TMS THERAPY:
A UNIQUE AND PROVEN APPROACH TO TREATING DEPRESSION

Clinical TMS Society

www.clinicaltmssociety.org

This slide has been produced and edited by the Outreach Committee and the Education Committee of the Clinical TMS Society. The Board of the Society initially approved the slide deck for educating other clinicians in September 2017 and it has been revised since this time. As this is a product of the society, and it can not be altered in any way.

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.

Clinical Presentation of Major Depression per *DSM 5*

- **At least 5 of the following for two weeks, uninterrupted**
  - *Depressed mood*
  - *Loss of interest/pleasure*
  - *Weight loss or gain*
  - *Insomnia or hypersomnia*
  - *Psychomotor agitation or retardation*
  - *Feeling worthless or excessive/inappropriate guilt*
  - *Decreased concentration*
  - *Thoughts of death/suicide*
- **Additional required criteria**
  - *Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning*
  - *Episode not attributable to physiological effects of a substance or another medical condition*
  - *Episode not better explained by schizoaffective disorder, schizophrenia.*
  - *No history of manic or hypomanic episode*
  - *NOT substance-induced or are attributable to physiological effects of another medical condition*

DSM 5 MDD specifiers

Specify:

With anxious distress

With mixed features

With melancholic features

With atypical features

With psychotic features

With catatonia

With peripartum onset

With seasonal pattern

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, https://www.who.int/news-room/fact-sheets/detail/depression.

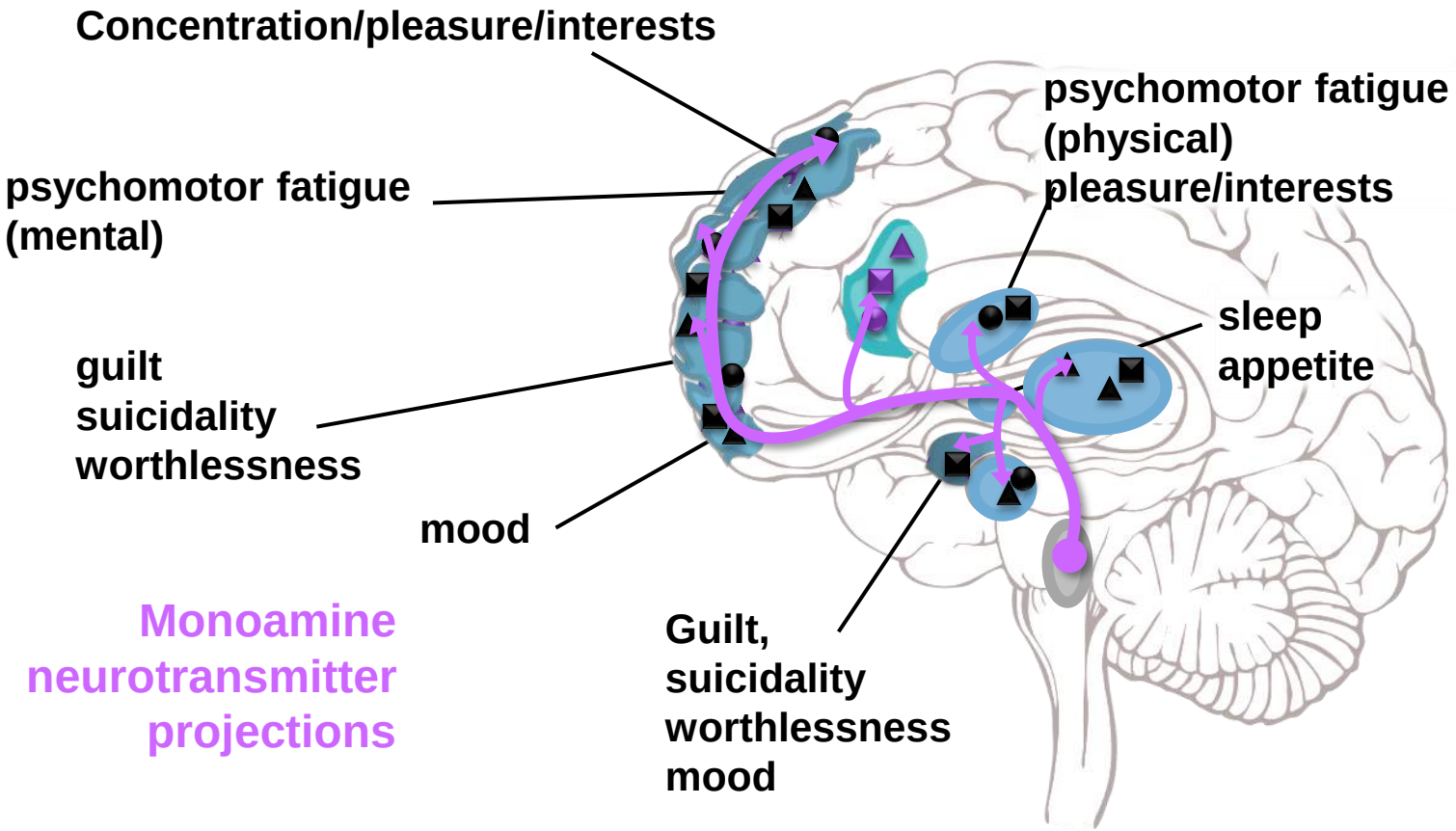
Treatment Resistant Depression

- Treatment resistant, and treatment refractory (highly resistant)
- Depression is not a standardized term
- Suggested definition: MDD episodes, not responding to two adequate trials of antidepressants, based mainly on STAR*D study

Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatments steps: A STAR*D report. *Am J Psychiatry* 2006; 163: 1905; Kessler RC, Berglund P, Demier O, et al. The epidemiology of major depressive disorder: Results from the National comorbidity Survey Replication (NCS-R). *JAMA* 2003; 289:3095.

THE BIOLOGY OF DEPRESSION

Major Depressive Disorder: Circuits and Neurotransmitters



- Monoamine dysfunction is linked to MDD
- Malfunctioning circuits lead to specific symptoms

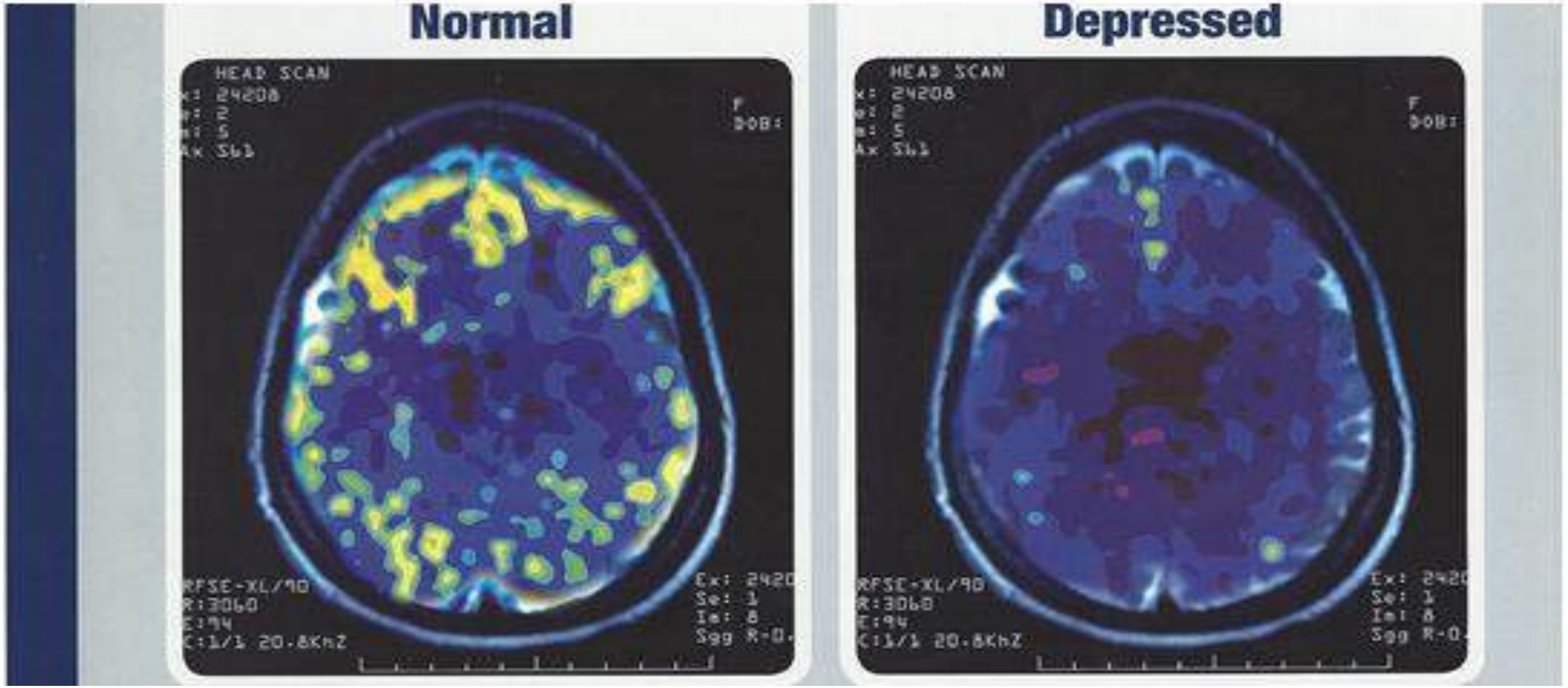
Regions implicated in MDD are connected to the brainstem via monoaminergic circuits

Monoamine Neurotransmitters: Serotonin (5-HT), Dopamine (DA), Norepinephrine (NE)

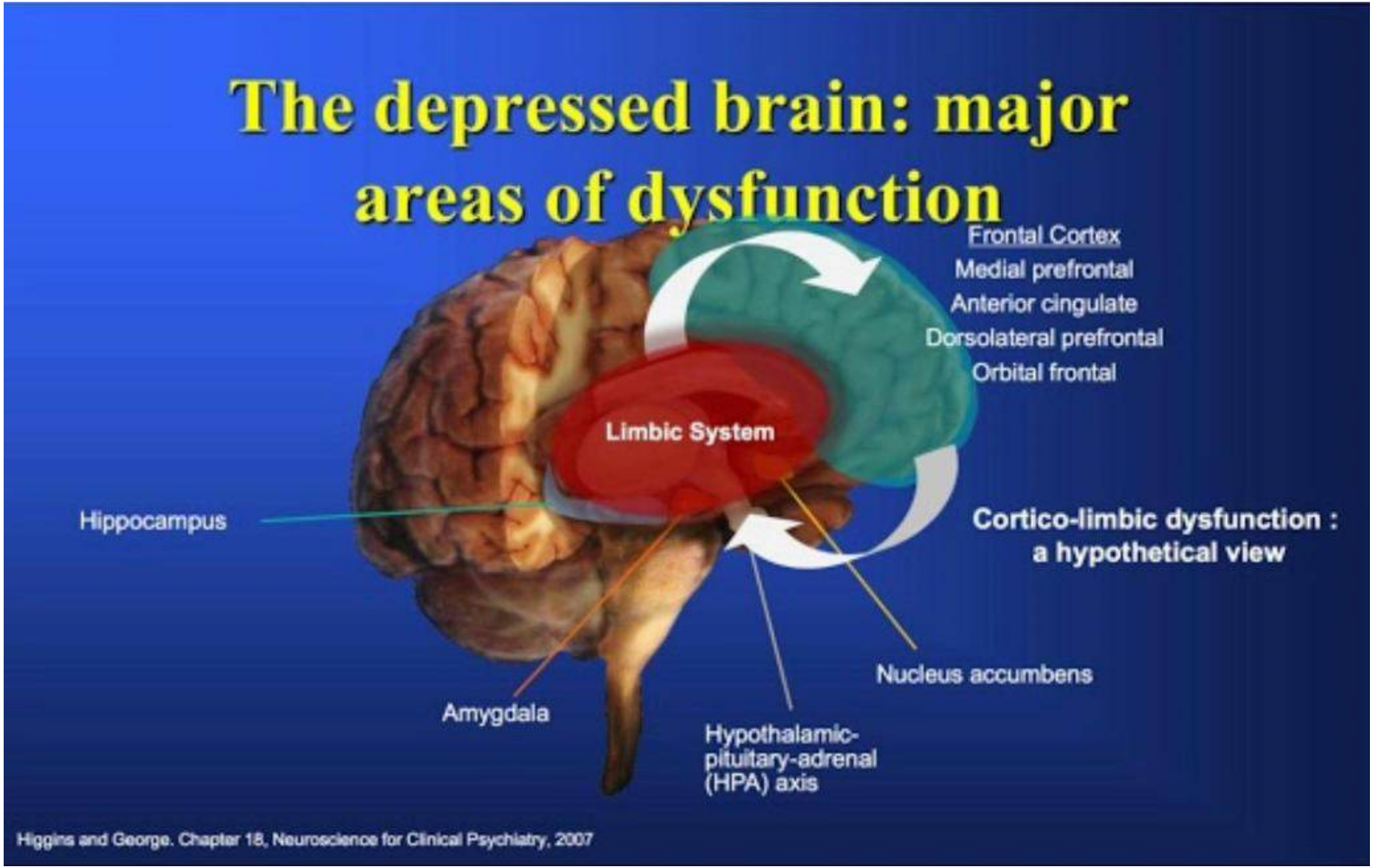
Stahl SM. Cambridge University Press; 2008.

Major Depression is a Brain Disease

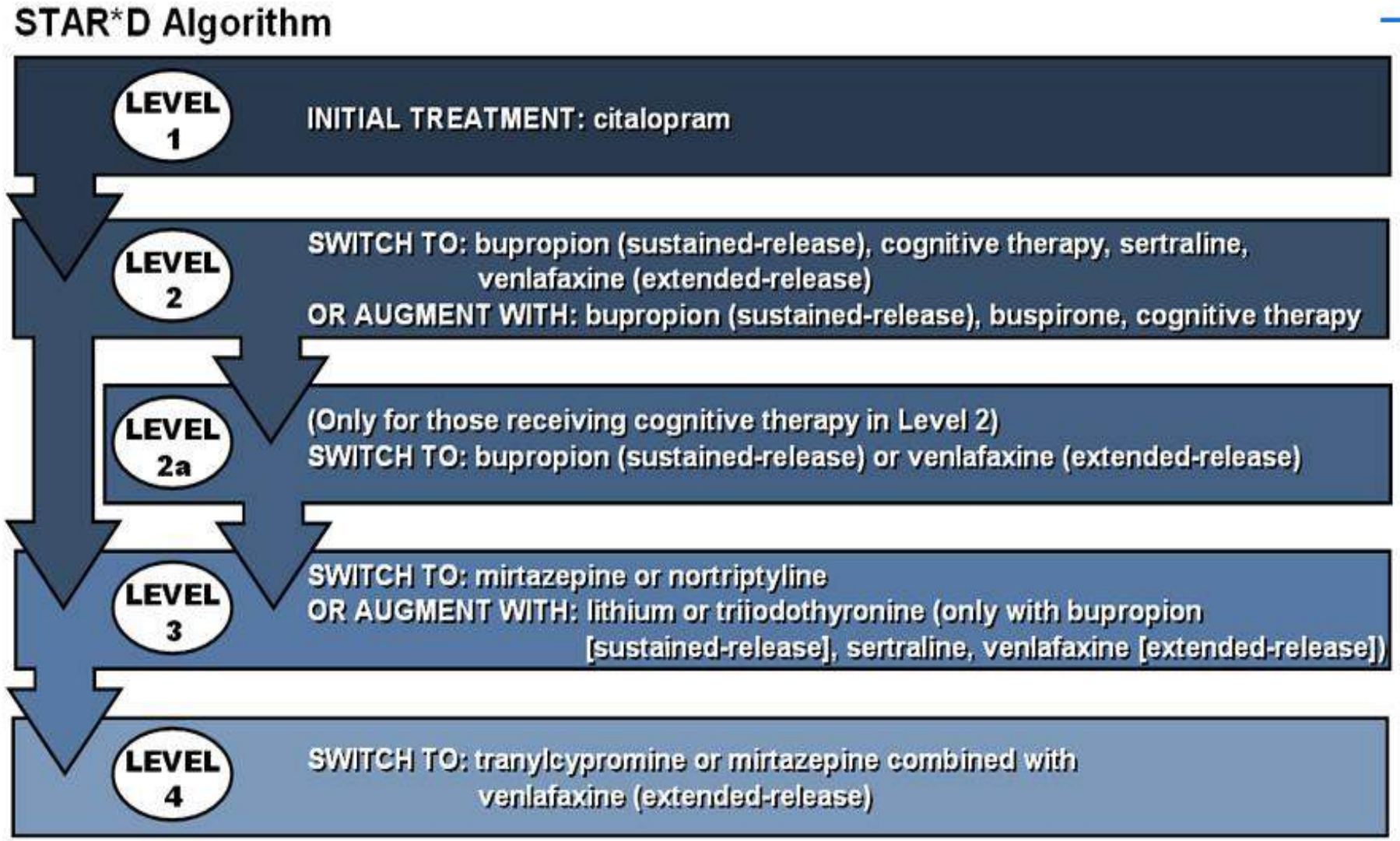
In some patients the PFC was hypometabolic



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

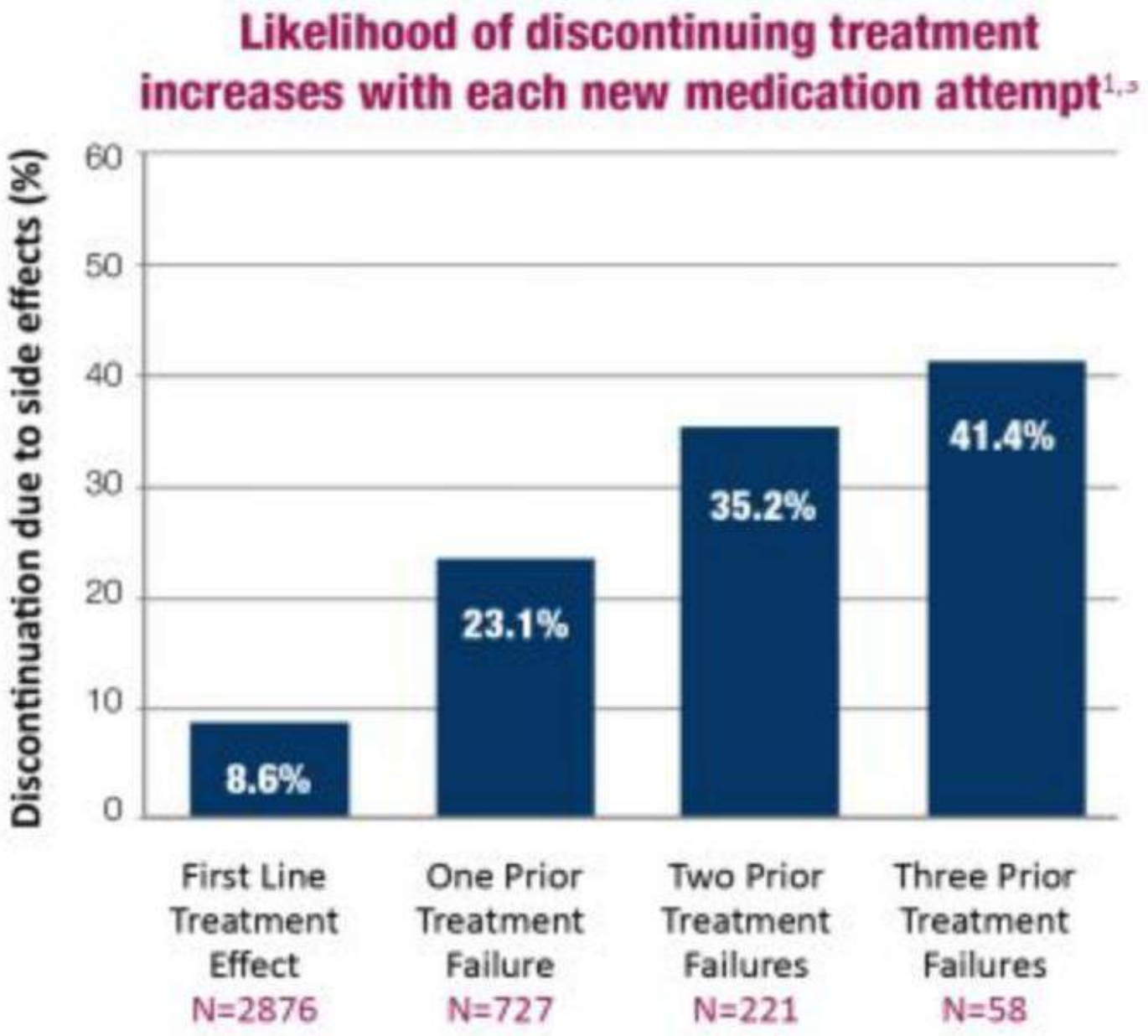

The depressed brain: major areas of dysfunction
Frontal Cortex
Medial prefrontal
Anterior cingulate
Dorsolateral prefrontal
Orbital frontal
Limbic System
Hippocampus
Cortico-limbic dysfunction : a hypothetical view
Nucleus accumbens
Amygdala
Hypothalamic-pituitary-adrenal (HPA) axis
Higgins and George. Chapter 18, Neuroscience for Clinical Psychiatry, 2007

STAR*D Treatment Algorithm



Trivedi et al. *Am J Psychiatry*. 2006; Rush et al. *NEJM*. 2006; Fava et al. *Am J Psychiatry*. 2006; McGrath et al. *Am J Psychiatry. 2006.*

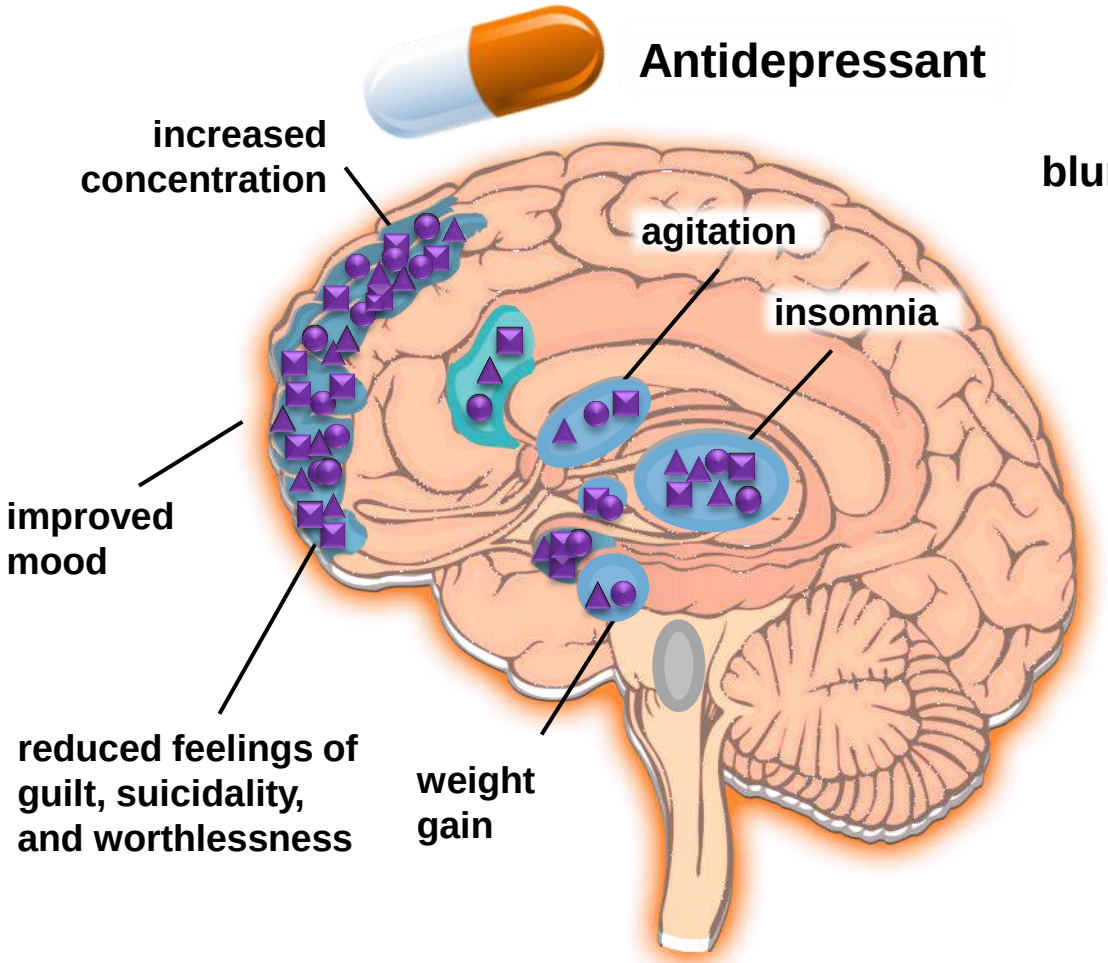
STAR*D Data Support Need for Other Treatment Options



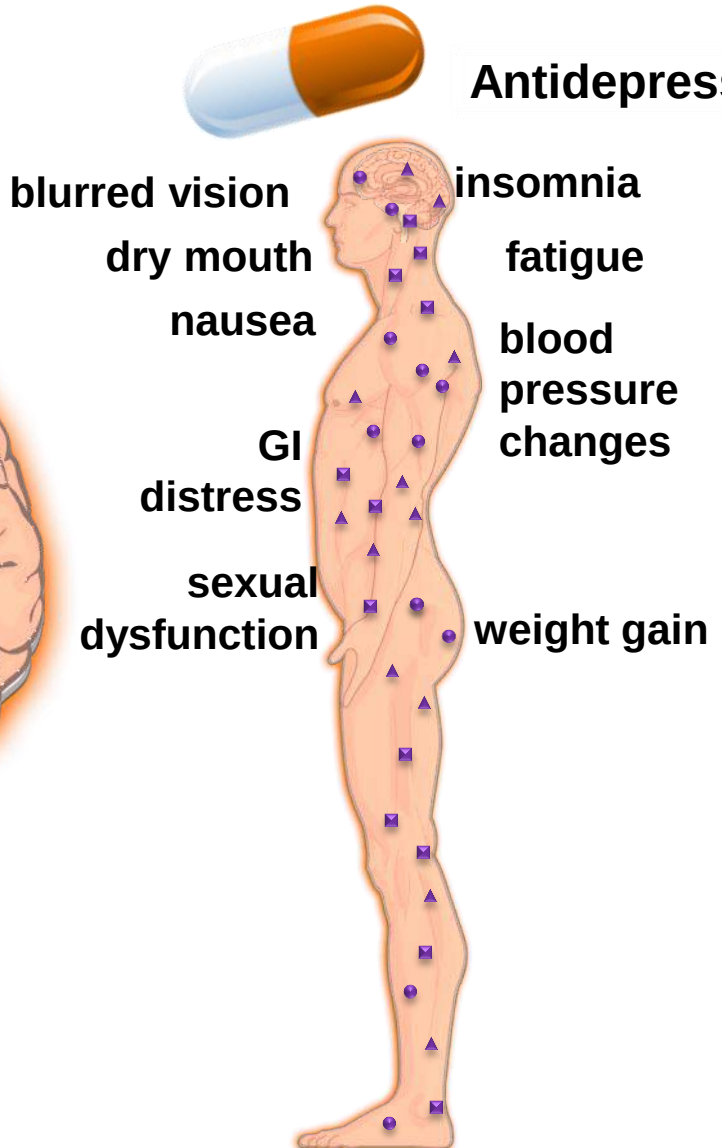
Trivedi et al. *Am J Psychiatry. 2006.* Fava et al. *Am J Psychiatry.* 2006.

Monoaminergic Effects of Antidepressant Medications

Therapeutic Effects such as:

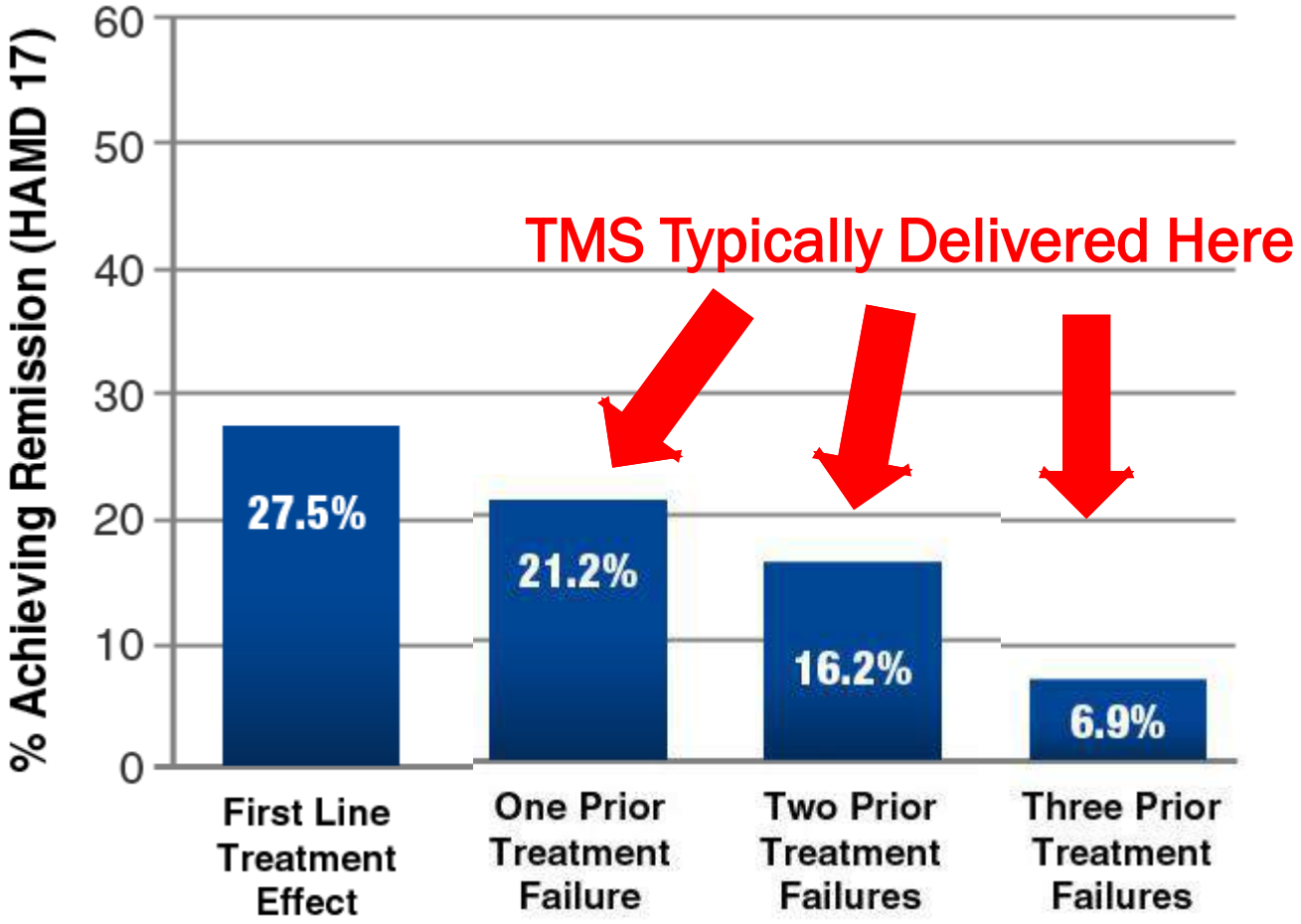


Side Effects such as:



Stahl SM. Cambridge University Press; 2008

STAR*D Demonstrated Decreased Remission Rates with Each Treatment Trial



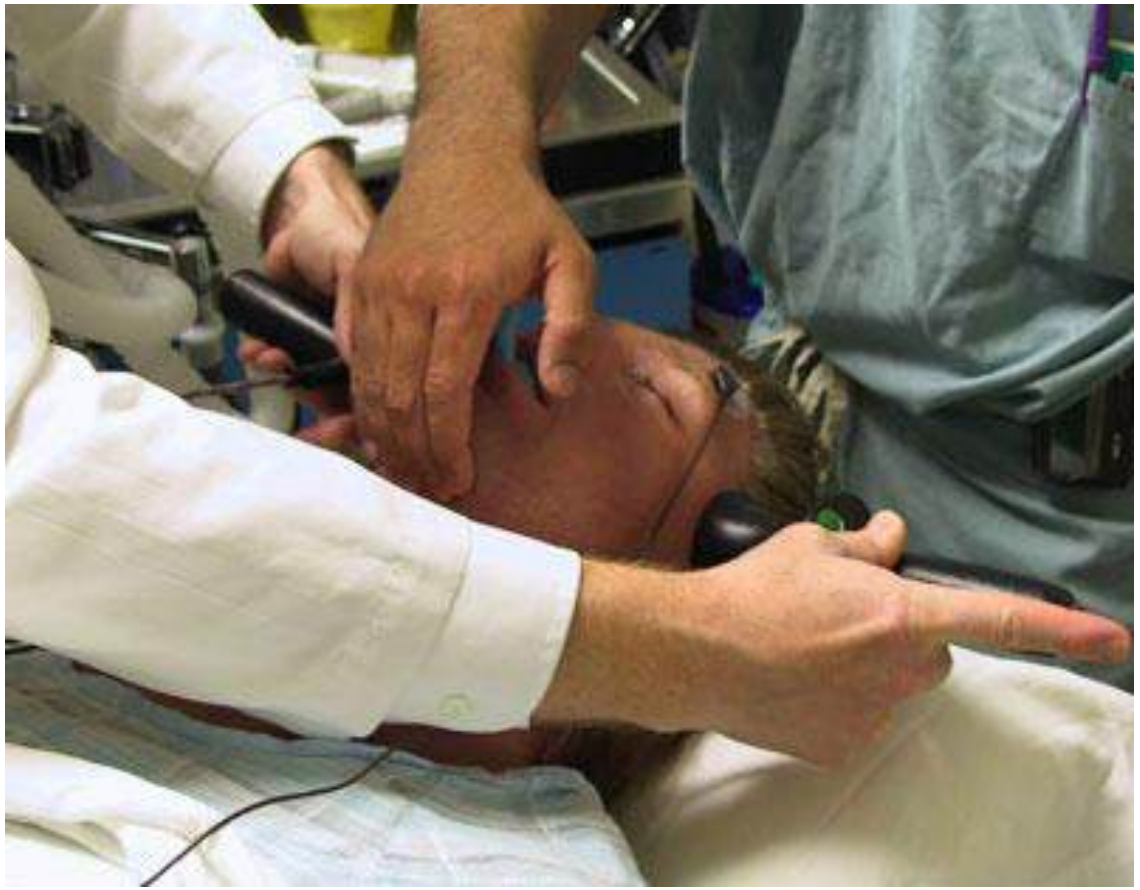
Trivedi (2006) *Am J Psychiatry*; Rush (2006) *Am J Psychiatry*; Fava (2006) *Am J Psychiatry*; McGrath (2006) *Am J Psychiatry*

TMS is NOT ECT

- TMS is not a replacement for ECT but is a different modality of therapeutic intervention in the algorithm of managing depression
- ECT is still best for MDD with psychotic features, acute suicidality, or catatonia
- Some patients who fail ECT respond to TMS and vice versa
- Head-to-head trials comparing ECT and TMS are not done with double blind due to the challenge of creating “double-dummy” sham design
- “It has been well established that, regardless of continuation treatment, relapse following ECT concentrates heavily in the weeks immediately following ECT termination, indicating that ECT has little intrinsic durability of benefit.”

Quote from H Sackeim, *Brain Stimulation* 2016 (9) 313-319.

ECT



Images from University of Michigan
https://www.youtube.com/watch?v=W8Ypt-vKI2U

About ECT

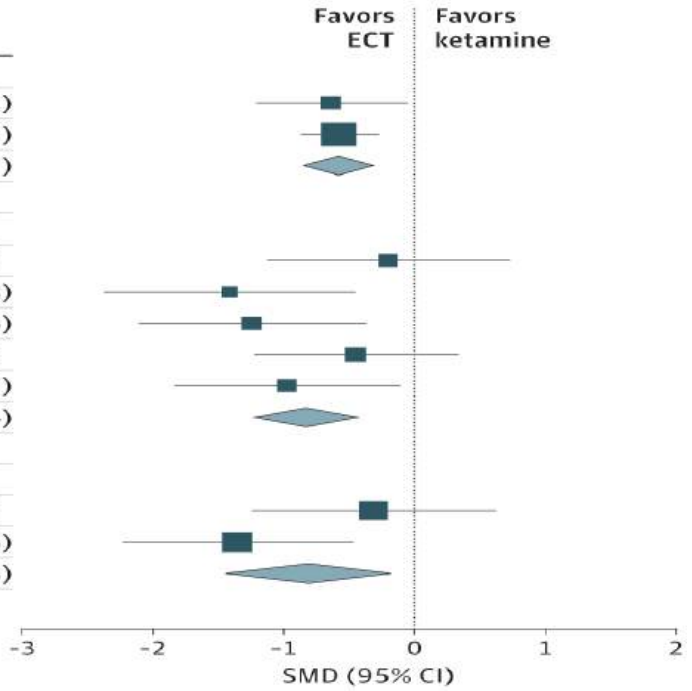
- Still considered the gold standard treatment for depression
  - *Especially effective for older patients, psychotic depression, and melancholic depression*
- Also highly effective for mania and catatonia
- Does have more side effects but the biggest risk of major side effects comes from general anesthesia.
- May require 6-8 weeks of leave of absence from work/school and assistance from others driving during that time
- Development of ultra brief pulse width electric current and unilateral electrode placement have greatly reduced the cognitive side effects.

Haq AU, Sitzmann AF, Goldman ML, Maixner DF, Mickey BJ. Response of depression to electroconvulsive therapy: a meta-analysis of clinical predictors. J Clin Psychiatry. 2015 Oct;76(10):1374-84.

ECT vs Ketamine

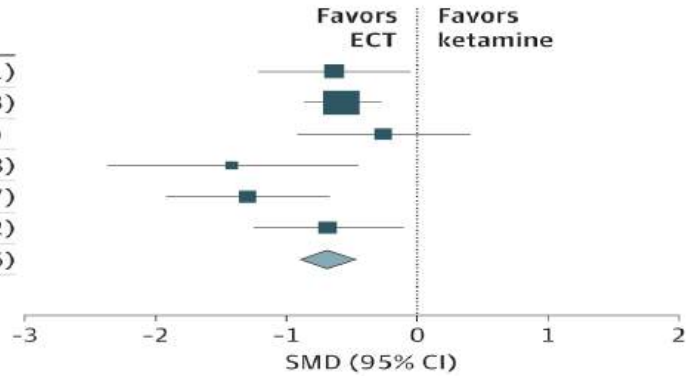
A Severity of depressive symptoms by measure

Study	ECT Total	ECT Mean (SD)	Ketamine Total	Ketamine Mean (SD)	SMD (95% CI)
MADRS					
Basso et al,[36] 2020	24	-17.420 (7.4900)	25	-13.000 (6.1500)	-0.636 (-1.211 to -0.061)
Ekstrand et al,[37] 2022	91	-22.300 (9.6100)	95	-16.200 (11.3500)	-0.577 (-0.870 to -0.283)
Total (95% CI)	115		120		-0.589 (-0.850 to -0.327)
Heterogeneity: $\tau^2 = 0$; $\chi^2 = 0.03$; $df = 1$; $P = .86$; $I^2 = 0\%$					
HDRS					
Ghasemi et al,[38] 2014	9	-21.880 (5.8500)	9	-20.670 (5.4200)	-0.204 (-1.131 to 0.723)
Kheirabadi et al,[39] 2019	12	-12.500 (3.5000)	10	-7.700 (2.9500)	-1.415 (-2.371 to -0.458)
Sharma et al,[41] 2020	13	-21.190 (5.8400)	12	-14.500 (4.3800)	-1.246 (-2.115 to -0.376)
Kheirabadi et al,[40] 2020 (IM)	12	-12.330 (5.0300)	15	-10.140 (4.4400)	-0.451 (-1.221 to 0.319)
Kheirabadi et al,[40] 2020 (oral)	12	-12.330 (5.0300)	12	-8.170 (2.9800)	-0.972 (-1.826 to -0.117)
Total (95% CI)	58		58		-0.832 (-1.221 to -0.444)
Heterogeneity: $\tau^2 = 0.0475$; $\chi^2 = 5.1$; $df = 4$; $P = .28$; $I^2 = 22\%$					
BDI					
Ghasemi et al,[38] 2014	9	-26.780 (8.7000)	9	-23.780 (9.5100)	-0.313 (-1.245 to 0.618)
Sharma et al,[41] 2020	13	-30.650 (5.7700)	12	-20.450 (8.6800)	-1.350 (-2.233 to -0.466)
Total (95% CI)	22		21		-0.859 (-1.500 to -0.218)
Heterogeneity: $\tau^2 = 0.3225$; $\chi^2 = 2.5$; $df = 1$; $P = .11$; $I^2 = 60\%$					



B Overall effect size for severity of depressive symptoms

Study	N	SMD (95% CI)
Basso et al,[36] 2020	50	-0.636 (-1.211 to -0.061)
Ekstrand et al,[37] 2022	186	-0.577 (-0.870 to -0.283)
Ghasemi et al,[38] 2014	18	-0.259 (-0.916 to 0.398)
Kheirabadi et al,[39] 2019	22	-1.415 (-2.371 to -0.458)
Sharma et al,[41] 2020	25	-1.297 (-1.916 to -0.677)
Kheirabadi et al,[40] 2022	39	-0.684 (-1.256 to -0.112)
Total (95% CI)		-0.685 (-0.890 to -0.476)
Heterogeneity: $\tau^2 = 0.0368$; $\chi^2 = 8.15$; $df = 5$; $P = .15$; $I^2 = 39\%$		

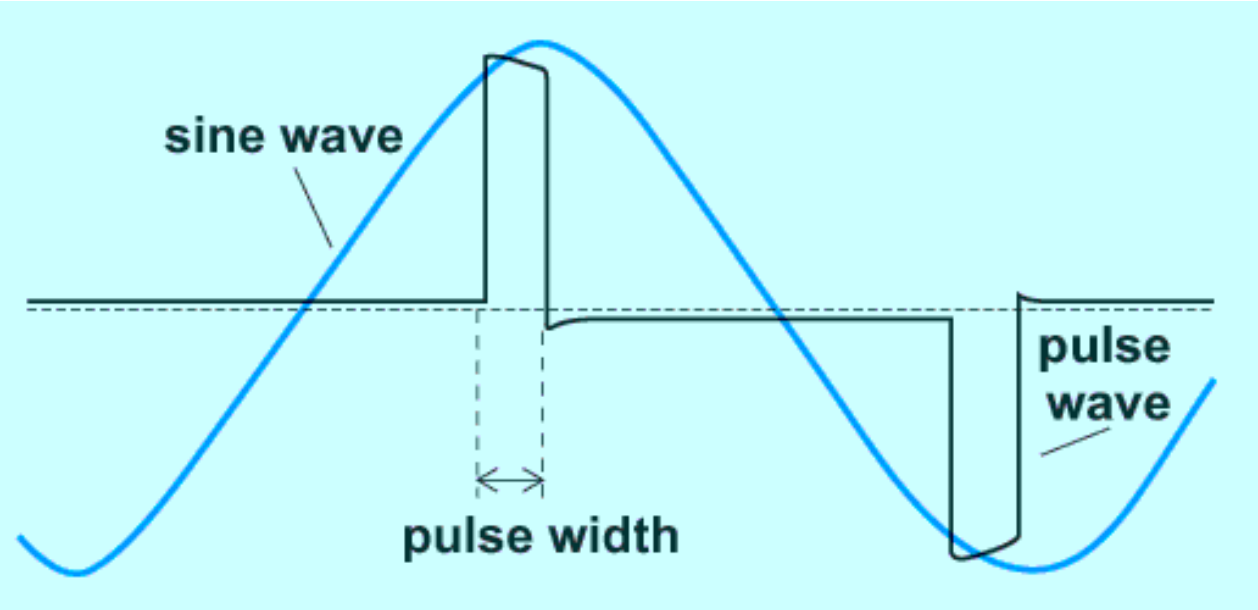


Unilateral ECT Treatment

Unilateral

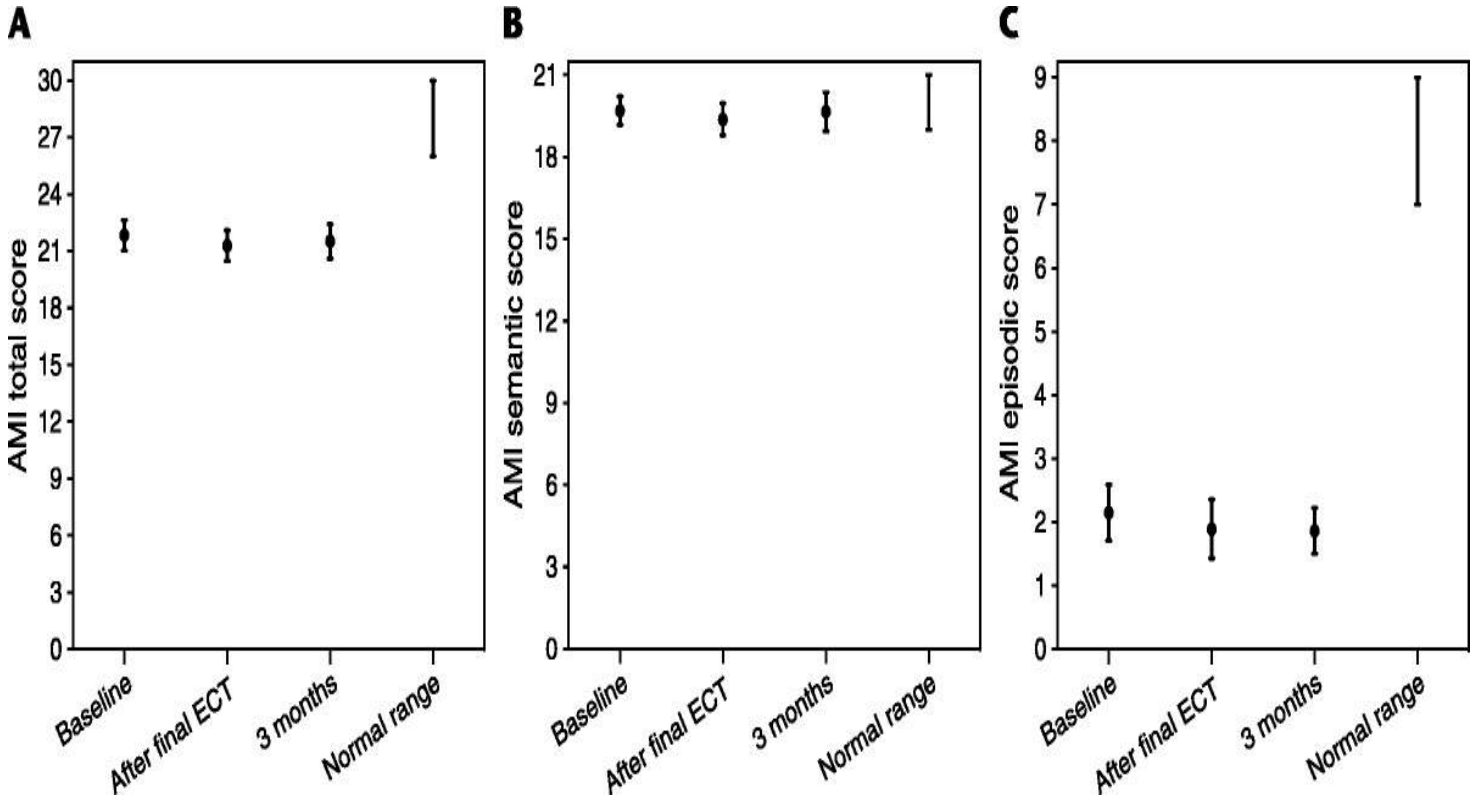
- Using unilateral placement significantly reduces cognitive side effects
- Does take more sessions to reach remission compared to bilateral placement

Ultra Brief pulse width



- Initially ECT used sine wave electrical current from a standard outlet
- Modern ECT machines convert sine wave to pulses of electrical current that are less cognitive impairing

Cognitive Side Effects



- Depression is associated with deficits in autobiographical episodic memory at baseline
- ECT showed no change in these deficits 3 months post ECT
- This metanalysis included mostly bitemporal electrode placement

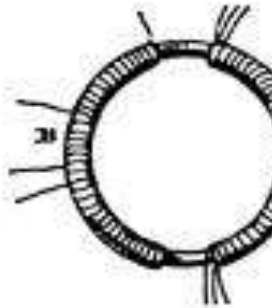
Jelovac, A. O'Connor, S. et al. Autobiographical Memory Specificity in Major Depression Treated With Electroconvulsive Therapy. *J ECT.* 2016 Mar;32(1):38-43.

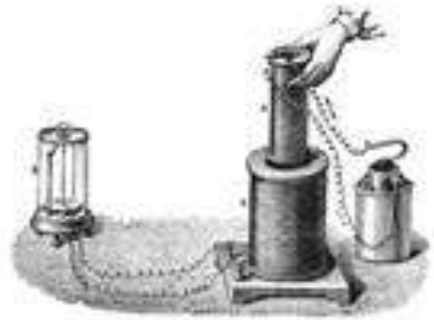
TRANSCRANIAL MAGNETIC STIMULATION: MECHANISM OF ACTION

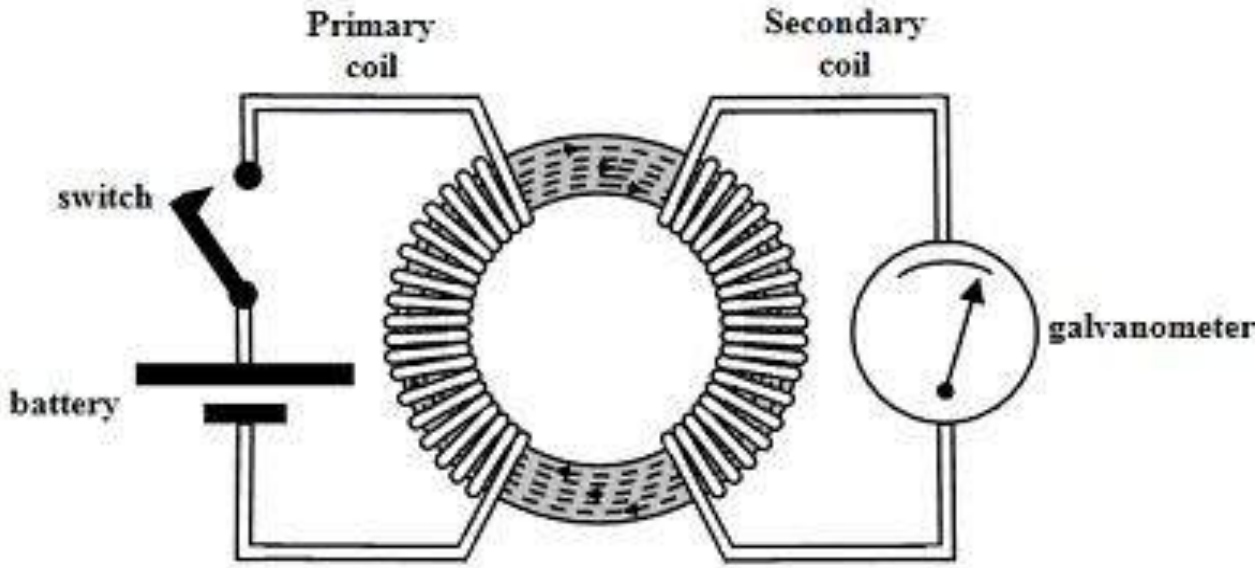
Science Behind TMS: 1831 Michael Faraday

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.

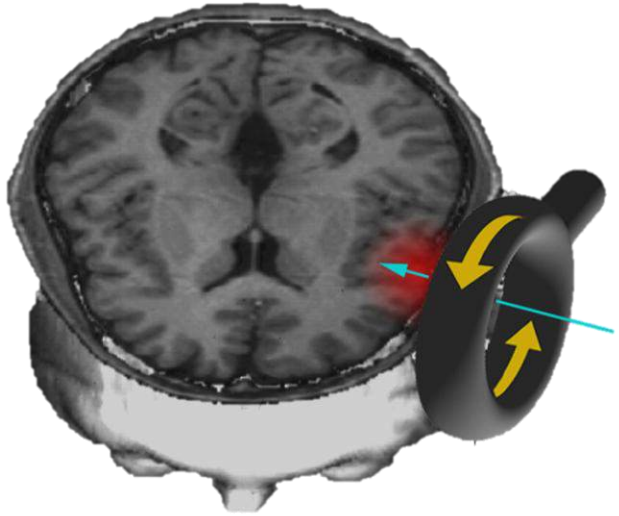
The rate of change (flux) of this magnetic field determines the induction of a secondary current in a nearby conductor that is placed in a perpendicular plane.



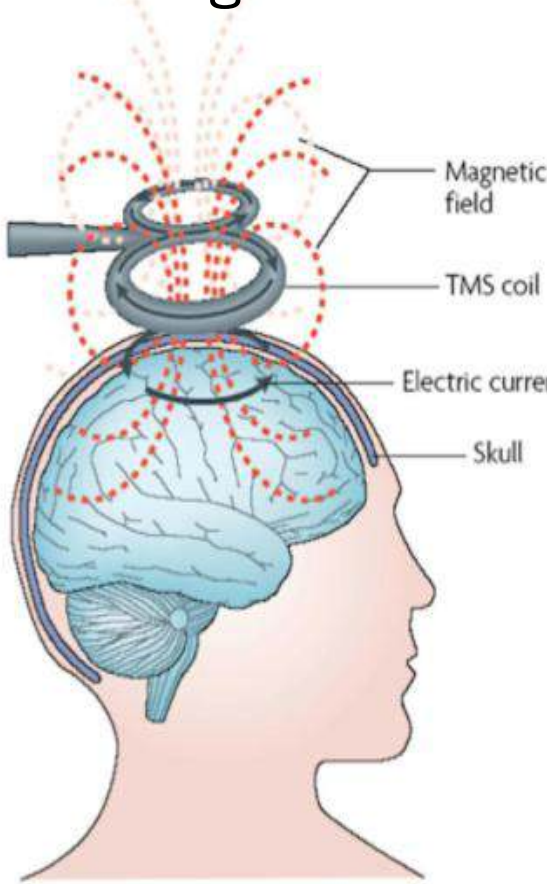


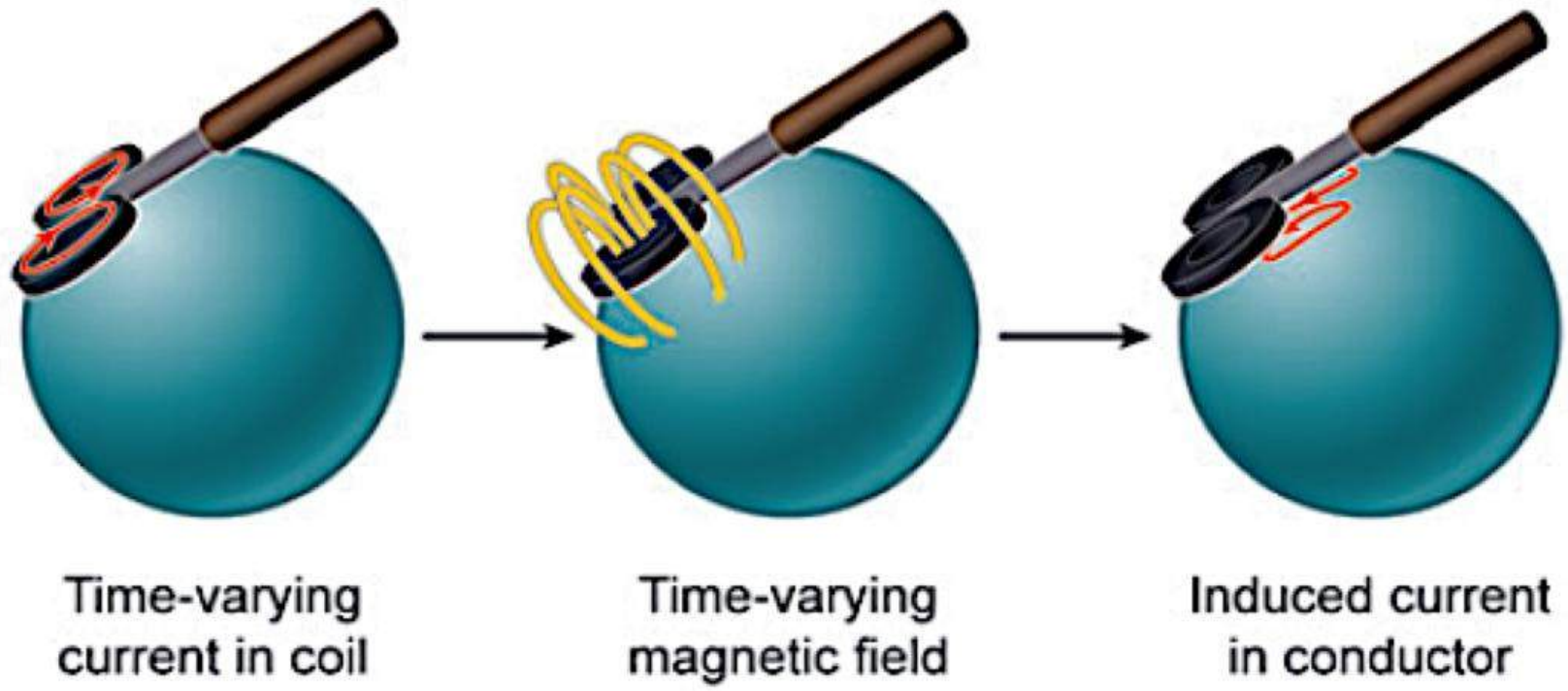


TMS Physics: Faraday's Law

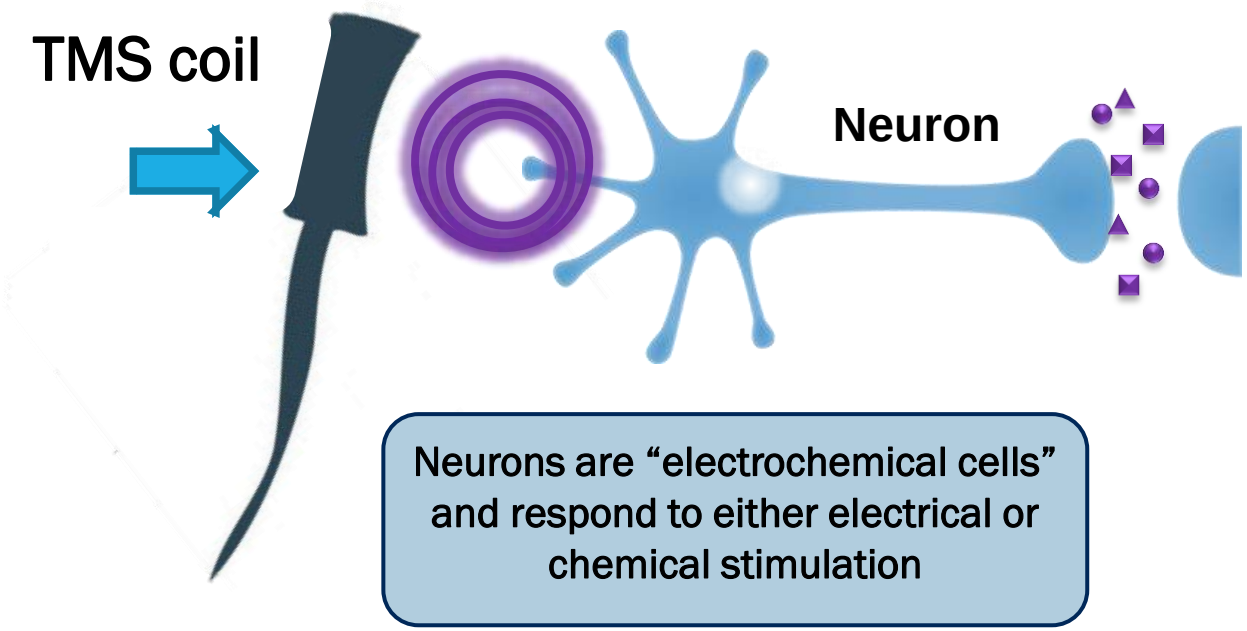


Magnetic Field Passes through Scalp and Skull Unimpeded
Cortical Neurons Act as Conductors, Like Copper Wire
Pulsed Magnetic Field Induces Current in Neurons





TMS Directly Depolarizes Cortical Neurons to Produce an Action Potential

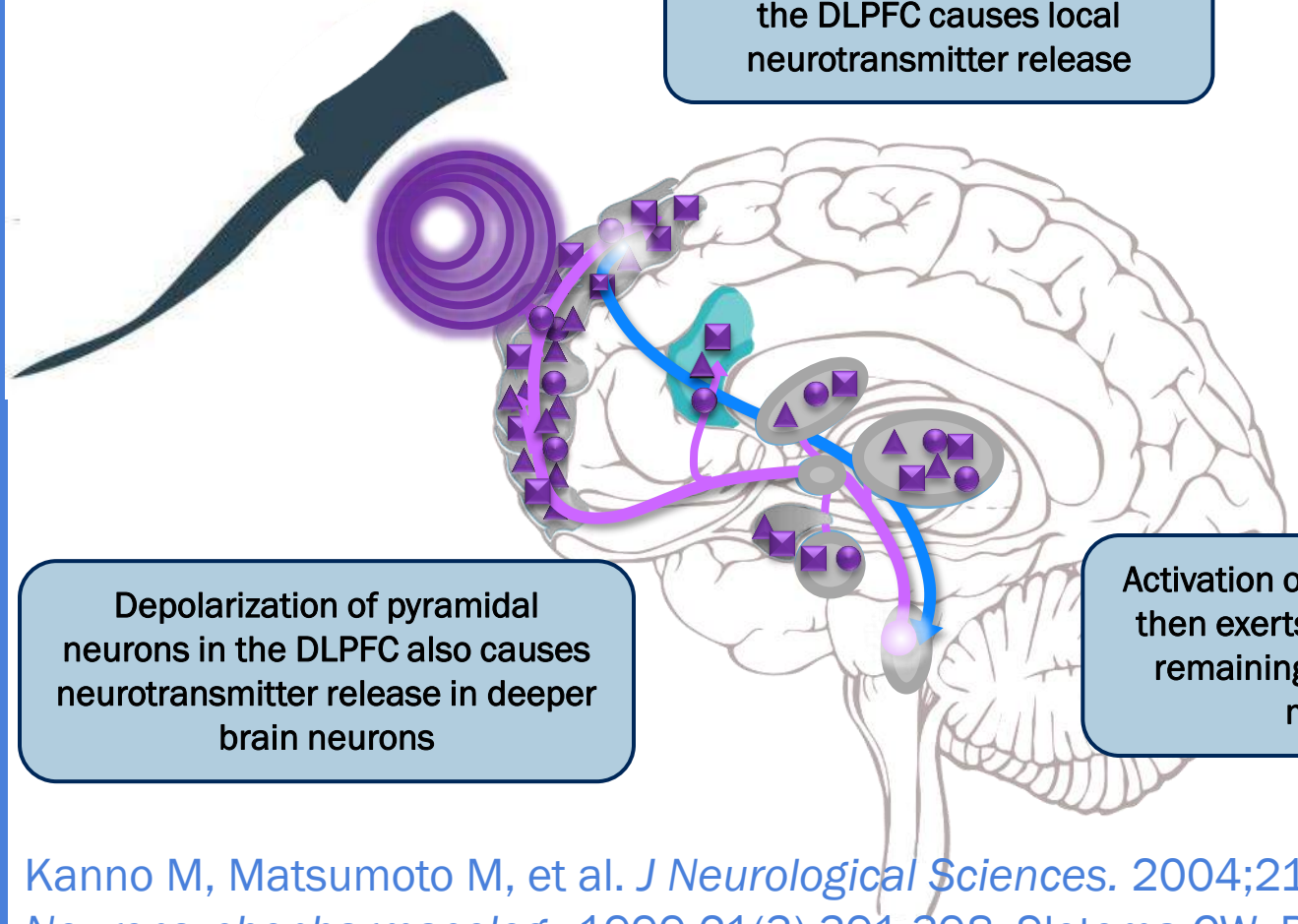


Sequence of Effects of TMS Pulsed Magnetic Fields:

- induces a local electric current in the superficial cortex
- depolarizes neurons (change in charge differential across the membrane)
- elicits an action potential (neuron fires)
- release of chemical neurotransmitters at synapse
- propagation of signal to other brain regions and structures

Post A, Keck ME. J Psychiatric Research. 2001;35: 193-215.

Neuronal Firing Releases Neurotransmitters into the Synapse



Depolarization of neurons in the DLPFC causes local neurotransmitter release

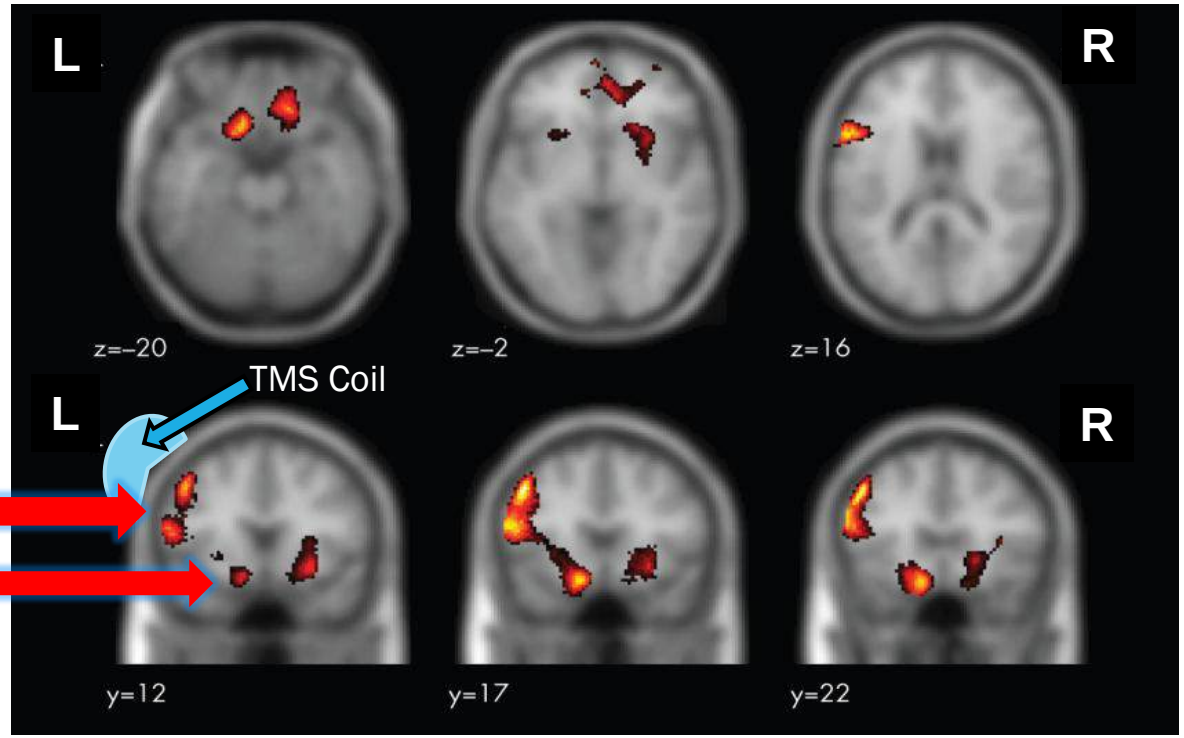
Depolarization of pyramidal neurons in the DLPFC also causes neurotransmitter release in deeper brain neurons

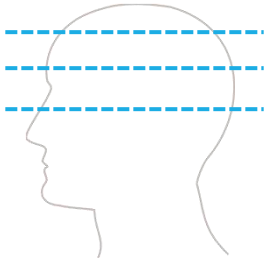
Activation of deeper brain neurons then exerts secondary effects on remaining portions of targeted mood circuits

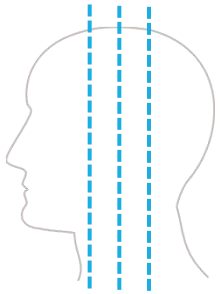
These effects are associated with improvements in depressive symptoms

Kanno M, Matsumoto M, et al. *J Neurological Sciences.* 2004;217:73-81.Juckel G, Mendlin MA, et al. *Neuropsychopharmacology.*1999;21(3):391-398. Slotema CW, Blom JD, et al. *J Clin Psychiatry.* 2010;71(7):873-884.

Targeted Effects on Mood Circuits in the Brain



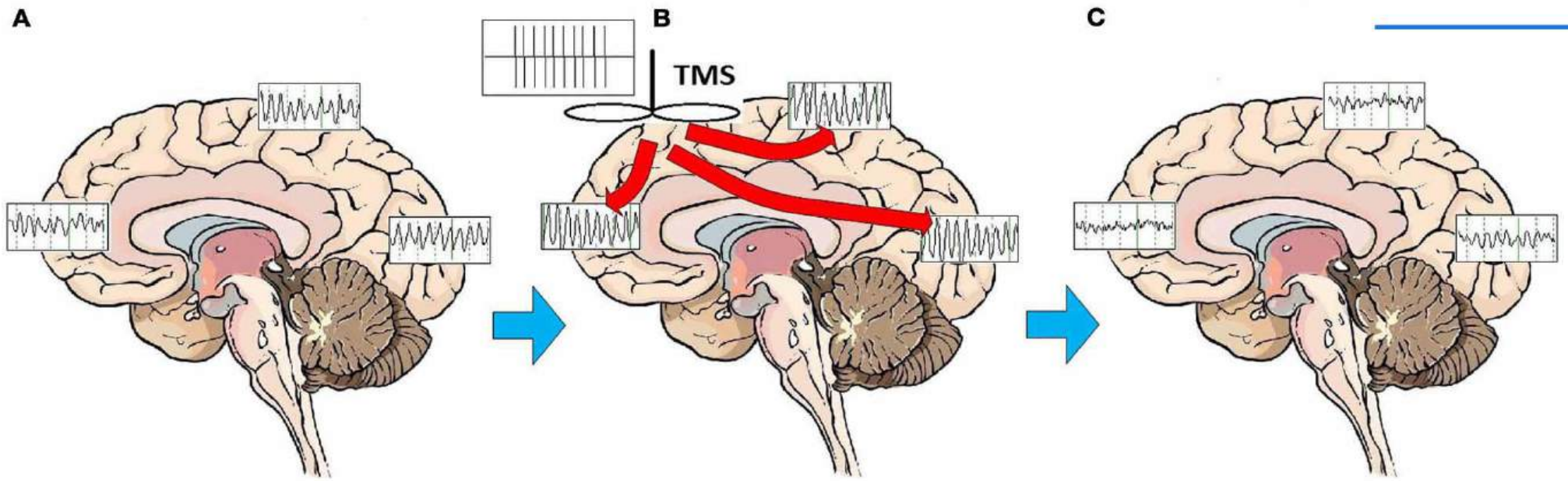




Activation of fronto-cingulate brain circuit following a course of TMS applied to the left dorsolateral prefrontal cortex in patients with Major Depression

Kito, *J Neuropsychiatry Clin Neurosci*. 2008

Other Theory of TMS Mechanism of Action



- MDD is marked by disturbances in brain functional connectivity, thalamocortical dysrhythmia. This connectivity is modulated by rhythmic oscillations of brain electrical activity.

- 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

Leuchter A et al Frontiers in Human Neuroscience 2013; 7(37): 1-10.

Biological & Behavioral Effects of TMS

Effects Seen After Chronic Exposure (Repeated TMS Applications):

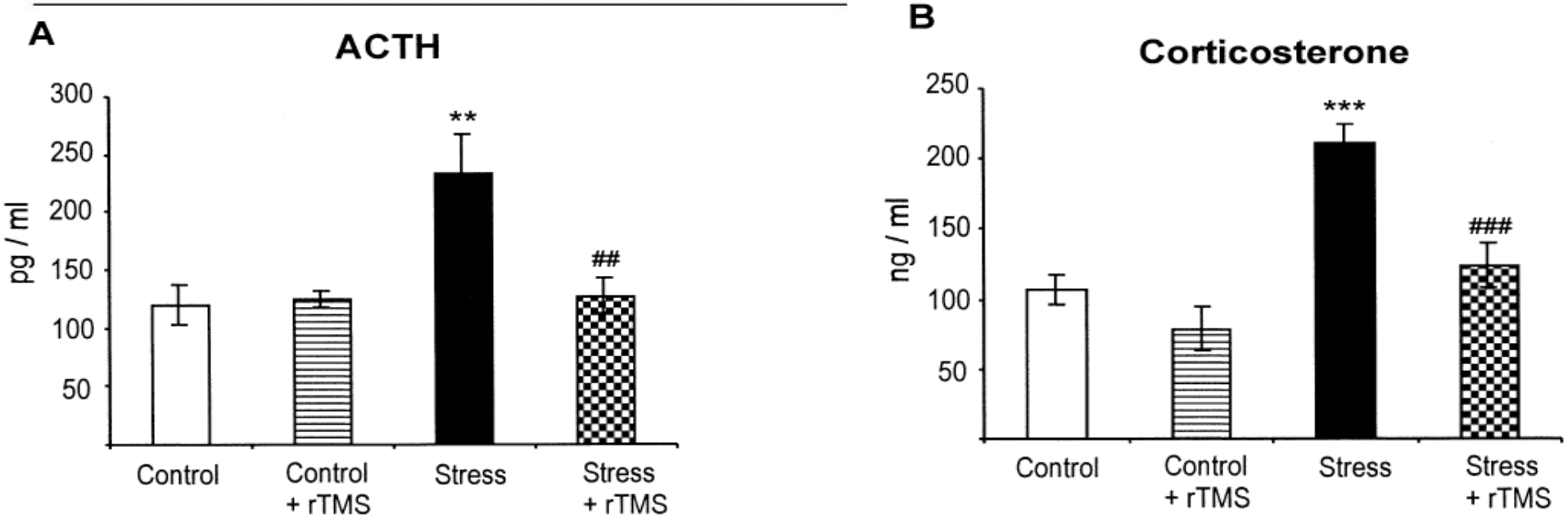
- Specific outcome is dependent upon stimulation parameters
- Alteration of monoamine concentrations
- Beta-receptor, serotonin-receptor modulation
- Evidence of induction of neurogenesis genes (eg, BDNF)
- Plasticity-like actions (ie, LTD/LTP-like effects)
- Local GABA, glutamate effects
- Stimulation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

TMS Restrains the Activation of HPA Axis During Chronic Stress

Chronic Psychosocial Stress and Concomitant Repetitive Transcranial Magnetic Stimulation: Effects on Stress Hormone Levels and Adult Hippocampal Neurogenesis

Boldizsár Czéh, Tobias Welt, Anja K. Fischer, Angelika Erhardt, Wolfram Schmitt, Marianne B. Müller, Nicola Toschi, Eberhard Fuchs, and Martin E. Keck

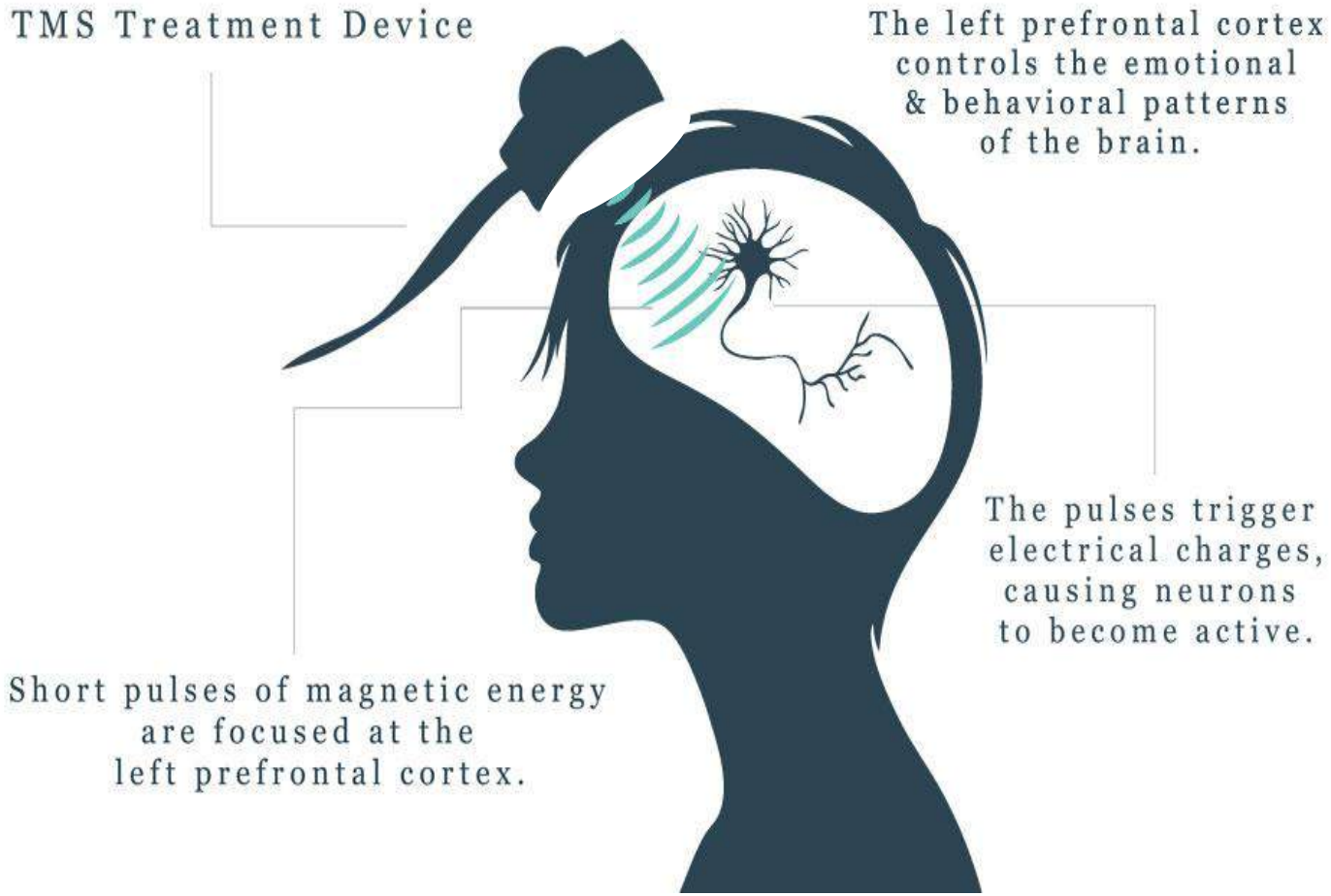


Czeh, B., et al., *Biol Psychiatry*. 2002;52:1057-1065

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

TMS: is a Well-Tolerated Antidepressant

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

TMS Side Effects:

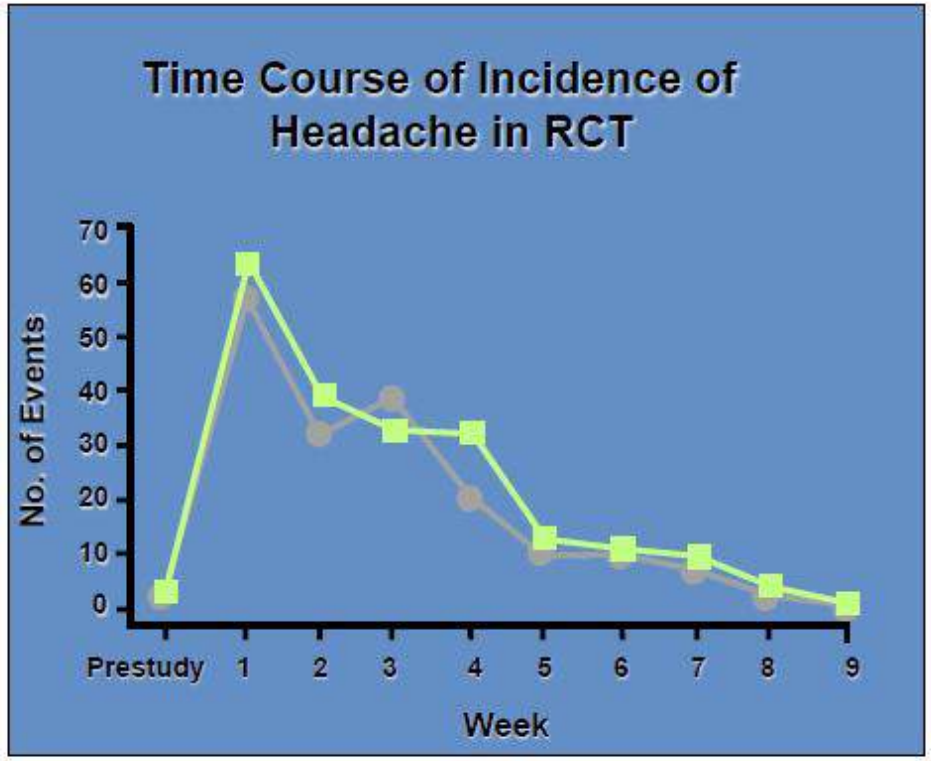
Scalp/Head Pain at Treatment Site and Headache

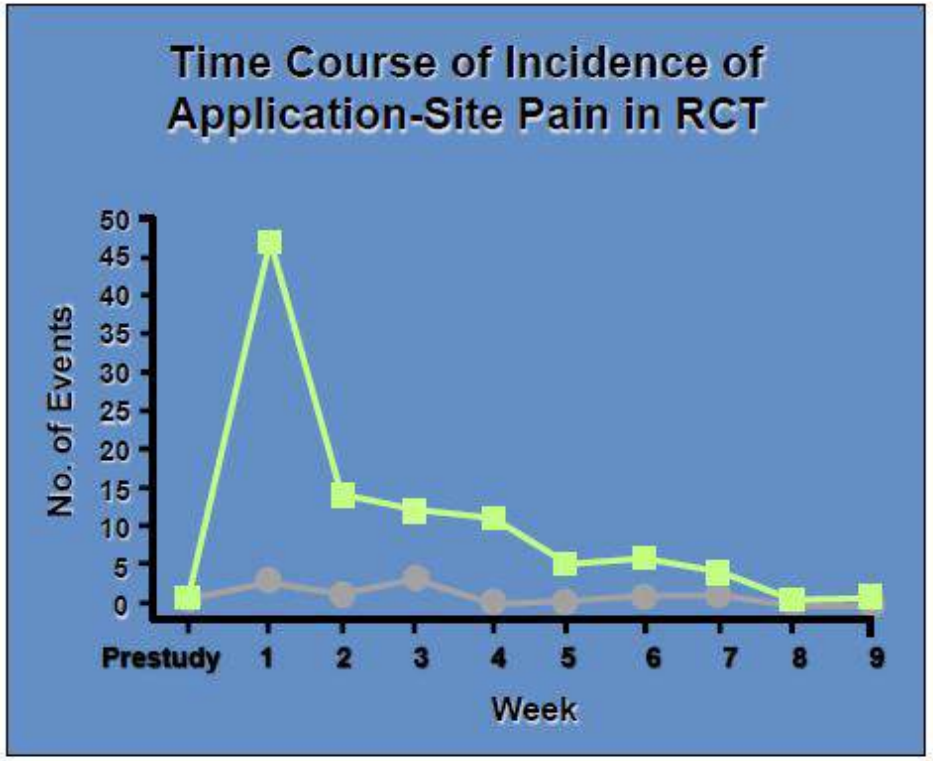
No Systemic Side Effects:

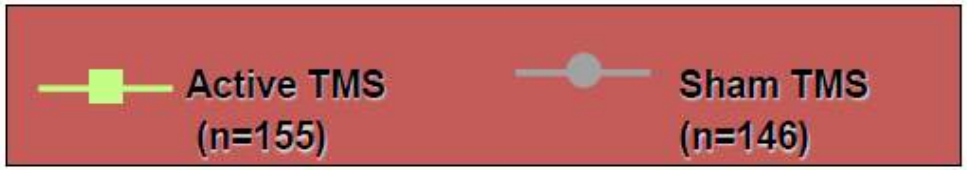
Weight Gain	Nausea	Dry Mouth
Weight Loss	Nervousness/Anxiety	Sweating
Appetite changes	Sexual side effects	Tremor
Constipation	Impotence	Fatigue
Diarrhea	Weakness	Treatment Discontinuation symptoms

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

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







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

Serious Adverse Events That Have Been Studied

Hearing Loss

- Small proportion of adult human have experienced transient increases in auditory thresholds
- Permanent threshold shift in single patient who did not wear ear plugs and was stimulated with the H1 coil
- Majority of studies which hearing protection was used report no change in hearing after TMS

<u>Recommendations:</u>

Patients and TMS Technicians should be required to wear ear plugs that meet a minimum standard of 30dB protection.

Loo et al. Biol Psychiat 2001; Zangen et al. Clin Neurophysiol 2005; Folmer et al. Acta Otolaryngol 2006; Rossi et al. J Neurol Neurosurg Psychiat 2007; Janicak et al. J Clin Psychiat 2008

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

Emergence of Suicidal Ideation: Multicenter Study

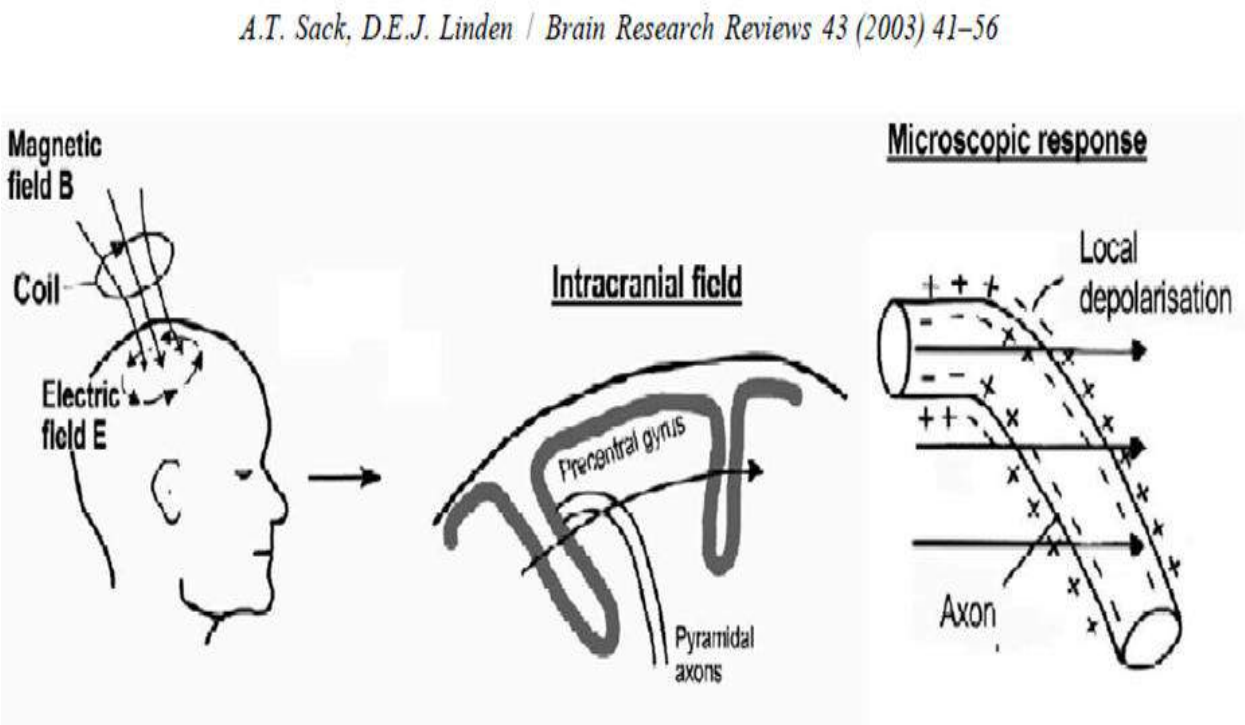
- Treatment emergent disease exacerbation
  - *Population with increased severity of clinical condition*
- 1.9% with sham; 0.6% active TMS

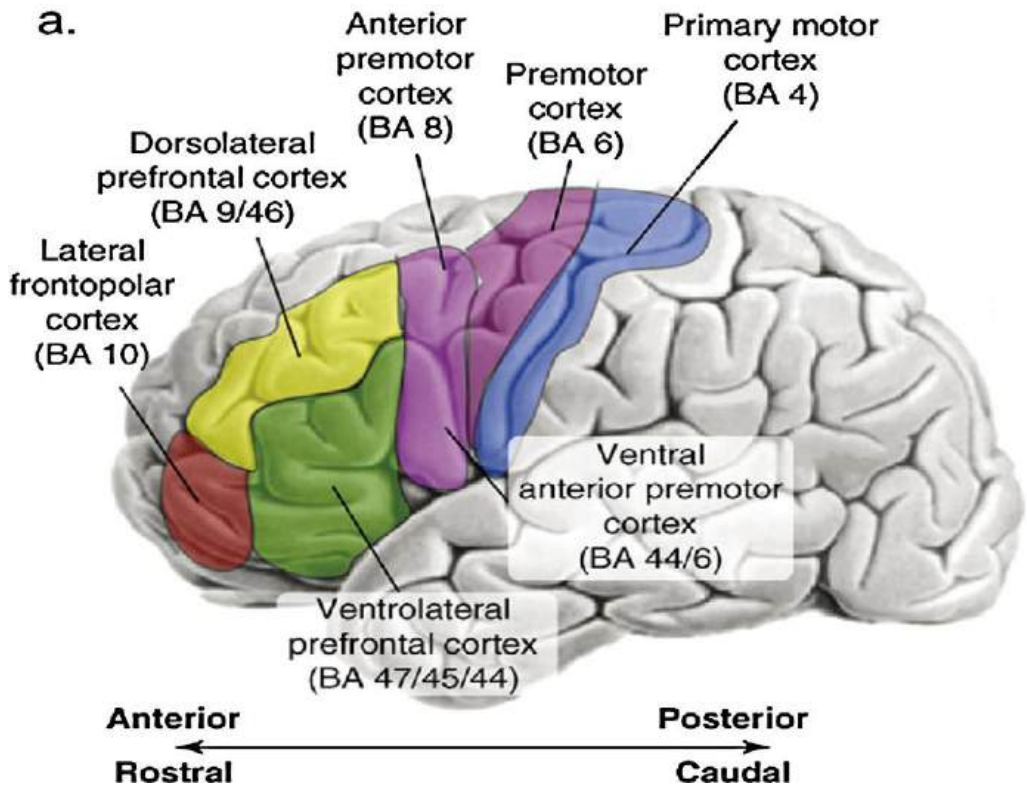
- One non-lethal overdose in sham treatment group

Janicak PG et al. J Clinical 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.





Developmental Cognitive Neuroscience 2014 (10) 57-76.

TMS and Seizures

- Most cases associated with TMS were prior to the publication of the TMS safety guidelines in 1998 [1]
- 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 could be considered very low. [1]
- The risk is less than or comparable to risk of seizure associated with antidepressant medications [2]

[1]Wassermann, E. Electroencephalography and Clinical Neurophysiology, 108, 1998; [2]George MS et al Curr Opin Psychiatry. 2013 Jan 26(1): 13-18

SCIENTIFIC EVIDENCE OF EFFICACY FOR TMS THERAPY

Large - Scale Randomized Controlled Trials - RCT's

- Four large-scale studies (sample size > 100), 3 studies patients off medications and 1 study patients on medications concurrently
- Two large multicenter industry supported trials that lead to FDA approval for two devices
- One NIH-funded study with dosage parameters similar to those in the industry-sponsored study but with sham design enhancements
- One European study of the augmentation effects of TMS when used in combination with pharmacotherapy

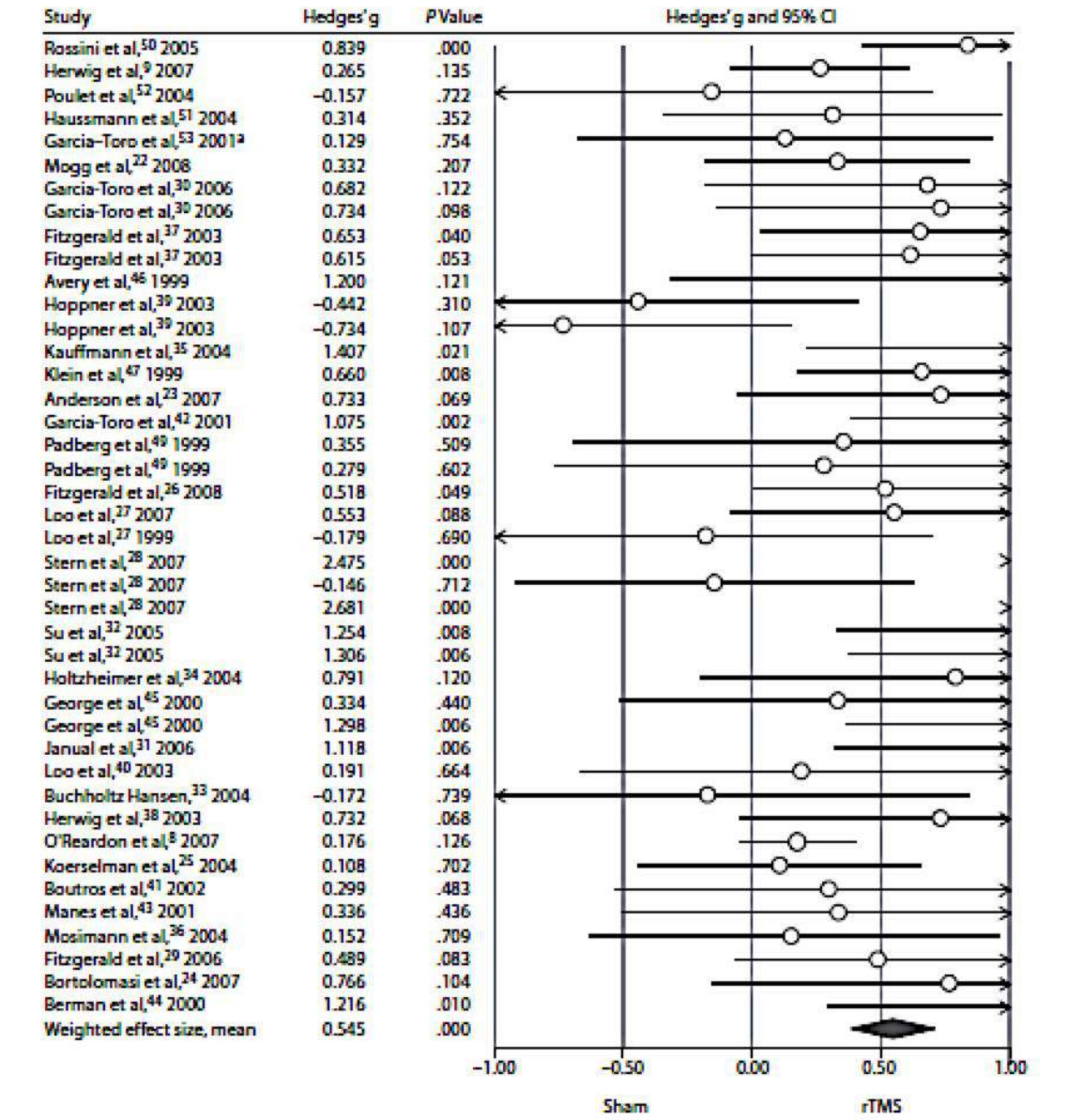
George et al., *Archives of General Psychiatry.* 2010(67);507-516 Herwig et al., *British Journal Psychiatry. 2007;*191, 441-448 Levkovitz et al., *World Psychiatry*. 2015(14); 64-73 O'Reardon et al., *Biological Psychiatry*. 2008(62); 1208-1216

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
  - Increase intensity
  - Increase pulse number
- Most recent
  - 34 individual trails, 1383 patients and found
  - TMS to be more effective than sham TMS
  - with a large effect size = 0.55.

Slotema CW et al J Clin Psychiatry 2010;71(7):873–84

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



[a]Add-on therapy.
Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

Multisite Naturalistic Observational Study of TMS for MDD: Acute Treatment Outcomes & 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

Acute Phase

Treatment course driven by patient clinical response

Long-term Outcomes

Measured at 3, 6, 9 and 12 months

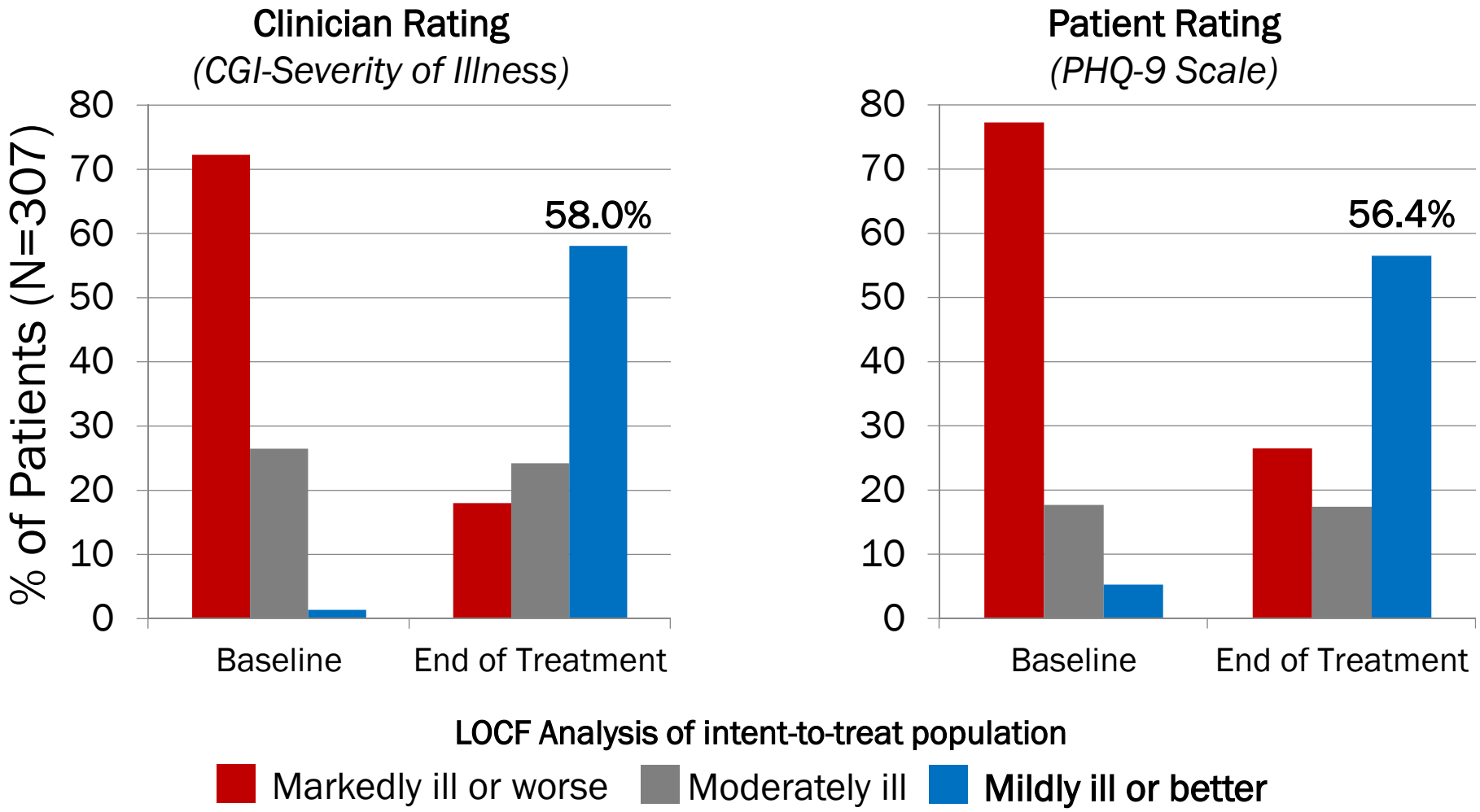
Carpenter et al, *Depression and Anxiety*, 2012; Dunner et al, *J Clin* Psychiatry 2014

Patients Who Entered Study Had Significant Morbidity

Patient and Treatment Characteristics	N = 307
N (%) Female	205 (66.8)
Age in years, mean (SD)	48.6 (14.2)
Disease and Treatment History N(%) - Recurrent Major Depression - Comorbid Anxiety Disorder	 285 (92.8) 46 (15.0)
Psychiatric Treatment History N(%) - History of Inpatient Hospitalization - History of ECT Treatment	 133 (43.3) 15 (4.9)
Prior Antidepressant Medication Treatment mean (SD) - Average Number of Adequate Treatments in Current Episode	 2.5 (2.3)
Mean (SD) Number of TMS Sessions During Acute Treatment	28 (10.1)

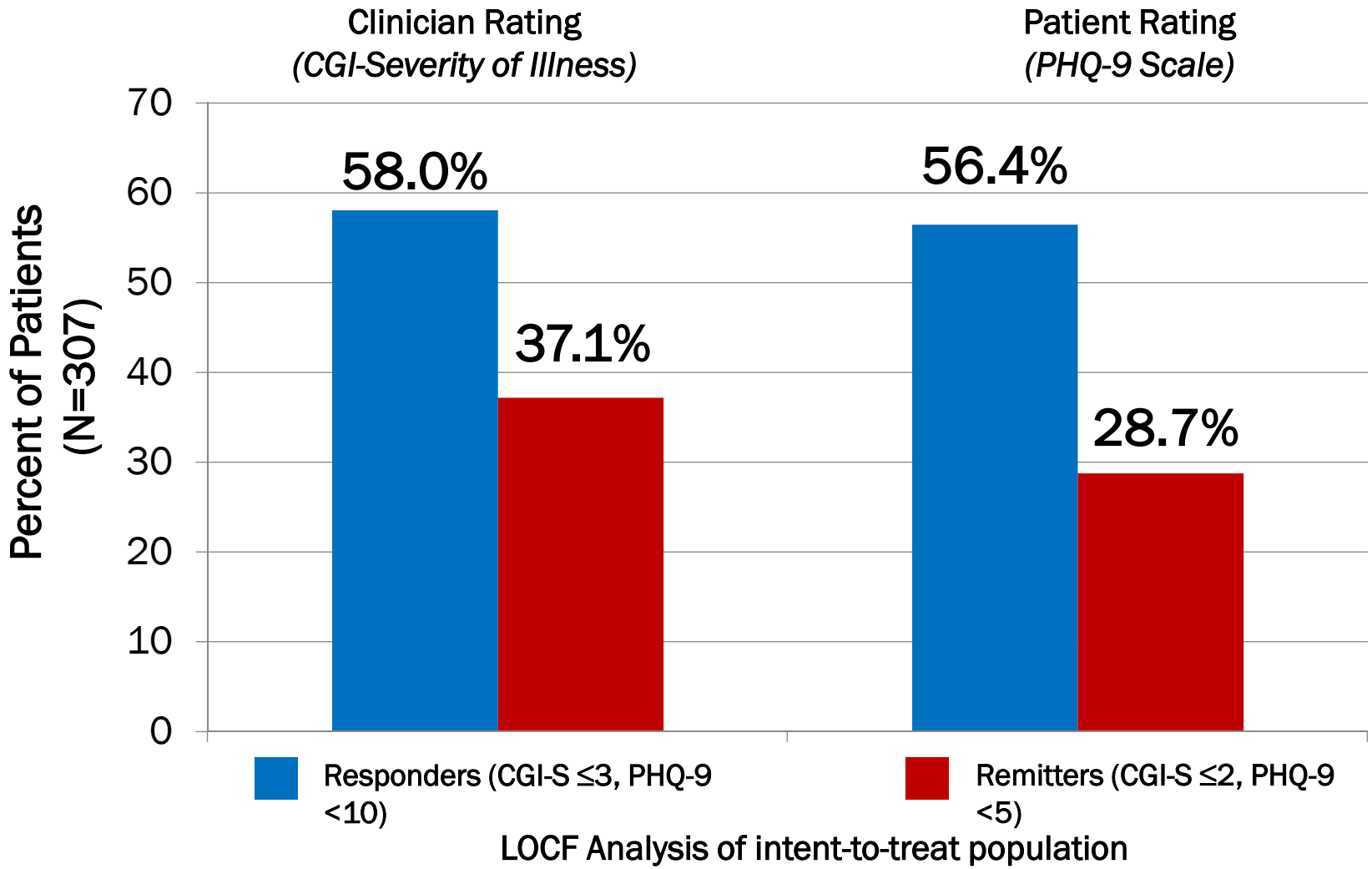
Carpenter et al, *Depression and Anxiety*, 2012

Comparison of End of Acute Treatment Clinician & Patient-Assessed Outcomes



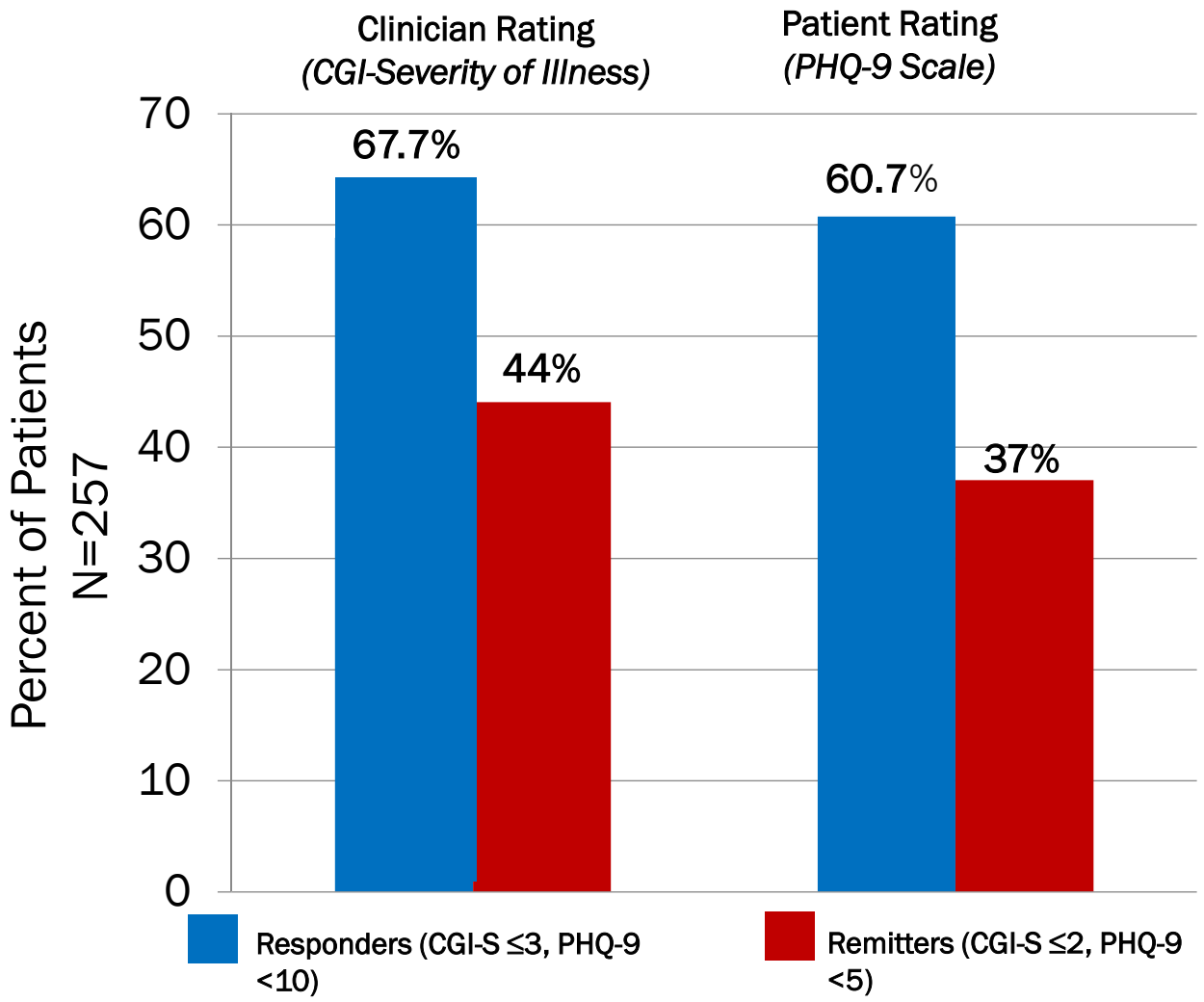
Carpenter et al, *Depression and Anxiety. 2012*

1 in 2 Patients Responded, 1 in 3 reached Remission



Carpenter et al, *Depression and Anxiety.* 2012

Long-Term Phase Results, 12 Months



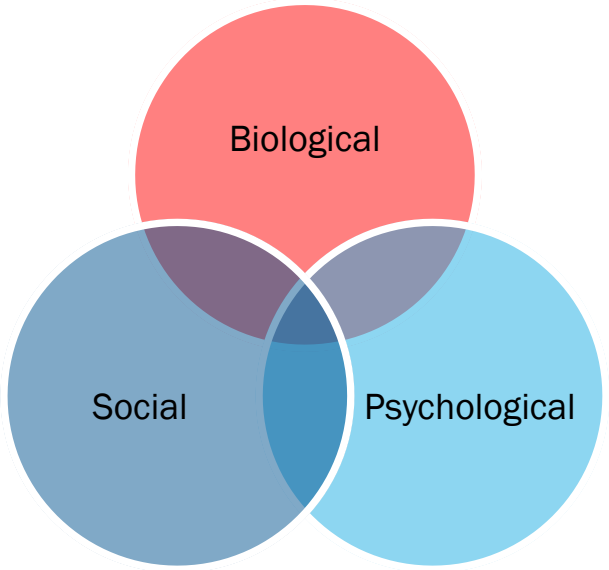
Outcomes measured for one year following following acute treatment

- Physician directed standard of care
- 36.2% of patients received TMS reintroduction
- Average number of TMS treatment days = 16

Dunner et al., *J. Clin Psych.* 2014

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.

Maintenance TMS

- No approved maintenance protocol
- TMS is consistently effective for recapturing prior level of response when introduced in the face of symptom relapse

"It is notable that TMS reintroduction was successful in rescuing most patients with threshold deterioration and returning them to their prior level of depressive symptom relief."

<u>Important observation given:</u>

- The chronic and relapsing nature of pharmacoresistant major depression
- Absence of definitive data suggesting that re-treatment with previously effective medications is capable of doing the same.

The results provide support for long-term treatment strategy that incorporates retreatment with TMS for patients who showed positive response to an initial acute course.

Phillip et al., *Brain Stimulation* 2016 (9): 251-257


"LISA"
Treated with TMS Therapy

WHO MAY BE CANDIDATES FOR TMS THERAPY?

Why Do We Need to Consider TMS as a Treatment Option?

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

World Health Organization Feb 2017

Who is Right for TMS Therapy?

Indicated for:

- TMS Therapy is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medications

Best Practices:

- In recurrent episode
- Multiple medication attempts, yet still symptomatic
- Prescribed a complex drug regimen
- Experience frequent side effects from medications

McIntyre R et al. J Clinical Psychiatry June 2017 78:6, 703-713

TMS is Included in Practice Guidelines, first line & after medication failure(s)

Since 2010, American Psychiatric Association (APA) has included TMS in guidelines: "…acute phase treatment may include pharmacotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy, transcranial magnetic stimulation or light therapy…"

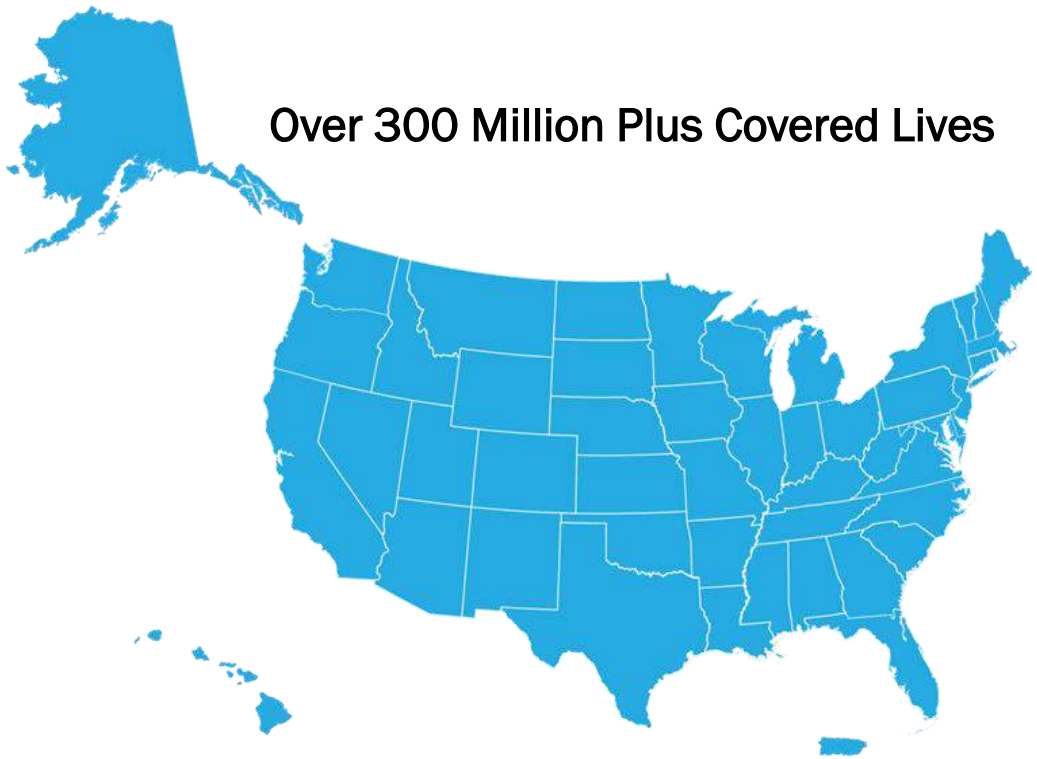
Since 2009 World Federation of Societies for Biological Psychiatry

Since 2009 Canadian Network for Mood and Anxiety Treatments

Since 2010, Institute for Clinical Systems Improvement

Schlaepfer, et al. *World J Biol Psychiatry*, 2009, 2015; Kennedy, et al *J Aff Disorders* (2009); Milev, et al, *Canadian Journal of Psychiatry,* 2016, Institute for Clinical Systems Improvement, 2010, 2016; APA 2010

TMS Insurance Coverage in US



- TMS has coverage in every state for Major Depressive Disorder
- Covered by all major private insurance companies
- Covered by Medicare in every state
- Coverage policies vary, but most typically require a failure of 3-6 antidepressant medications from different classes and Psychotherapy

Conclusion

- TMS is focal non-invasive form of brain stimulation based on principles of electromagnetic induction of current that has been well established for nearly 200 years.
- TMS is a safe and effective treatment of moderate to severe MDD and research supporting its efficacy in treatment of other mental and neurological disorders.
- TMS is well-tolerated and without risks of systemic side effects
- TMS should be considered a treatment option for patients with MDD.