

SPONSORED TOPICAL WEBINAR

An Educational Resource for APA members
from McLean Hospital.

Efficacy and Clinical Implementation of TMS, ECT and Ketamine

November 3, 2023

PAID FOR BY



APA DISCLAIMER

Dr. Steve Seiner and Dr. Joshua Brown have working relationships with McLean Hospital. As such, they have both a financial and intellectual interest in the webinar content. The purpose of this presentation is to provide a balanced view on the efficacy and clinical implementation of Neurotherapeutic options.

The content was created by McLean Hospital and does not reflect the views of APA or its editorial staff. Email advertising@apa.org to learn more.

ATTENDANCE

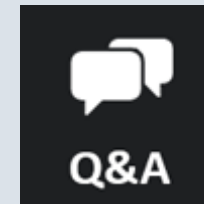
- No CE credit will be offered for this webinar.
- A “Certificate of Attendance” will be emailed to live attendees only.
- You must attend for 45 minutes to receive the certificate.

RECORDING

- A recording of this presentation will be emailed to everyone in 2 weeks' time.
- The recording will include the presentation slides.

HAVE A QUESTION?

- You are on mute. Communicate using the **Q&A box** in the webinar screen. Submit your questions for our speakers using the Q&A box.
- Presentation slides will be posted in the **chat box** of your webinar screen.





Stephen Seiner, MD



Joshua Brown, PhD, MD

PRESENTERS

Stephen Seiner, MD

- Director of Psychiatric Neurotherapeutics Program and Medical Director of Electroconvulsive Therapy (ECT) Service, McLean Hospital
- Assistant Professor of Psychiatry, Harvard Medical School

Joshua Brown, PhD, MD

- Medical Director of Transcranial Magnetic Stimulation (TMS) Service, Director of Transcranial Magnetic Stimulation Research in the Division of Depression and Anxiety Disorders, and Director of Brain Stimulation Mechanisms Laboratory, McLean Hospital
- Member of the Faculty of Psychiatry, Harvard Medical School

MCLEAN HOSPITAL DISCLAIMERS

- Dr. Stephen Seiner
 - *Will be talking about off label uses of treatments*
- Dr. Joshua Brown
 - *Receives support from Philanthropy*
 - NIH, DARPA, and Brain & Behavior Research Foundation (BBRF)

The Efficacy and Clinical Implementation of TMS, ECT and Ketamine

Stephen Seiner MD and Joshua Brown, MD, PhD

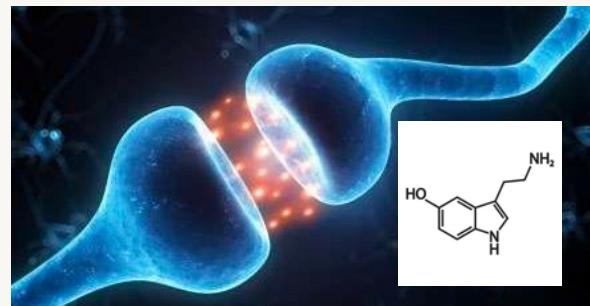
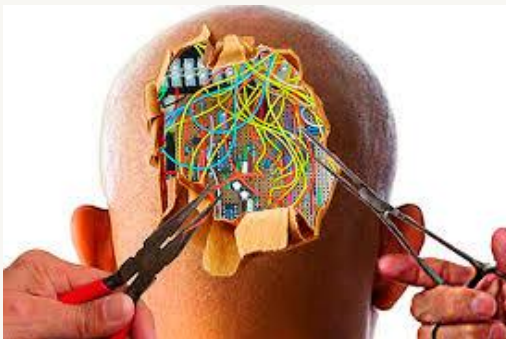
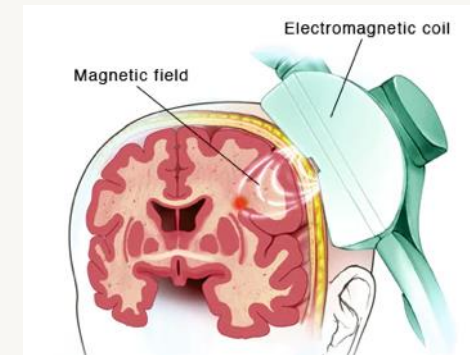
Clinical Approaches for the Brain



TRD

~30% do not respond =
Treatment – resistant
depression

280 million world-wide =
~90 million with TRD



How The Brain Works

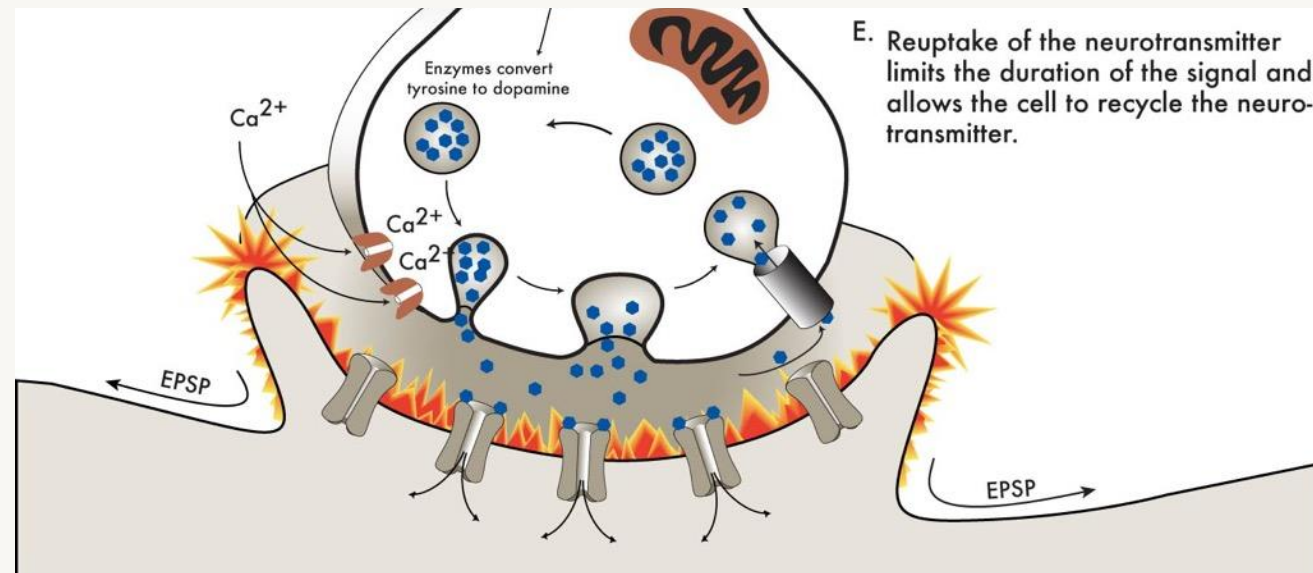
Electro

Chemical

The Brain is an **Electro**chemical Organ

Electricity is the Currency of the Brain

All of synaptic pharmacology simply serves to transmit electrical signals to the next neuron



Overview of FDA-Cleared Brain Stimulation Modalities

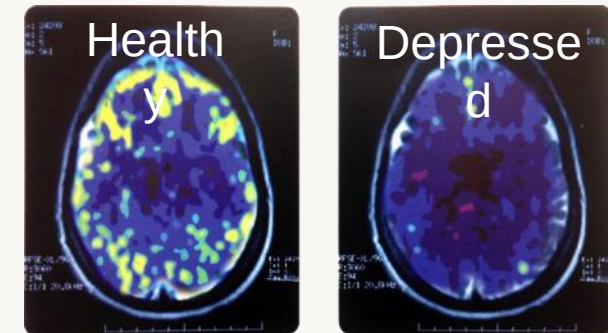
Non-Invasive

- Electroconvulsive Therapy (ECT)
 - *Catatonia (1976- “Grandfathered in”)*
 - *Severe Depressive Episode (Unipolar or Bipolar (1976- “Grandfathered in”)*
- Transcranial Magnetic Stimulation (TMS)
 - *MDD, non-psychotic, moderate-severe (2008)*
 - *OCD (2018)*
 - *Smoking Cessation (2020)*
 - *Neurology: Migraine (2013)*

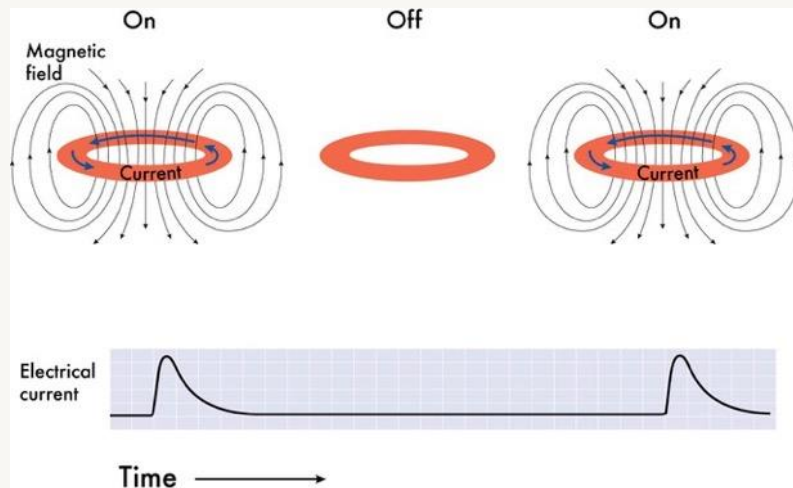
Invasive

- Deep Brain Stimulation (DBS)
 - *OCD (2009-HDE)*
 - *Neurology:*
 - *PD (1997, 2002)*
 - *ET (1997)*
 - *Dystonia (2003-HDE)*
- Vagus Nerve Stimulation (VNS)
 - *MDD (2005)*
 - *Neurology: Epilepsy (1997)*

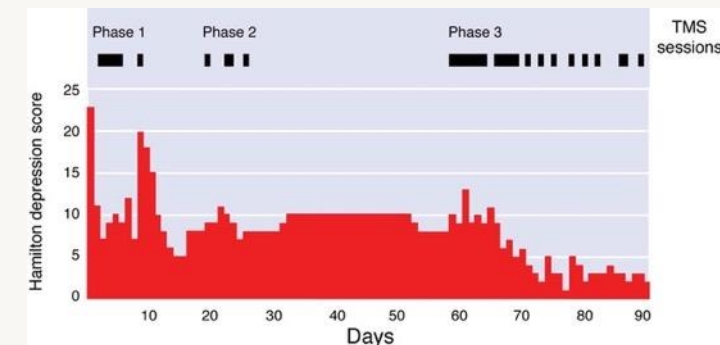
How TMS Came to Be—for TRD



Source: Mark George, MD Biological Psychiatry Branch Division of Intramural Research Programs, NIMH 1993



Higgins & George, *Brain Stimulation Therapies for Clinicians*, 2019



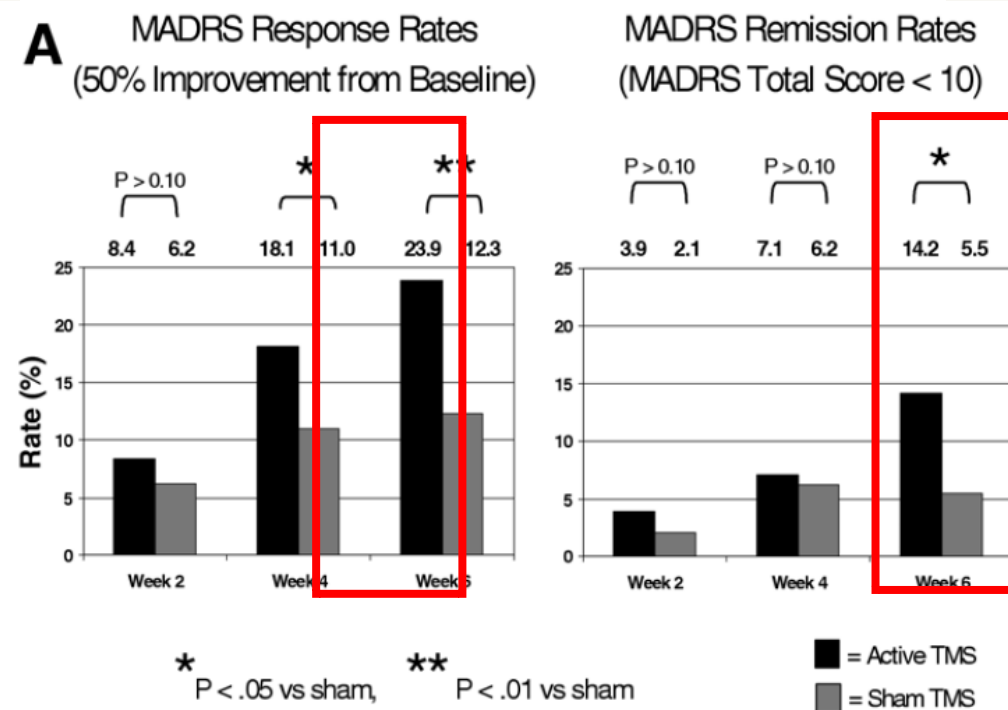
Adapted from George et al, *Neuroreport*, 1995

ORIGINAL ARTICLE

Daily Left Prefrontal Transcranial Magnetic Stimulation Therapy for Major Depressive Disorder

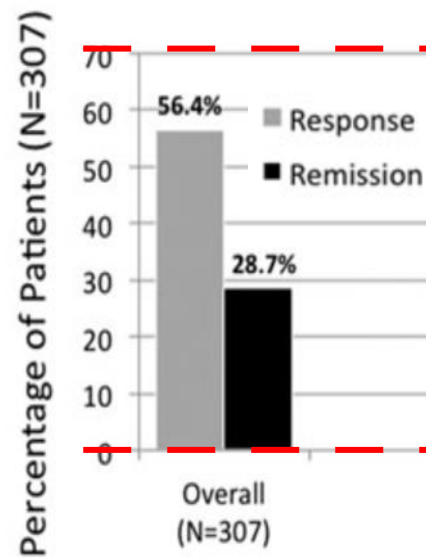
A Sham-Controlled Randomized Trial

Mark S. George, MD; Sarah H. Lisanby, MD; David Avery, MD; William M. McDonald, MD; Valerie Durkalski, PhD; Martina Pavlicova, PhD; Berry Anderson, PhD, RN; Ziad Nahas, MD; Peter Bulow, MD; Paul Zarkowski, MD; Paul E. Holtzheimer III, MD; Theresa Schwartz, MS; Harold A. Sackeim, PhD

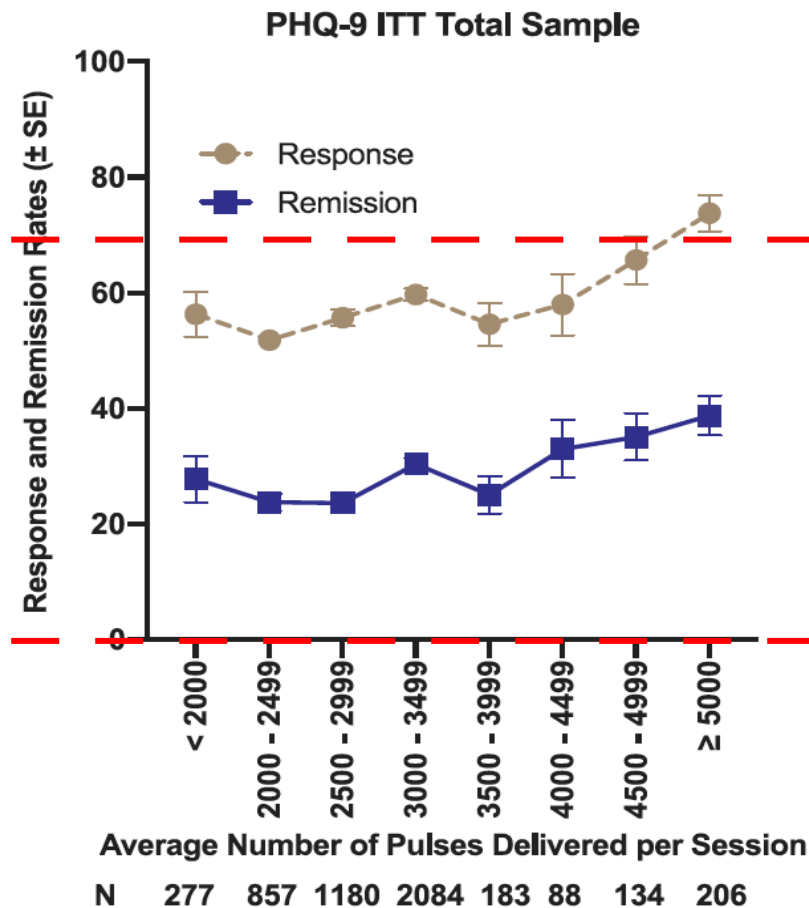


How Effective is TMS?

PHQ-9 Outcomes

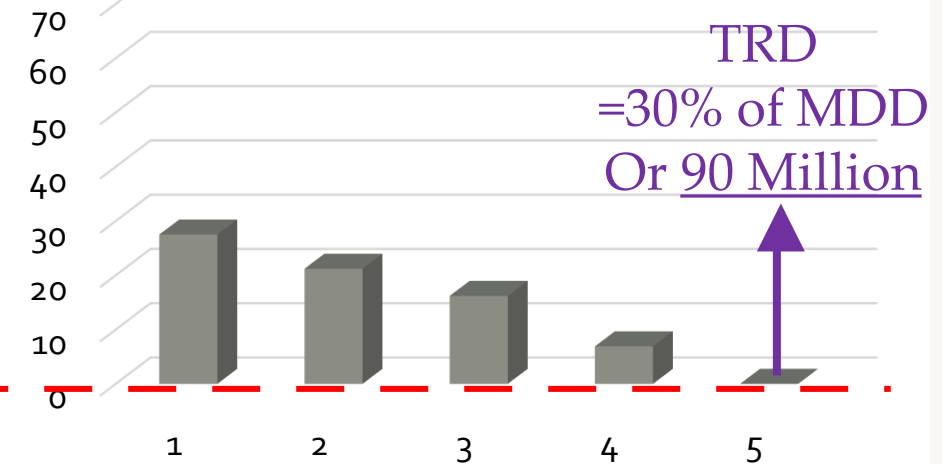


Carpenter et al.,
Depress Anxiety, 2012



Sackeim et al., *J Affect Dis*, 2020

% Chance of Response



(Adapted from STAR-D trial, Rush et al., 2006)

Does TMS have side effects?

DRUG THERAPY

OTHER ADVERSE EVENTS

Nervousness
Weakness
Abnormal Ejaculation
Constipation
Anxiety
Impotence
Diarrhea
Increased Appetite
Dizziness
Sweating
Decreased Appetite
Tremor
Drowsiness
Decreased Sexual Interest
Headache/Migraine
Treatment Discontinuation
Side Effects



TMS THERAPY

Scalp Pain or Discomfort

OTHER ADVERSE EVENTS

Eye Pain
Toothache
Muscle Twitching
Facial Pain
Pain of Skin

In clinical trials, fewer than 5% of patients discontinued treatment with NeuroStar TMS Therapy due to adverse events.



Who Gets TMS?

FDA-cleared:

1. *MDD (2008)*
 - a) Unipolar
 - b) Non-psychotic
 - c) Moderate-Severe
2. *OCD (2018)*
3. *Migraines (2013)*
4. *Smoking Cessation (2020)*
5. *Anxious Depression (2021)*

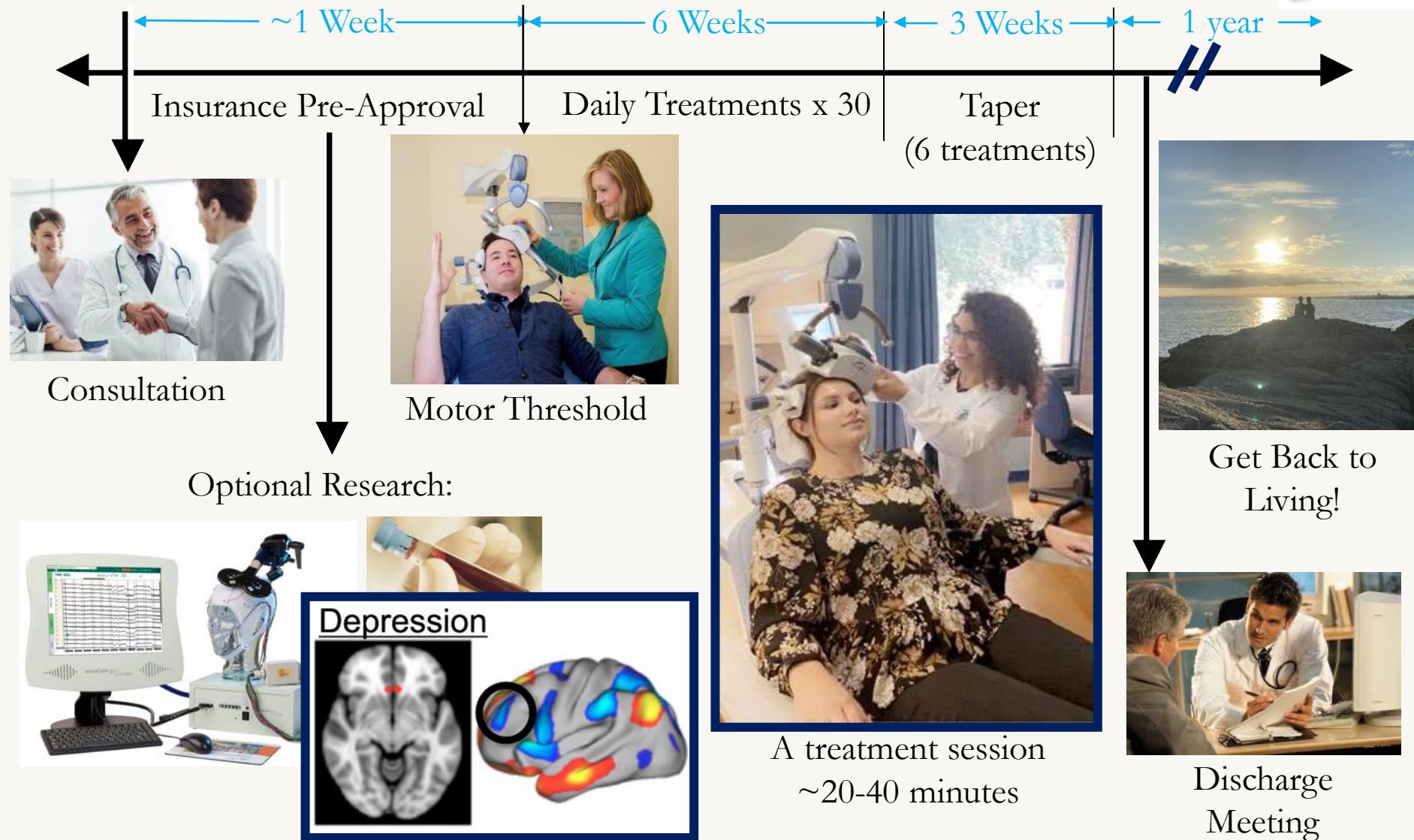
TRD Indications & Contraindications

- Inadequate/Intolerable response to medications and psychotherapy
- No metal or devices in head or neck

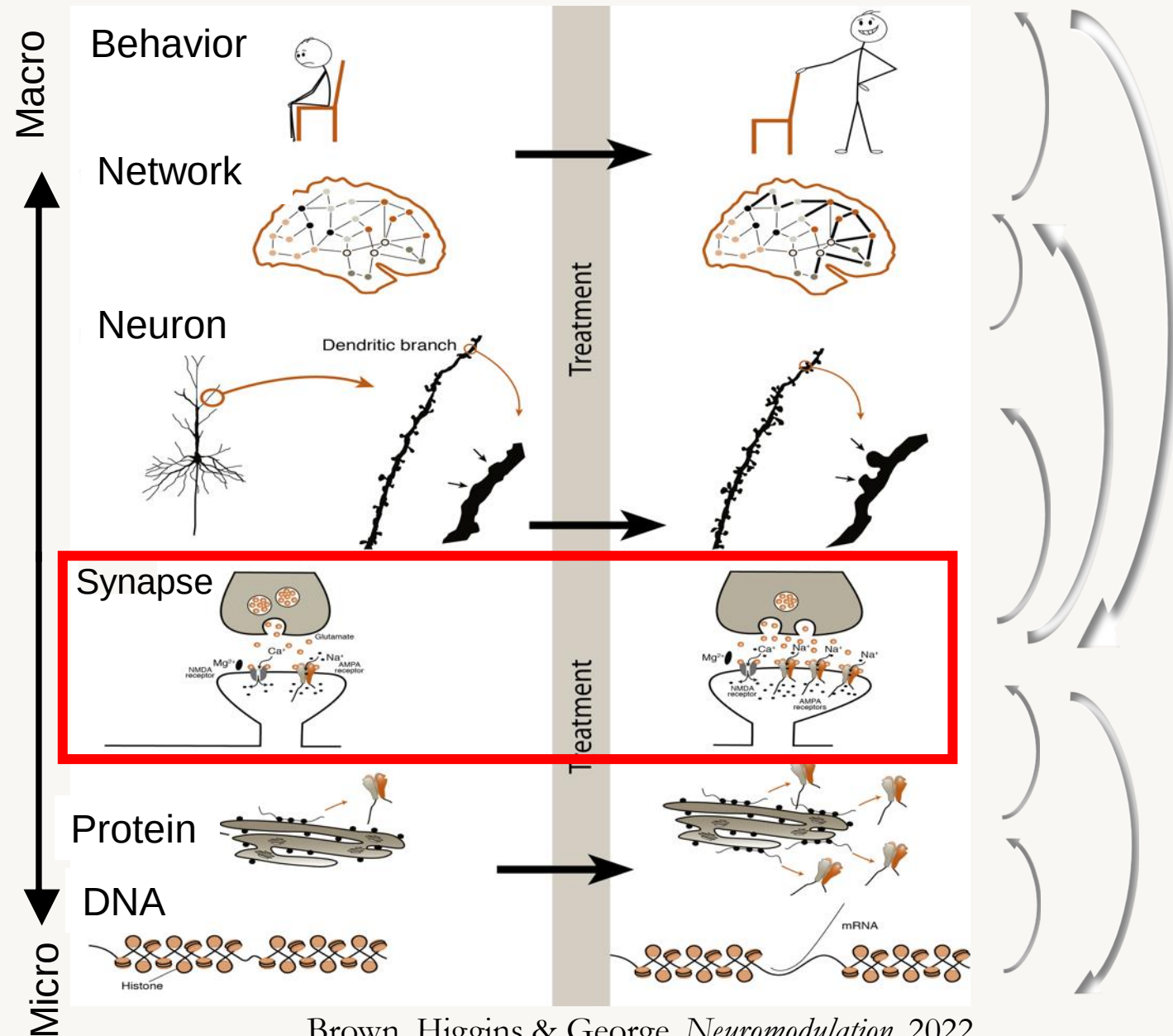
Possible exclusions:

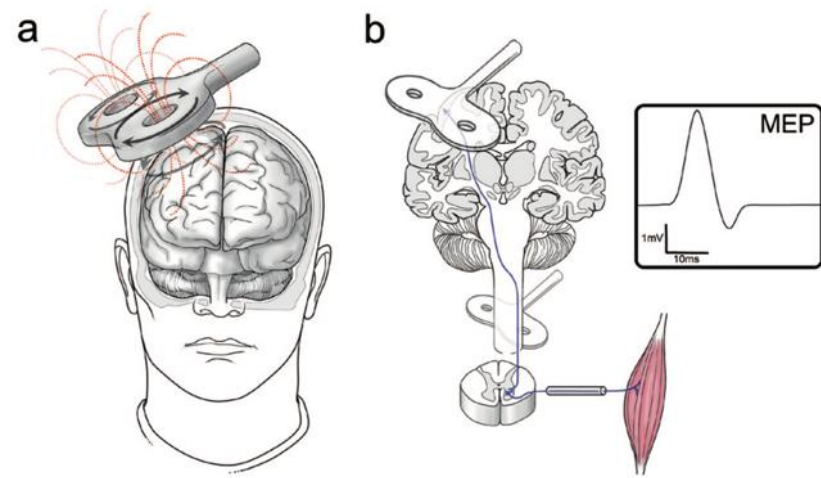
1. Seizure History
2. Neurologic Problems
3. Active Substance Use Disorder
4. Any Other Secondary Cause of Depression

What's the Process of TMS?

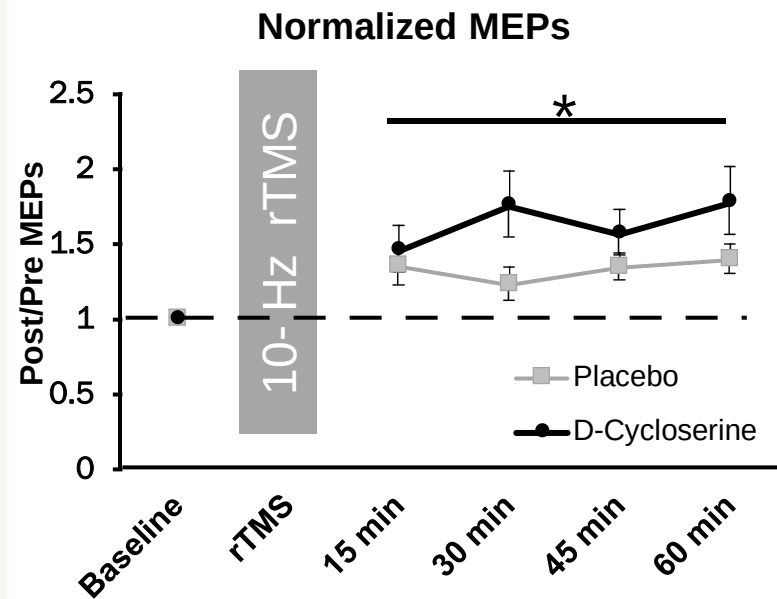


How Does TMS Change the Brain?





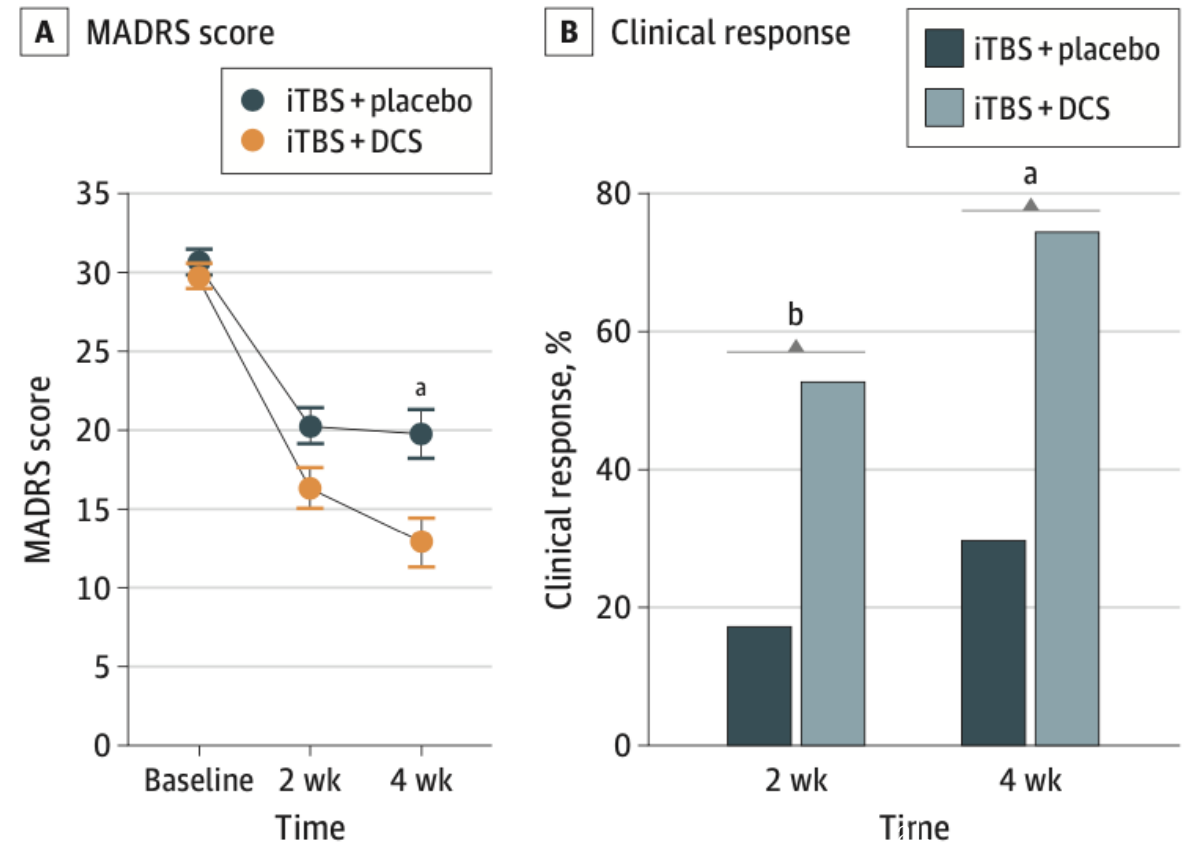
Vlachos et al., *Neuroforum*, 2017



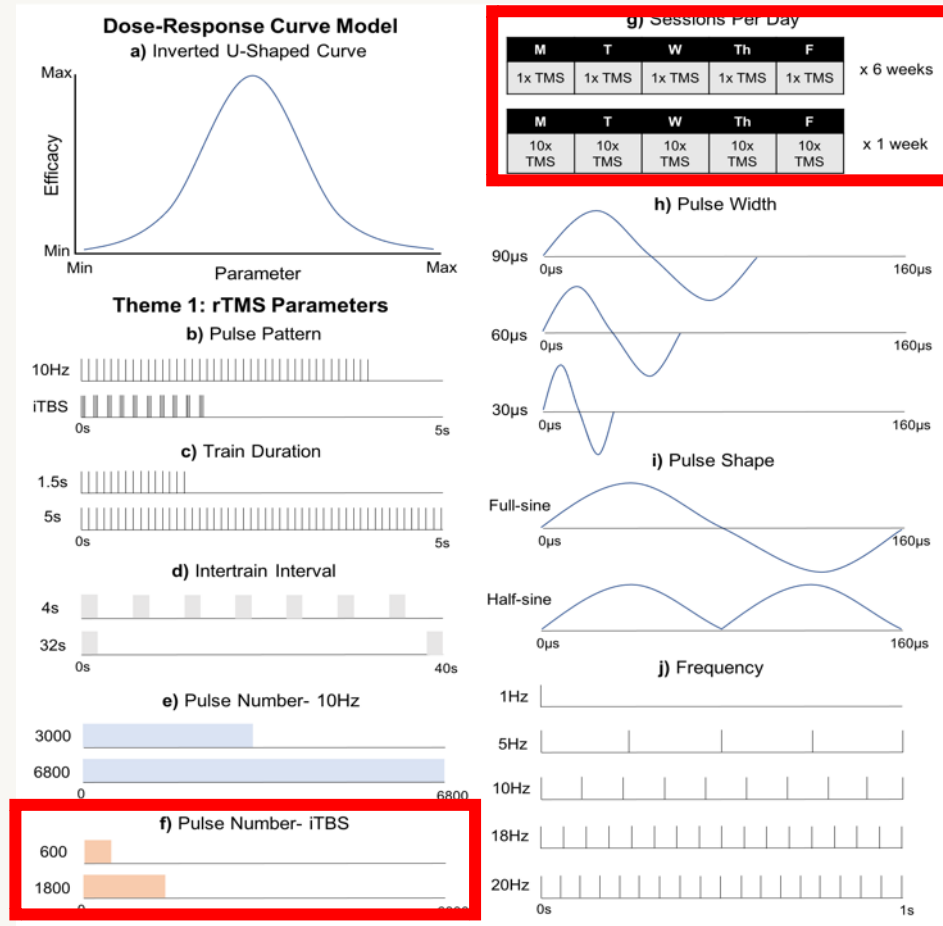
Adapted from Brown et al., *Brain Stimulation*, 2020

Enhancing TMS Effects

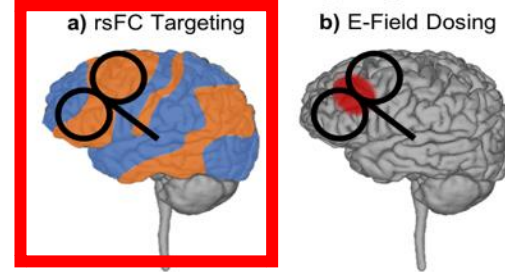
Figure 2. Clinical Outcomes in Participants Who Received Intermittent Plus Placebo and iTBS Plus D-Cycloserine (DCS)



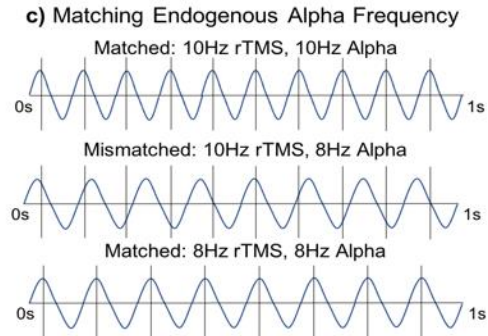
Potential The Problem of TMS' Infinite Parameter Space



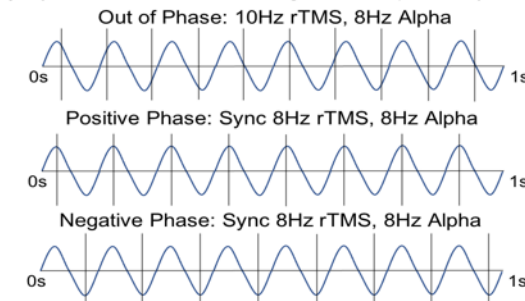
Theme 2: Personalized Targeting and Intensity



Theme 3: Personalized Stimulation Frequency



d) Synchronization to Endogenous Alpha Rhythm

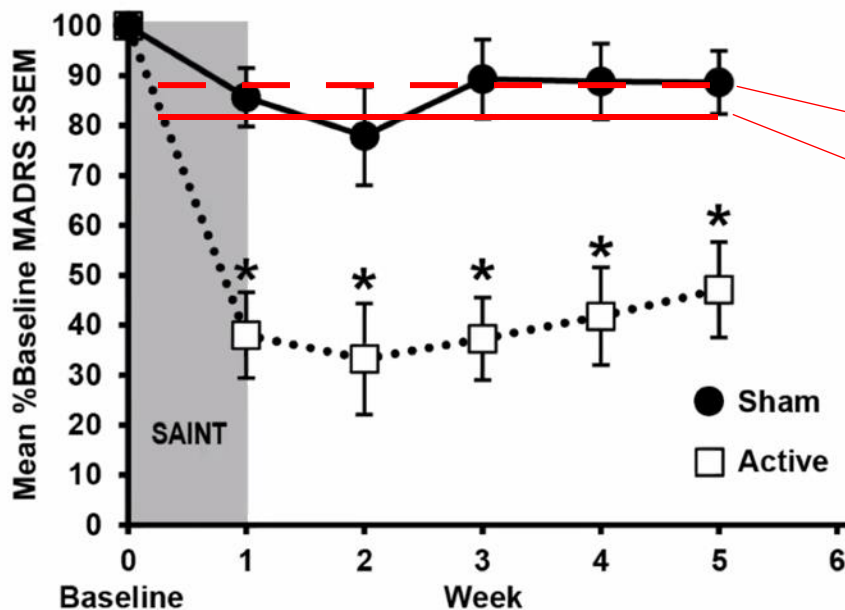


Can parameter optimization improve TMS outcomes?

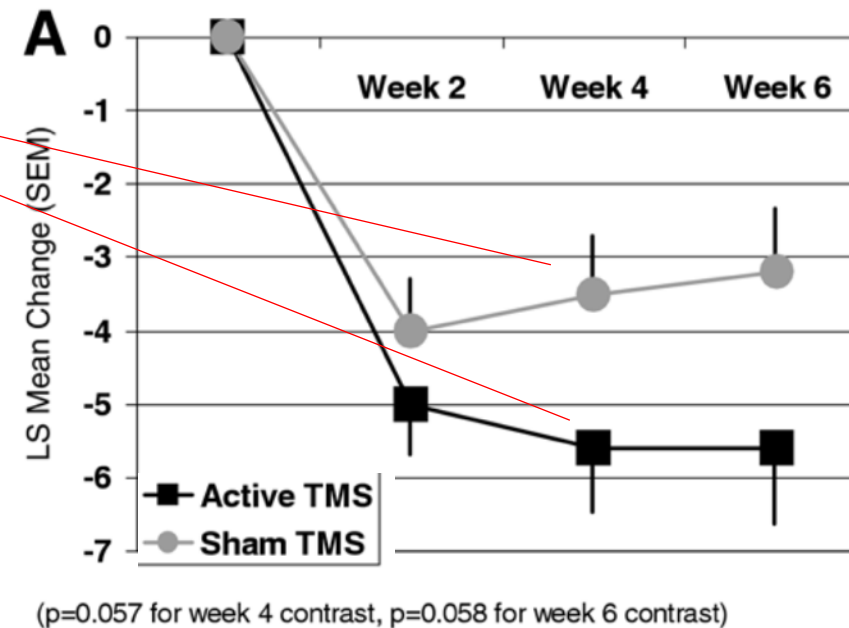


- Δ Pulse # (total and per day)
- Δ Session # (total and per day)
- Δ Targeting

32.8 → 26.8 = 18.3% improvement



Cole et al., *AJP*, 2021



O'Reardon et al., *Biol Psych*, 2007

TMS changes the (*____*) brain



Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Review article

Transcranial magnetic stimulation: Emerging biomarkers and novel therapeutics in Alzheimer's disease

Giacomo Koch^{a,b,*}, Alessandro Martorana^b, Carlo

Contents lists available at ScienceDirect

Brain Stimulation

<http://www.journals.elsevier.com/brain-stimulation>

Multiple Sclerosis and Related Disorders 36 (2019) 101375

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

Non-invasive brain stimulation for fatigue in multiple sclerosis patients: A systematic review and meta-analysis

Mange Liu, Siyuan Fan, Yan Xu, Liying Cui*

ELSEVIER

journal homepage: www.elsevier.com/locate/clinph

Journal of the Neurological Sciences

Bilateral and unilateral movement train

chronic stroke patients Review

Transcranial magnetic stimulation in hereditary ataxias: Diagnostic utility, pathophysiological insight and treatment

Roberto Rodríguez-Labrada^{a,b}, Luis Velázquez-Pérez^{a,b,c,*}, Ulf Ziemann^{d,*}

Theta-Burst Transcranial Magnetic Stimulation for Posttraumatic Stress Disorder

Noah S. Philip, M.D., Jennifer Barredo, Ph.D., Emily Aiken, M.A., Victoria Larson, B.S., Richard N. Jones, Sc.D., M. Tracie Shea, Ph.D., Benjamin D. Greenberg, M.D., Ph.D., Mascha van 't Wout-Frank, Ph.D.

Am J Psychiatry 176:11, November 2019

ajp.psychiatryonline.org

Review

Transcranial Magnetic Stimulation in Tourette Syndrome: A Historical Perspective, Its Current Use and the Influence of Comorbidities in Treatment Response

Marco Grados^{1,*}, Rachel Huselid² and Laura Duque-Serrano³

Oranuclear palsy

Am J Psychiatry 176:11, November 2019

Review

Transcranial Magnetic Stimulation in Tourette Syndrome: A Historical Perspective, Its Current Use and the Influence of Comorbidities in Treatment Response

Marco Grados^{1,*}, Rachel Huselid² and Laura Duque-Serrano³

Currents

les

Brain Stimulation 13 (2020) 1271–1279

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: <http://www.journals.elsevier.com/brain-stimulation>

Two weeks of image-guided left dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation improves smoking cessation: A double-blind, sham-controlled, randomized clinical trial

ECT

Stephen Seiner MD

Director of Psychiatric Neurotherapeutics
Program

Director of ECT

McLean Hospital

Role of therapist and outpatient team

- Recognize patients who are not responding to adequate therapy and medication trials who may benefit from ECT
- Be able to discuss these options with your patients
- Make an appropriate referral
- Support the patient through the process and treatment and be knowledgeable about expected side effects
- Help the patients after the treatment is through

What is ECT?

ECT = Electroconvulsive Therapy

- Done under brief general anesthesia – asleep for whole treatment, with muscle relaxant – no significant convulsion or movement.
- Brief electrical stimulus administered for a couple of seconds, inducing a short (minute or so) seizure while under anesthesia. Can be administered to one side (unilateral) or both sides (bilateral).
- Safe & Painless, except for occasional post-treatment headache (usually mild)
- Very quick – Only a few minutes and patients can go home after 2 hours
- An acute course is generally 8 to 15 treatments done 2-3 times a week
- If successful, often followed by a taper of treatments (continuation ECT) or ongoing treatments (maintenance ECT)

Case Example

- **MWM in his 70's, history of MDD, admitted for worsening depression and an attempt to cut his wrist, in setting of worsening financial concerns around real estate deal**
- Severe ruminative thinking, describes agitation “churning inside.” Poor sleep, concentration, appetite and describes anhedonia.
- Became paranoid about others talking about him and became convinced his financial lender was trying to steal from him.
- Multiple medication trials (SSRIs, NSRIs, and anti-psychotics). Meds at admission were Mirtazapine 45 mg and Olanzapine 20mg
- He felt that no treatment could possibly help because his situation was hopeless.

ECT— Indications and Efficacy

Psychotic depression

- ECT sometimes first line treatment
- Psychotic depressed patients may respond faster than non-psychotic, with response rates as high as 95% (Petrides 2001)

Catatonia

- Response rates in most modern studies range from 80 to 100% (Lloyd 2020 review)
- Should be considered when Lorazepam fails or in cases of malignant catatonia or when rapid resolution is needed

ECT— Indications and Efficacy

Major depression

- No trial has ever found any medication to be superior in efficacy to ECT
- Responses range from 50-60% in patients who are medication resistant to 80-90% in medication naive or intolerant patients

(American Psychiatric Association Task Force, second edition, 2001)

ECT— Indications and Efficacy

Bipolar disorder – depression

- Very effective – Meta-analysis of 6 studies found ECT to be equally effective for both bipolar and unipolar depression (Remission rate of 53.2% in 316 bipolar depression). (Dierckx et al., Bipolar Disorders, 2012)
- Randomized Control Study – (Schoeyen et al., Am J Psychiatry 2015) - compared ECT to Goodwin and Jamison medication algorithm
 - *Remission rates similar (34.8 % ECT vs 30.0% meds)*
 - **Response rates much better for ECT (73.9% vs. 35%)**

ECT— Indications and Efficacy

Other Effective Uses of ECT

- Bipolar mania – Well established treatment – very effective in severe cases or in delirious mania.
- Treatment Resistant Schizophrenia
- Schizoaffective disorder – both affective symptoms and can help with psychosis
- Severe agitation in dementia

Memory Loss

Anterograde Memory (ability to form new memories)

■ Studies

- Meta-Analysis and Systematic Review in Biological Psychiatry (Semkovska 2010) found that “cognitive abnormalities associated with ECT are mainly limited to the first 3 days post-treatment. Pretreatment functioning levels are subsequently recovered. After 15 days, processing speed, working memory, anterograde memory, and some aspects of executive function improve beyond baseline levels.”
- They found no evidence of long term affect on anterograde memory

■ How to Explain to patients

- Short term memory can be impacted significantly during the acute course of ECT. Most commonly presents as forgetfulness – forgetting conversations, asking same questions, directions etc.
- During or soon after the acute course, not a great time to go on a job interview or first date, do estate planning, or other activities requiring memory to be sharp.
- This reliably improves over the course of 2 to 4 weeks after ECT.
- May actually be better a month after ECT than before ECT if depression remits (because concentration, focus and processing often all improve as depression improves).

Memory Loss

Retrograde Memory (remembering past memories)

■ Studies

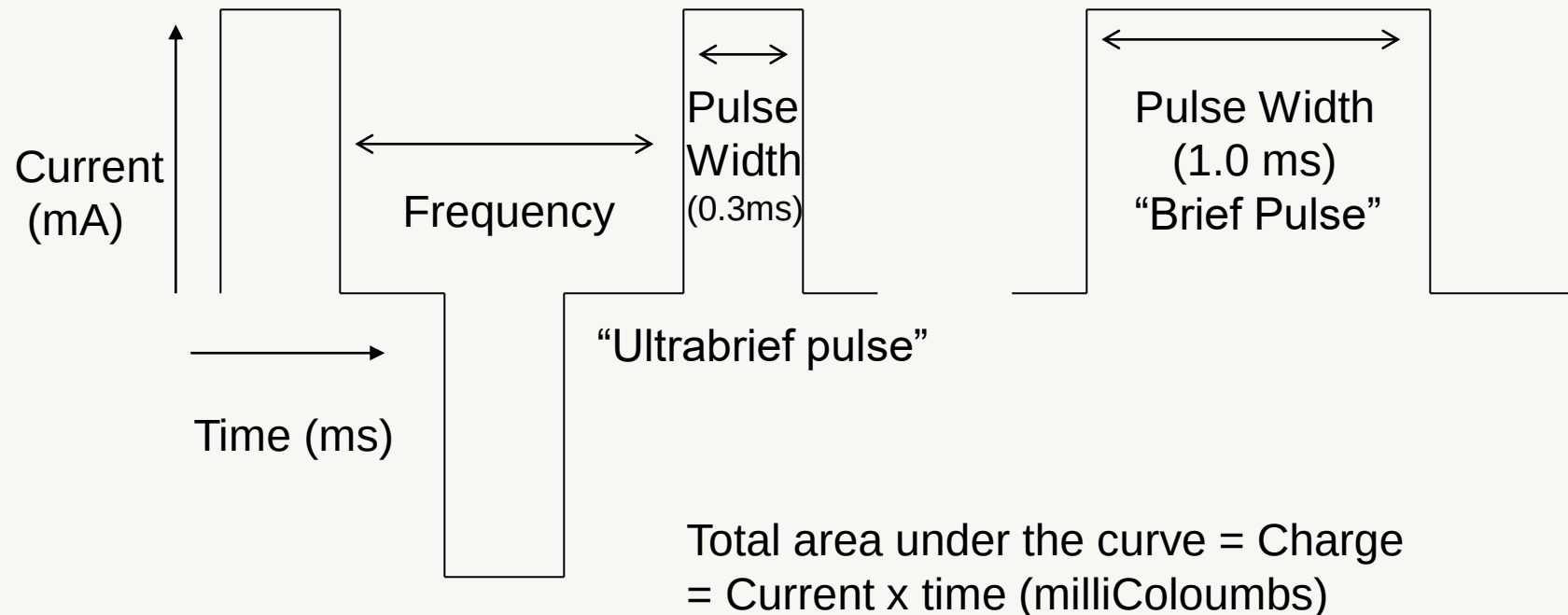
- Retrograde memory very difficult to test
- Large naturalistic community study suggested bilateral placement more associated with sustained autobiographical memory effects at 6 months than RUL (Sackeim 2007)
- Newer “ultrabrief pulse” RUL ECT – associated with little sustained retrograde memory loss. (Sackeim 2008)
- Studies suggest ECT technique matters

■ How to explain to patients

- Many patients experience gaps in their memory for the period during ECT and for some period before that. Sometimes these memories will return with prompting or time, but some memories are sometimes lost permanently.
- The events closer to the ECT in time (especially when they were most depressed) – are more likely to be lost.
- Most commonly lost memories are things they did once and then didn’t think about much again (a person they met once or piano recital).
- ECT technique can affect the amount of retrograde memory lost, so major changes such as electrode placement should be reviewed with the patient.

What's New: Ultrabrief pulse

- Pulse width is reduced to 0.3ms (from 1ms) to take advantage of the optimal duration for neuronal depolarization time (0.1 to 0.2ms) – More efficient and physiologic.
- Studies show significantly less memory loss – *especially retrograde memory*
- We have extensive experience, and have noted significant cognitive advantage to ultrabrief pulse, but probably a milder form of ECT that doesn't work for everyone.



Ketamine

***** INCLUDES OFF LABEL/EXPERIMENTAL TREATMENT *****

How does Ketamine work?

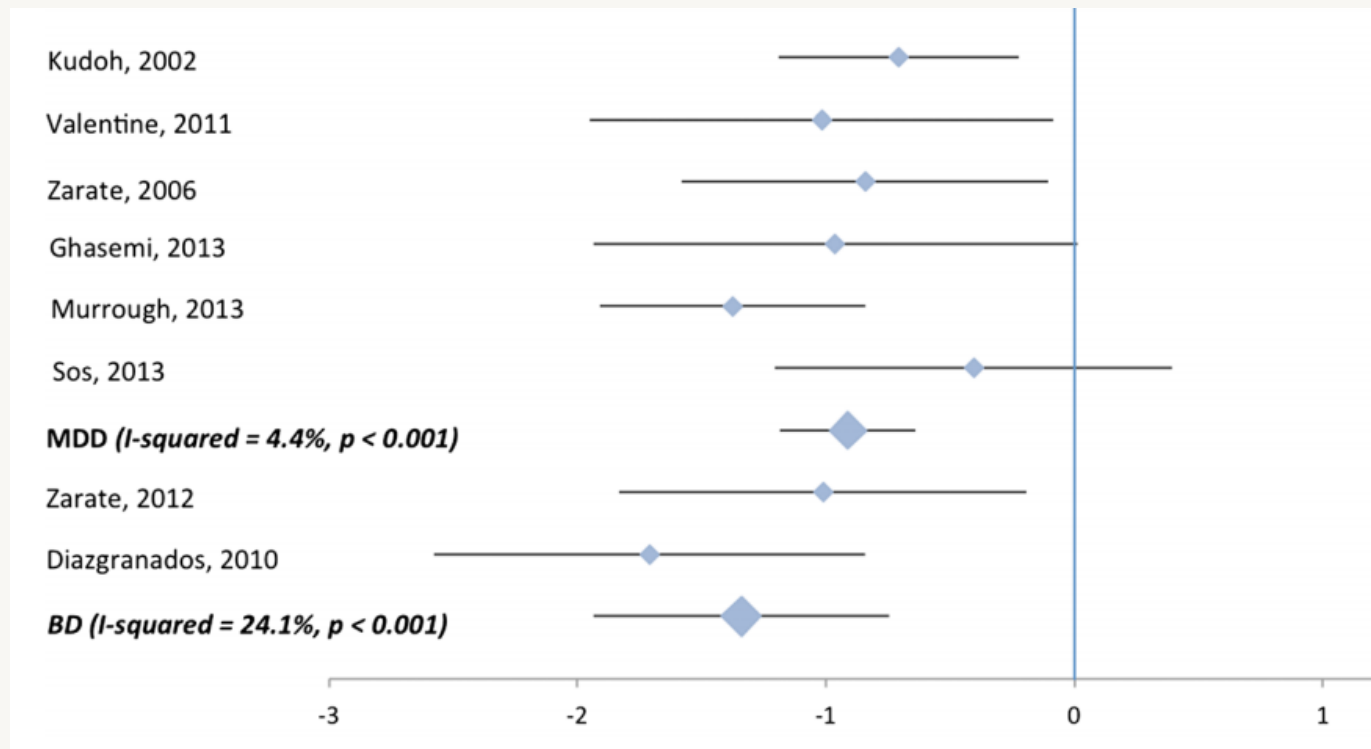
NMDA glutamate receptor antagonism – may or may not be causal action of antidepressant effect

Other possible actions include:

- AMPA-R: Subtype of glutamate receptor – targeted by ketamine metabolite, which showed anti-depressant effect (Nature 2016)
- BDNF: Brain Derived Neurotrophic Factor
- eEF2: inhibiting eEF2 increases BDNF
- IGF-1: Insulin like Growth Factor 1

Esketamine intranasal recently FDA APPROVED (s-enantiomer has 3 to 4 fold higher affinity for NMDA glutamate receptors than r-enantiomer).

Ketamine Administration in Depressive Disorders: Results from a Recent Meta-Analysis



Slide courtesy of Diego Piazzagalli Ph.D

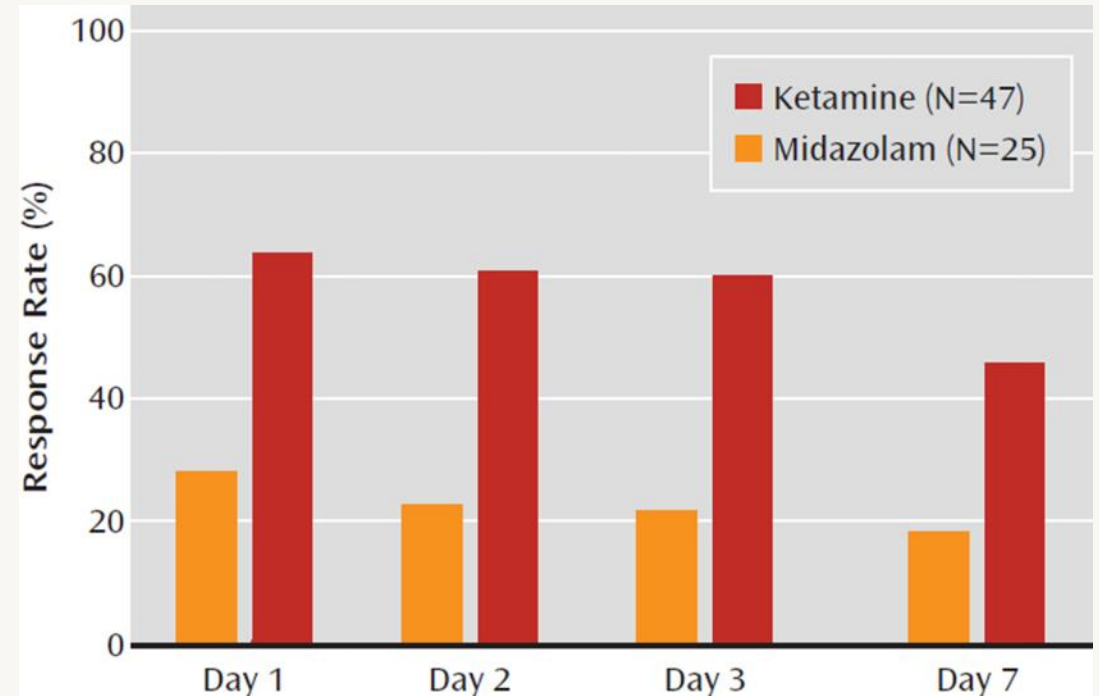
Fond et al., 2014

Randomized Controlled Trial of Ketamine IV infusion

- **Murrough et al. Am J Psychiatry 2013**
- **40 minute IV infusion at 0.5mg/kg-subanesthetic dose**
- Study with treatment resistant depression – patients had failed at least 3 antidepressant trials.
- Midazolam used as control to mimic effects of ketamine
- Much larger sample – 47 ketamine patients, 25 midazolam
- Most common adverse events in ketamine group: dizziness, blurred vision, headache, nausea or vomiting, dry mouth, poor coordination, poor concentration and restlessness.
- **17% had significant dissociative symptoms** – resolving by 2 hours post-treatment.
- Ketamine infusion discontinued for 2 patients due to hemodynamic changes.

RESULTS

- Significant response rate to Ketamine vs. Midazolam (decrease from baseline of at least 50% on MADRS)
- After 7 days, the differences were no longer statistically significant

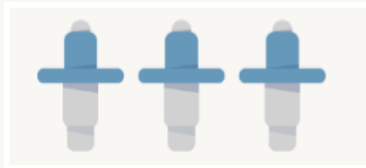


Am J Psychiatry 170:10, October 2013

ESKETAMINE

Esketamine and Placebo

- Esketamine was provided in a disposable single-use nasal spray device which delivered 28 mg of esketamine per device ^{1,2}



Up to 3 devices may be needed, used 5 minutes apart.



Self-Administration with HCP observation

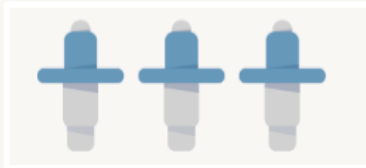
- In study, given twice a week for 4 week
- **Antidepressant**
- Open-label oral antidepressant, initiated with esketamine nasal spray or intranasal placebo, assigned by the investigator (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR])
- Dosing of the oral antidepressant followed a fixed titration schedule

***Courtesy of Janssen Pharmaceutical

ESKETAMINE

Esketamine and Placebo

- Esketamine was provided in a disposable single-use nasal spray device which delivered 28 mg of esketamine per device ^{1,2}



Up to 3 devices may be needed, used 5 minutes apart.



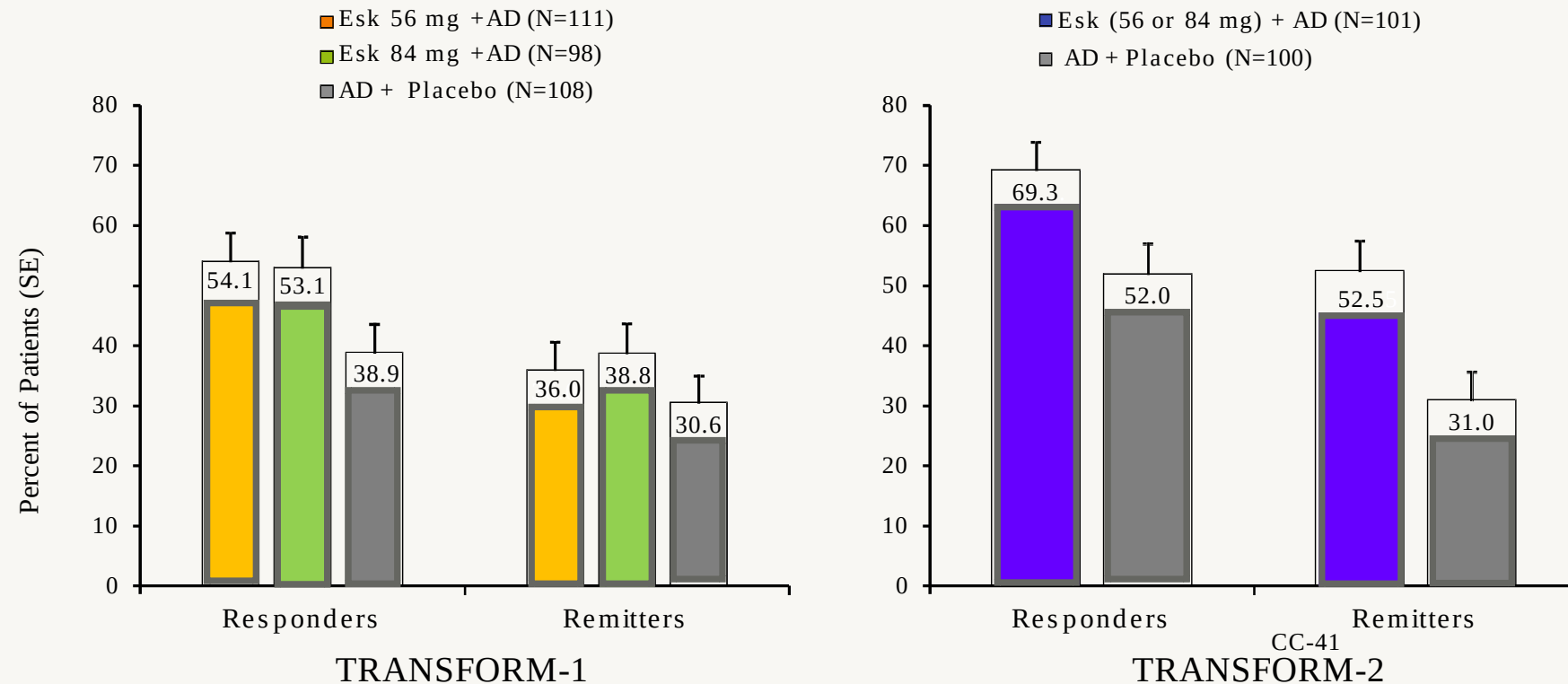
Self-Administration with HCP observation

- In study, given twice a week for 4 week
- **Antidepressant**
- Open-label oral antidepressant, initiated with esketamine nasal spray or intranasal placebo, assigned by the investigator (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR])
- Dosing of the oral antidepressant followed a fixed titration schedule

***Courtesy of Janssen Pharmaceutical

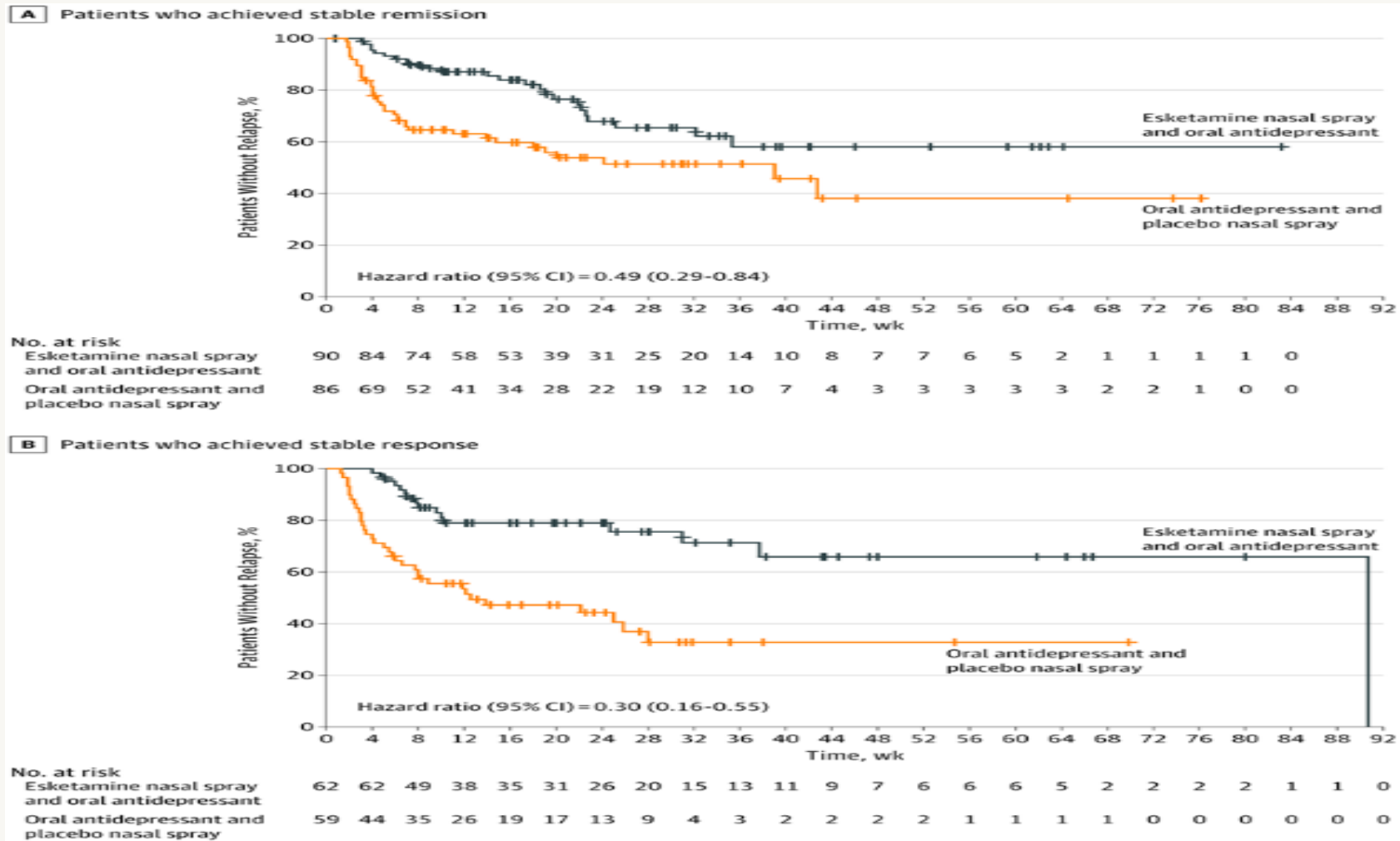
Response and Remission Rates at Day 28

TRANSFORM-1 (3001) and -2 (3002)



**Courtesy of Janssen Pharmaceutical

Esketamine plus AD Maintenance Therapy



**Esketamine –
Phase 3 Pooled
Most Common
Adverse Events
> 5%**

<u>Side Effect</u>	<u>Esketamine + AD</u>	<u>Placebo +AD</u>
Nausea	28.3	8.6
<u>Dissociation</u>	<u>28.6</u>	<u>3.6</u>
Dizziness	23.7	6.8
Vertigo	22.5	2.3
Headache	20.2	17.1

*****Prescribing Program requires BP monitoring
and 2 hour post-tx observation.**

Our Ketamine Clinic

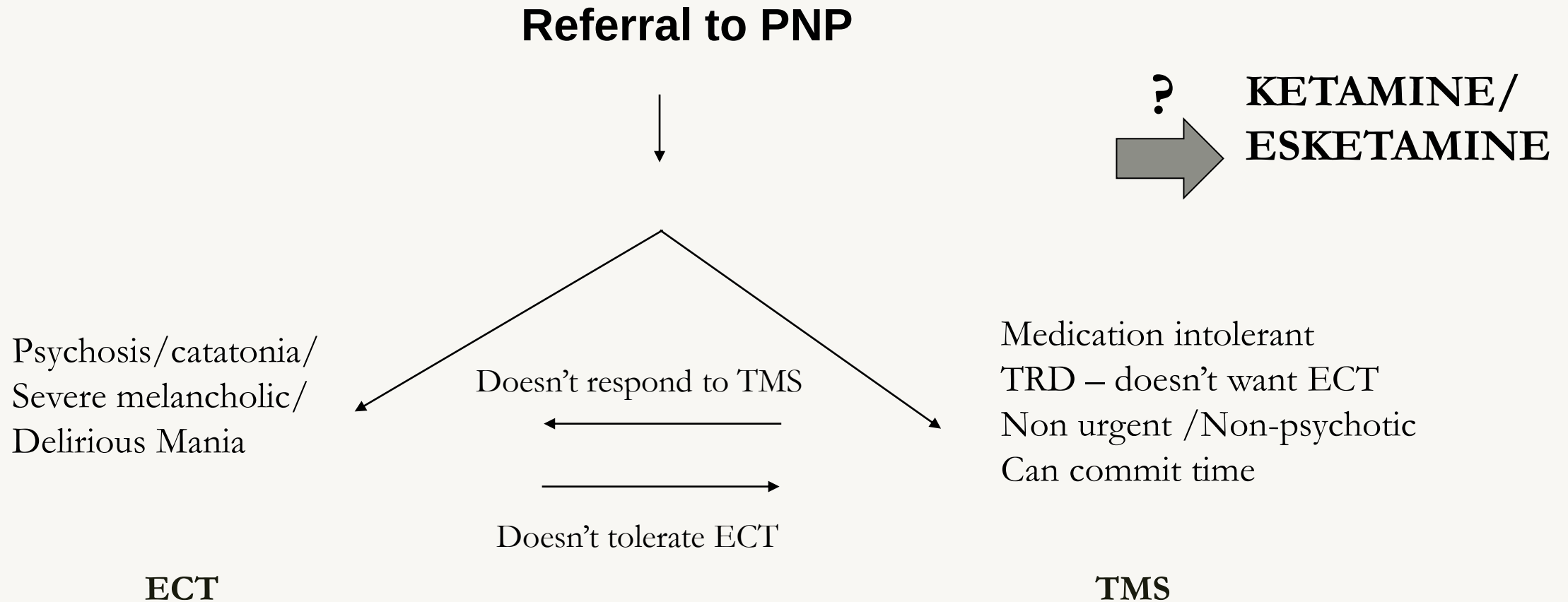
■ IV Ketamine infusions

- Twice a week IV ketamine up to 8 treatments
- After treatment 4, if no improvement, unlikely to respond, so consider stopping or possibly making dose adjustments to treatment
- If responding, generally finish acute series of 8 treatments.
- Once in remission or acute phase completed, we observe the duration of the remission window. Maintenance in select cases, but in general designed to help alleviate symptoms acutely and help kick off a multidisciplinary treatment plan, with “rescue” ketamine treatments available if relapse occurs.

■ Esketamine intranasal

- Recommended treatment course is twice a week for 4 weeks.
- Potential dose increase after first week if no improvement
- Maintenance treatment is possible – usually every one to two weeks

Fitting it together -Currently at McLean's PNP



Summary

- Treatment Resistant Depression is common
- When Therapy and medications are not enough, other neurotherapeutic options can be very helpful.
- TMS can be a useful option – with very few side effects for most patients. This modality is rapidly evolving with exciting new avenues of treatment with impressive response rates.
- ECT can be life-saving, particularly for patients with psychotic depression, catatonia or intense SI. However, with improved side-effect profile, can be used for broader patient population
- The role of Ketamine and Esketamine are yet to fully be determined, but are very effective in many cases of severe treatment resistant depression, often when even ECT is not effective.

AUDIENCE Q&A

FINAL THOUGHTS

- A recording will be emailed to you in 2 weeks. It will include the presentation slides.
- Take our survey immediately after the webinar has concluded.

THANK YOU!

PAID FOR BY



Mass General Brigham
McLean