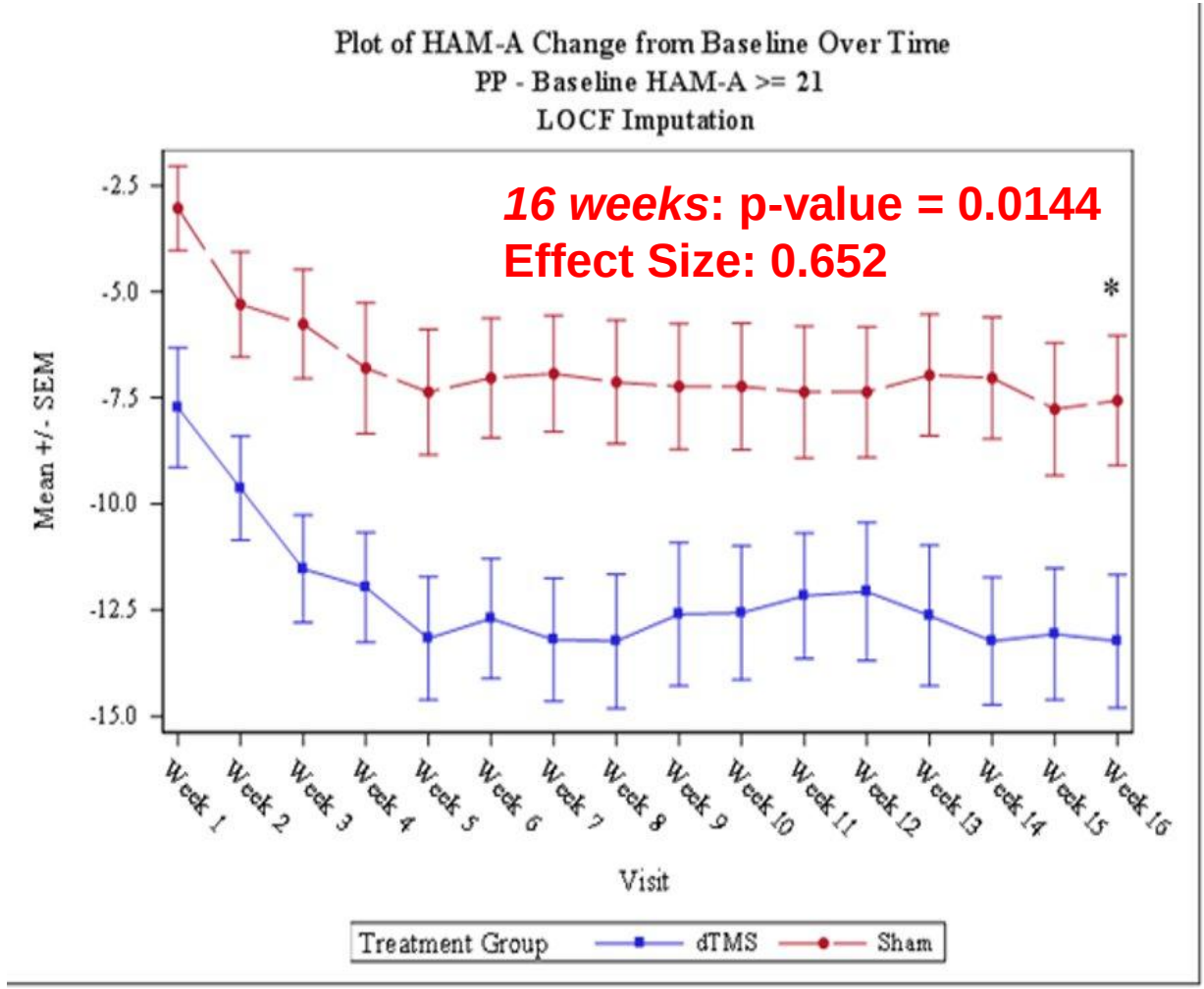




[1] CTMSS communication with Brainsway CMO A. Tendler; [2] Levkovitz Y, et al. 2015

Anxious Depression: Supporting Evidence for FDA-Clearance II





[1] CTMSS communication with Brainsway CMO A. Tendler; [2] Levkovitz Y, et al. 2015

TMS:
Migraine Headache

Migraine

One device as of 2013

- Single pulse TMS (sTMS)
- Portable, battery-operated device generates a 0.9T pulse lasting less than a millisecond
- First FDA cleared in 2013 for abortive acute treatment in migraine with aura
- FDA cleared in 2017 for acute and preventative treatment of migraine headaches in adolescents (age 12 and older) and adults

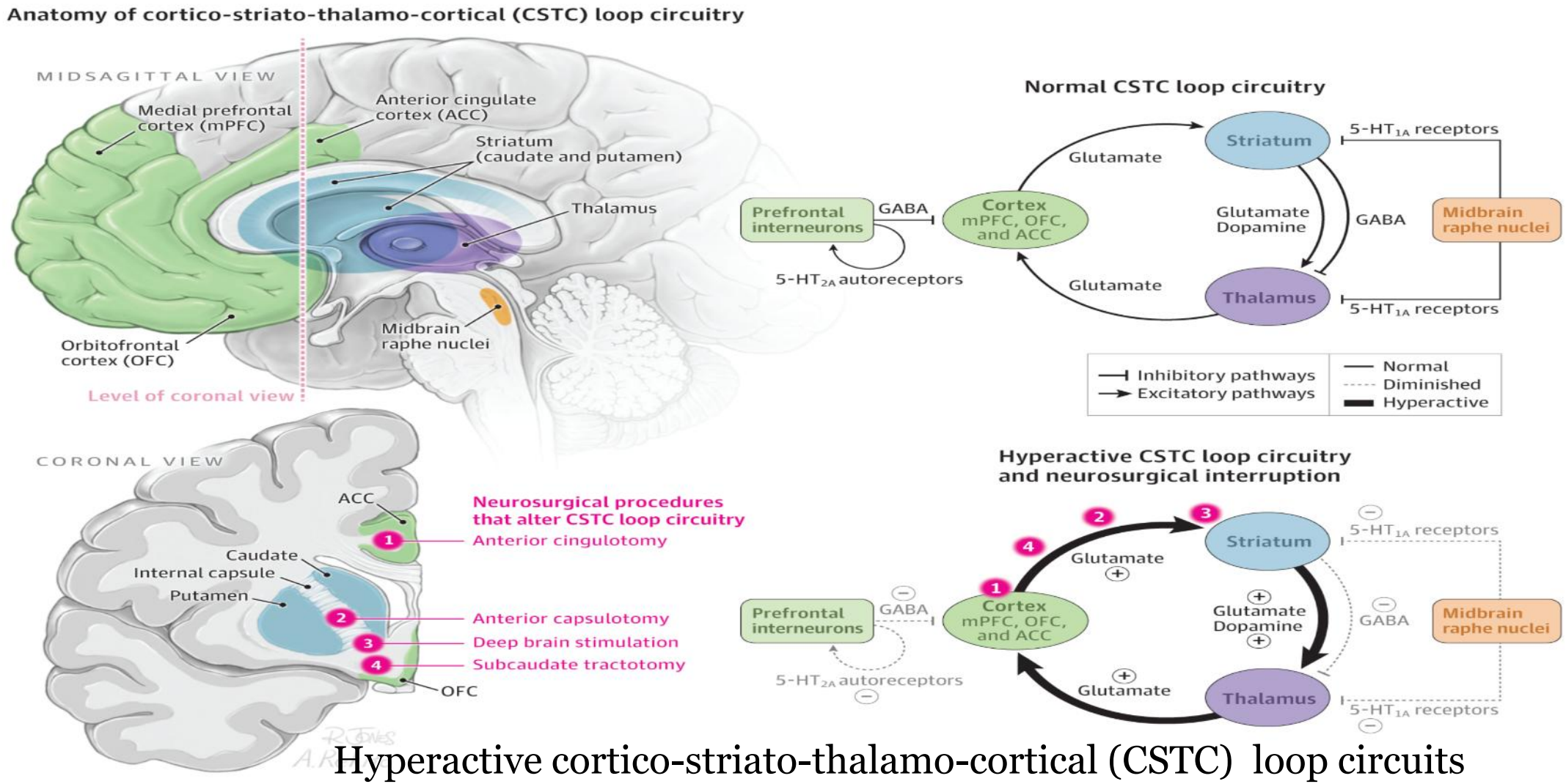
TMS: Obsessive-Compulsive Disorder (OCD)

OCD Treatment Challenges

- OCD has a lifetime prevalence of 2.3%[1]
- 10% of patients have no meaningful response to traditional treatments including pharmacotherapy (SSRIs, TCAs, atypical antipsychotics) and cognitive behavioral therapy (e.g., ERP)[2]
- Psychosurgeries (DBS, ablative procedures) come with risk of severe complications (infection, bleeding, device malfunction, agitation/mania, etc.)

[1]Russio et al. (2010);
[2]Pallanti et al. (2006)

Proposed Mechanism of OCD

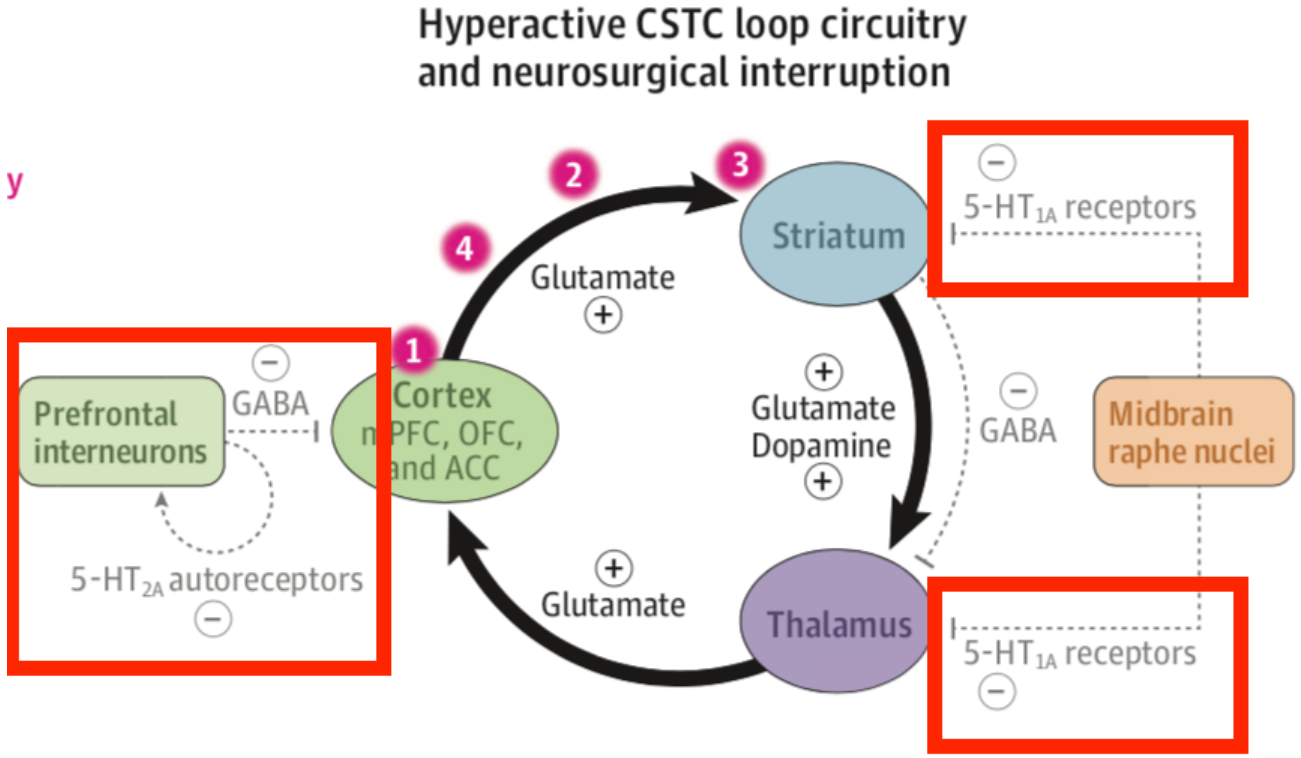


Hyperactive cortico-striato-thalamo-cortical (CSTC) loop circuits

Dougherty et al. (2018) *JAMA Psychiatry*

A Neurochemical Explanation of Hyperactive CSTC Circuits

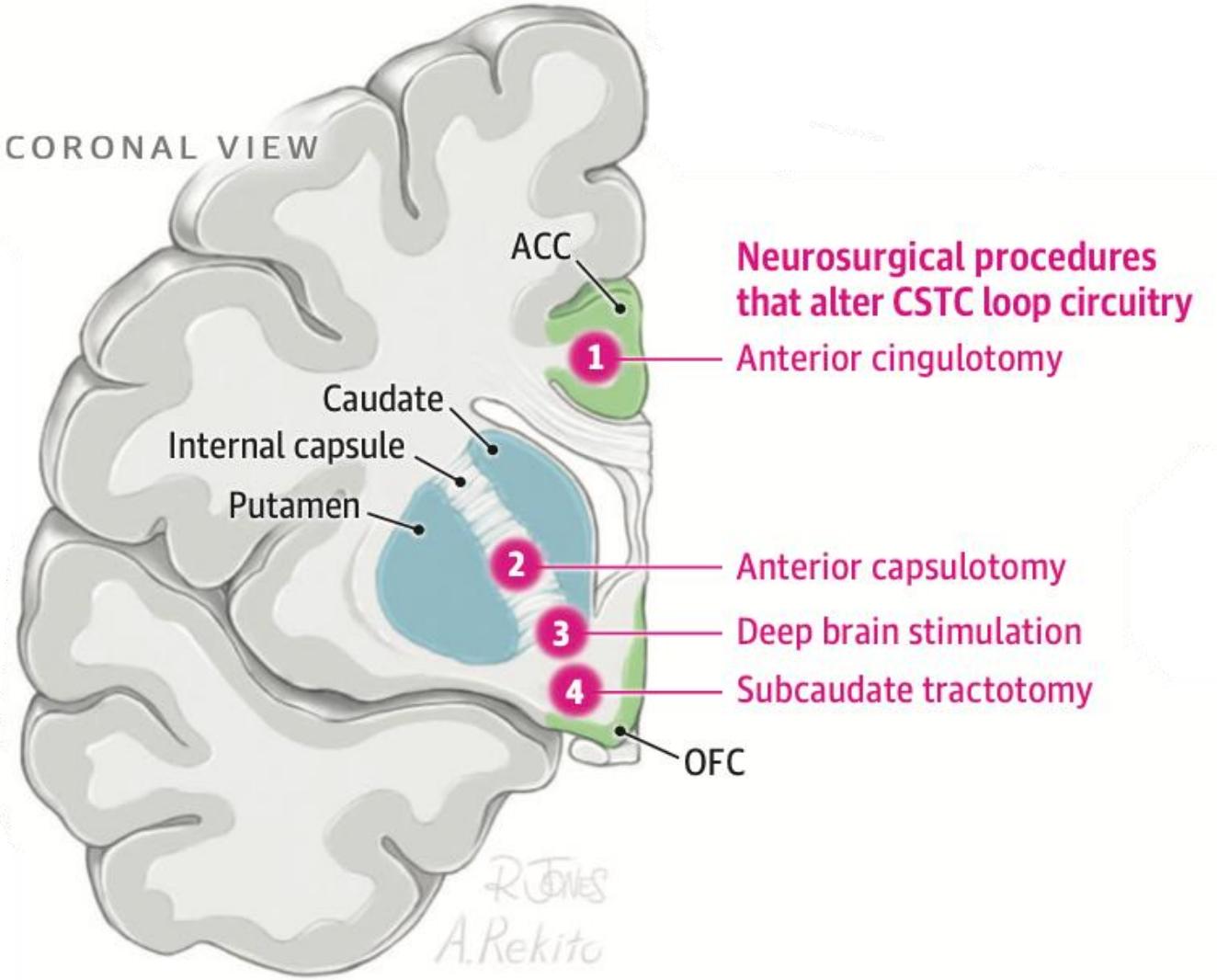
- Hyperactive CSTC Circuits due to decreased "breaks" and increased "acceleration"
- "Breaks" in OCD – diminished serotonin & GABA activity in mid-brain & mPFC
- "Acceleration" in OCD – increased glutamate & dopamine activity in cortex, striatum, & thalamus



Dougherty et al. (2018) *JAMA Psychiatry*

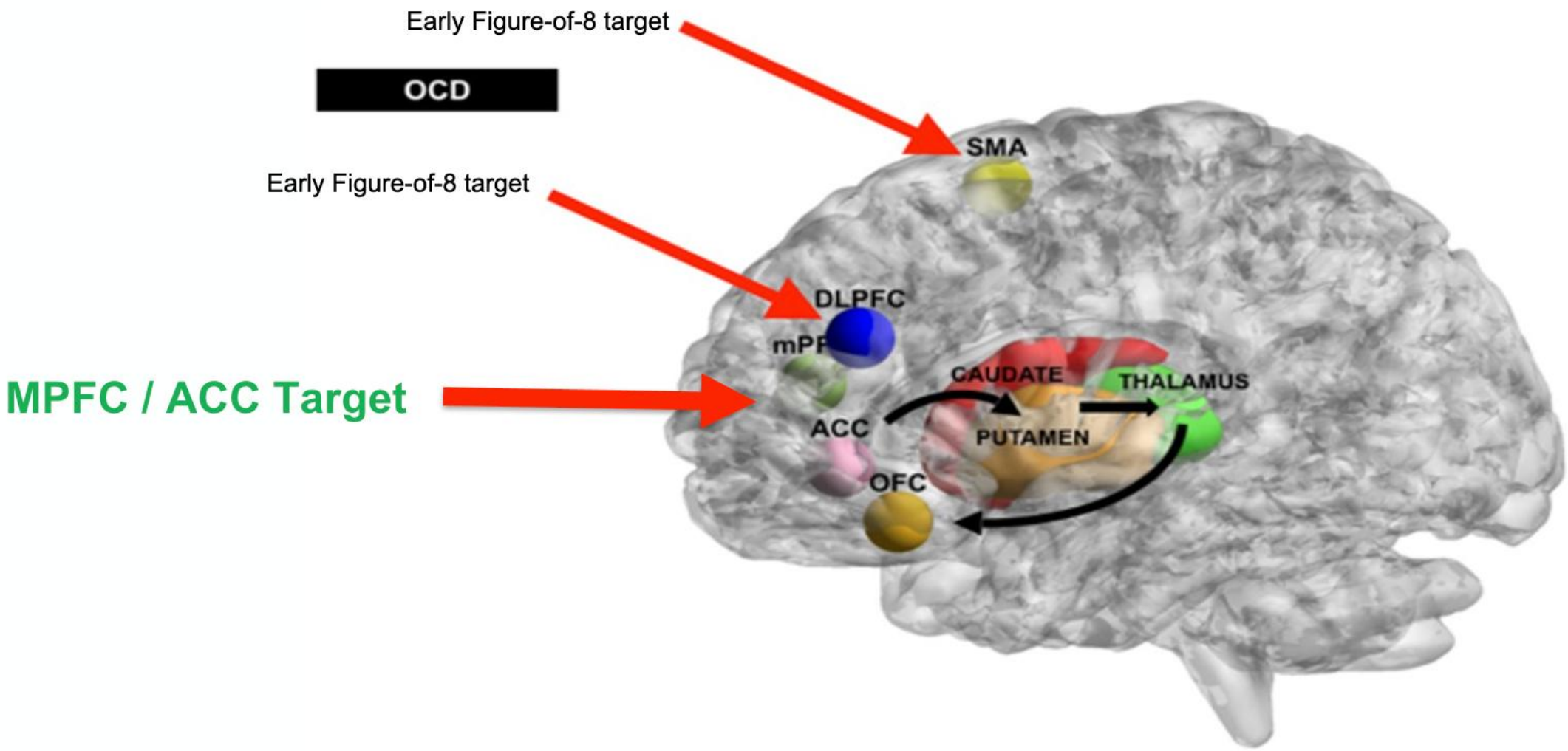
Neurosurgical Intervention Sites That Alter CSTC loop circuitry

- *Anterior cingulotomy*
- *Anterior capsulotomy*
- *Deep brain stimulation (VCVS)*
- *Subcaudate tractotomy*



Dougherty, et al. (2018)

Obsessive Compulsive Disorder Targets



Williams NR et al. 2018

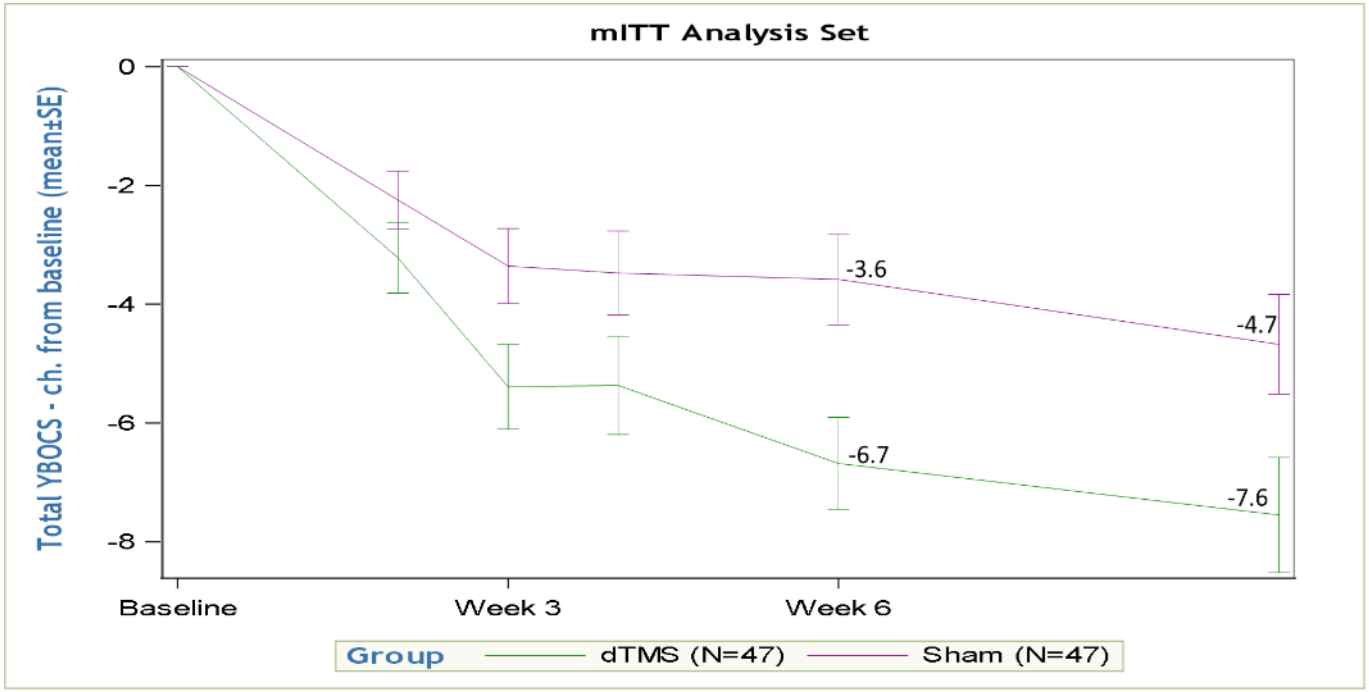
OCD TMS Pivotal Study

- Randomized, multi-center study (n = 100)
- Patients receiving medications for OCD were maintained at current dosages
- 49 patients received treatment with H-Coil targeting ACC & MPFC, and 51 received treatment with a sham device
- Protocol: 20 Hz, 2 sec on, 20 sec off, for 50 trains= 2000 total pulses for 29 sessions
- "PERSONALIZED SYMPTOM PROVOCATION" before treatment (Theory: Prime the circuit before treatment)

Press Release by FDA on 8-17-2018:
Carmi et al. (2018) *Brain Stimulation*

Results of OCD TMS Pivotal Study

- 38% of patients responded (>30% reduction in YBOCS) to TMS verses 11% of patients undergoing sham
- Likely best used as adjunct to exposure therapy and medications
- Remission is rare, as is the case with SSRI treatment
- Effect sizes are modes (Y-BOCS reduction ~6-9); similar to SSRI outcomes
- Large, long-term durability studies are not yet available



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

Press Release by FDA on 8-17-2018:
Carmi et al. (2018) *Brain Stimulation*

TMS:
Smoking Cessation

Smoking Cessation Treatment: Challenges

- 34 million people and an estimated 14% of adults in the US smoke cigarettes
- Individuals who attempt to quit smoking average approximately 6 quit attempts before achieving long-term abstinence
- The EAGLES trial, an RCT of 8144 people who smoked found a significantly higher 6-month quit rate for varenicline (21.8%) than for bupropion (16.2%) and the nicotine patch (15.7%). Each therapy was more effective than placebo (9.4%).
- One RCT of 446 participants found significantly higher 6-month cessation rates from combining varenicline & NRT than from varenicline alone (65.1% vs 46.7%)

Rigotti et al. (2022) *JAMA*

Brain Targets in Addiction

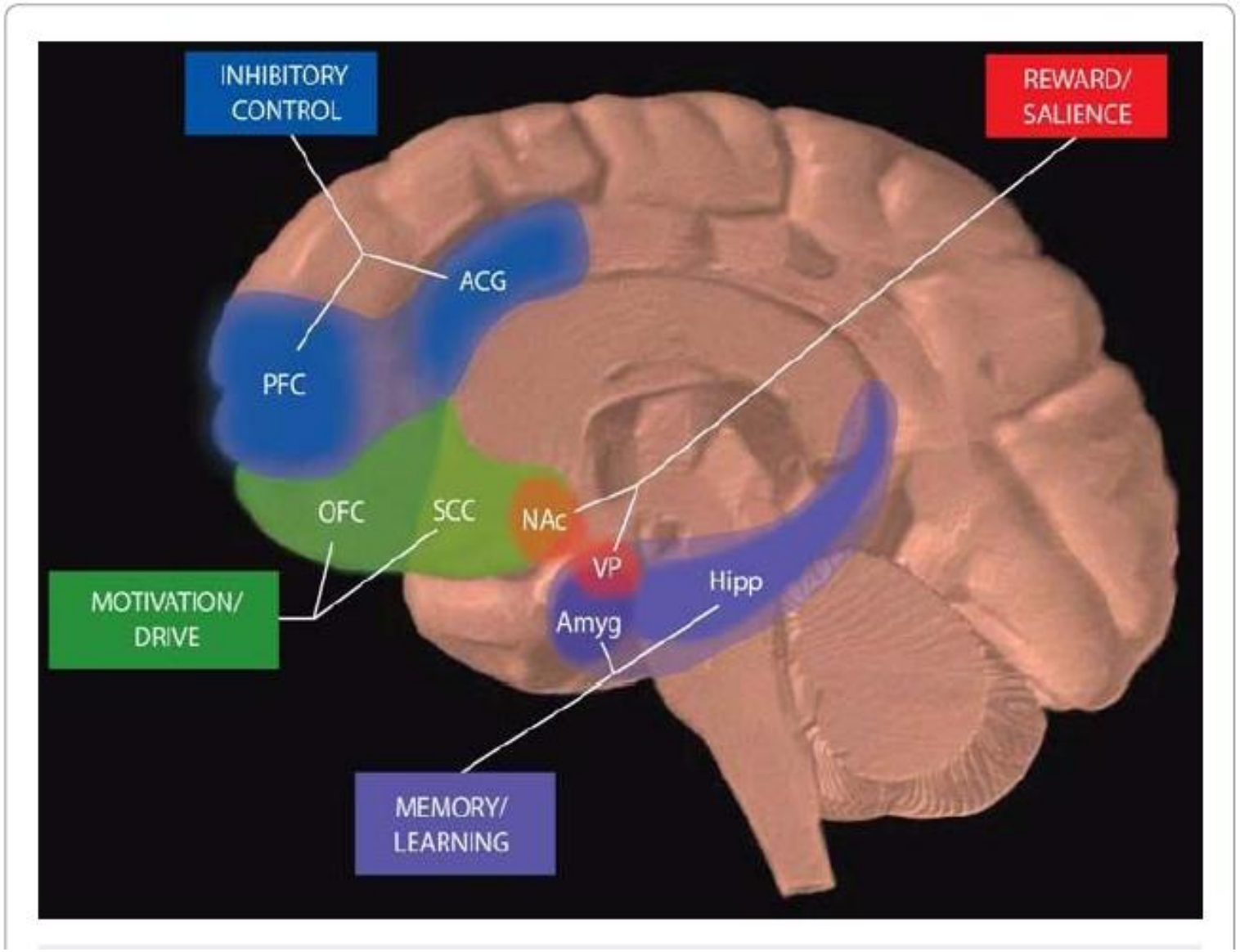
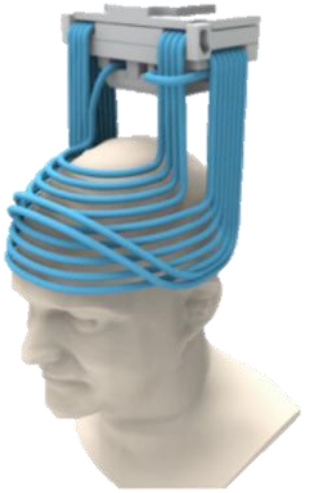


Image from NIDA website

Smoking Cessation Pivotal Study: Design

- RCT using Brainsway's proprietary H-4 coil
- 262 heavy smokers (168 completed the study plus 3 weeks of follow-up)
- 5 treatments/week for 3 weeks then 1 treatment/week for 3 weeks (total = 18)
- 10 Hz, 120% RMT, 3 sec train (30 pulses), 15 sec IPI, 1800 pulses
- H4 stimulation site: insular and lateral prefrontal cortices
- 5-minute pre-treatment provocation procedure
- After TMS, a 2-minute motivational talk was read



Zangen et al. (2021) *Lancet*

Smoking Cessation Pivotal Study*: Results

- Primary end point was 4-week Continuous Quit Rate (CQR)
- CQR was 28.4% in the treatment group vs 11.7% in the sham group (p=0.0063)
- ITTQR was 19.4% in the treatment group vs 8.7% in the sham group (p=0.0238)
- A secondary end point, reduction in the number of cigarettes smoked:

	Active	Sham	
Average no. smoked/ week	132	127	
After 3 weeks treatment	38	57	p = 0.0018
After 6 weeks of the study	31	48	p = 0.0125

Zangen et al. (2021) *Lancet*

**Large, long-term durability studies are not available*

TMS:
Adverse Events

TMS Therapy Well-Tolerated

Most common adverse events with all coils (incidence < 5%):

TMS Side Effects:

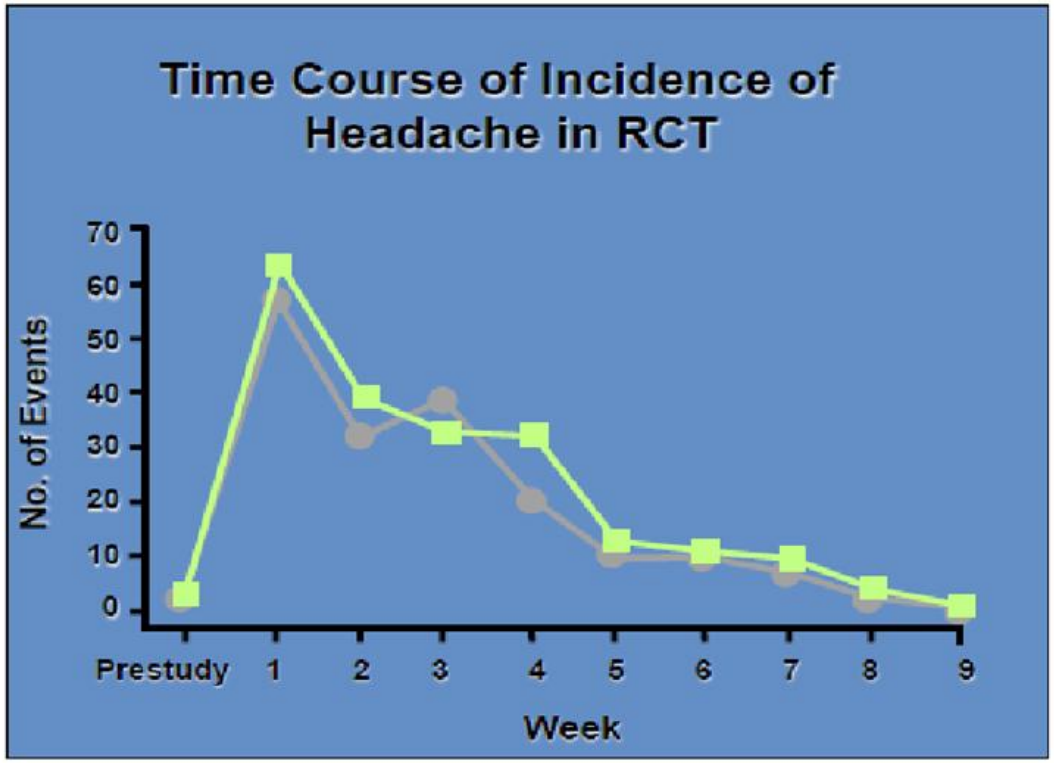
- Application site discomfort/pain
- Headache
- Referred (eye, tooth, jaw) discomfort/pain
- Insomnia
- Anxiety

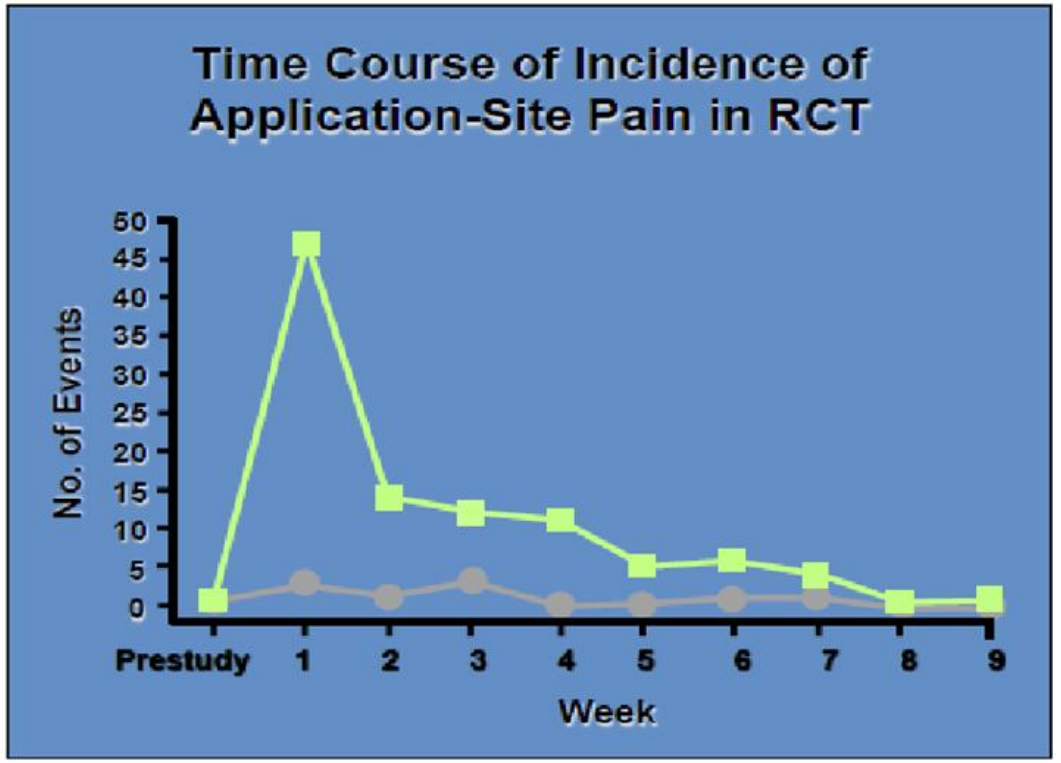
No Systemic Effects:

- Changes in sleep
- Fatigue
- Anxiety / Agitation
- Blurred vision
- Dry mouth
- Weight and Appetite changes
- Sexual dysfunction
- Autonomic Changes / Instability
- Gastrointestinal distress
- Tremor
- Negative changes in cognition

510(k) applications for Neuronetics & Brainsway devices for MDD (2008, 2012);
Janicak et al. (2008) *J Clin Psychiatry*

Time Course for Most Common Adverse Events with Figure-8 TMS Coil

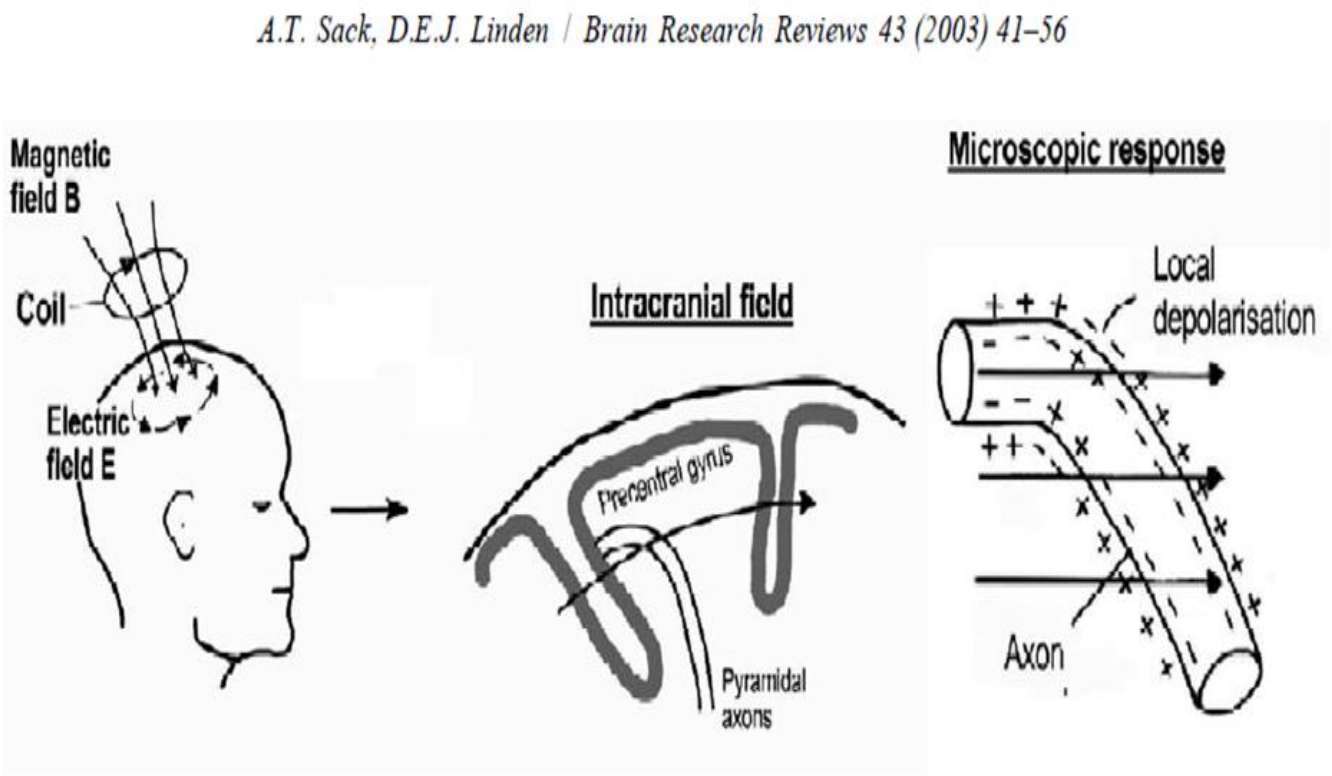


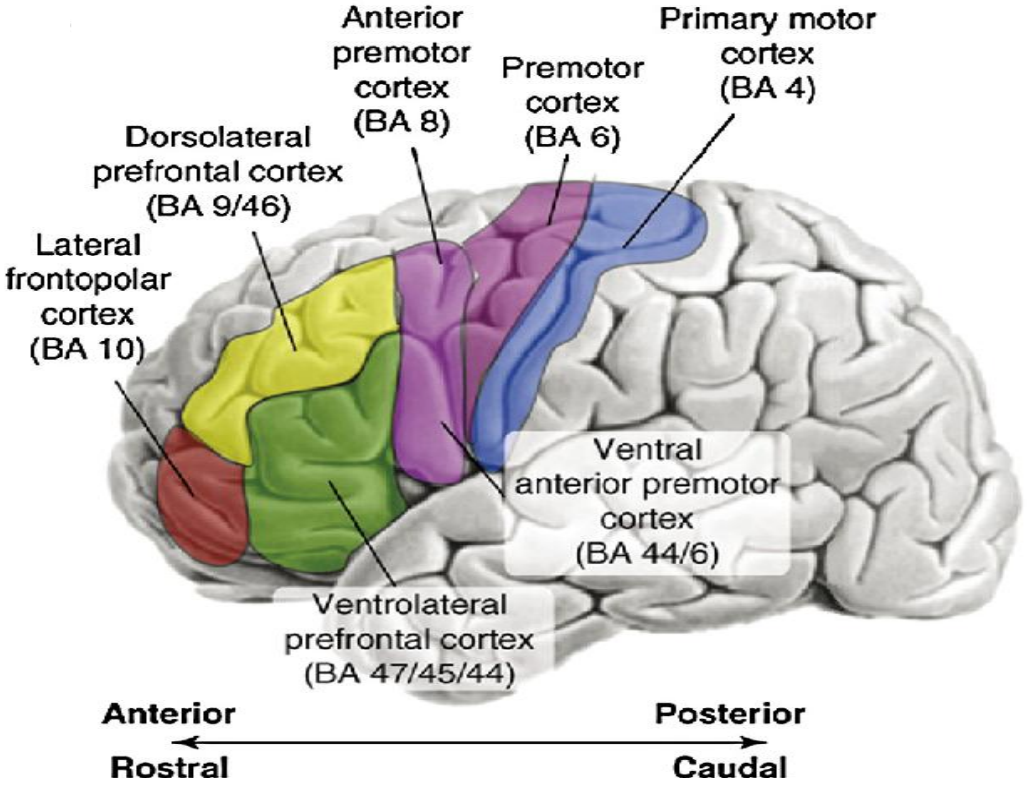


Janicak et al. (2008) J Clin Psychiatry

TMS: Seizures I

- Seizure most serious adverse event associated with TMS.
- The risk of seizures is < 0.1% per treatment course





Dumontheil. (2014) *Developmental Cognitive Neuroscience*

TMS: Seizures II

- Most cases associated with TMS were prior to the publication of safety guidelines in 1998 [1]
- The risk is less than or comparable to that associated with antidepressant medications [2]
- All reported TMS induced seizures have occurred during treatment session itself and have stopped with no sequelae and no progression to epilepsy.

1. Wassermann. (1998) *Electroencephalography and Clinical Neurophysiology*
2. George et al. (2013) *Curr Opin Psychiatry*

TMS: 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 in which hearing protection was used report no changes in hearing[3]
- Recent study examining the sound of 7 different TMS coils found airborne sound exceeded some exposure limits for TMS subjects and, in some cases, for operators.[4]

[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; [4]Koponen et al. (2020) Brain Stim*

TMS:
Hearing Recommendations:

- Patients and TMS technicians are required to use earplugs that meet a minimum standard of 30dB of protection

- Consider hearing protections for visitors or clinicians that stay in the room during treatments, especially with higher stimulation intensities

TMS:
Treatment Emergent Mania (TEM)

Review of 10 TMS studies involving both depressed and bipolar patients reported[1]:

- TEM was 0.84% for active treatment group and 0.73% for sham group
- The switch rate for unipolar patients was 0.34%
- The switch rate for bipolar patients was 3.1%

More recent review of all TEM reported up to 2015 found that[2]:

- Both high and low frequency stimulation could result in TEM
- Although, many of the cases of TEM coincided with antidepressant medication changes.

[1]Xia et al. (2008) *Int J of Neuropsychopharmacology*
[2]Rachid (2017) *J of Psych Practice*

TMS:
Emergence of Suicidal Ideation in Pivotal Study

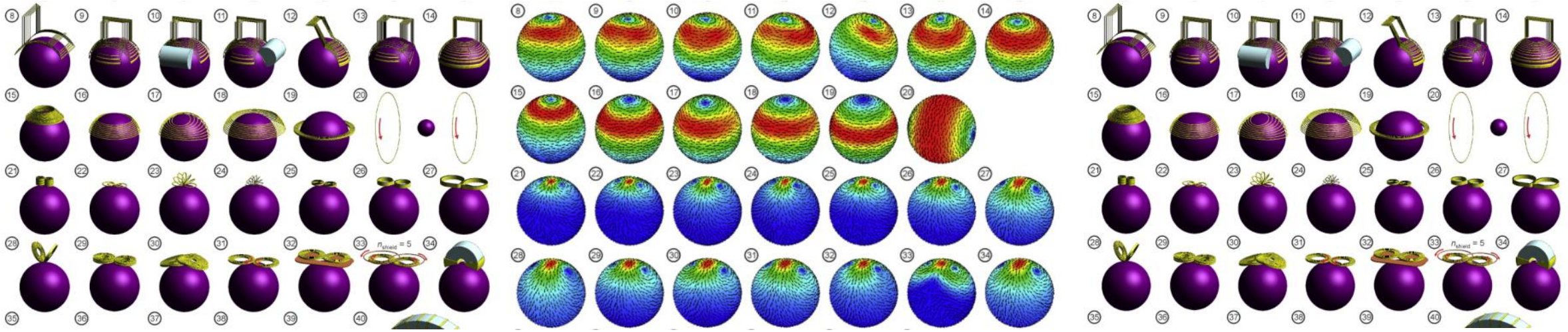
- Treatment emergent disease exacerbation in a population with increased severity of clinical condition
- 1.9% with sham; 0.6% active TMS
- One non-lethal overdose in a sham-treated patient

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

Summary

TMS is:

- Focal, non-invasive form of brain stimulation
- Based on principles of electromagnetic induction of current
- Well studied in its current form for >30 years
- FDA-cleared for >10 years
- Well-tolerated and without risk of systemic side effects



Images Deng Z et al. 2013

Who is Right for TMS Therapy?

TMS Therapy is FDA cleared for:

- MDD in adult patients who have failed to receive satisfactory improvement from one prior antidepressant medication
- Refractory MDD with the SAINT neuromodulation system (accelerated protocol and personalized neuro-navigation)
- Anxious depression
- Treatment refractory OCD
- As an aid in short-term smoking cessation
- Acute and preventative treatment of migraine (single pulse device)

Who is Right for TMS Therapy?

Best Practices:

- In MDD that has failed to respond to 2+ antidepressant medication trials from at least 2 different classes, with or without anxious features
- In OCD that has failed to respond to evidence-based medication trials from at least 2 different classes AND a trial of evidence-based psychotherapy (e.g. ERP)
- In smoking cessation, for patients who have failed to respond to standard medications and behavioral interventions
- For patients with multiple sensitivities or contraindications to medications
- For patients who have responded to a prior course of TMS

Where to Learn more:

Textbooks:

- *Transcranial Magnetic Stimulation in Clinical Psychiatry,* Edited by M. George and R. Belmaker. 2007; ISBN 978-1-58562-197-2
- *Transcranial Magnetic Stimulation: Clinical Applications for Psychiatric Practice*. Edited by Bermudes, Lanocha, and Janicak, 2018; ISBN 978-1-61537-105-1

Consensus statements for TMS for depression:

- NNDC-APA consensus - McClintock et al. *Journal of Clinical Psychiatry* 2017
- CTMSS consensus – Perera, George, Grammer, Janicak, Pascual-Leone, and Wirecki; *Brain Stimulation* 2016.
- European Consensus– Lefaucheur et al. *Clinical Neurophysiology* 2014

Educational Courses:

CME Courses:

- CTMSS CME course, PULSES: Introductory & Refresher Course on TMS, CME program with Hands-on Device Training- Two Day course. Society hosts now four courses per year, both U.S. and International locations, www.clinicaltmssociety.com
- CTMSS Annual Education Meeting; >14 hours of CME on Advanced TMS topics; www.clinicaltmssociety.com
- APA's Master's course: Transcranial Magnetic Stimulation: Clinical Applications for Psychiatric Practice; 8 hr CME; www.psychiatry.org

University based CME training courses:

- Medical University of South Carolina
- Berenson-Allen Center for Non-Invasive Stimulation (MGH-Harvard)
- Duke University Medical Center

Thank You !

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