Innovation in Neuromodulation: Transcranial Magnetic Stimulation

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Assistance provided from Clinical TMS Society (CTMSS)

Faculty Disclosure

Dr. Lowell:

- Clinical TMS Society
  - Education Committee Co-Chair
    - PULSES Task Force
    - Resident Task Force
  - Membership Committee
  - Clinical Standards Committee 2016-2019

- Owner of the TMS Institute of Ohio 2013-present

- This continuing medical education activity includes device or medicine brand names for participant clarity purposes only, due to the presence of different branded versions of the same product. No product promotion or recommendation should be inferred.

Disclosure

- I, as a faculty member, have been informed of my responsibility to disclose to you, the audience, if I will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved – or cleared, as in the case of devices – by the US Food and Drug Administration).
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.
- There was no industry involvement in the content of the slide deck.
- This slide deck was generated with assistance from CTMSS Education committee.

Disclosure

- Clinical TMS Society (CTMSS) is an international professional association of over 1000 clinicians, researchers, technicians, students, and industry partners dedicated to:
  - Optimizing clinical practice of TMS treatment
  - Increasing awareness of TMS therapy
  - Improving accessibility of TMS therapy

Disclosure

- This slide deck was built from a slide deck which was originally conceived, produced, and edited by the Outreach Committee of Clinical TMS Society.
- The society's board of directors approved the original slide decks for educating other clinicians in September 2017, since this time the slide deck has evolved into multiple slide decks and have been edited and updated by the Education Committee.
- This slide deck has been updated from the original 2017 version; subsequent versions have been used in conjunction with CTMSS by the American Psychiatric Association (APA); the Southern Psychiatric Association (SPA), and now with Psych Congress.
- There are other FDA treatment clearances for repetitive TMS: OCD, as Aid to Smoking Cessation, MDD with Anxious features, and Single pulse TMS has been cleared for Migraine. These clearances will be introduced but will not be thoroughly reviewed.
- Most of this presentation will center on repetitive Transcranial Magnetic Stimulation (rTMS or TMS) for MDD.

MDD = major depressive disorder; OCD = obsessive-compulsive disorder.

Learning Objectives

Understand the evidence for Transcranial Magnetic Stimulation as a treatment for depression

Describe where TMS falls in the Major Depressive Disorder treatment algorithm

Know the history of TMS

Know the efficacy rate for TMS for Major Depressive Disorder from the scientific literature

Assess whether TMS would be appropriate for a patient

Costs of Untreated Depression

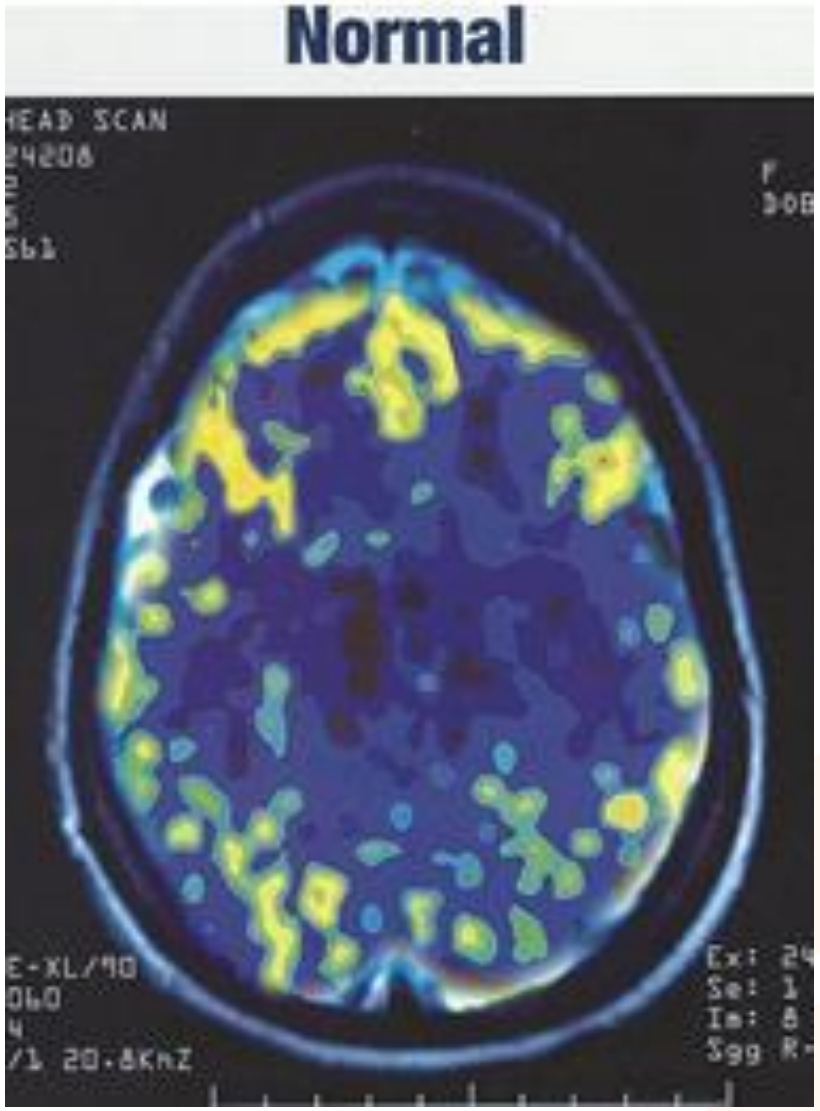
- Depression is a common mental disorder
- Globally, more than 350 million people of all ages suffer
- Depression is the leading cause of disability worldwide and a major contributor to the global burden of disease
- Only 50% of individuals with depression seek help
- More than 30% do not receive adequate treatment from medication or psychotherapy

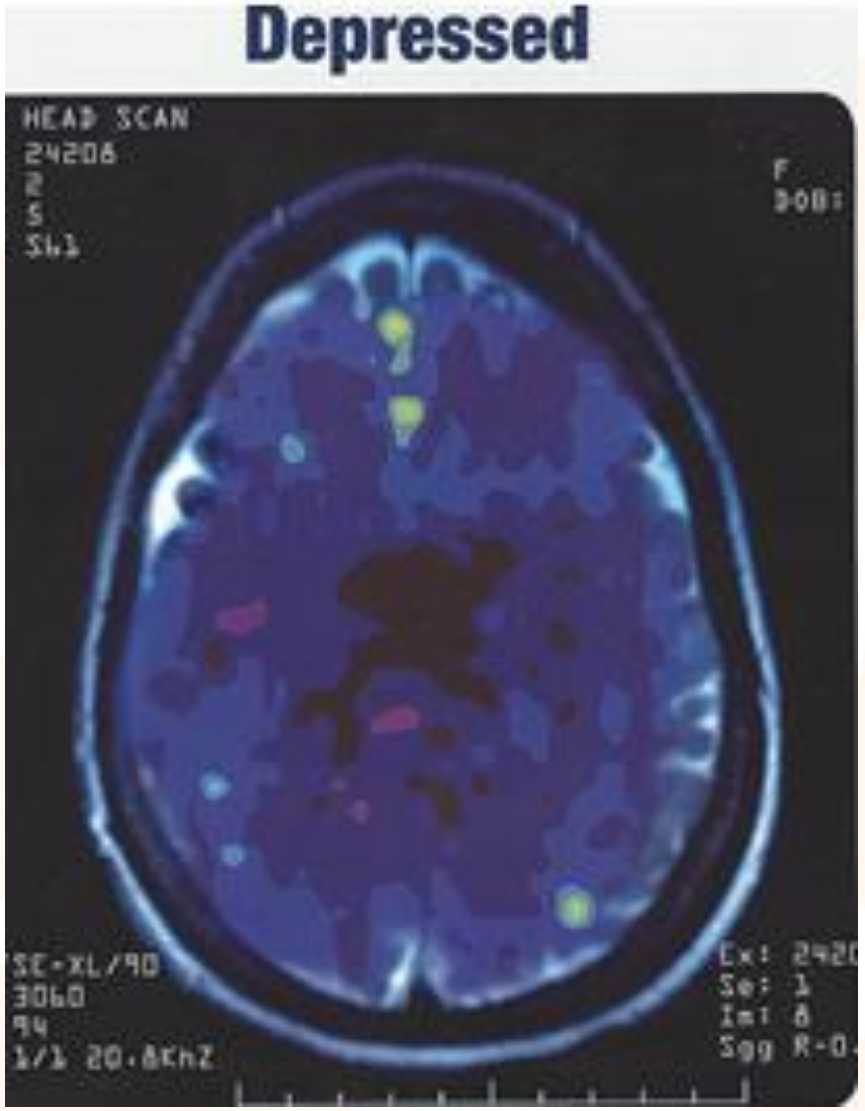
World Health Organization. 2017

Depression, *A Brain Circuit Problem*

- Despite the predominance of pharmaceutical agents for treatment of depression, monoamine transmitters are only part of the depression picture; *the brain is an electro-chemical organ*
- Sophisticated forms of brain imaging are permitting scientists to understand the working brain and its circuitry
- These imaging technologies are leading towards understanding which brain circuits regulate mood and anxiety disorders

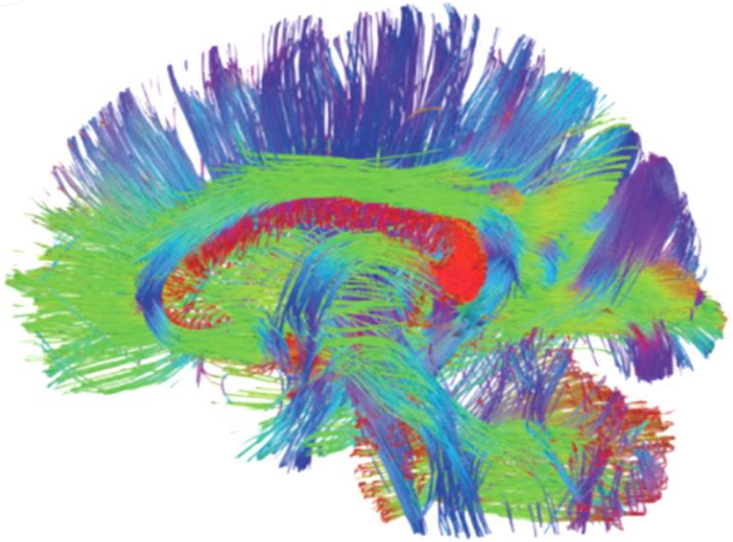
Major Depression is a Brain Disease



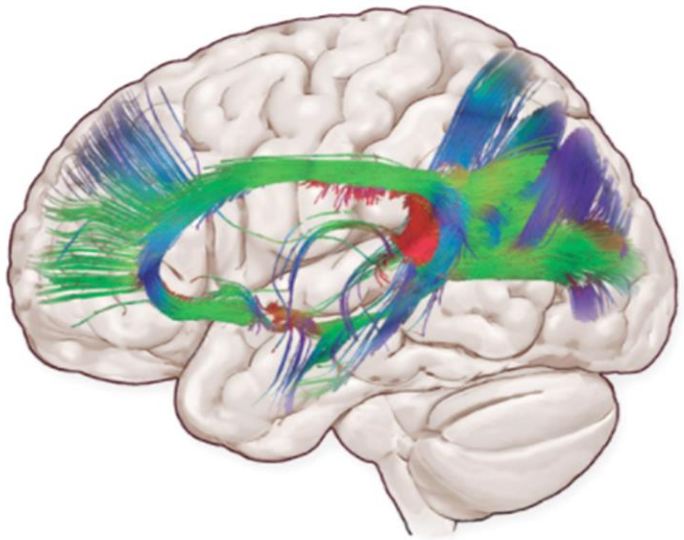


Mark S. George, MD. Fluorodeoxyglucose Positron Emission Tomography (PET) images acquired at the National Institute of Mental Health (NIMH), Bethesda, MD, 1994.

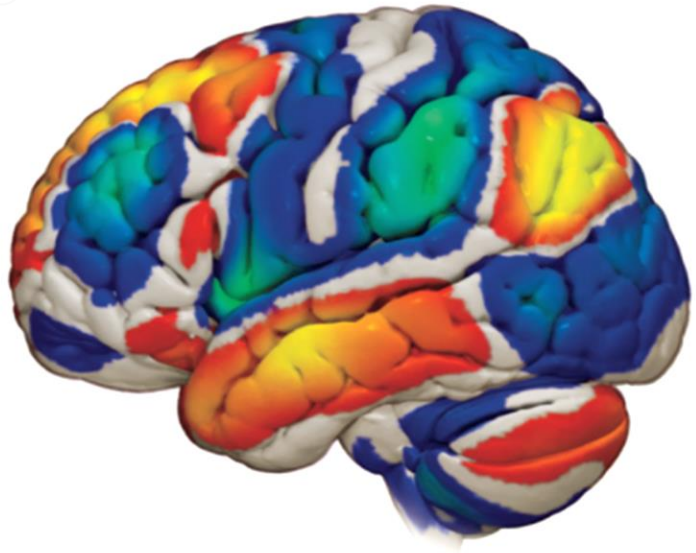
Map of Anatomical Connectivity



Specific Fiber Tracts



Map of Functional Connectivity



In depression, studies have found structural and functional dysfunction in frontal and prefrontal cortex, the anterior cingulate, and the limbic systems (amygdala, hippocampus, and the dorsomedial thalamus).

Image from: Fox MD. *N Engl J Med*. 2018;379(23):2237-2245.

Antidepressant Medications

- When used first-line, antidepressant medications help patients reach remission about one-third of the time[1,2]
- A recent meta-analysis revealed that antidepressants had a small to modest effect size of approximately 0.3[3]
- With medication combinations and the development of pharmacogenomic testing we likely may improve outcomes
- Unfortunately, many patients still do not respond to medications or do not tolerate the side effects associated with the medications

[1]Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40. [2]Fava M, et al. *Am J Psychiatry*. 2006;163(7):1161-1172. [3]Cipriani A, et al. *Lancet*. 2018;391(10128):1357-1366.

Neuromodulation Options for Depression

Medications (chemical neuromodulation)

SSRIs, SNRIs, TCAs, MAOIs, lithium, esketamine, other augmentation agents

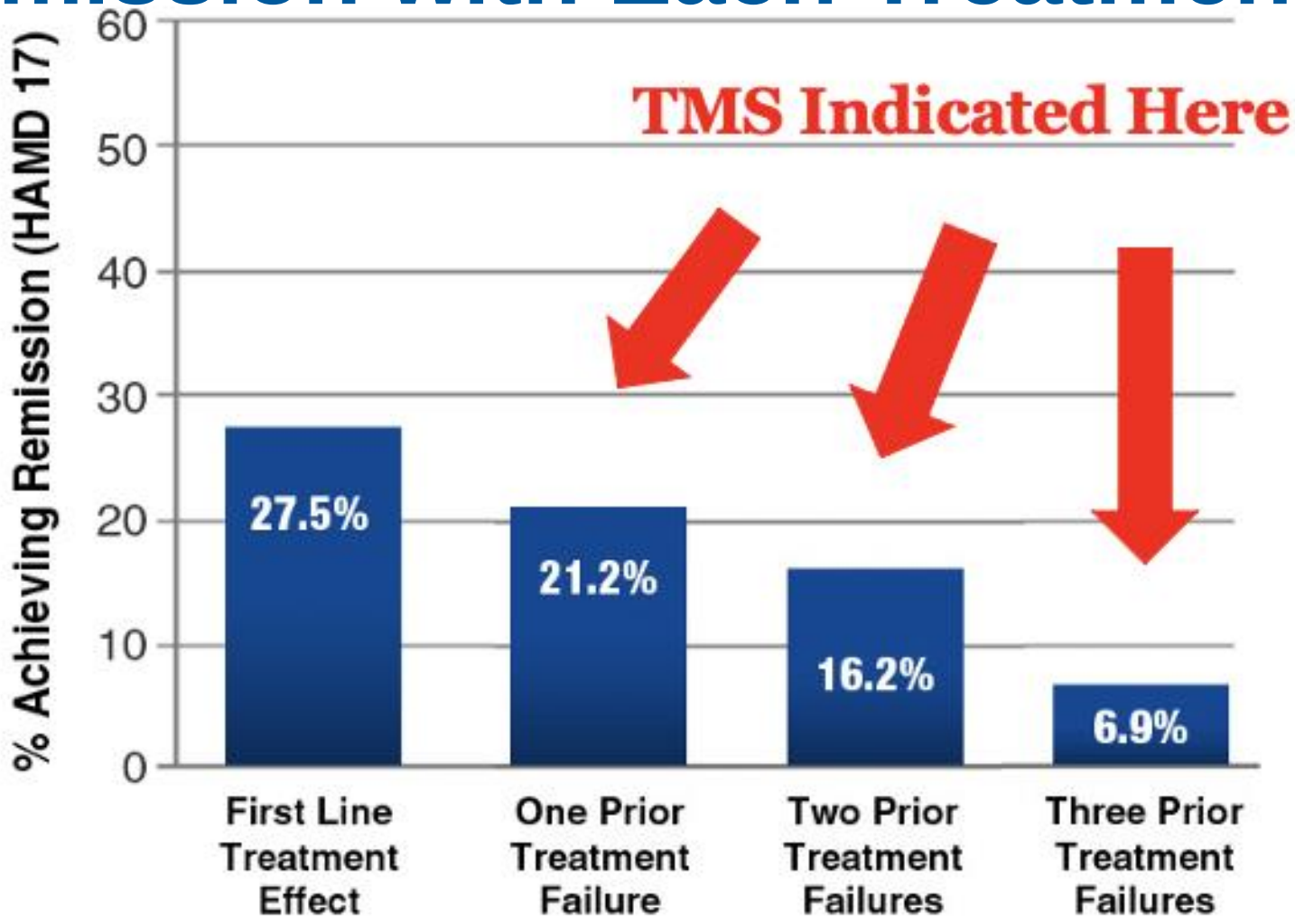
Psychotherapy (behavioral neuromodulation)

CBT (Cognitive-Behavioral Therapy), DBT (Dialectical Behavioral Therapy), ACT (Acceptance and Commitment Therapy), Psychodynamic Therapy, Interpersonal Therapy, and Group Therapy

Neurostimulation (electrical neuromodulation)

ECT (Electroconvulsive Therapy), VNS (Vagus Nerve Stimulation), DBS (Deep Brain Stimulation), rTMS or TMS (repetitive Transcranial Magnetic Stimulation)

STAR*D Revealed Reduced Likelihood of Remission with Each Treatment Trial

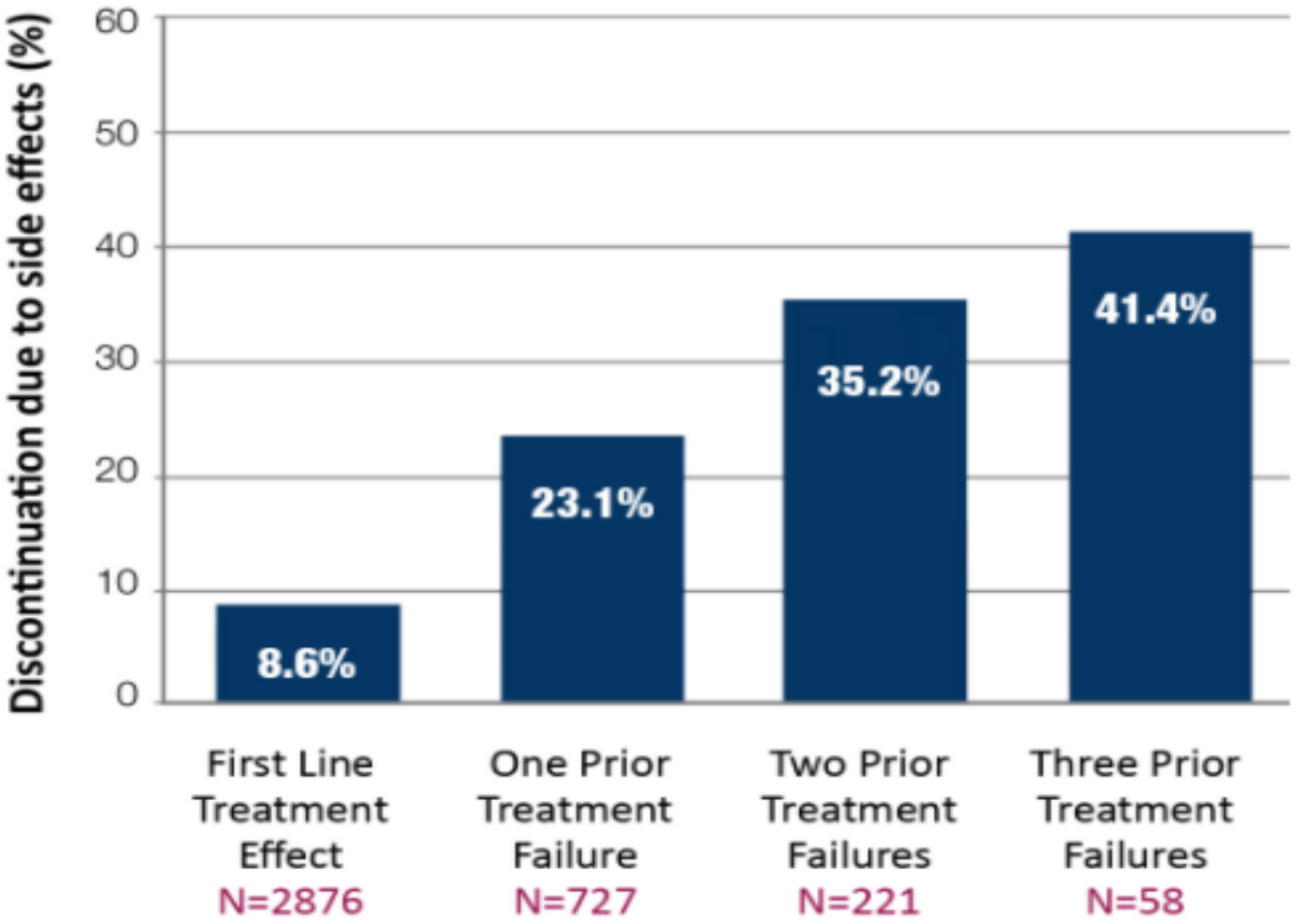


Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40. Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917. Fava M, et al. *Am J Psychiatry*. 2006;163(7):1161-1172. McGrath PJ, et al. *Am J Psychiatry*. 2006;163(9):1531-1541.

STAR*D: Discontinuing Treatment Increases with Each New Medication Attempt

Medication Side Effects

- Increased or decreased sleep
- Changes in energy and fatigue
- Blurred vision
- Dry mouth
- Weight changes
- Appetite changes
- Sexual dysfunction
- Vital sign changes: blood pressure and pulse
- Gastrointestinal distress: nausea, vomiting, diarrhea, constipation



Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40. Fava M, et al. *Am J Psychiatry*. 2006;163(7):1161-1172.

Advantages of TMS Over TAU

- 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
- TMS, like other neuromodulation, has proven to be effective in TRD for patients who have not responded to several medication trials

TAU = treatment as usual; TRD = treatment-resistant depression.

Carpenter LL, et al. *Depress Anxiety*. 2012;29(7):587-596. Connolly KR, et al. *J Clin Psychiatry*. 2012;73(4):e567-e573.

TMS vs Other Neuromodulation

- FDA cleared for earlier in course of care, although some patients who fail ECT, respond to TMS and vice versa
- Non-invasive
- Office-based procedure that requires no sedation, anesthesia, hospitalization, or recovery time
- No known cognitive side effects with TMS

- ECT is ideal for MDD with psychotic features, acute hospitalized patients with suicidality, or catatonia
- ECT and VNS are ideal for highly refractory patients who have failed TMS and other outpatient treatments

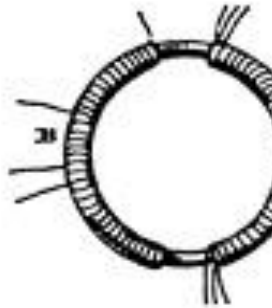
Transcranial Magnetic Stimulation

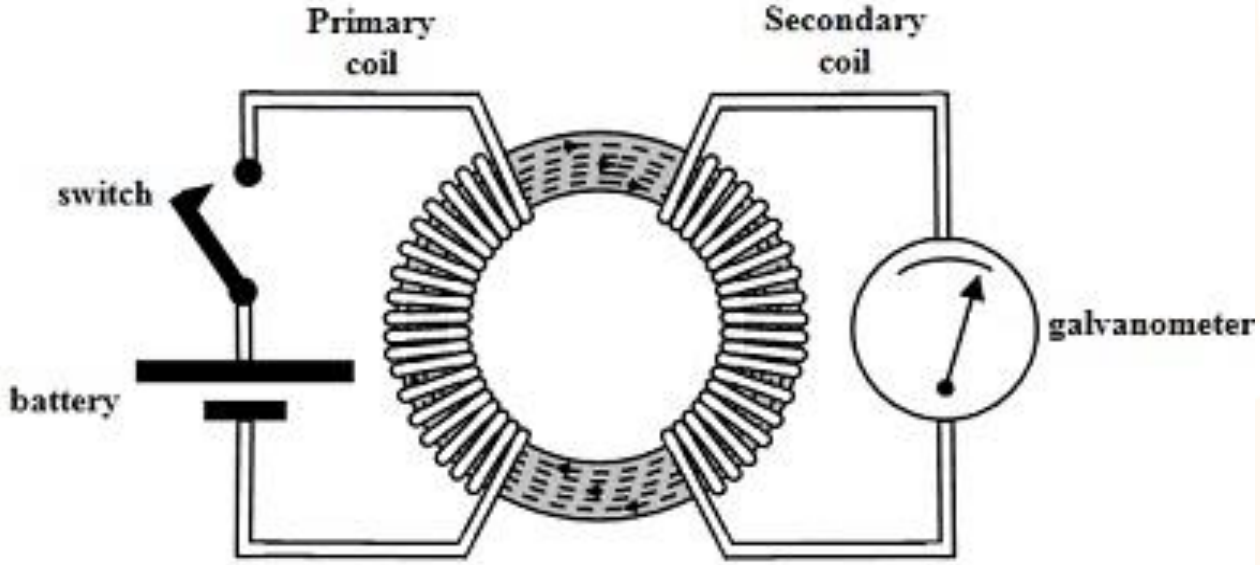
History and Mechanism of Action

Science of TMS: 1831 Michael Faraday

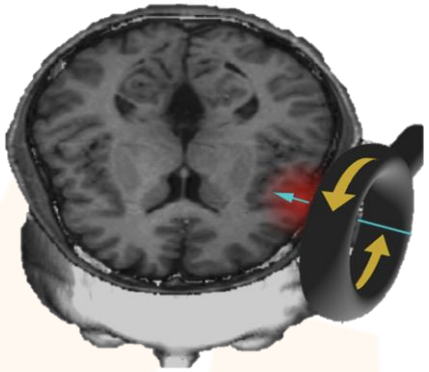
- Physical principles of electromagnetism were discovered in 1831 by Michael Faraday; he observed that a pulse of electric current passing through wire coil generates a magnetic field

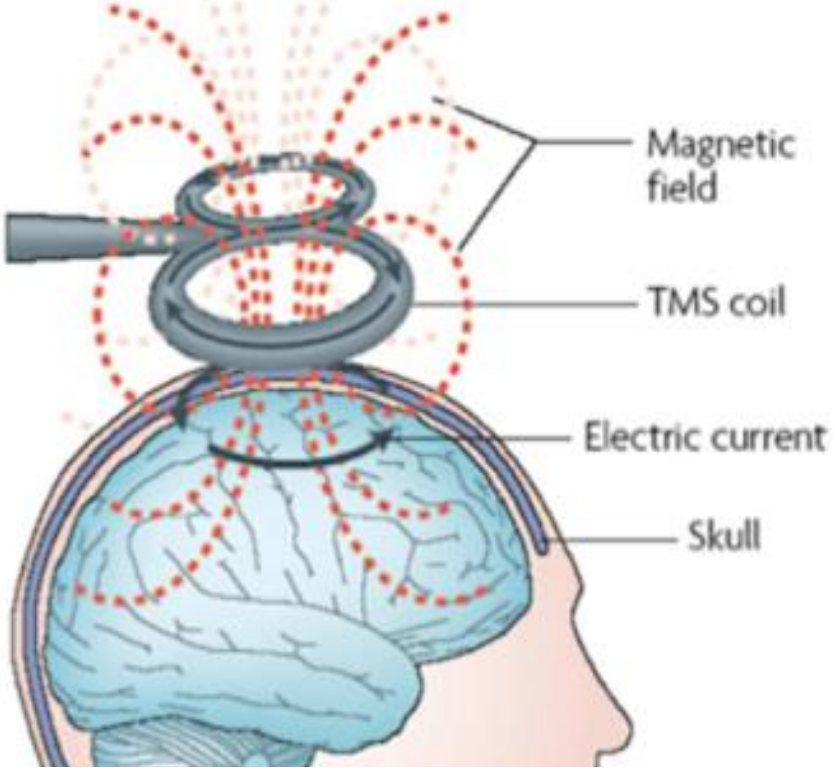
- Rate of change (flux) of magnetic field determines the induction of a secondary current in a nearby conductor placed in a perpendicular plane

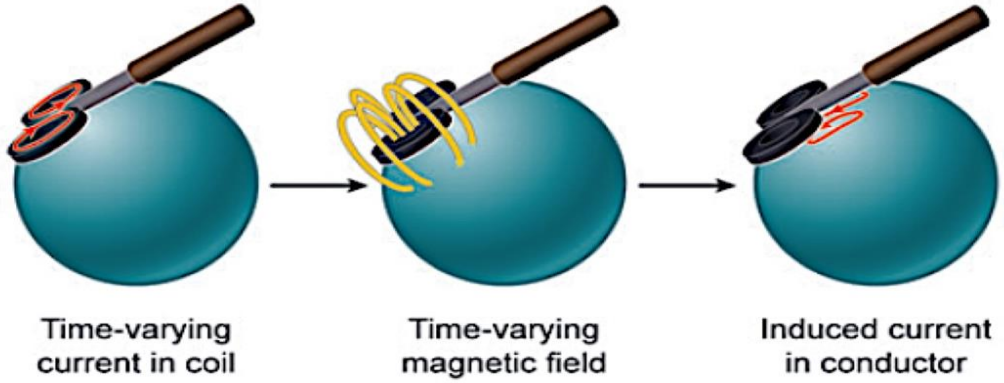




TMS Physics, Using Faraday's Law



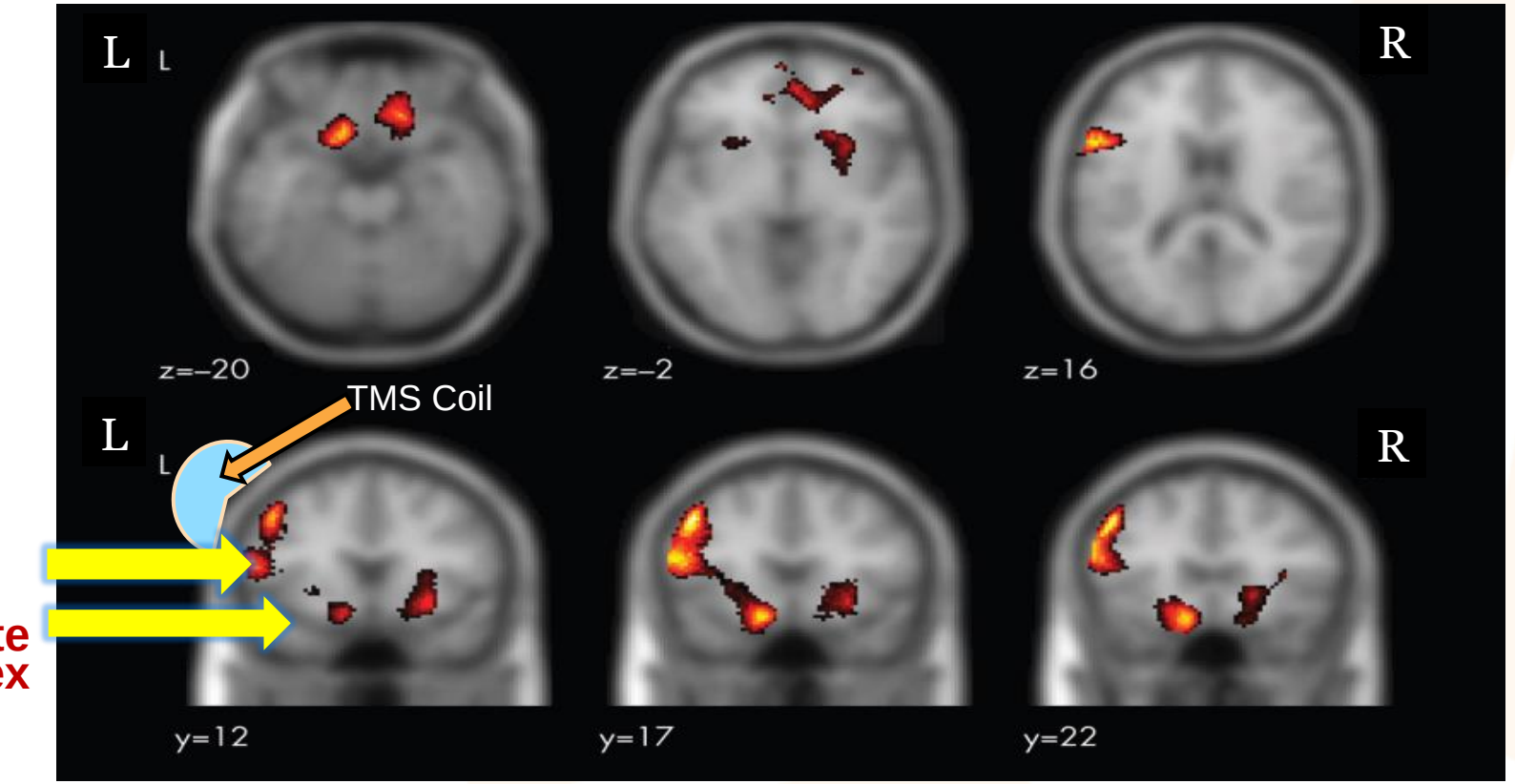




- Time varying electrical current flows from Stimulator
- Time varying (pulsed) magnetic field emits from the TMS coil
- Induced Electrical current in cortical and subcortical tissue of the brain (conductor)
- Neurons become depolarized
- Action potential propagates along the neuron
- Release neurotransmitters at synapse and continues propagation of signal to other brain regions and structures

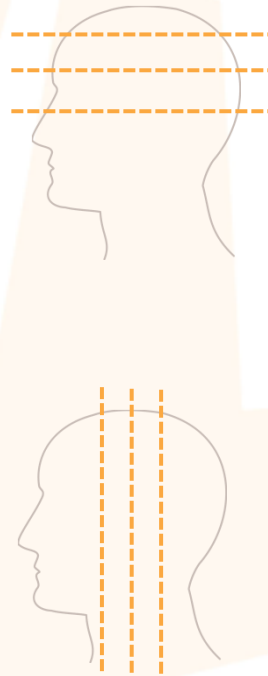
Post A, et al. *J Psychiatr Res*. 2001;35(4):193-215.

Targeted Effects on Brain Mood Circuits



Dorsolateral prefrontal cortex

Anterior cingulate cortex



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

Kito S, et al. *J Neuropsychiatry Clin Neurosci*. 2008;20(1):74-80.

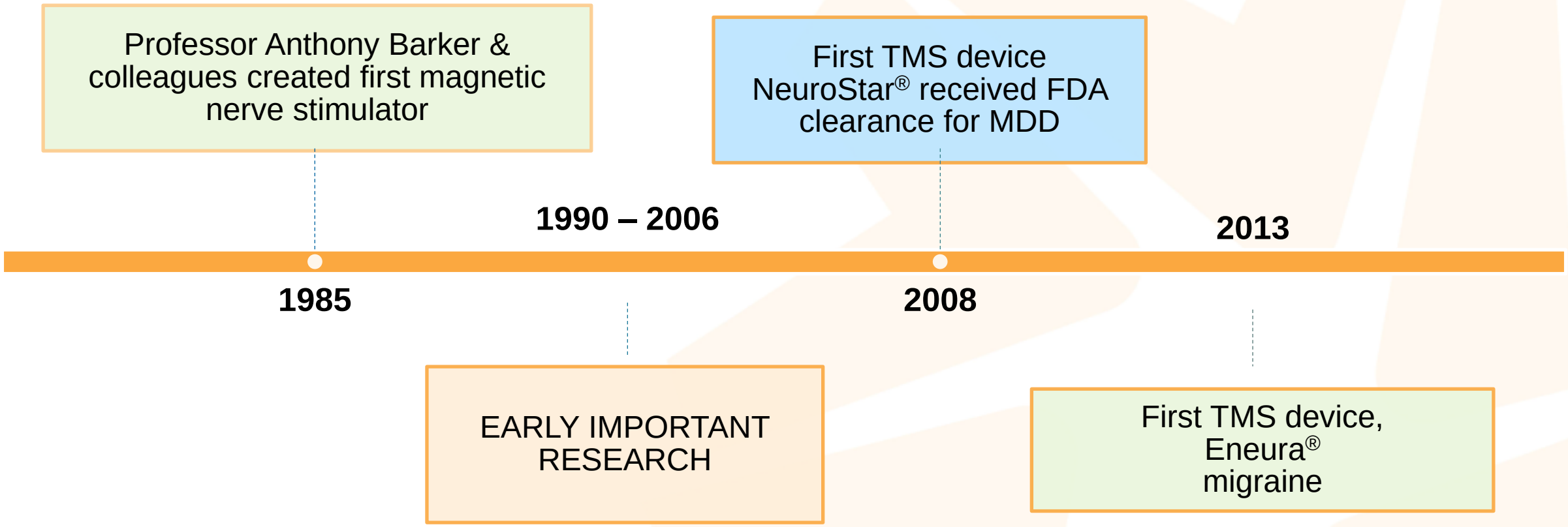
Biological and Behavioral Effects of Repeated TMS

- 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 and glutamate effects
- Effects on thyroid hormones and HPA axis
- Evidence of neurogenesis gene induction (eg, BDNF upregulation)
- Plasticity-like actions (ie, 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)
- TMS entrains and resets thalamocortical oscillators, normalizes regulation, and facilitates reemergence of intrinsic cerebral rhythms and through this mechanism of action restores normal brain function

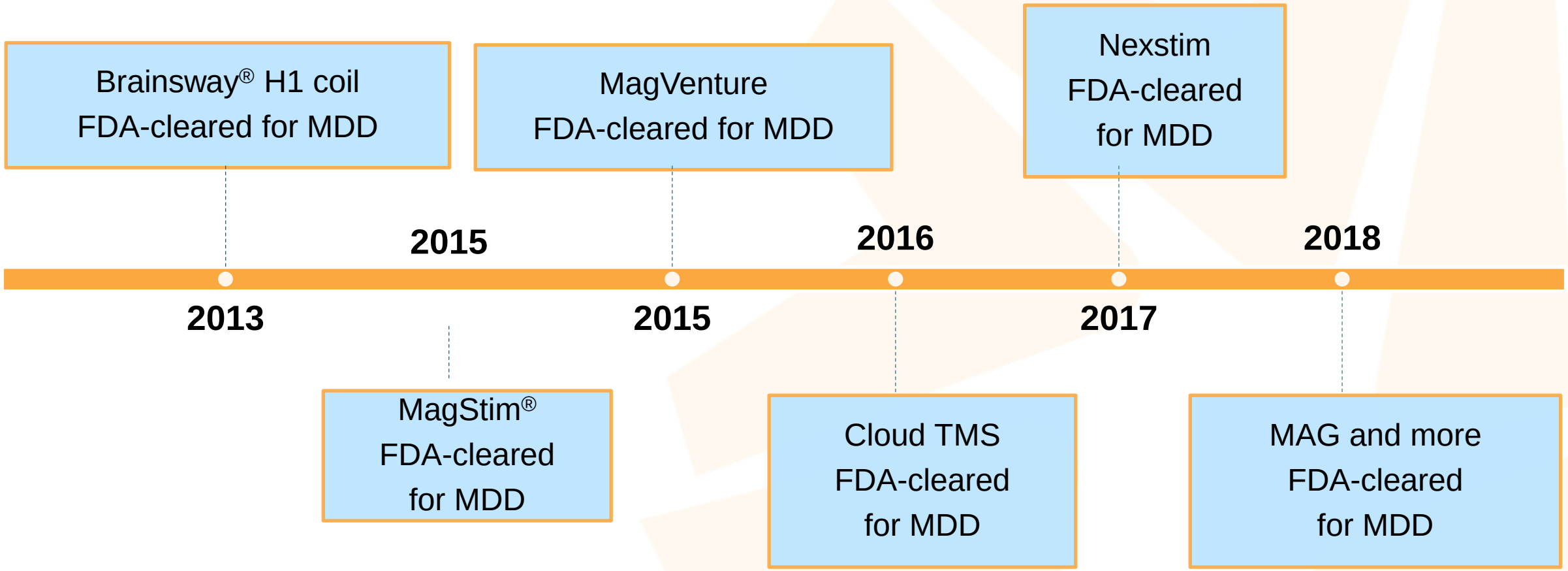
BDNF = brain-derived neurotrophic factor; DLPFC = dorsolateral prefrontal cortex; GABA = gamma-aminobutyric acid; HPA = hypothalamic–pituitary–adrenal.

Lisanby SH, et al. *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. *J 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. Czéh B, et al. *Biol Psychiatry*. 2002;52(11):1057-1065. Leuchter AF, et al. *Front Hum Neurosci*. 2013;7:37.

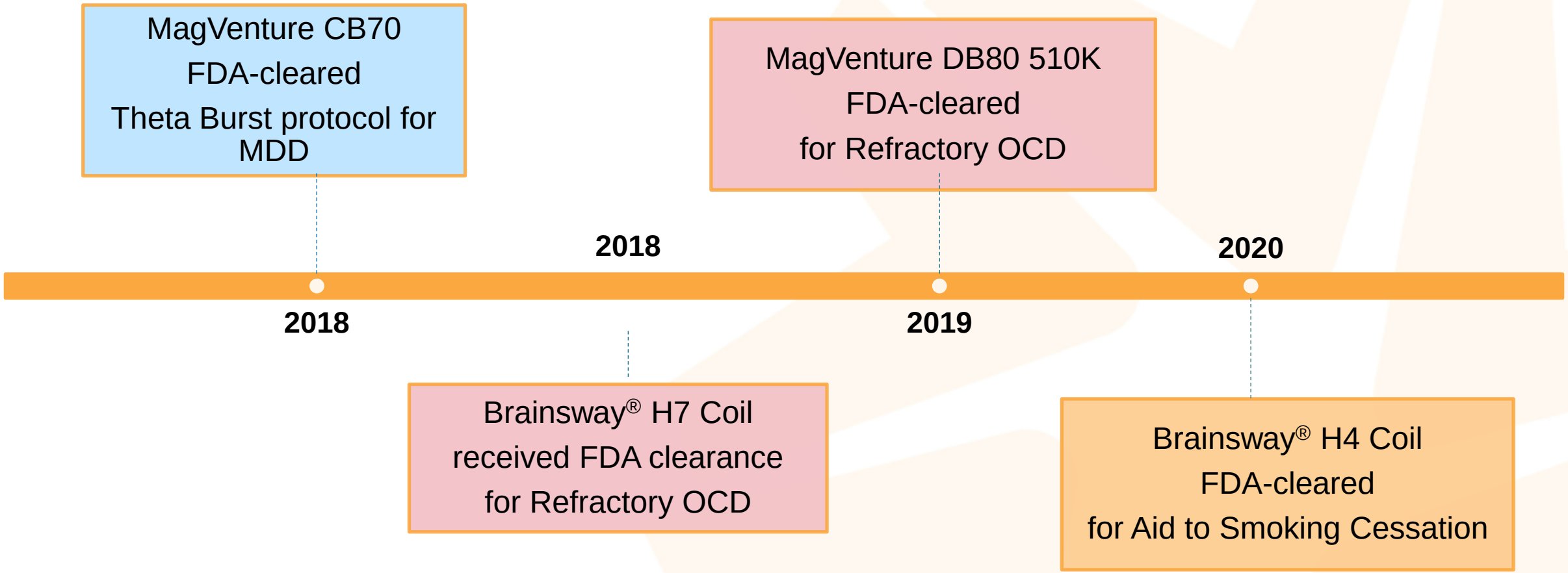
TMS Field is Evolving Quickly



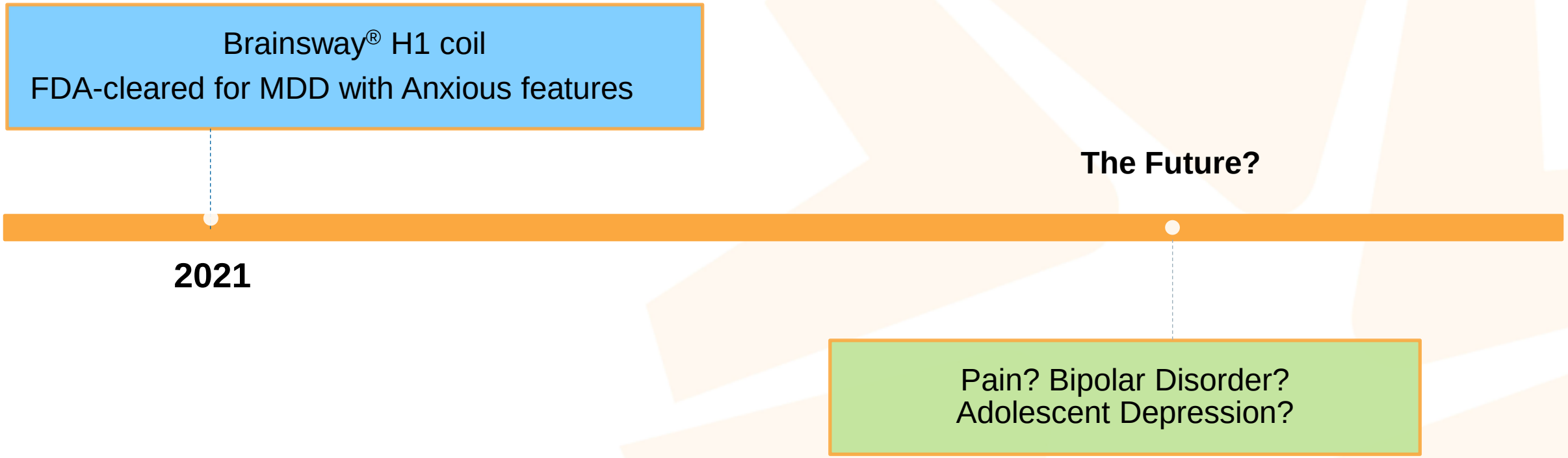
TMS Field is Evolving Quickly



TMS Field is Evolving Quickly



TMS Field is Evolving Quickly



FDA-Cleared Devices in the United States for Major Depressive Disorder

2008
NeuroStar
Figure 8 iron core
neurostar.com

2015
Magstim
Figure 8
magstim.com

2016
Cloud TMS
Figure 8
neurosoft.com

2018
Apollo
Figure 8
magandmore.com

2013
Brainsway
Hesed coil
brainsway.com

2015
MagVenture
Figure 8
magventure.com

2017
Nexstim NBT
Figure 8
nexstim.com

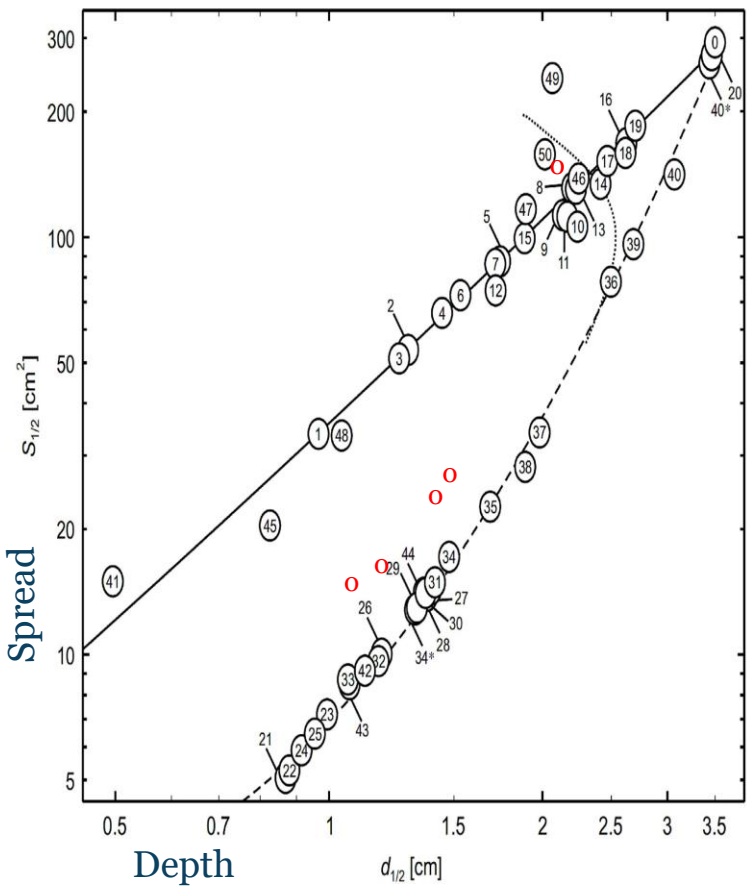
FDA-Cleared Devices in the United States for Other Indications

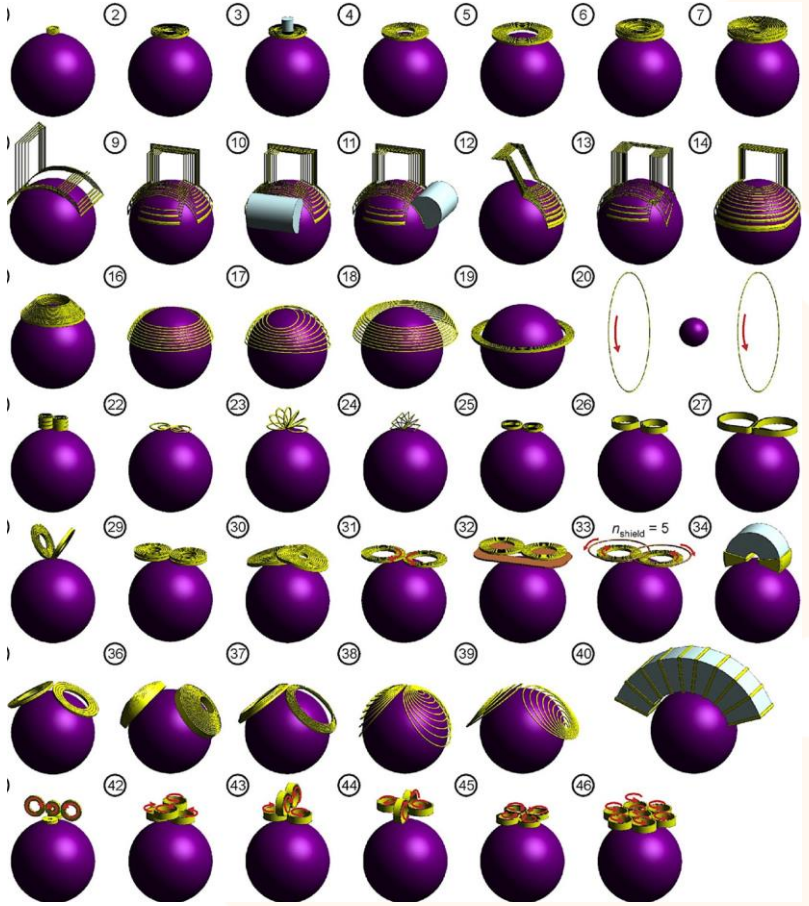
eNeura
1 Special device for Migraine
(Single pulse device –sTMS)
eneura.com

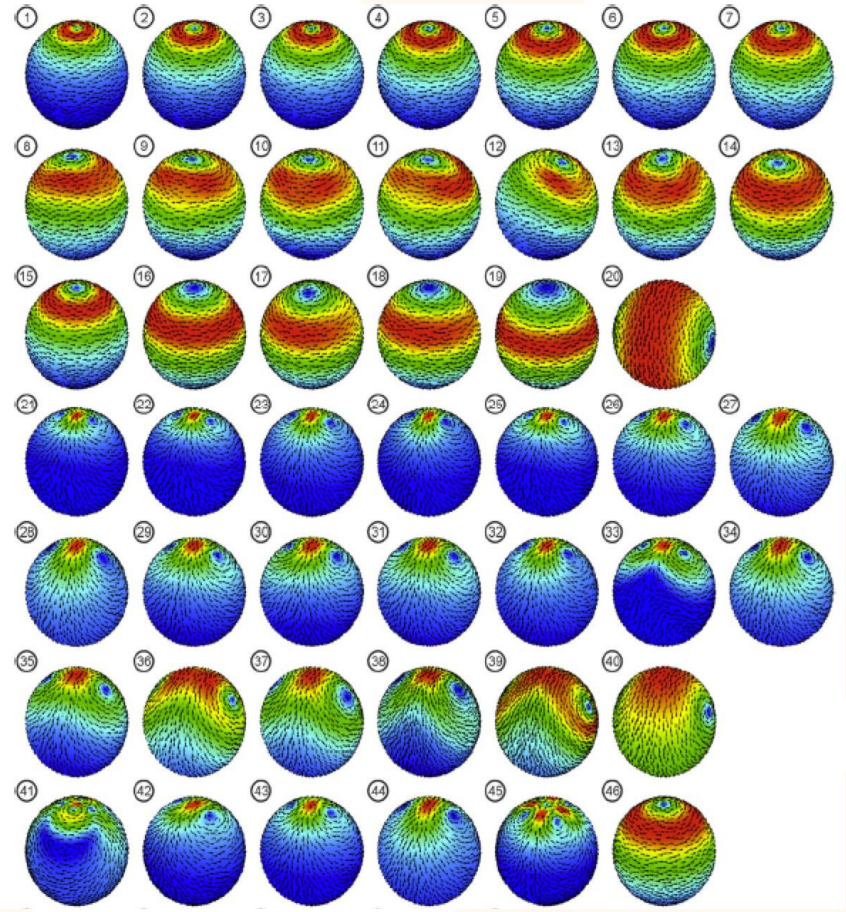
Brainsway
Other Special coils
1- for smoking cessation,
1 for OCD
brainsway.com

MagVenture
1 Special coil for OCD
magventure.com

Design Depth and Width of Stimulation







Deng ZD, et al. *Brain Stimul*. 2013;6(1):1-13.

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
- Treatment of OCD that has not responded to other modalities of treatment
- Augmentation of Smoking Cessation Treatment
- Abortive treatment for migraines

Best Practices:

- In a recurrent episodes of depression, inadequately treated OCD, intractable migraines, smoking cessation that has failed standard care
- Multiple medication attempts, yet still symptomatic
- Prescribed a complex drug regimen
- Experience frequent side effects from medication

McIntyre RS, et al. *J Clin Psychiatry*. 2017;78(6):703-713. Press Release from FDA. 2018.

TMS: *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
- Other concerns
  - 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 D, et al. *J ECT*. 2011;27(1):18-25. Philip NS, et al. *Brain Stimul*. 2014;7(4):608-612. Schrader LM, et al. *Clin Neurophysiol*. 2005;116(10):2501-2504.

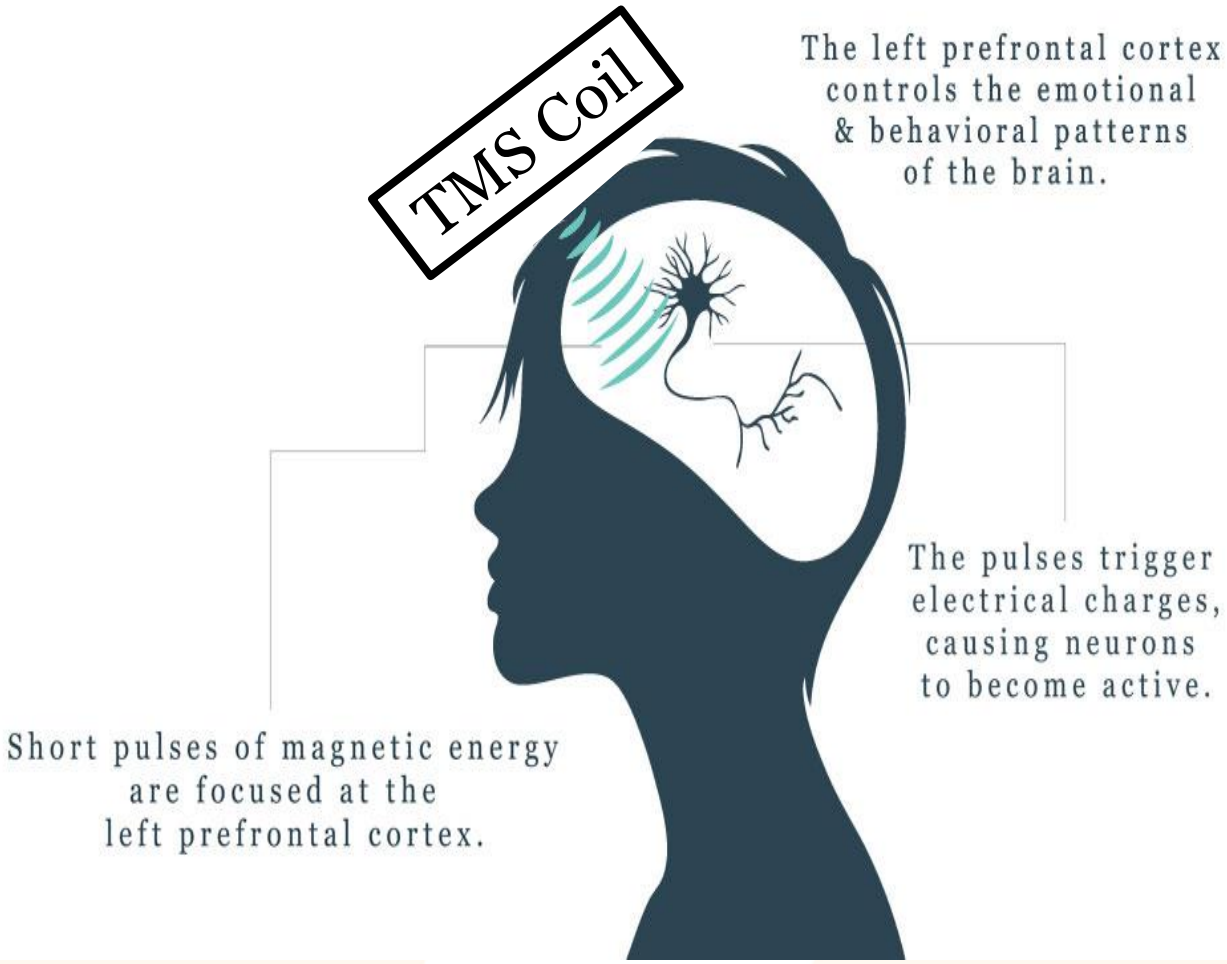
Transcranial Magnetic Stimulation

Patient Experience of 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

*Time and frequency of session varies based on device and indication being treated



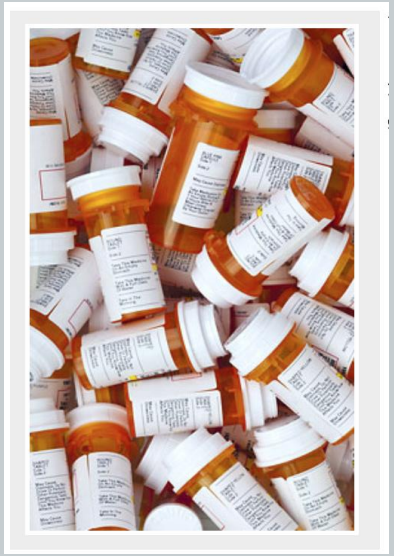
TMS Therapy is Well Tolerated

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

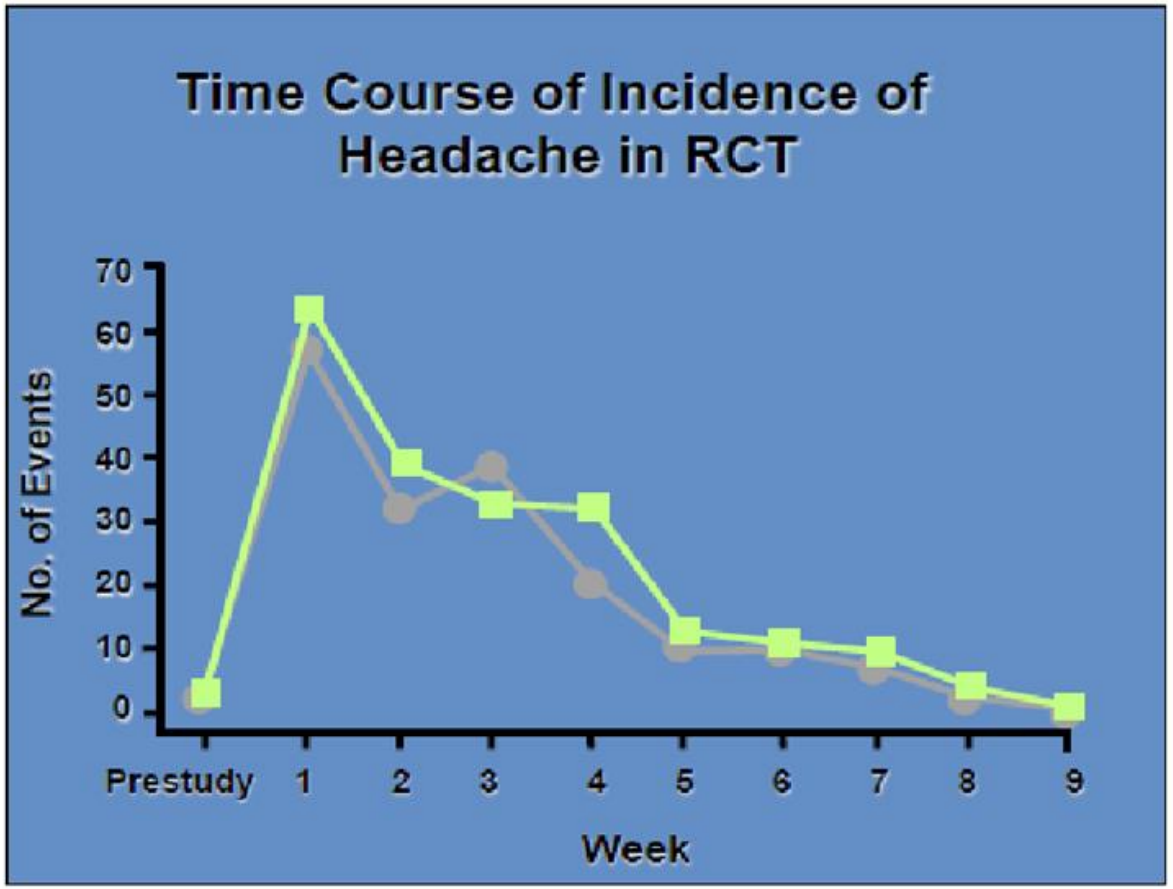
No Systemic Side Effects

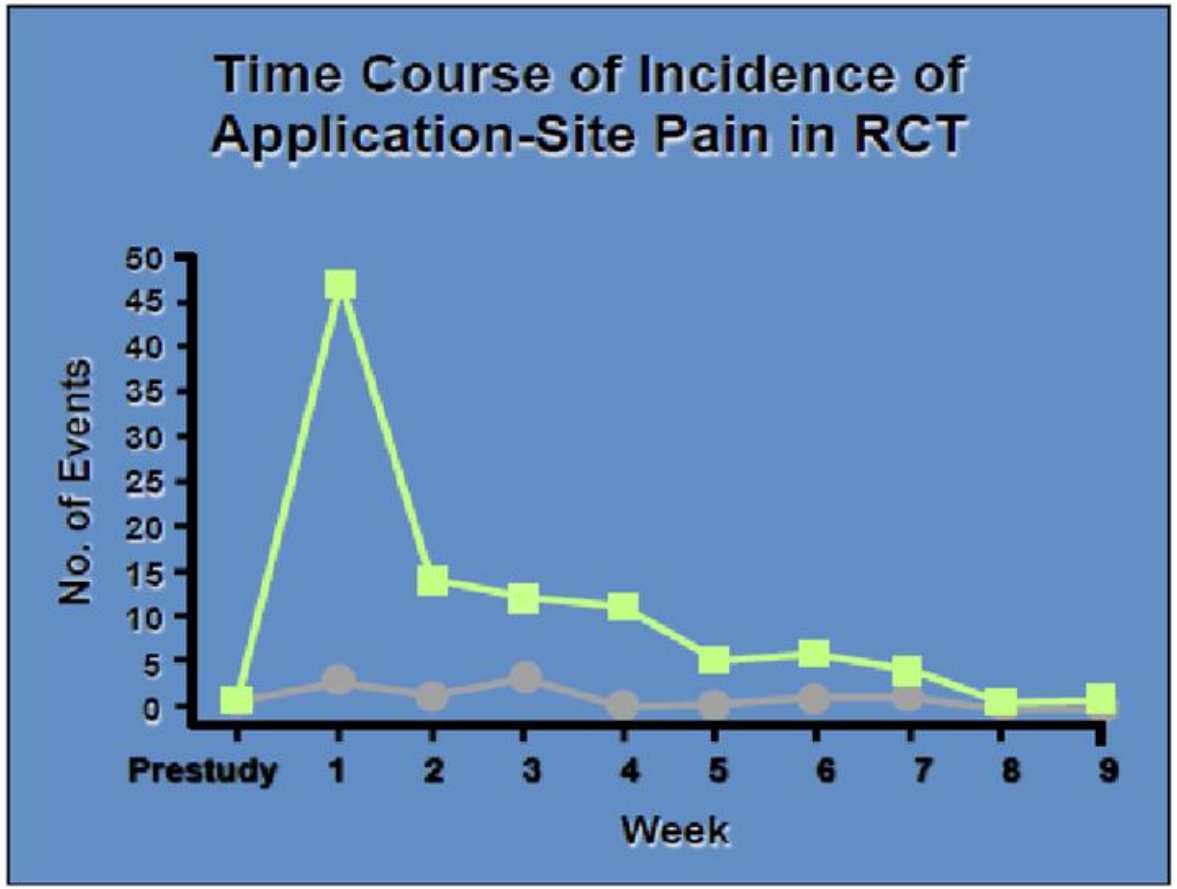


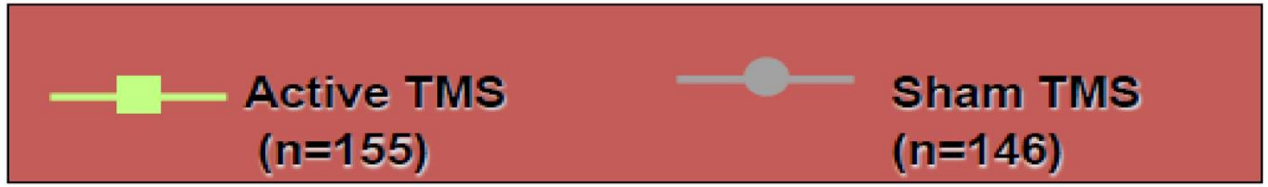
- Other changes in sleep
- Fatigue
- Agitation
- Blurred vision
- Dry mouth
- Weight and Appetite changes
- Sexual dysfunction
- Autonomic changes / Instability
- Gastrointestinal distress
- Tremor
- Negative changes in cognition

510(k) applications for Neuronetics and Brainsway devices for MDD (2008, 2012).
Janicak PG, et al. *J Clin Psychiatry*. 2008;69(2):222-232.

Most Common Adverse Events with Figure-8 TMS Coil







Janicak PG, et al. *J Clin Psychiatry*. 2008;69(2):222-232.

Rare, But Serious Adverse Events Have Been Studied

Hearing Loss

- Small # of adults have experienced transient increase in auditory threshold and one patient who did not wear ear plugs with H1 coil had permanent threshold shift
- Most studies with hearing protection report no hearing changes after TMS
- All persons in Treatment room are required to use earplugs that meet a min standard of 30dB protection

Treatment-Emergent Mania

- Early pooled data from treating MDD and depressed Bipolar patients reported treatment emergent mania was 0.84% for active treatment group (less for sham)
- Difference was not statistically different
  unipolar patients = 0.34%
  for bipolar patients = 3.1%

Treatment-Emergent Suicidal Ideation

- Treatment emergent disease exacerbation
- Population with increased severity of clinical condition
- Commonly reported event in RCT
  - 1.9% with sham*;
  - 0.6% active TMS

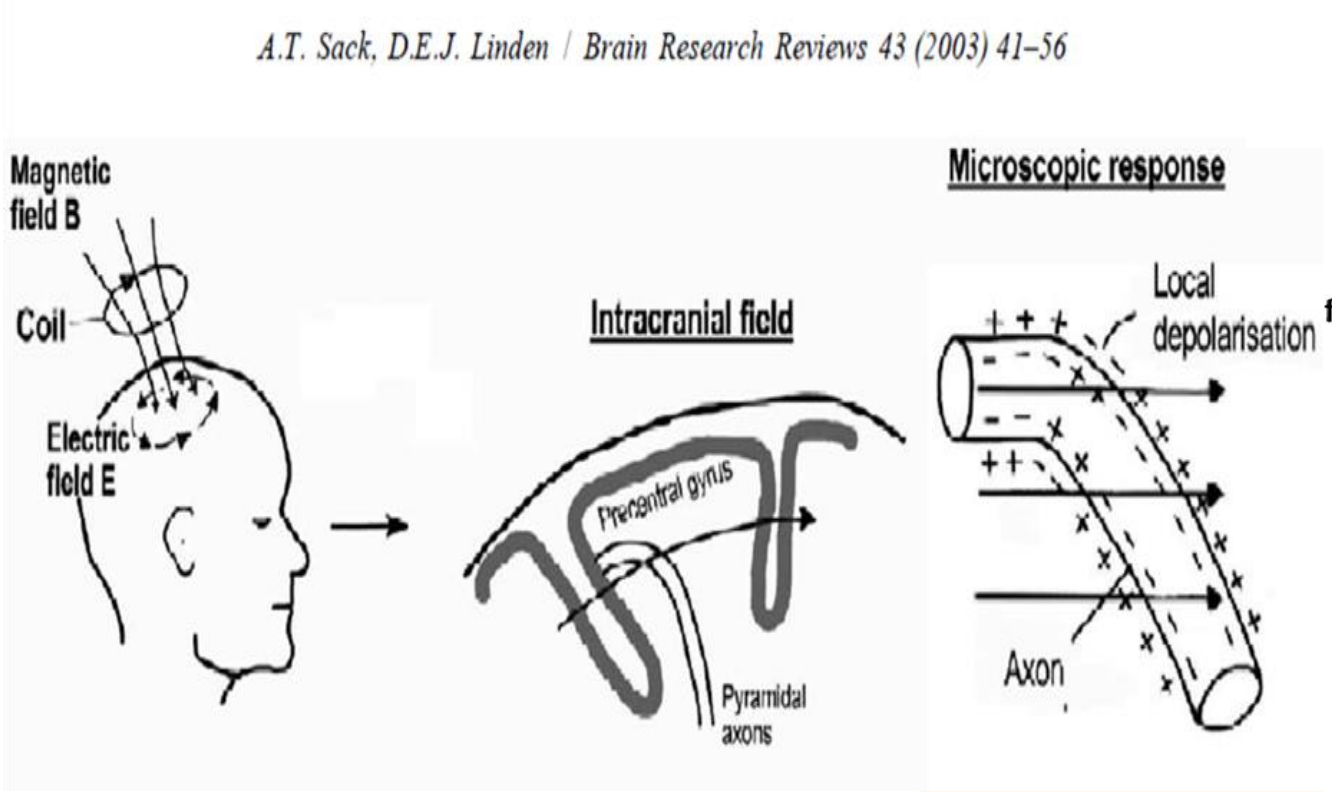
*1 non-lethal OD in sham group

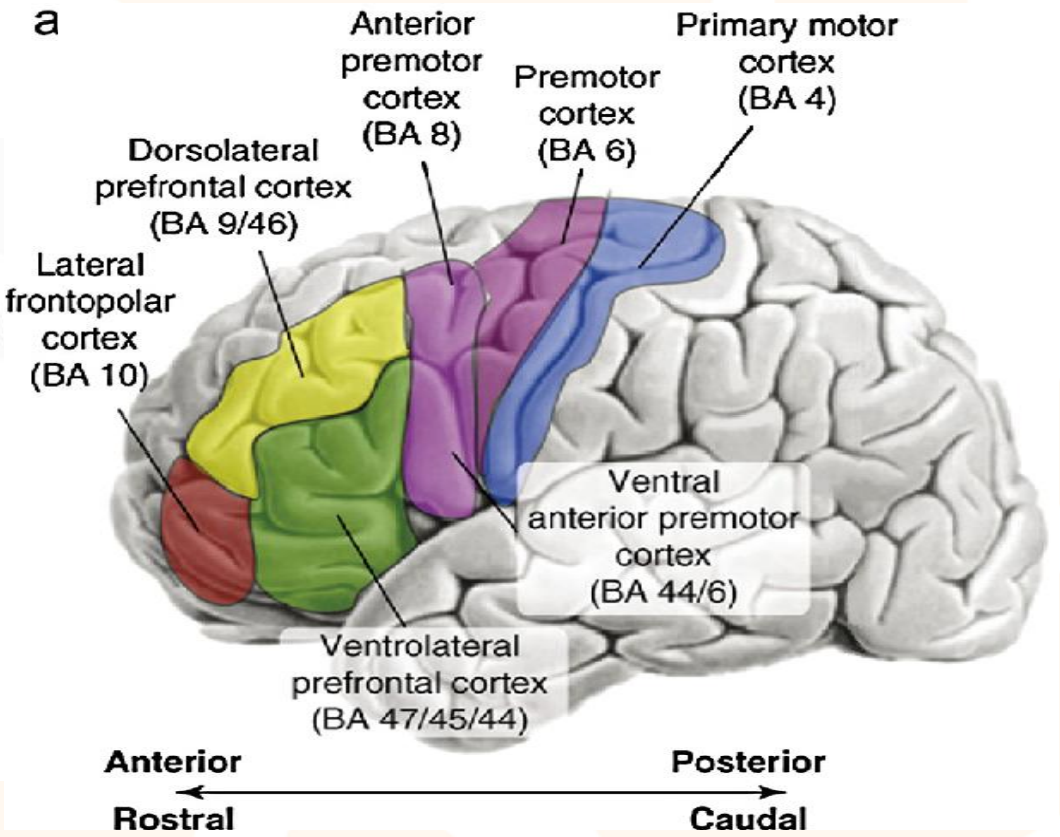
Loo C, et al. *Biol Psychiatry*. 2001;49(7):615-623. Zangen A, et al. *Clin Neurophysiol*. 2005;116(4):775-779. Folmer RL, et al. *Acta Otolaryngol Suppl*. 2006;(556):96-101. Rossi S, et al. *J Neurol Neurosurg Psychiatry*. 2007; 78(8): 857-863. Xia G, et al. *Int J Neuropsychopharmacol*. 2008;11(1):119-130. Janicak PG, et al. *J Clin Psychiatry*.2008; 69(2):222-232.

TMS and Seizures

Seizure is the most serious side effect associated with TMS

The risk of seizures is **<0.1% per treatment course**





Dumontheil I. *Dev Cogn Neurosci*. 2014;10:57-76.

TMS and Seizures

- Most cases associated with TMS were prior to the publication of the TMS safety guidelines in 1998
- Considering the large number of healthy individuals and patients who have undergone TMS sessions since 1998 and the small number of seizures reported, the risk of TMS to induce seizures is very low
- The risk is less than or comparable to risk of seizure associated with antidepressant medications
- TMS induced seizures occur primarily during treatment session itself; seizures could happen while calibrating a dosage (finding MT); no sequelae and no progression to epilepsy

Wassermann EM. *Electroencephalogr Clin Neurophysiol*. 1998;108(1):1-16. George MS, et al. *Curr Opin Psychiatry*. 2013;26(1):13-18.

Scientific Evidence

Supporting TMS for MDD

Large-Scale RCTs

- 4 large-scale studies (sample sizes >100), 3 studies patients took no medications and in 1 study patients took medication concurrently
  - 2 large multicenter industry supported trials that led to FDA approval for 2 devices
  - NIH-funded study 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

RCT = randomized controlled trial.

O'Reardon JP, et al. *Biol Psychiatry*. 2007;62(11):1208-1216. Levkovitz Y, et al. *World Psychiatry*. 2015;14(1):64-73. George MS, et al. *Arch Gen Psychiatry*. 2010;67(5):507-516. Herwig U, et al. *Br J Psychiatry*. 2007;191:441-448.

Evidence for Efficacy of TMS for MDD

- 30+ clinical trials in adults
- Numerous meta-analyses
- Greater effects in more recent studies
  - Longer duration of treatment
  - Increased intensity
  - Increased pulse number
- Large meta-analysis in 2010
  - 34 individual trials, 1383 patients
  - Found TMS to have large effect size of 0.55

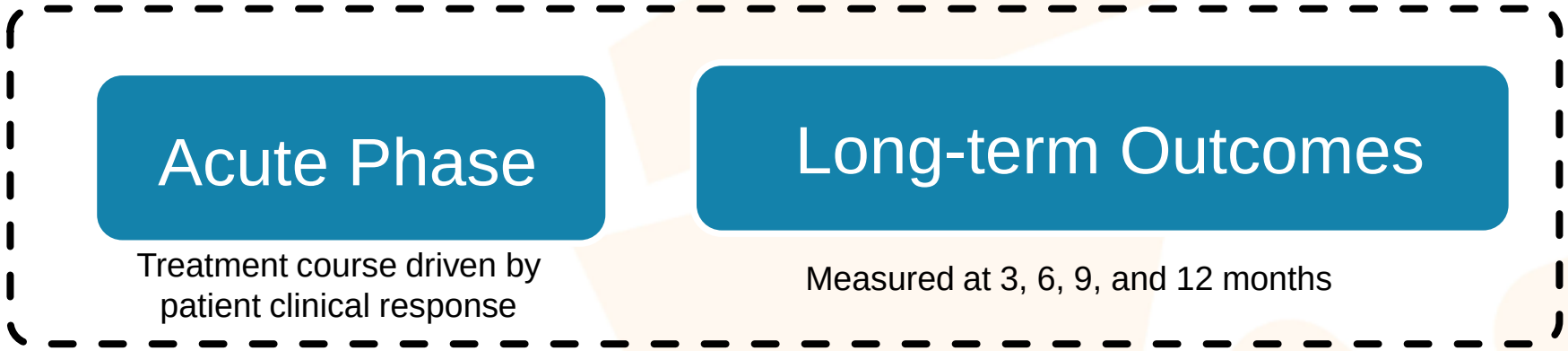
Slotema CW, et al. *J Clin Psychiatry*. 2010;71(7):873-884.

Multisite Naturalistic Observational Study of TMS for MDD:
Acute Treatment Outcomes and One-Year Follow-Up

Study Goal: Define real world outcomes associated with TMS therapy across a broad spectrum of patients and practitioners

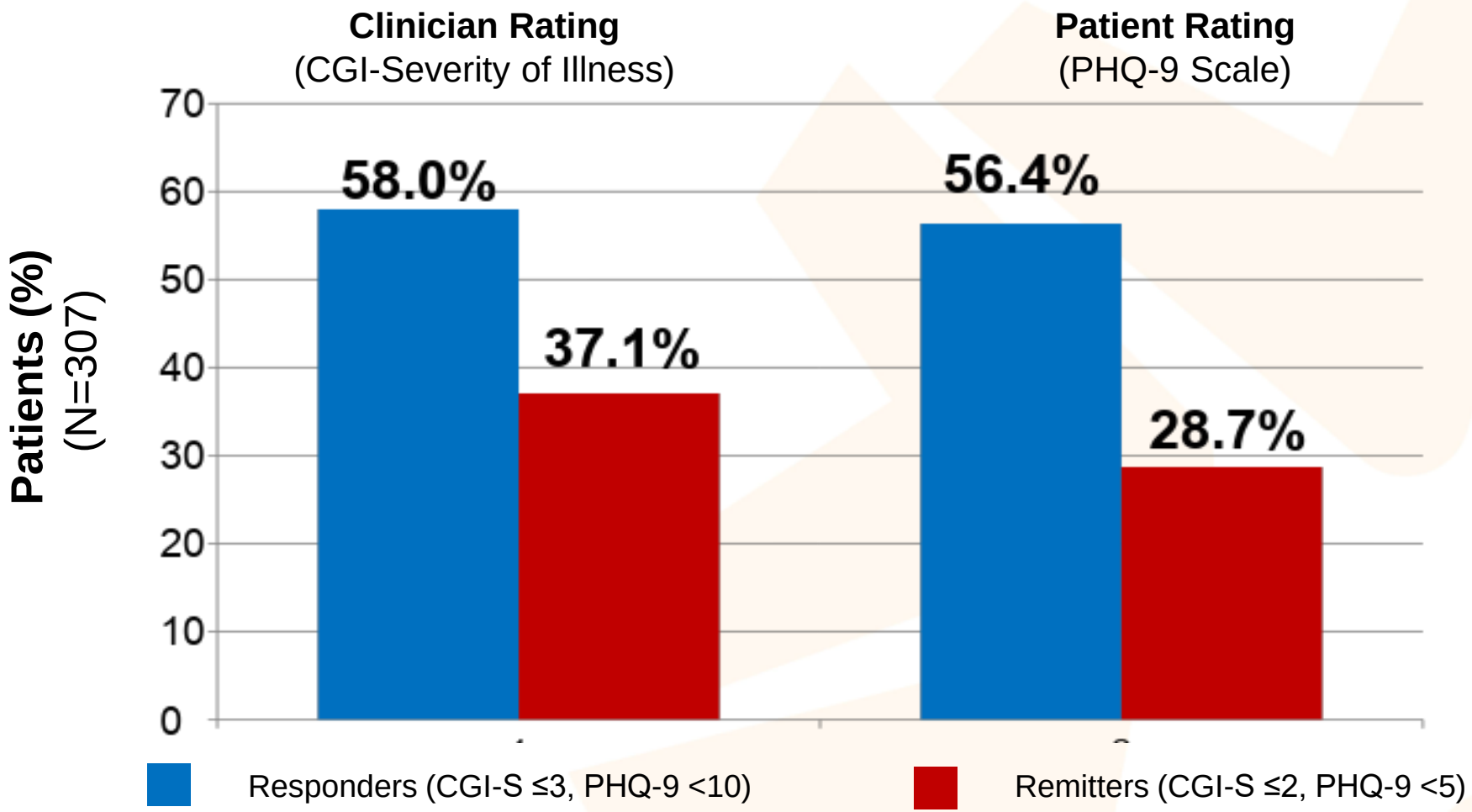
42 Sites:
Comprised of institutions and private practice

307 Patients:
Unipolar, non-psychotic MDD patients in acute phase



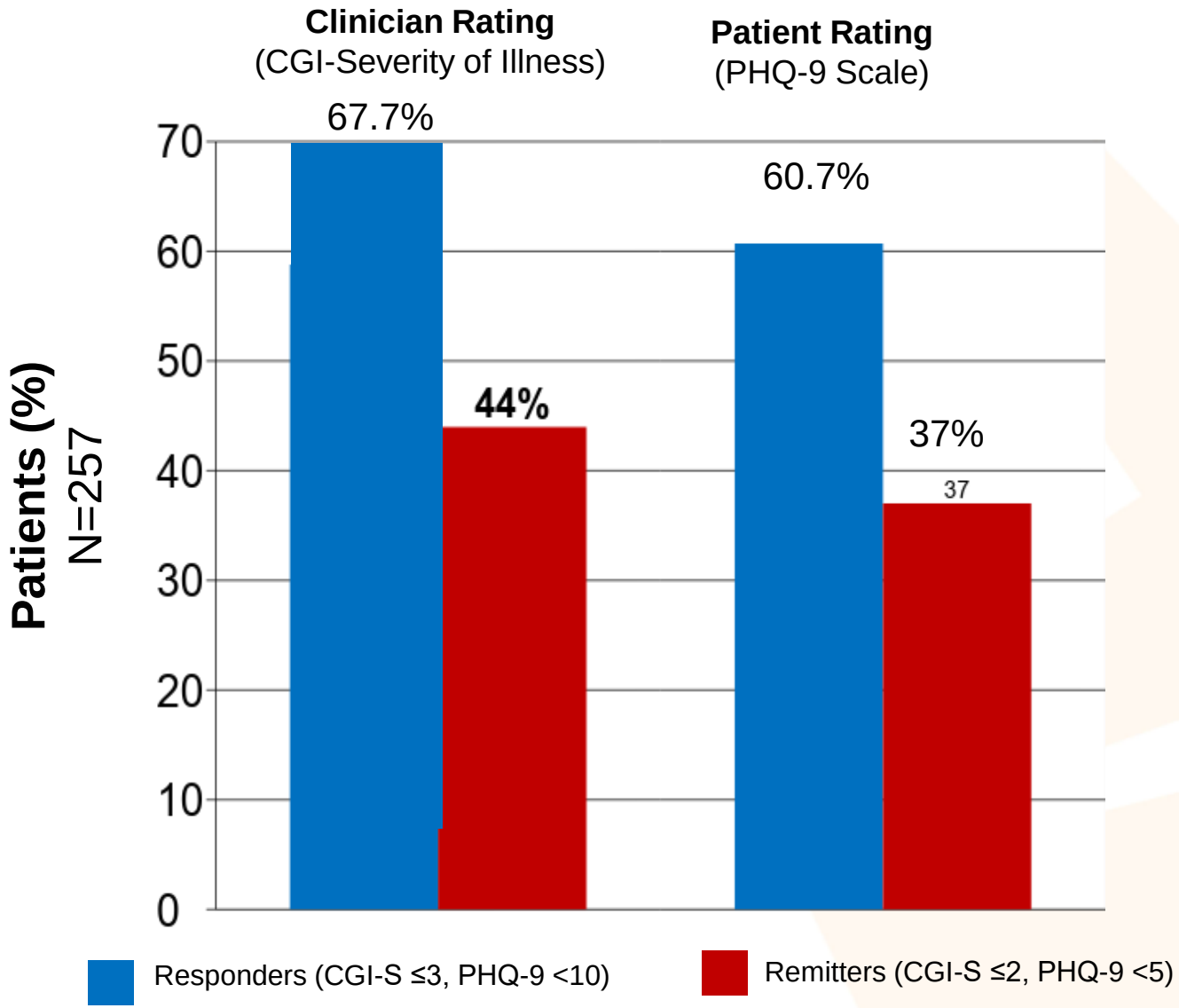
Carpenter LL, et al. *Depress Anxiety*. 2012;29(7):587-596. Dunner DL, et al. *J Clin Psychiatry*. 2014;75(12):1394-1401.

Remission is Possible with TMS Therapy: 1 in 2 Patients Respond, 1 in 3 Achieve Remission



Carpenter LL, et al. *Depress Anxiety*. 2012;29(7):587-596.

Long-Term Phase Results (12 Months)



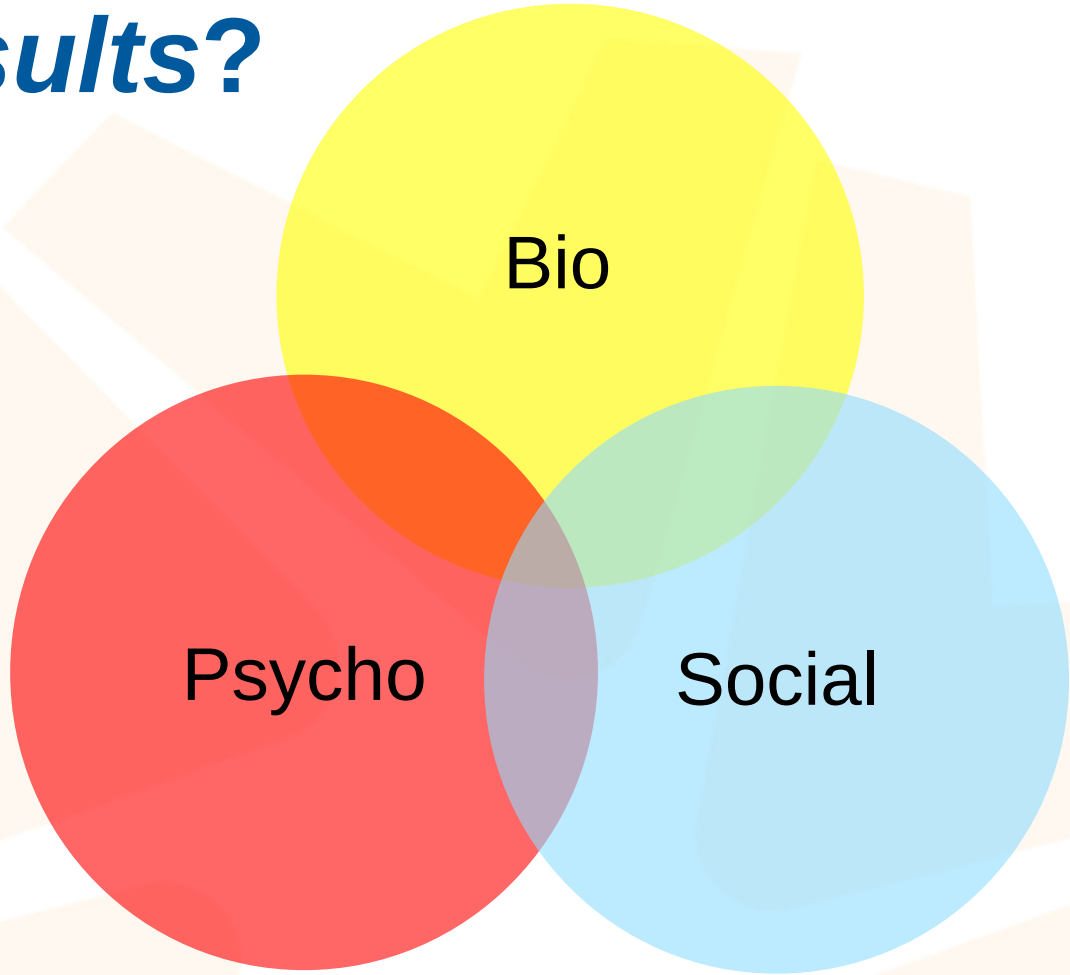
Outcomes measured 1 year following acute treatment

- Physician directed standard of care
- 36.2% of patients received TMS reintroduction
- Average # of TMS sessions during year = 16

Dunner DL, et al. *J Clin Psychiatry*. 2014;75(12):1394-1401.

Why are real world results better than clinical trial results?

- Combination Strategies
  - Well-tolerated with many medications
  - Psychotherapy and Behavioral Activation
- Patients who enroll in studies may not reflect clinical populations in a variety of ways
- Engagement in Life
    - Intensive Outpatient Program
    - Routine
    - Positive Human Interaction



Rossi S, et al. *J Neurol Neurosurg Psychiatry*. 2007;78(8):857-863. Donse L, et al. *Brain Stimul*. 2018;11(2):337-345. Russo GB, et al. *J Affect Disord*. 2018;236:101-104. Vedeniapin A, et al. *Brain Stimul*. 2010;3(4):207-210.

After Acute Treatment of Depression

- Combination Strategies
  - Well-tolerated with many medications
  - Psychotherapy and Behavioral Activation
- Patients who enroll in studies may not reflect clinical populations in a variety of ways
- Engagement in Life
    - Intensive Outpatient Program
    - Routine
    - Positive Human Interaction

Philip NS, et al. *Brain Stimul*. 2016;9(2):251-257. Rossi S, et al. *J Neurol Neurosurg Psychiatry*. 2007;78(8):857-863. Donse L, et al. *Brain Stimul*. 2018;11(2):337-345. Russo GB, et al. *J Affect Disord*. 2018;236:101-104.