Harvard TMS Course

Pharmacology and TMS

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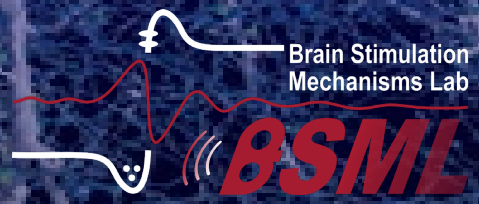

Disclosures

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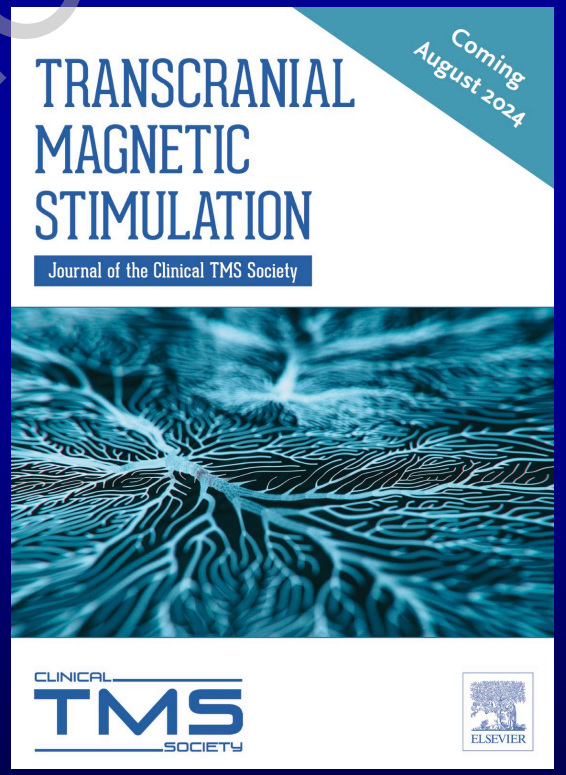


*50% off in 2025

Learning Objectives

1. The brain is an electrochemical organ.
2. What are the effects of daily medications on rTMS effectiveness.
   - Chronic effects: Homeostatic Plasticity
3. Putative mechanisms of repetitive rTMS.
4. Leveraging these mechanisms can enhance rTMS efficacy.

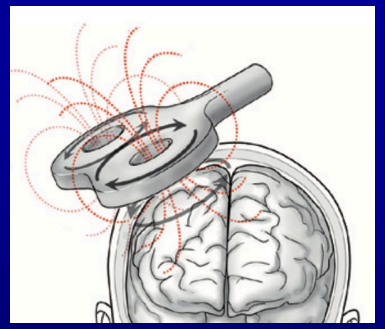
How The Brain Works

Electro Chemical

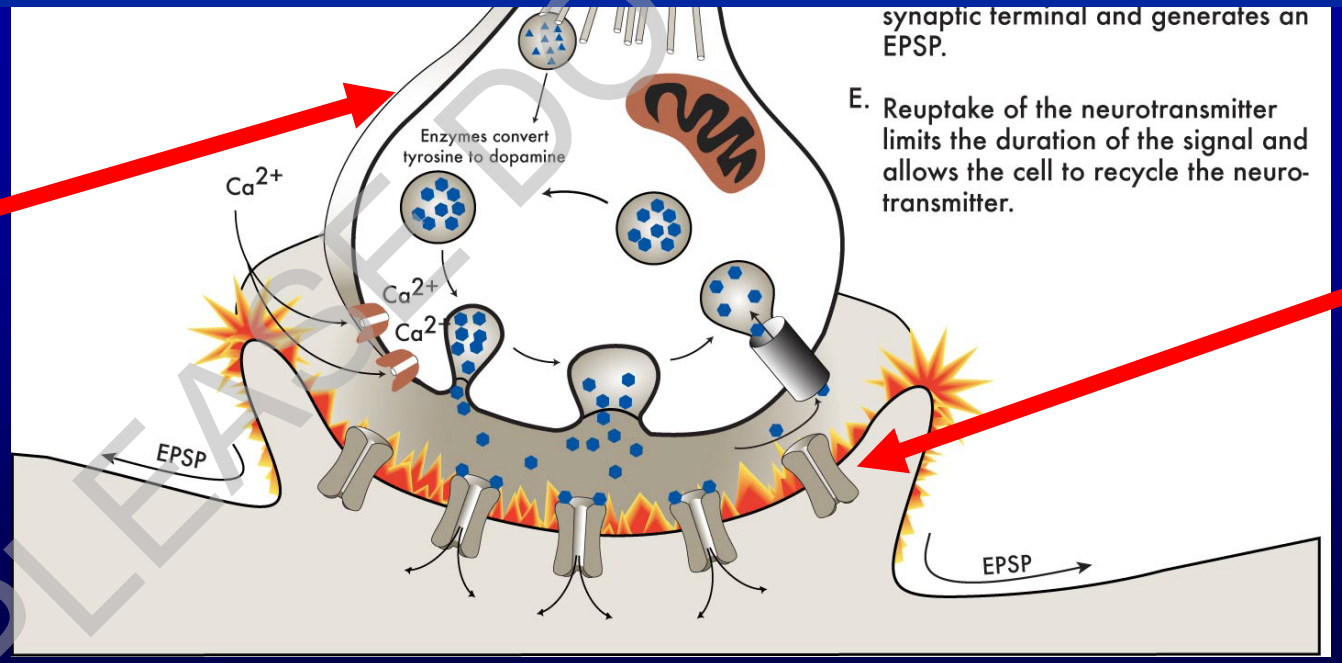
The Brain is an Electrochemical Organ

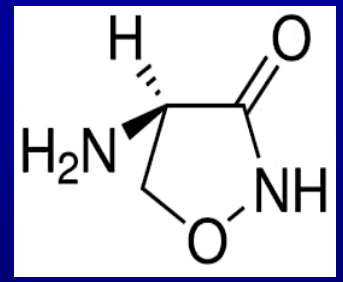
Electricity is the Currency of the Brain

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



TMS

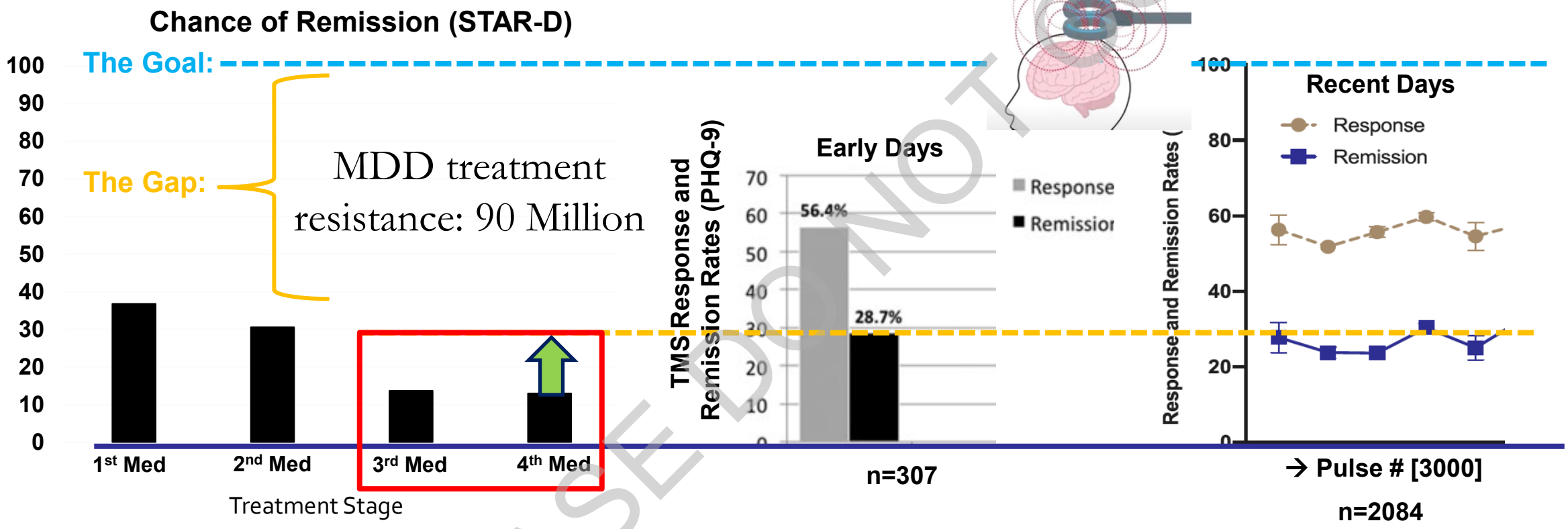




Drugs

Higgins & George, *Brain Stimulation Therapies for Clinicians*, 2019, slide adapted from Mark George

The Problem: The Gap



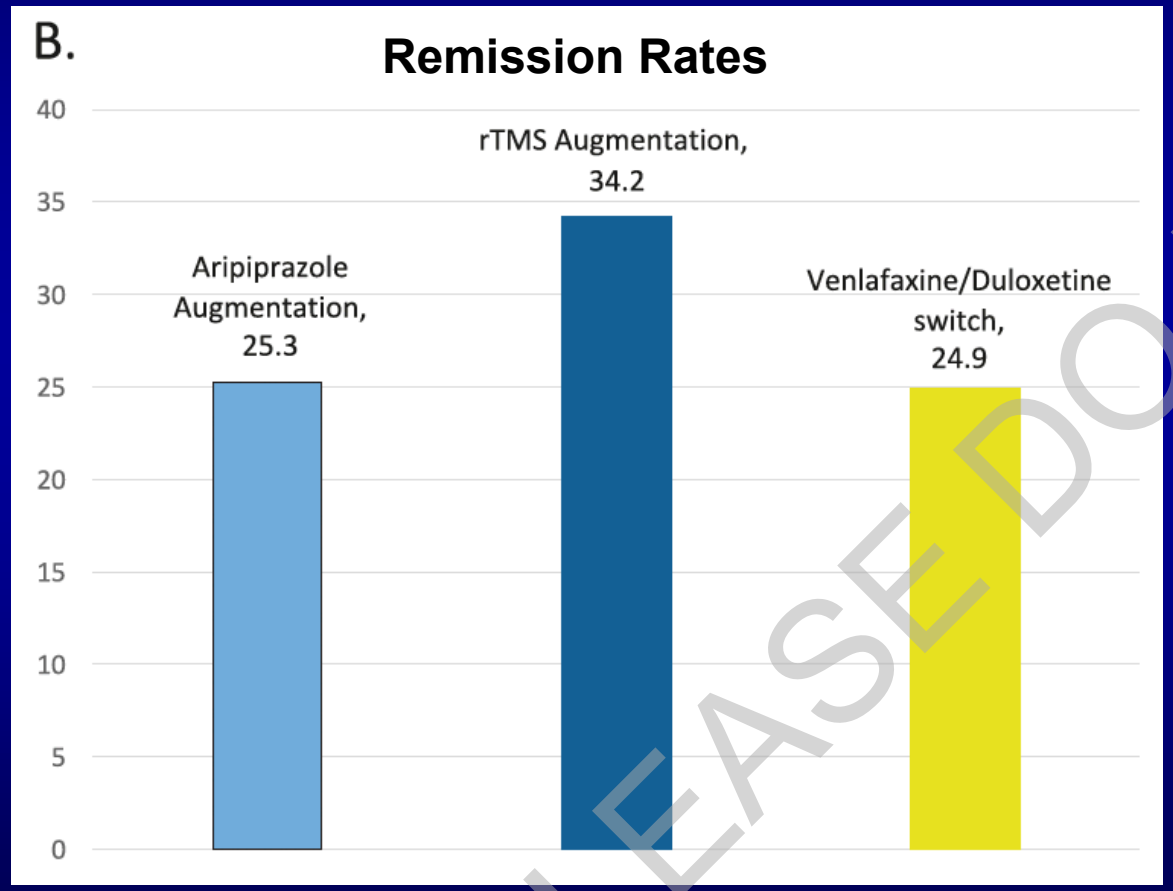
Adapted from Rush et al., *AJP*, 2006 (STAR-D)

Carpenter et al., *Depress Anxiety*, 2012

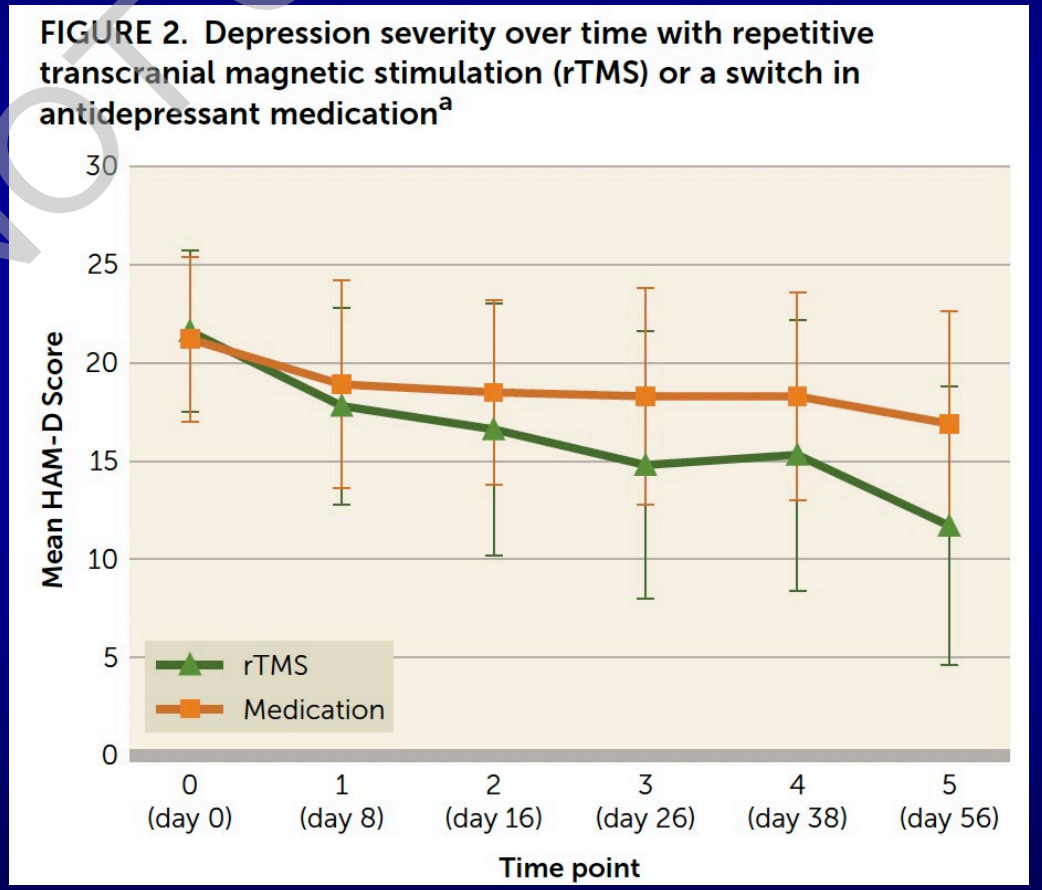
Sackeim et al., *J Affect Dis*, 2020

Our Q: How do we make TMS better?

Treatment resistant? More meds vs. TMS



Papakostas et al, *Molecular Psychiatry*, 2024



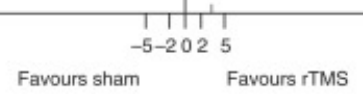
Dalhuisen, et al, *AJP*, 2024

What role do medications have in TMS response?

What recommendations should we make for our patients?

Is TMS better with Meds?

Author, year	Sessions (no.)	Intensity %MT	Frequency (Hz)	Train per session	Train duration (s)	Pulse per session (no.)	Total pulses (no.)	Mean difference from baseline (SD)	WMD (95% CI)	% Weight
On antidepressant										
Theleritis et al.,[18] 2017	15	100	20	40	2	1600	24 000	4 (5.99) , 15 (4.77)	11.00 (7.80 to 14.20)	7.39
Blumberger et al.,[23] 2016	30	120	10	70	3	2100	63 000	5 (4.8) , 6.4 (7)	1.40 (–1.22 to 4.02)	8.30
Chen et al.,[31] 2013	10	90	20	20	2	800	8000	12.6 (2.19) , 13.9 (2.25)	1.30 (–0.65 to 3.25)	9.34
Blumberger et al.,[16] 2012	15	100/120	10	29	5	1450	21 750	6.3 (6.76) , 5.7 (5.89)	–0.60 (–4.45 to 3.25)	6.44
Fitzgerald et al.,[32] 2012	15	120	10	30	5	1500	22 500	0.2 (5.85) , 4.1 (5.51)	3.90 (0.52 to 7.28)	7.12
Bakim et al.,[29] 2012	30	110	20	20	2	800	24 000	6.08 (8.21) , 12.45 (8.3)	6.37 (–0.39 to 13.13)	3.45
Triggs et al.,[34] 2010	10	100	5	50	8	2000	20 000	9.8 (10.3) , 8.4 (10.5)	–1.40 (–8.66 to 5.86)	3.12
Bretlau et al.,[27] 2008	15	90	8	20	8	1280	19 200	5.6 (5.61) , 8.9 (5.25)	3.30 (0.13 to 6.47)	7.43
Su et al.,[37] 2005	10	100	20	40	2	1600	16 000	3.7 (8.38) , 13.4 (9.59)	9.70 (1.81 to 17.59)	2.76
Mosimann et al.,[36] 2004	10	100	20	40	2	1600	16 000	4.1 (9.05) , 5.2 (8.16)	1.10 (–6.11 to 8.31)	3.15
Boutros et al.,[30] 2002	10	80	20	20	2	800	8000	7.33 (13.56) , 11.75 (16.52)	4.42 (–8.46 to 17.30)	1.23
Garcia-Toro et al.,[33] 2001	10	90	20	30	2	1200	12 000	1.77 (3.78) , 7.05 (5.66)	5.28 (2.30 to 8.26)	7.73
Avery et al.,[38] 1999	10	80	10	20	5	1000	10 000	6 (3.39) , 7.8 (9.77)	1.80 (–8.87 to 12.47)	1.70
Subtotal (I^2 = 69.6%, p = 0.000)									3.64 (1.52 to 5.76)	69.16
No antidepressant										
George et al.,[24] 2010	15	120	10	75	4	3000	45 000	3.13 (8.57) , 4.65 (10.43)	1.52 (–1.20 to 4.24)	8.13
O'Reardon et al.,[25] 2007	30	120	10	75	4	3000	90 000	3.3 (7.66) , 5.5 (8.4)	2.20 (0.36 to 4.04)	9.50
Avery et al.,[22] 2006	15	110	10	32	5	1600	24 000	3.7 (6.3) , 7.8 (7.8)	4.10 (0.74 to 7.46)	7.15
Holtzheimer et al.,[28] 2004	10	110	10	32	5	1600	16 000	3.2 (6.02) , 3.9 (5.22)	0.70 (–4.99 to 6.39)	4.31
Berman et al.,[26] 2000	10	80	20	20	2	800	8000	0.9 (11.51) , 12.5 (12.43)	11.60 (1.10 to 22.10)	1.75
Subtotal (I^2 = 15.3%, p = 0.317)									2.47 (0.90 to 4.05)	30.84
Overall (I^2 = 62.4%, p = 0.000)									3.36 (1.85 to 4.88)	100.00



Sehatzadeh et al., *J Psychiatry Neurosci*, 2019

Is TMS better with Meds?

REVIEW

A Review of Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation Combined with Medication and Psychotherapy for Depression

Brian Kochanowski, MA, Karina Kageki-Bonnert, Elizabeth A. Pinkerton, BS, Darin D. Dougherty, MD,* and Tina Chou, PhD*

"Concurrent antidepressant or mood stabilizer therapy was associated with a higher rate of response." (Fitzgerald, 2006)

TMS + MEDICATIONS									
Fitzgerald, et al. (2006)[55]	Phase 1: 67 received 1 Hz 63 received 2 Hz Phase 2: (offered to nonresponders) 16 received 5 Hz 14 received 10 Hz	Randomized, controlled	Different frequencies, different target	Phase 1: 1 or 2 Hz rTMS to right PFC at 110% MT, 900-1800 pulses Phase 2: 5 or 10 Hz rTMS to left PFC at 100% MT, ITI 20-25 seconds, 1500 pulses	10 rTMS sessions per phase	Stable dose of ongoing antidepressant or mood stabilizer	HAM-D BDI	1 Hz: HAM-D - 63.3% dec BDI - 63.5% dec 2 Hz: HAM-D - 66.4% dec BDI - 58.8% dec 5 Hz: HAM-D - 20.5% dec	Significant reduction in symptoms

"The medication-free patients…had given up on medication treatment usually after multiple failed trials…they may be a different… subgroup." (Fitzgerald, 2016)

TMS + MEDICATIONS									
Fitzgerald, et al. (2006)[55]	Phase 1: 67 received 1 Hz 63 received 2 Hz Phase 2: (offered to nonresponders) 16 received 5 Hz 14 received 10 Hz	Randomized, controlled	Different frequencies, different target	Phase 1: 1 or 2 Hz rTMS to right PFC at 110% MT, 900-1800 pulses Phase 2: 5 or 10 Hz rTMS to left PFC at 100% MT, ITI 20-25 seconds, 1500 pulses	10 rTMS sessions per phase	Stable dose of ongoing antidepressant or mood stabilizer	HAM-D BDI	1 Hz: HAM-D - 63.3% dec BDI - 63.5% dec 2 Hz: HAM-D - 66.4% dec BDI - 58.8% dec 5 Hz: HAM-D - 20.5% dec BDI - 22.4% dec 10 Hz: HAM-D - 37% dec BDI - 32.2% dec	Significant reduction in symptoms
Zhang, et al. (2019)[56]	117	Open-label	N/A	10 Hz over left dlPFC at 120% MT, 80 trains, ITI 12 seconds, 2400 pulses	At least 10 rTMS sessions	Stable dose of one antidepressant	HAM-D	51.5% dec	Significant reduction in symptoms
Wall, et al. (2011)[57]	8	Open-label	N/A	10 Hz over left dlPFC at 120%	30 rTMS sessions	Stable dose of ongoing SSRI and ongoing	CDRS-R	50.5% dec	Significant reduction in symptoms
Hansen, et al. (2004)[50]	6 active rTMS + medication 7 sham rTMS + medication (unipolar and bipolar depression)			60 seconds				MS + antidepressant: c MS + antidepressant: 54.6% dec	Poor tolerability of rTMS and high drop-out rates
Wilke, et al. (2022)[47]	37 rTMS + psychostimulants Wilke, et al. (2022) 53 rTMS only	Retrospective	rTMS only	10 Hz over left dlPFC at up to 120% MT, 40-pulse train, ITI 26 seconds, 3000 pulses	30 rTMS sessions	Stable dose of ongoing psychostimulant	IDS-SR	rTMS + Psychostimulant: 43.8% dec rTMS only: 29.8% dec	Combination superior
Berlim, et al. (2014)[58]	17	Open-label	N/A	20 Hz over left dlPFC at 120% MT, 75 trains of 2 seconds, ITI 20 seconds, 3000 pulses	20 rTMS sessions	Stable dose of ongoing medications (no benzodiazepines)	HAM-D QIDS	HAM-D - 50.9% dec QIDS - 27.1% dec	Significant reductions in symptoms
Garcia-Toro, et al. (2001)[52]	17 active rTMS + medication 18 sham rTMS + medication	Randomized, controlled, double-blind	Sham TMS (coil angled differently)	20 Hz over left dlPFC at 90% MT, 30 trains of 2 seconds, ITI 20-40 seconds	10 rTMS sessions	Stable dose of ongoing medications	HAM-D21 BDI	Active rTMS + medication: HAM-D21 - 26% dec BDI - 17.4% dec Sham rTMS + medication: HAM-D21 - 6.9% dec BDI - 9.7% dec	Combination superior

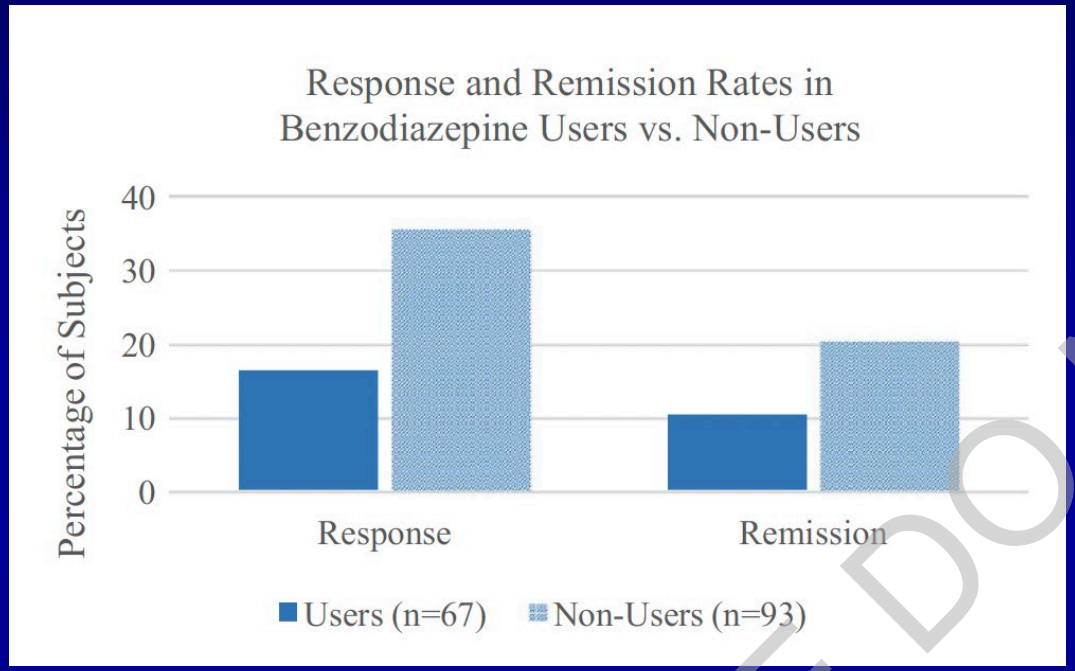
Psychostimulants: Enhances TMS response

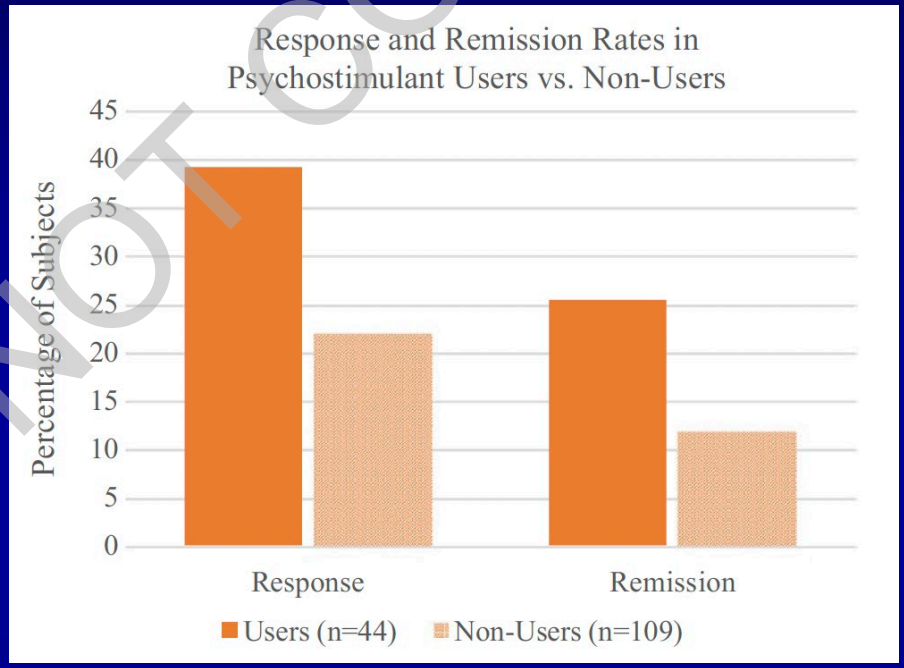
*Retrospective

TMS + MEDICATIONS									
Schüle, et al. (2003)[41]	26	Open-label	N/A	10 Hz over left dlPFC at 100% MT, 15 trains of 10 seconds, ITI 30 seconds	10-13 rTMS sessions	Mirtazapine, 45 mg/day or mirtazapine plus newly started lithium, carbamazepine or neuroleptics after full course of rTMS sessions	HAM-D	rTMS + mirtazapine (monotherapy): 38.8% dec	Combination reduced symptoms
Rumi, et al. (2005)[42]	22 active rTMS + amitriptyline 24 sham rTMS + amitriptyline	Randomized, controlled, double-blind	Sham TMS (sham coil)	5 Hz over left dlPFC at 120% MT, 25 trains of 10 seconds, ITI 20 seconds, 1250 pulses	20 rTMS sessions	Amitriptyline, average dose was 110 mg/day (clonazepam allowed)	HAMD-17 MADRS	*Estimated from graph Active rTMS + medication: HAMD-17 ~ 62% dec MADRS ~61% dec Sham rTMS + medication: HAMD-17 ~ 22% dec MADRS ~23% dec	Combination superior, also accelerated symptom reduction at 1 week into treatment
Hu, et al. (2016)[43]	12 left 10 Hz rTMS + quetiapine 13 right 1 Hz rTMS + quetiapine 13 sham + quetiapine (bipolar II depression)							ted from graph rTMS + medication: D17 ~ 46% dec S ~57% dec TMS + medication: D17 ~ 47% dec S~59% dec TMS + medication: D17 ~ 41% MADRS ~49% dec	Combination not superior
Hebel, et al. (2020)[44]	182 rTMS + drugs for psychosis 117 rTMS + no drugs for psychosis	Retrospective	rTMS only	Mostly 10 Hz over left dlPFC	Different protocols	Antipsychotics	HAM-D21 HAM-D17	rTMS + antipsychotics: HAM-D21 - 25.2% dec HAM-D17 - 25.4% dec rTMS only: HAM-D21 - 36.9% dec HAM-D17 - 38.9% dec	Antipsychotics interfere with TMS response
Deppe, et al. (2020)[45]	176 not taking benzodiazepines 73 taking lorazepam	Retrospective	Different protocols	Left, right, bilateral dorsolateral, or dorsomedial PFC	Different protocols	Lorazepam	HAM-D21 HAM-D17	No benzodiazepines: HAM-D21- 34.2% dec HAM-D17 - 35.7% dec Lorazepam: HAM-D21 - 18.8% dec HAM-D17 - 18.9% dec	Lorazepam interferes with TMS response
Cole, et al. (2022)[46]	25 iTBS + placebo 25 iTBS + D-CS	Randomized, controlled, double-blind	Placebo capsules	Left dlPFC at 80% MT, 20 trains of triplets at 50 Hz repeated at 5 Hz, 600 pulses	20 iTBS sessions	D-cycloserine, 100 mg at least 1 hour before iTBS	MADRS QIDS	iTBS + D-CS: MADRS - 56.8% dec QIDS - 44.4% dec iTBS + placebo: MADRS - 34.7% dec QIDS - 32.3% dec	Combination superior

Antipsychotics: interfere with TMS response
Lorazepam: interferes with TMS response
*Both Retrospective

Benzo's & Stimulants





Hunter et al., *Brain Behav*, 2019

Supported by: THREE-D study sub-analysis: 123/388 patients. (Kaster, AJP, 2019)

- BDZ users more likely NON-responders
- BDZ users more likely slower trajectory

BDZ Not Supported by: Two clinical trials: 64/121 patients. (Fitzgerald, Brain Stim, 2020)

More to come on Stimulants?

Drug effects on Cortical Excitability

Clinical Neurophysiology 126 (2015) 1847–1868

Contents lists available at ScienceDirect

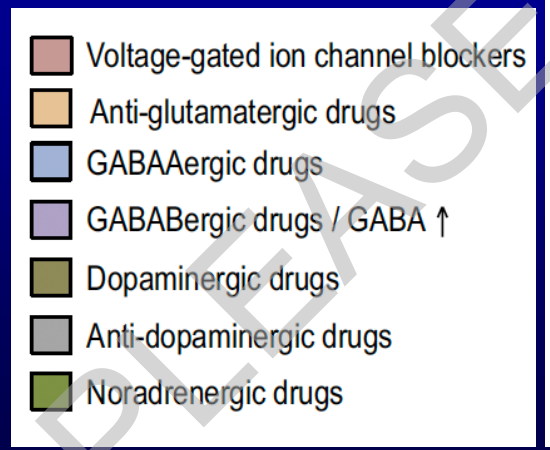
Clinical Neurophysiology

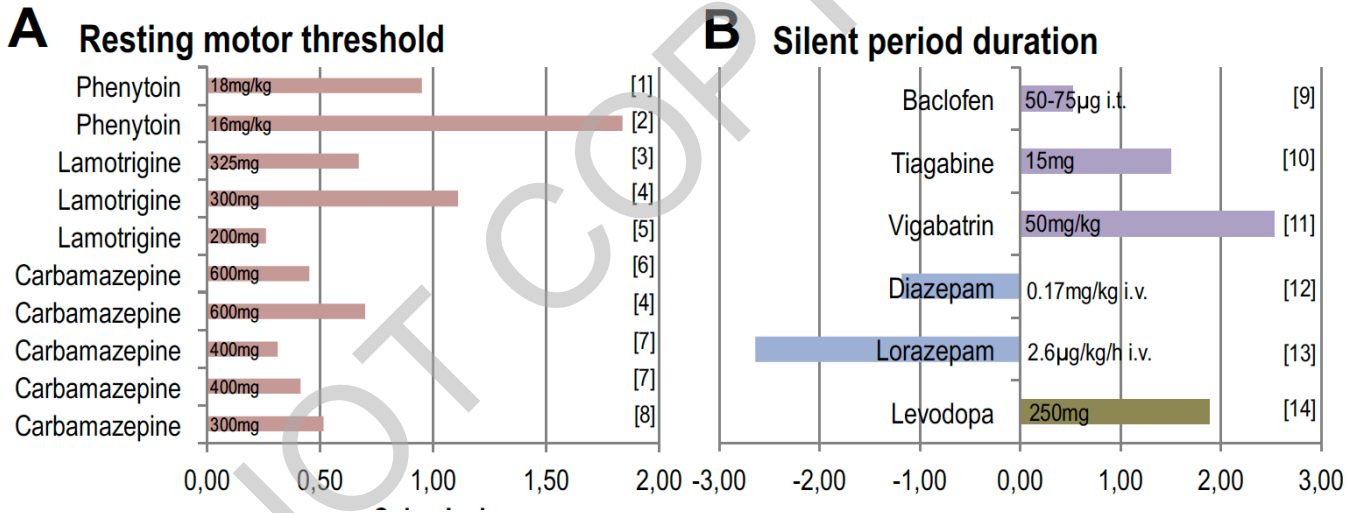
journal homepage: www.elsevier.com/locate/clinph

Review

TMS and drugs revisited 2014

Ulf Ziemann [a,*], Janine Reis [b], Peter Schwenkreis [c], Mario Rosanova [d,e], Antonio Strafella [f,g], Radwa Badawy [h,i], Florian Müller-Dahlhaus [a]



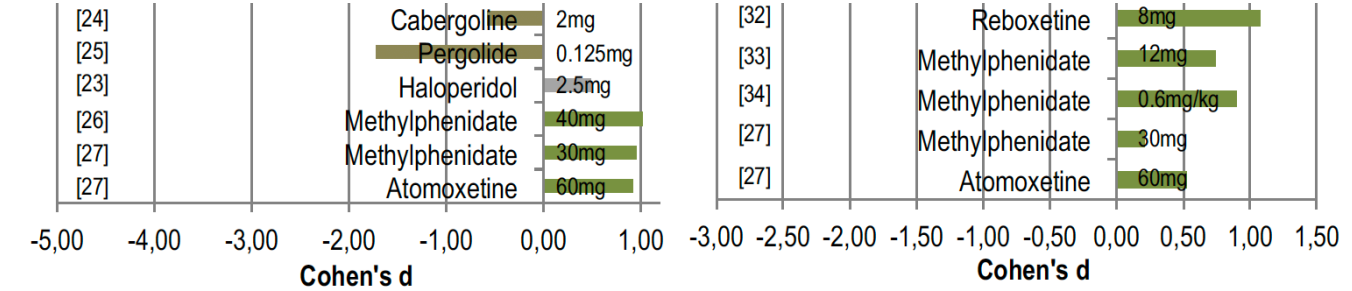


European Archives of Psychiatry and Clinical Neuroscience (2021) 271:1245–1253
https://doi.org/10.1007/s00406-021-01287-3

ORIGINAL PAPER

Antidepressant effect of repetitive transcranial magnetic stimulation is not impaired by intake of lithium or antiepileptic drugs

T. Hebel[1] · M. A. Abdelnaim[1] · M. Deppe[1] · P. M. Kreuzer[1] · A. Mohonko[1,2] · T. B. Poeppl[1,3] · R. Rupprecht[1] · B. Langguth[1] · M. Schecklmann[1]



Summary of Naturalistic Rx's

- 5 retrospective comparisons:
  - Antipsychotics and Benzo's (x2) (may) impair
  - Stimulants/dopaminergics (may) enhance (x2)
- *Non-controlled open-label data*

- What level of evidence do we need to change practice??

- What about NON-Rx drugs?

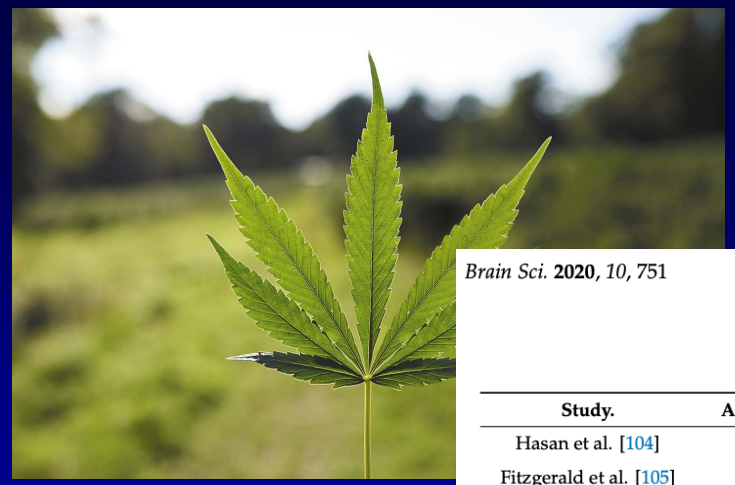


Table 2. Effects of cannabis on TMS measures.

Study.	AMT	RMT	MEP	CSP	iSP	SAI	LAI	SICI	ICF	SICF	LICI	SIHI	LIHI	Notes
Hasan et al. [104]	–	○	○	▲	–	–	–	▲	–	–	–	–	–	Acute intake
Fitzgerald et al. [105]	○	○	○	○	–	–	–	▼	○	–	○	–	–	Heavy and light cannabis users vs. non-users
Martin-Rodriguez et al. [106]	○	○	○	–	–	–	–	▼	–	–	–	–	–	CUD and daily cannabis users vs. non-users
Wobrock et al. [107]	–	○	–	–	–	–	–	▼	▲	–	–	–	–	Schizophrenia cannabis users vs. non-users
Flavel et al. [108]	–	○	○	○	–	–	–	–	–	○	○	–	–	Cannabis users vs. nonusers
Goodman et al. [109]	–	○	–	○	–	–	–	▲	○	–	○	–	–	Schizophrenia cannabis users vs. non-users
	–	○	–	○	–	–	–	▼	○	–	○	–	–	Control cannabis users vs. nonusers
Russo et al. [110]	○	○	○	○	–	○	○	▲	▼	–	–	–	–	MS patients on 1 month of Sativex
Leocani et al. [111]	–	○	○	–	–	–	–	○	○	–	–	–	–	MS patients on 1 month of Sativex
Calabrò et al. [112]	–	–	▲	–	–	–	–	▼	▼	–	–	–	–	MS patients on 6 weeks of Sativex + gait training

▲ increase; ▼decrease; ○ indicates no change; – indicates did not assess; CUD: cannabis use disorder; MS: multiple sclerosis.

Turco, *Brain Sci,* 2020

THC–Observational Data from Butler Hospital:

(*n* of 56, 28 THC users, 28 matched)

Users: 12/28 responders, 5/28 remitters

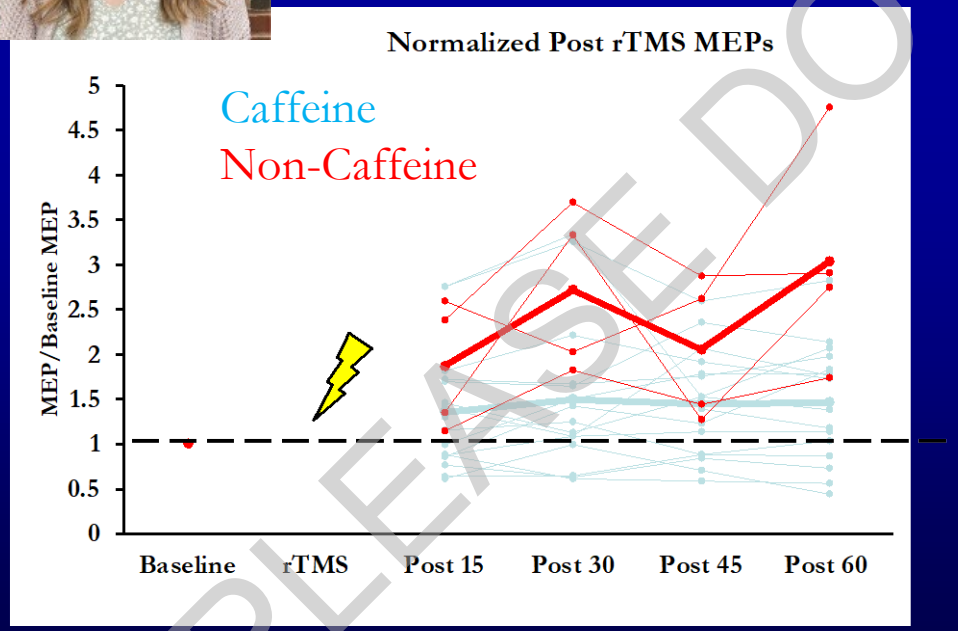
Matched: 16/28 responders, 11/28 remitters

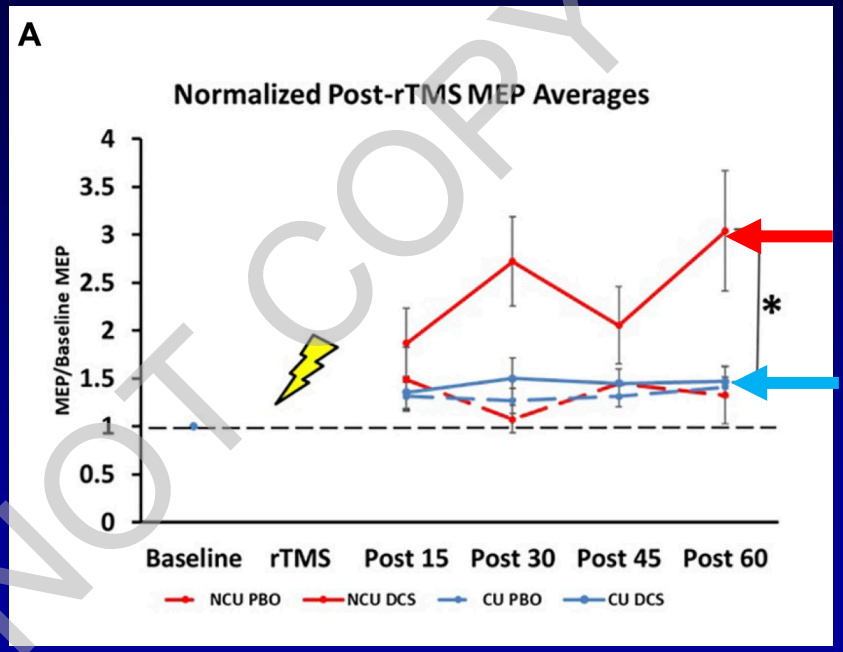
6 cases (Confusion, Psychosis, Sensory Changes, Panic)

-DePamphilis, *Brain Stimulation,* 2024

How about our Drug of Choice?

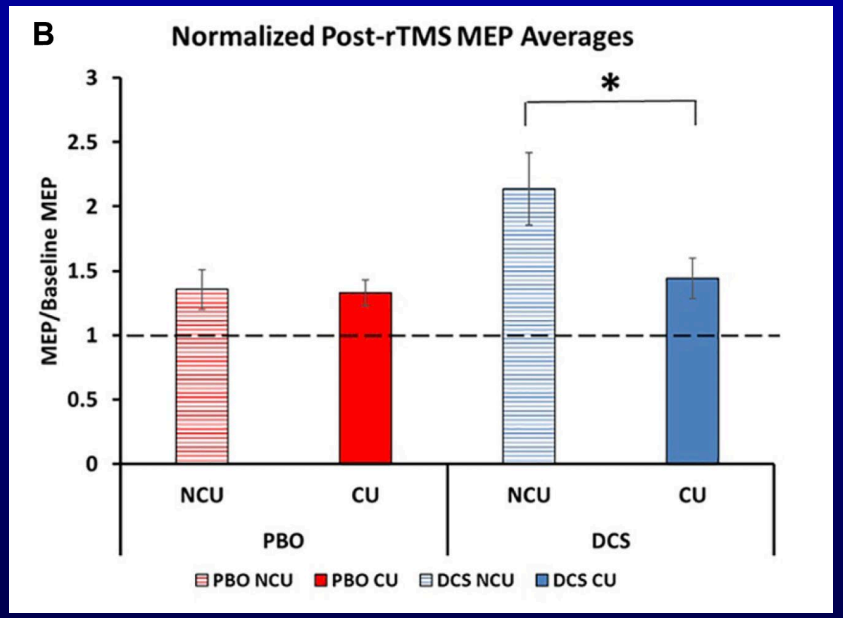
How Does the Most Common Stimulant (Caffeine) Effect TMS?





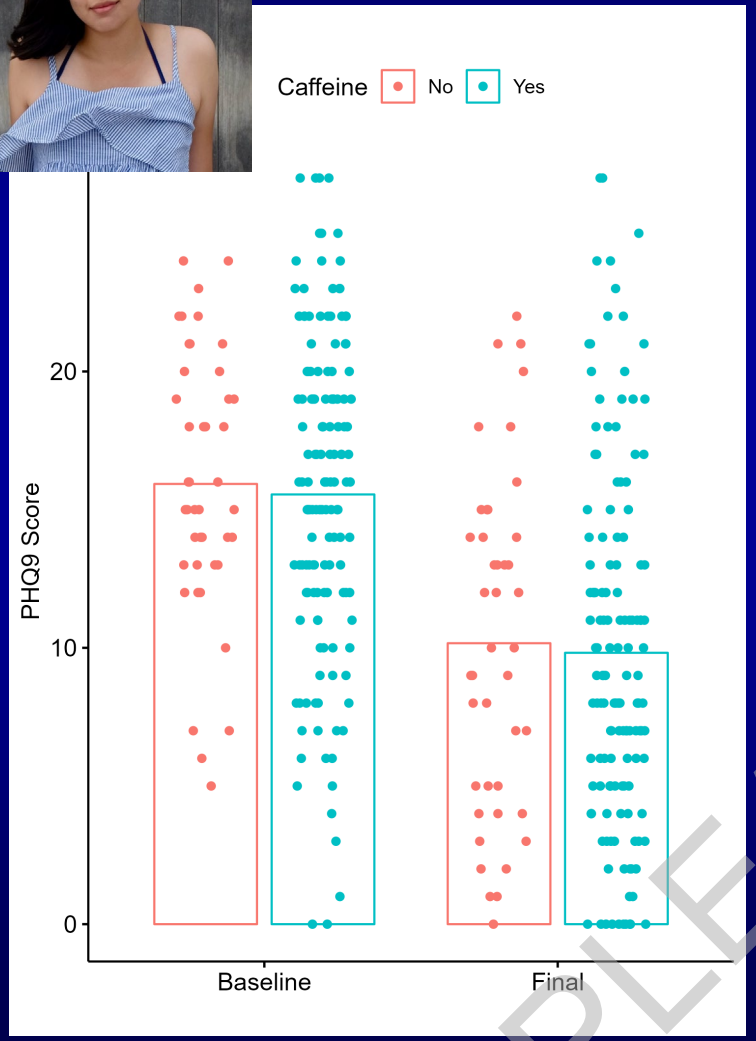
Caffeine-Free

Caffeine

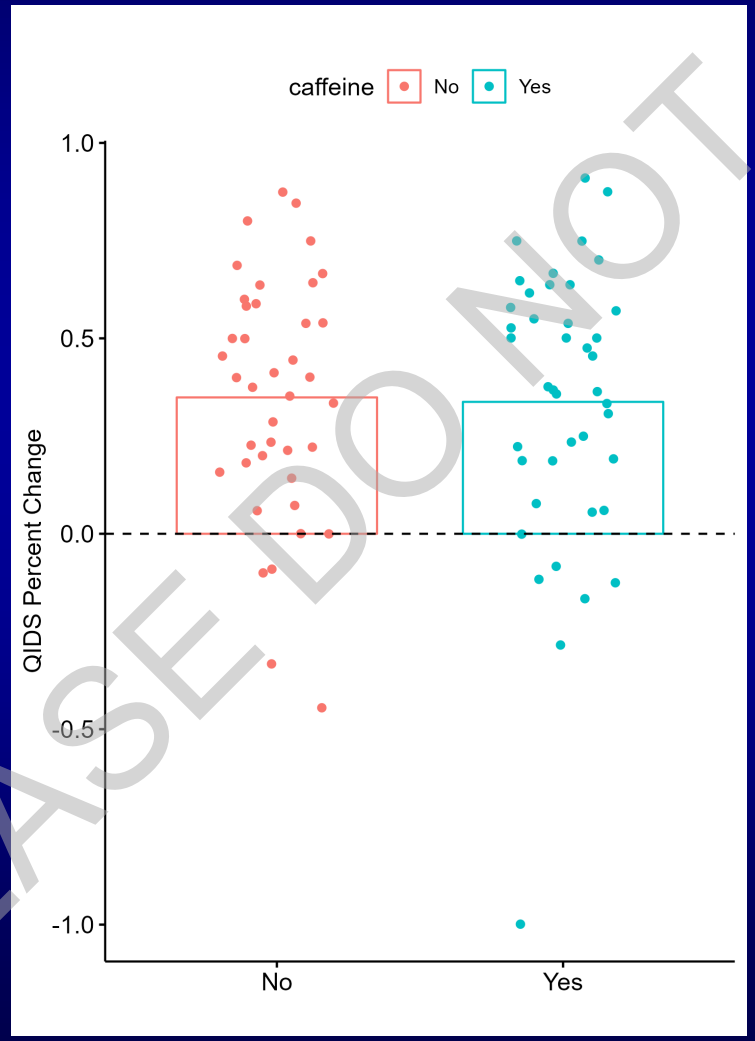


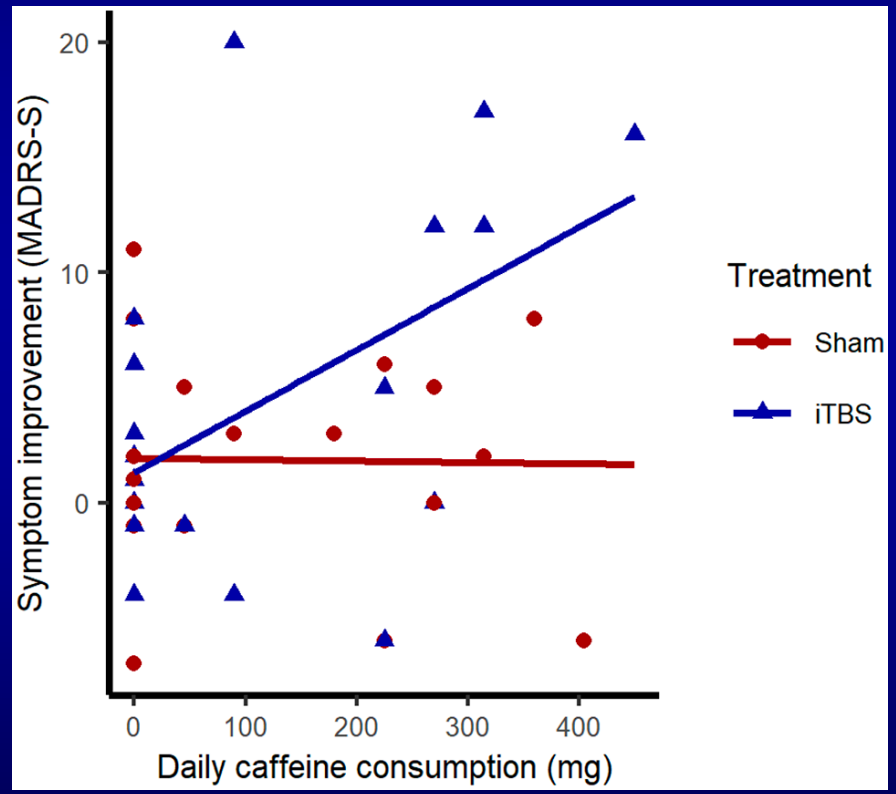
Vigne et al, *Front Psych*, 2023

Should we advise against caffeine use during TMS??

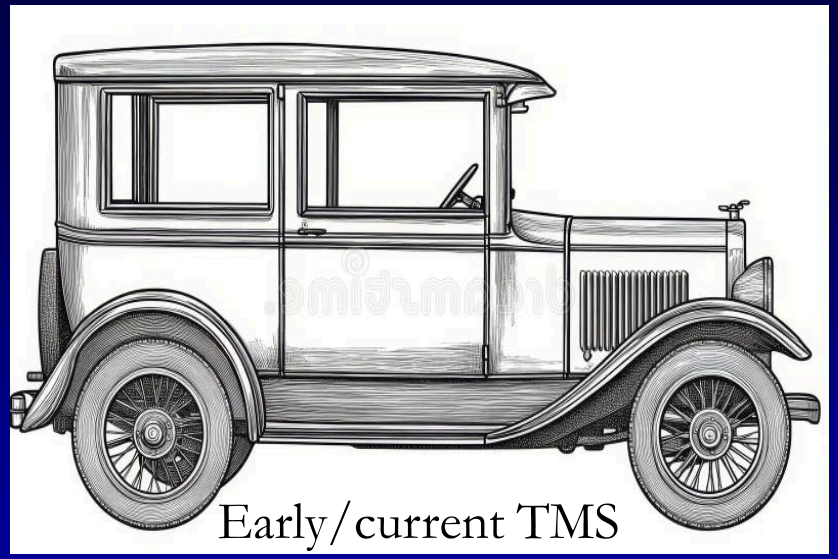


Kweon et al, *TMS*, 2025

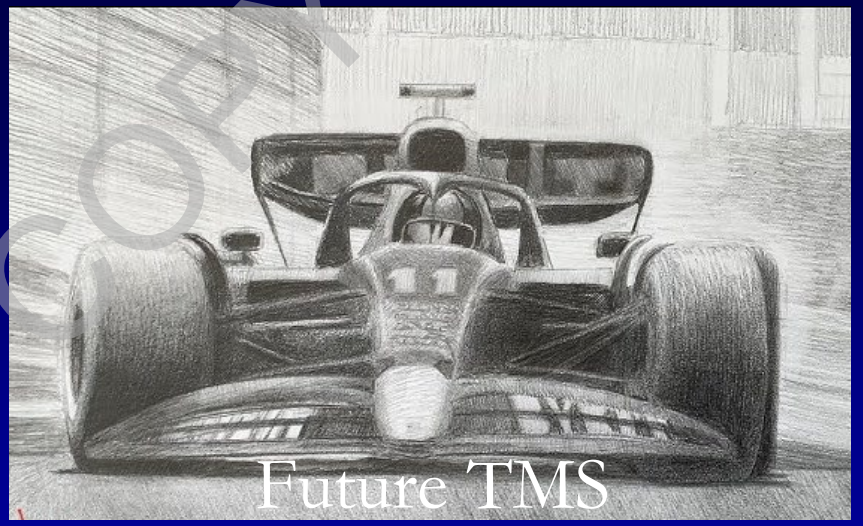


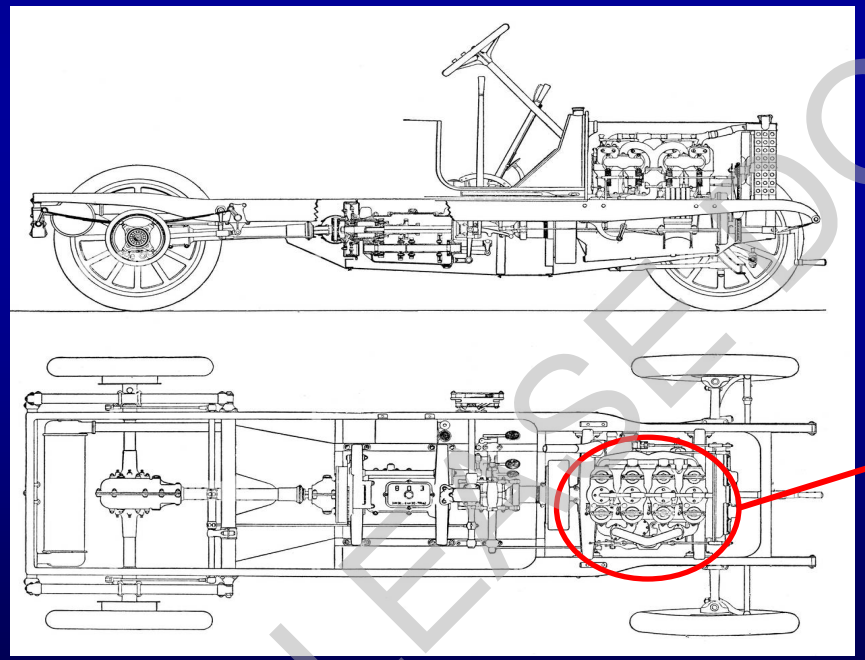


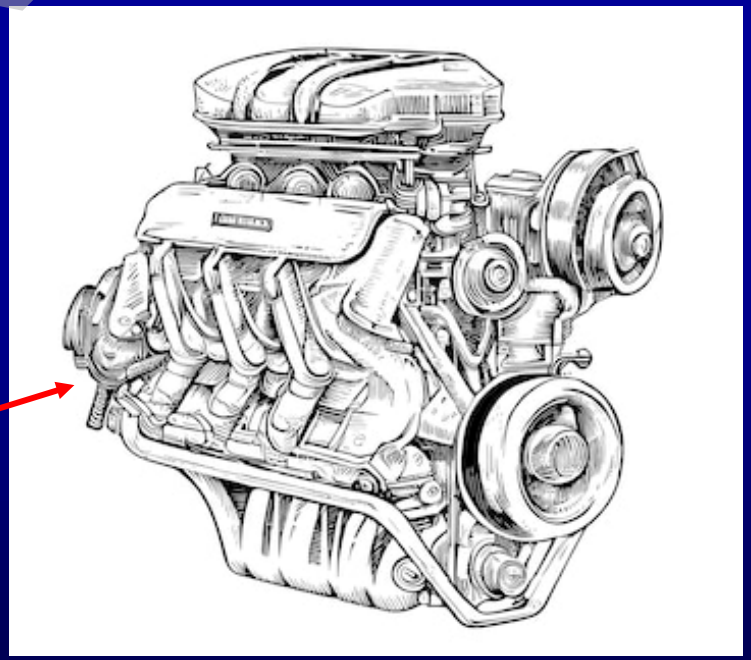
Frick et al, *Psychopharm*, 2021



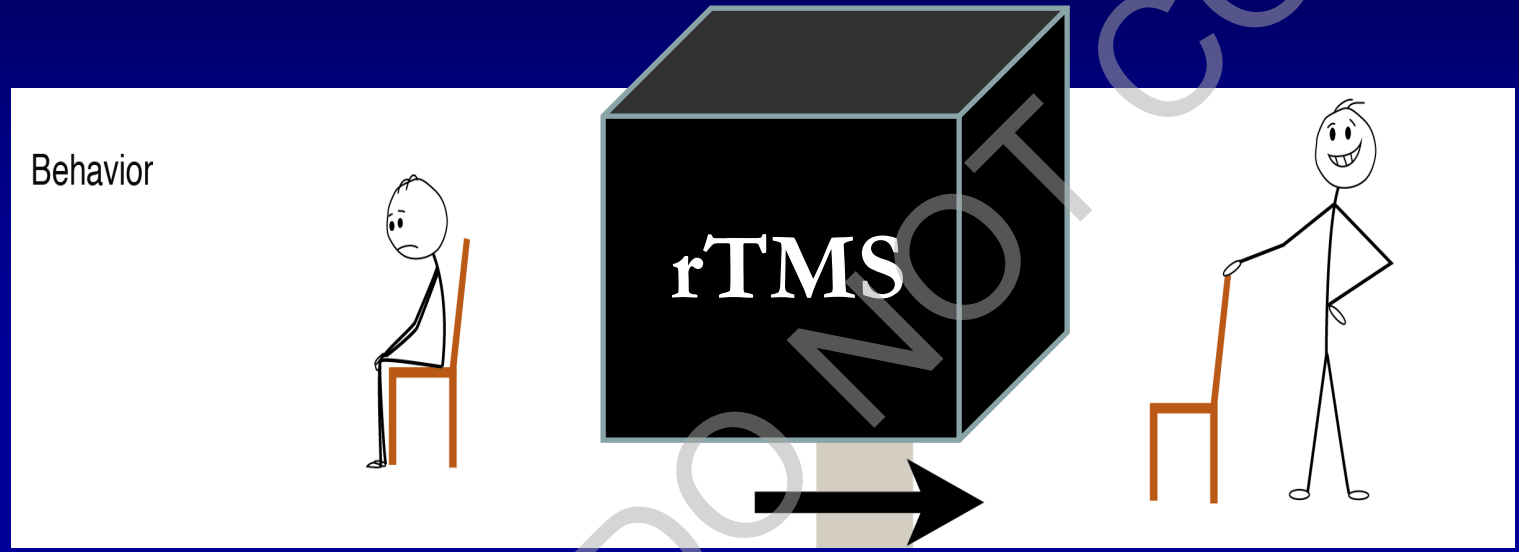
How did we get from Model T to F1?





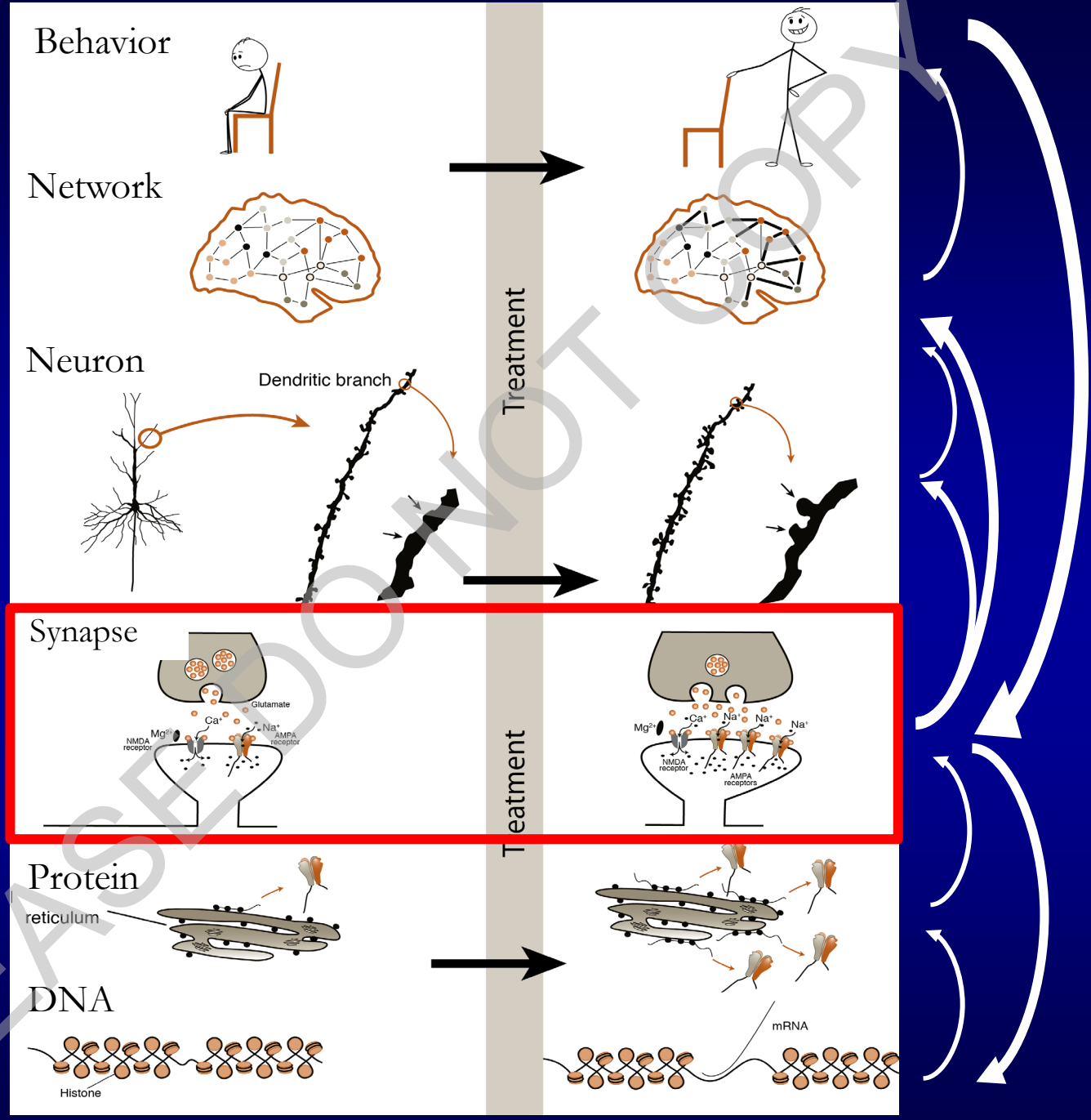


What is the rate-limited "engine" of TMS modulation of the brain?



How does rTMS produce lasting therapeutic changes in the brain?

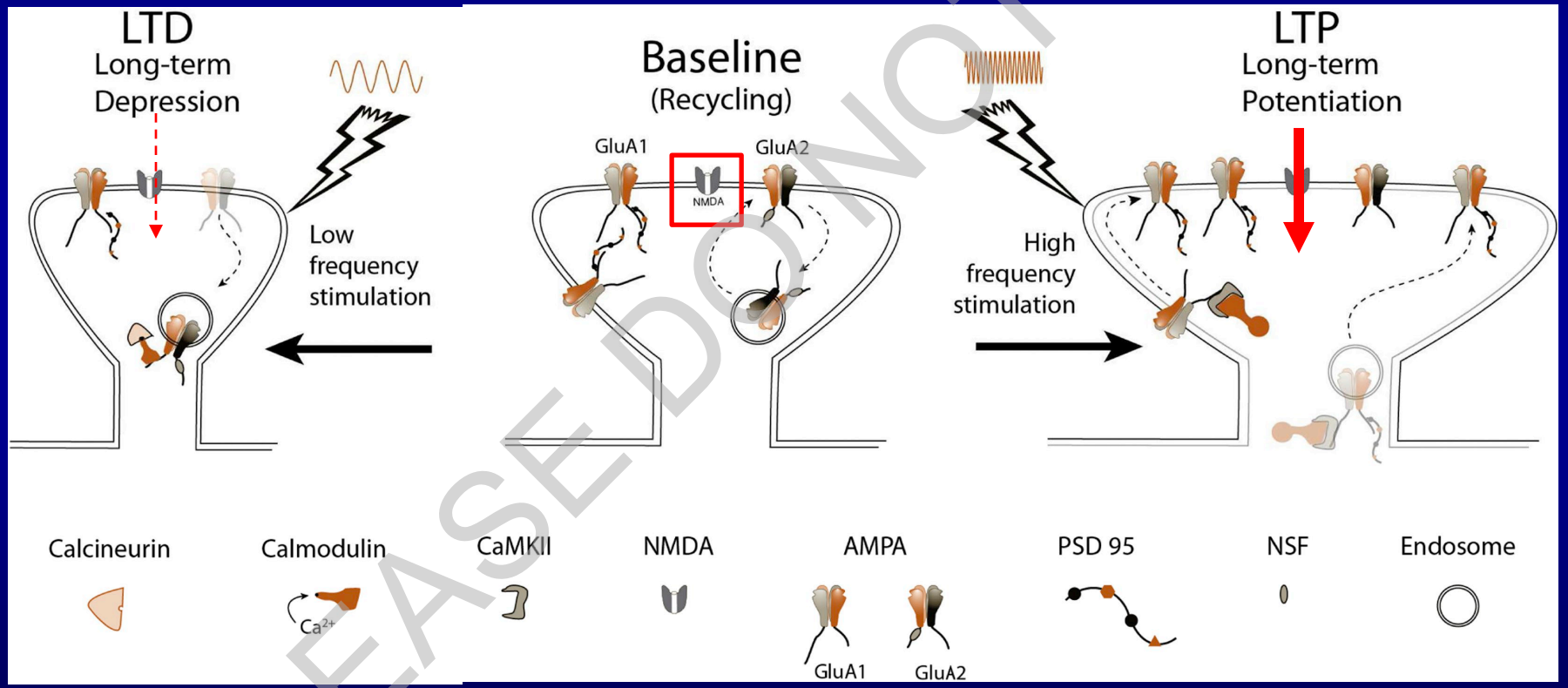
What Underlies
(aka causes?)
Network and Behavioral Effects?



Brown, Higgins & George, *Neuromodulation*, 2022

Synaptic Plasticity

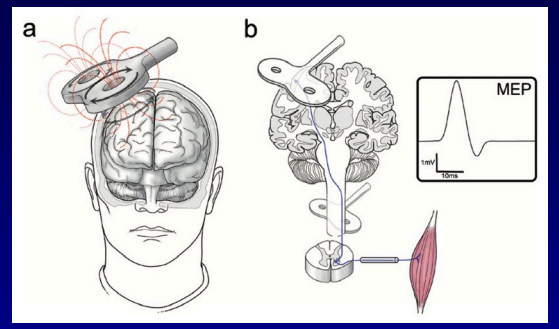
critically depends on NMDA receptors



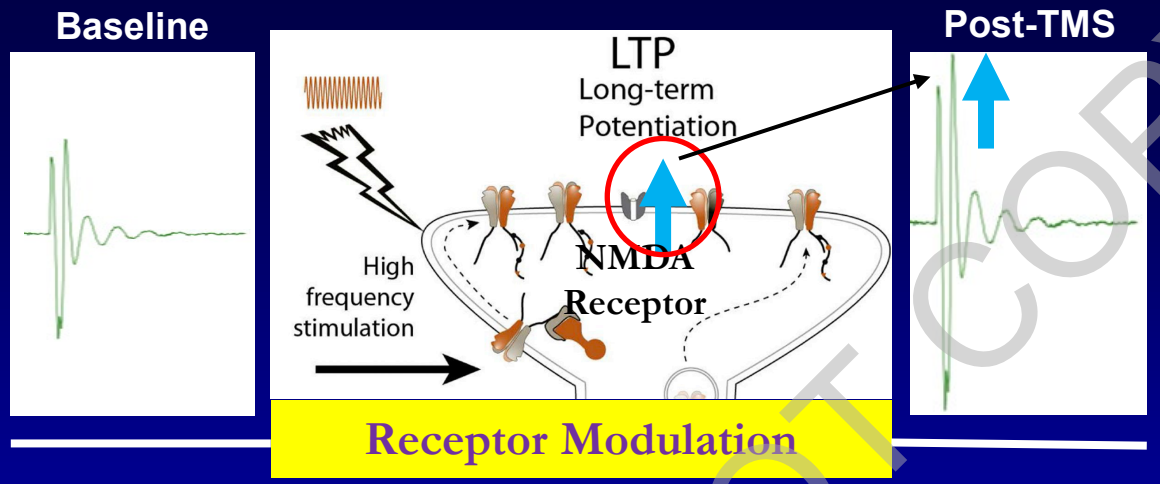
Brown et al, *Neuromodulation*, 2022

Vlachos, *J Neuro*, 2012

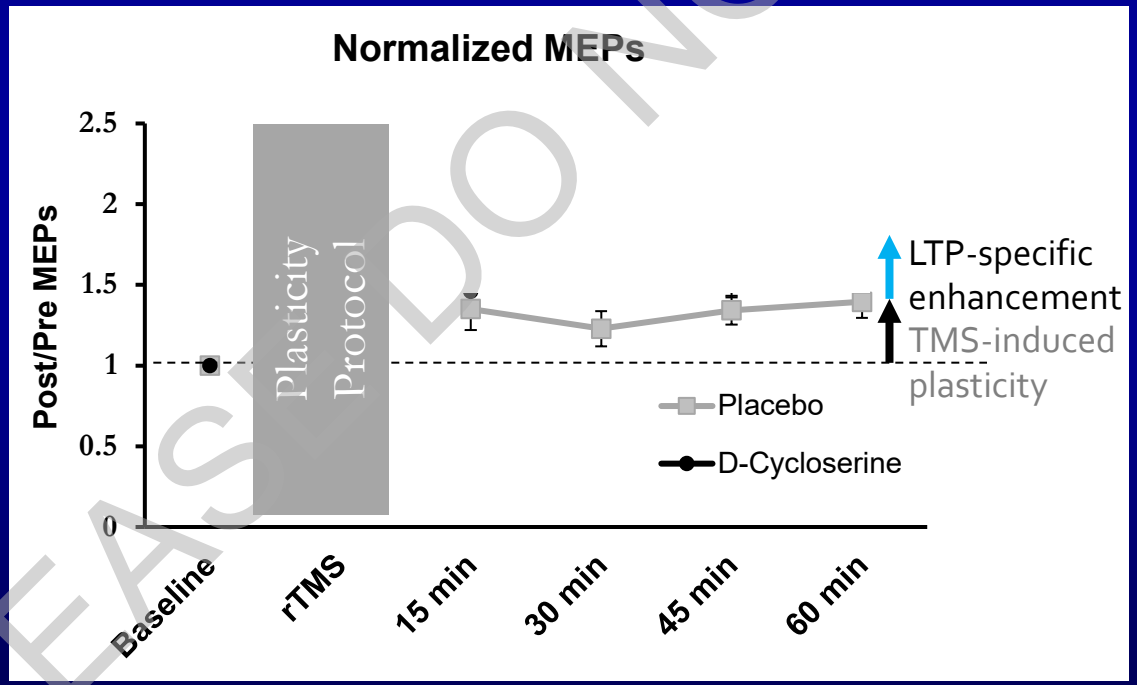
Huang, Clin Neurophys, 2007



Vlachos et al., *Neuroforum*, 2017



NMDAR Activation is Sufficient to Enhance Plasticity



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

Does TMS work through LTP?

Occlusion

- Brown et al., *Brain Stimul*, 2021

Homeostatic Depression

- Brown et al., *Brain Stimul*, 2021
- Vigne et al., *Front Psych*, 2023

Learning Augments

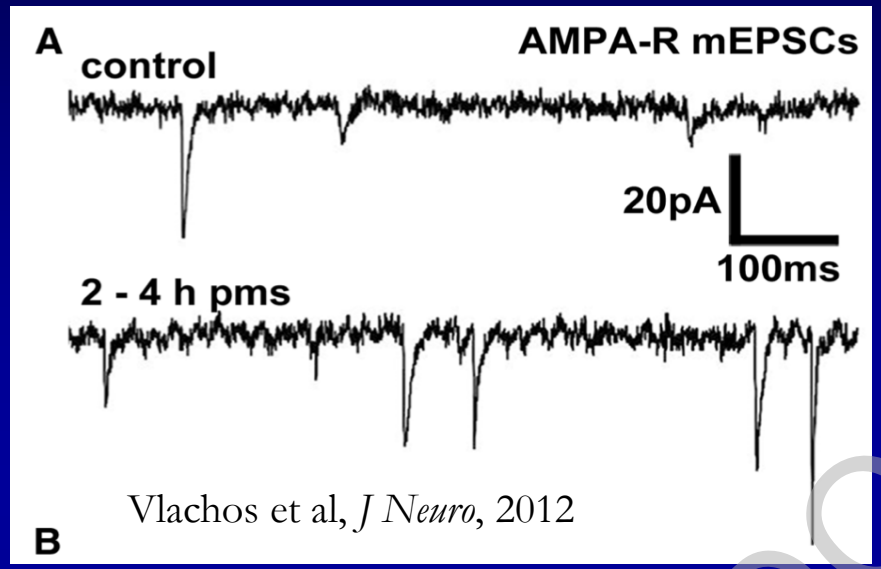
- Kweon et al., *Front Neural Circuits*, 2023

Enduring Effects

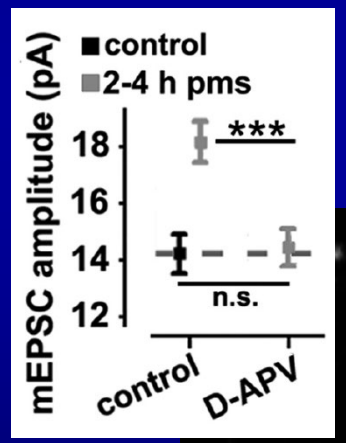
NMDAR-mediated

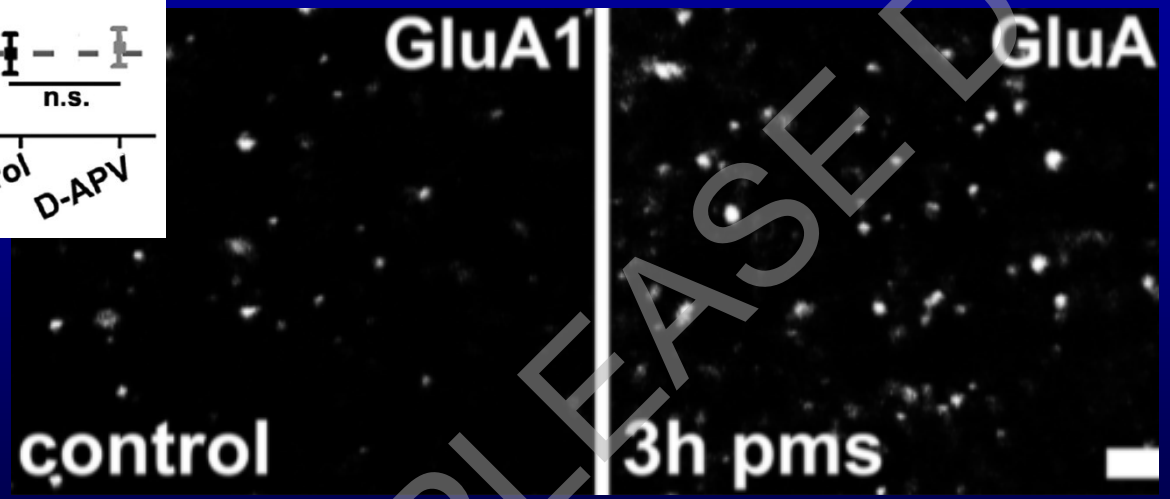
- Brown et al., *Brain Stimul*, 2020
- Kim et al., In prep
- Ganesh et al. Submitted
- Kweon et al, Submitted

Evidence for LTP



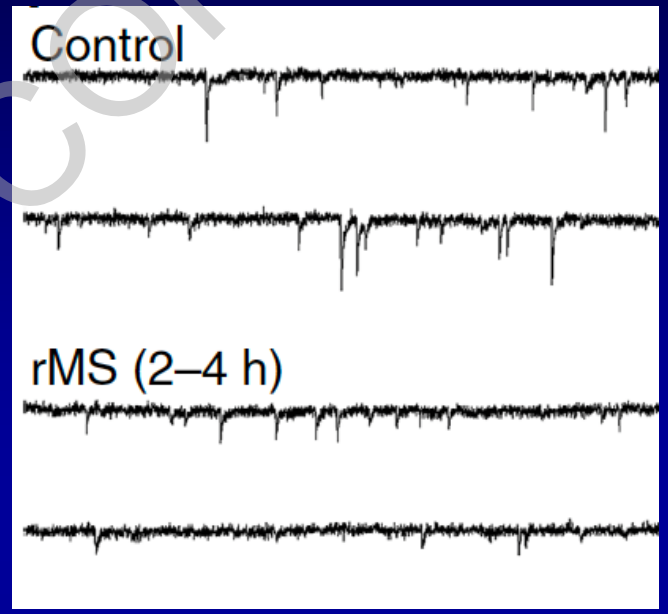
Vlachos et al, *J Neuro*, 2012

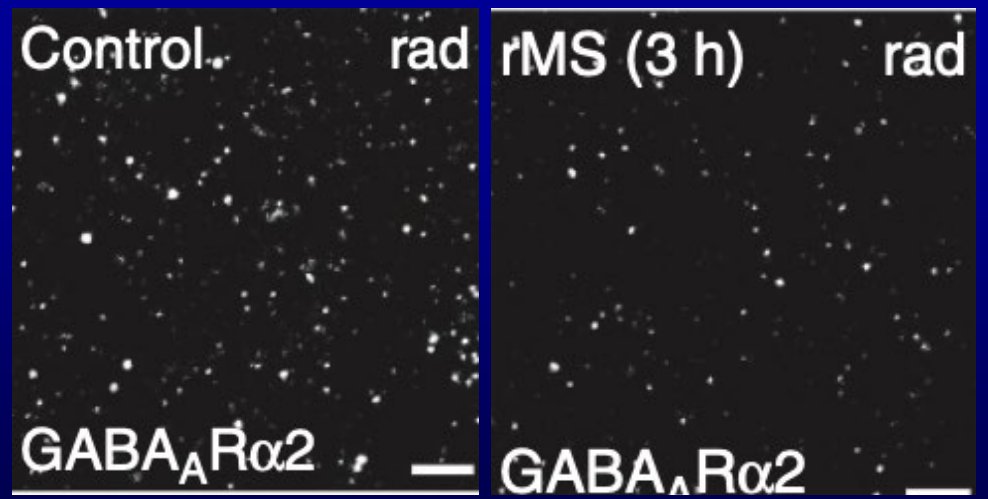




Vlachos et al, *J Neuro*, 2012

And ↓GABA!

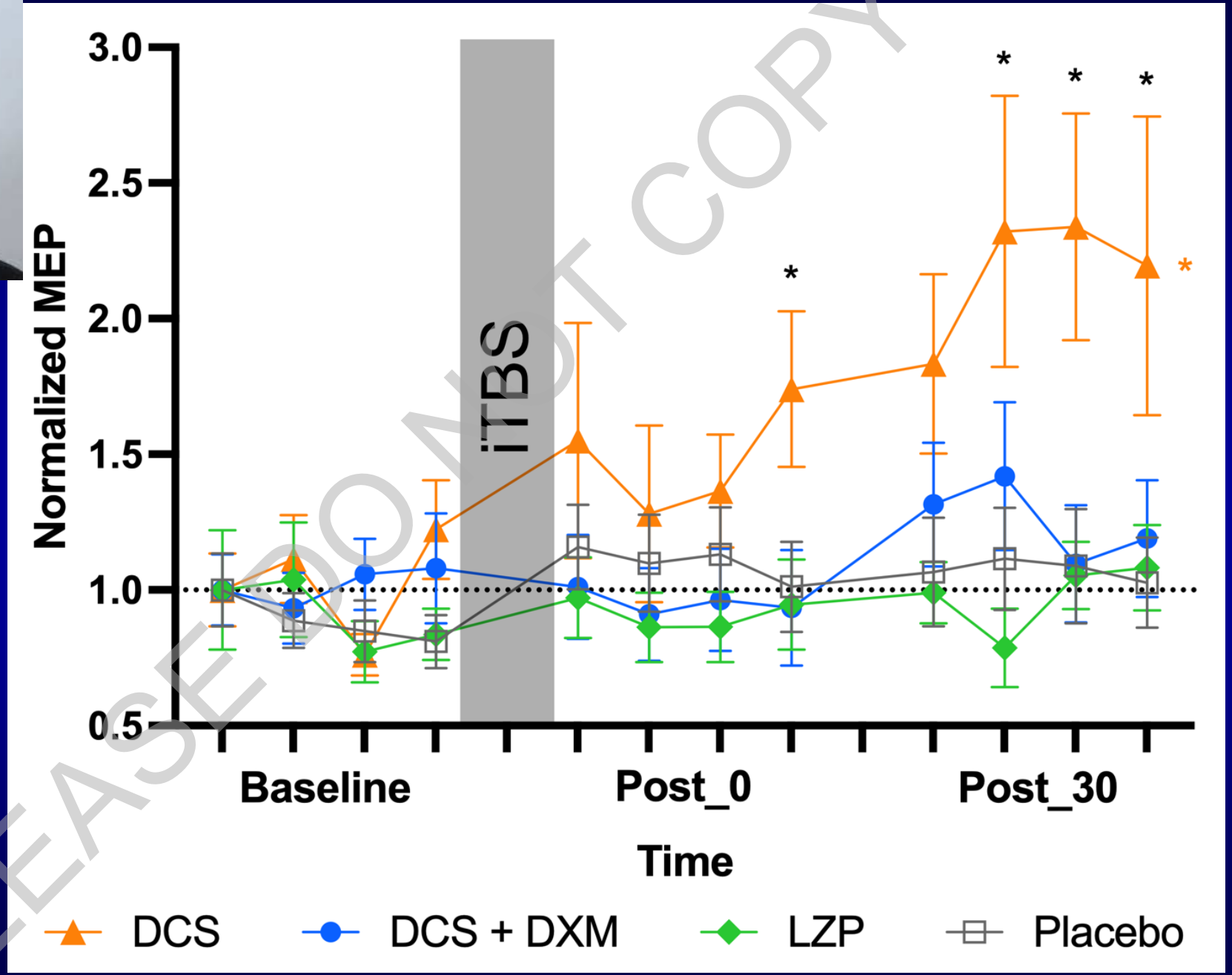




Lenz et al, *Nat Comm*, 2016

iTBS

- NMDAR agonism (DCS) enhances plasticity
- NMDAR antagonist (DXM) "knocks down"
- GABAR agonism NOT increased after TMS = No reduction in receptors



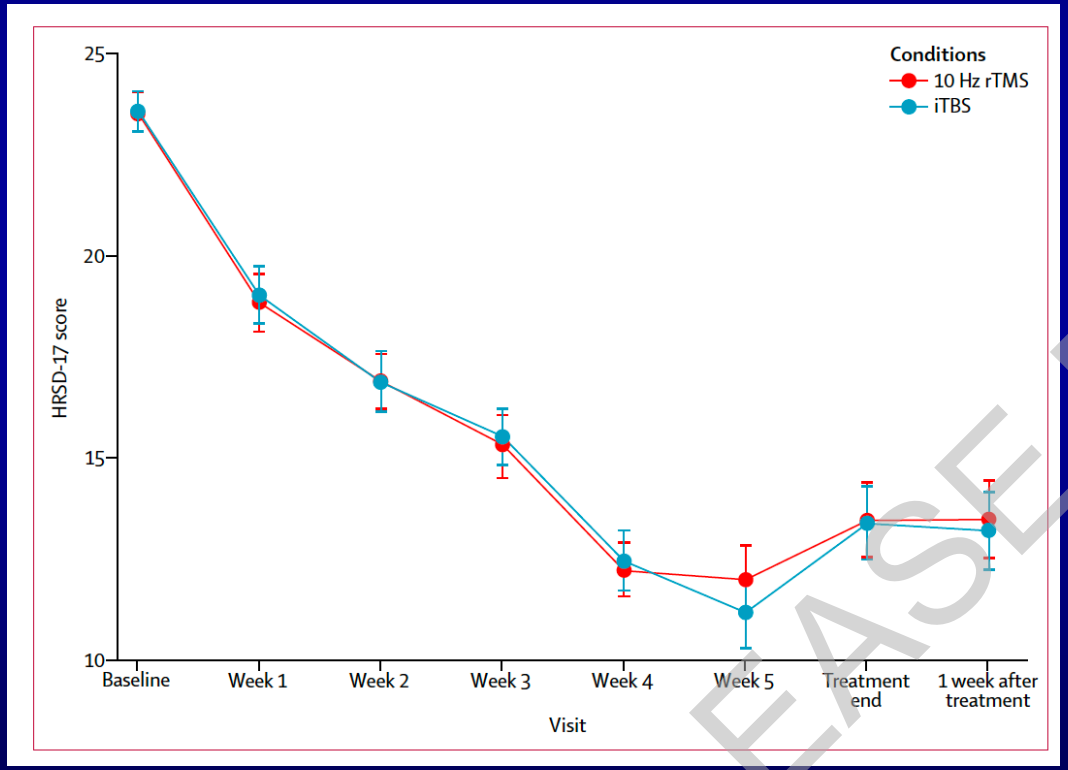
Kim et al., In Prep

10-Hz rTMS

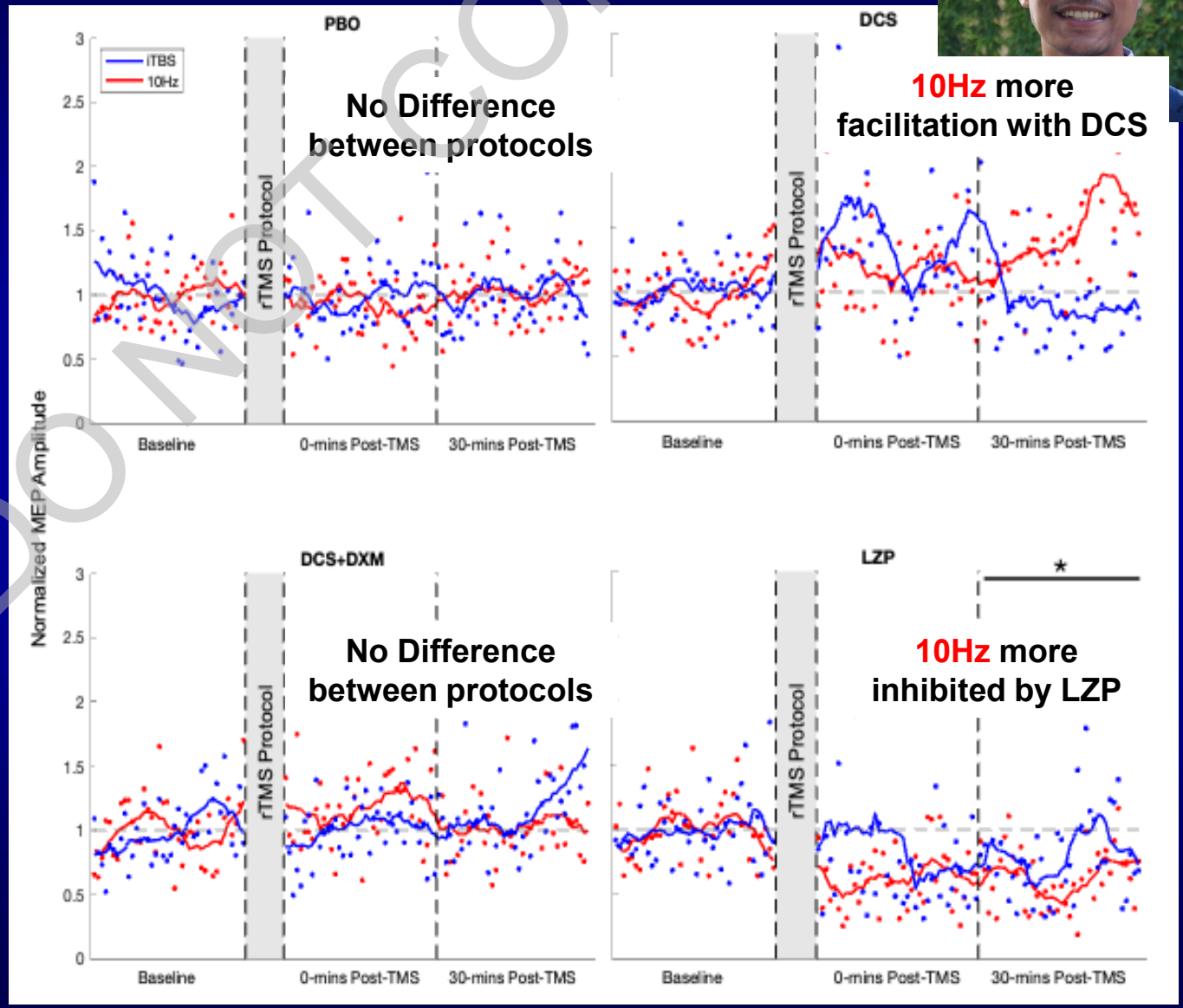
- NMDAR agonism (DCS) enhances plasticity
- NMDAR antagonist (DXM) "knocks down"
- GABAR agonism NOT increased after TMS = No reduction in receptors

Kweon et al., Submitted Manuscript

Does iTBS and 10-Hz work in the same way?



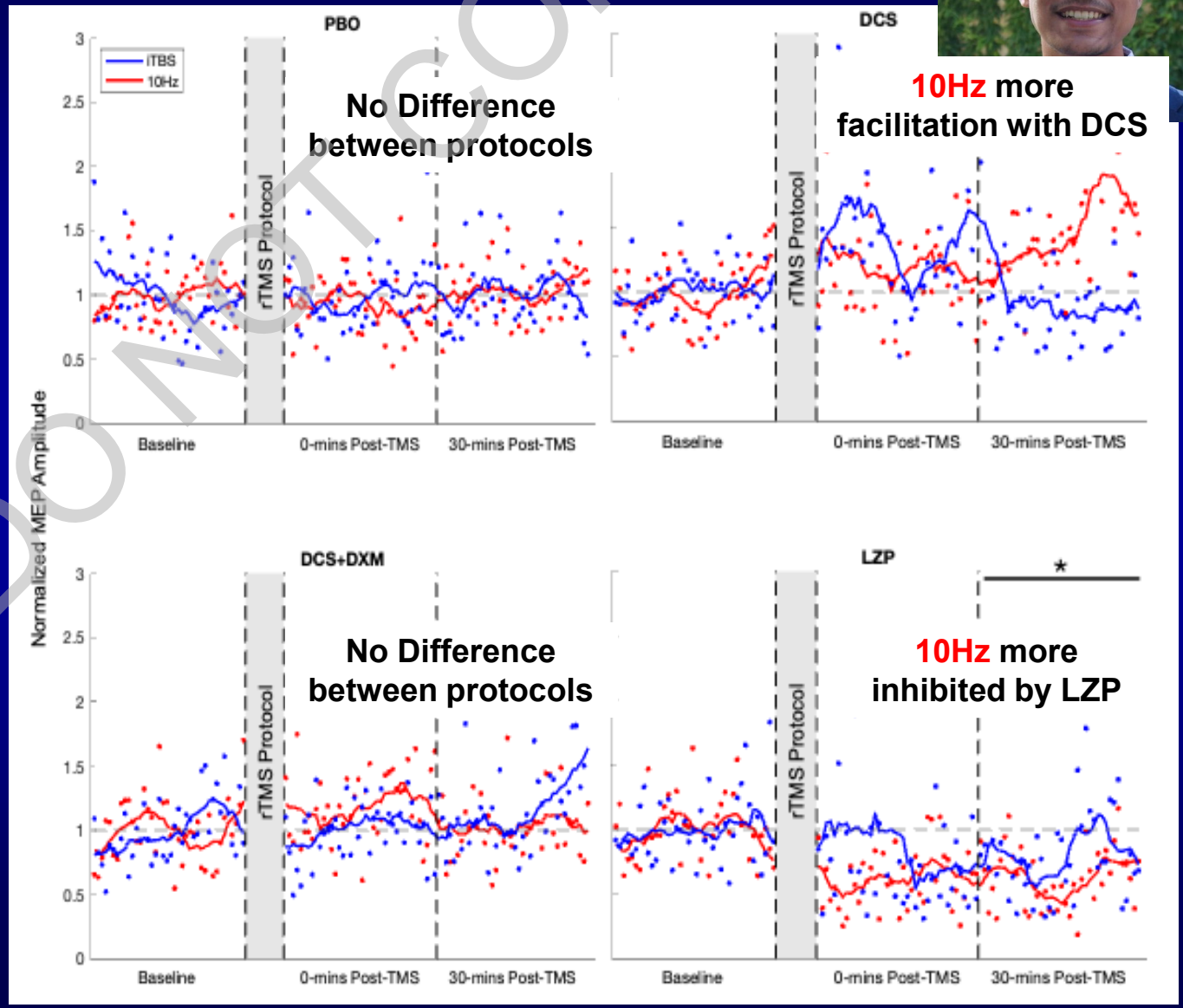
Blumberger et al., *Lancet*, 2018



Ganesh et al., Revised Manuscript Submitted

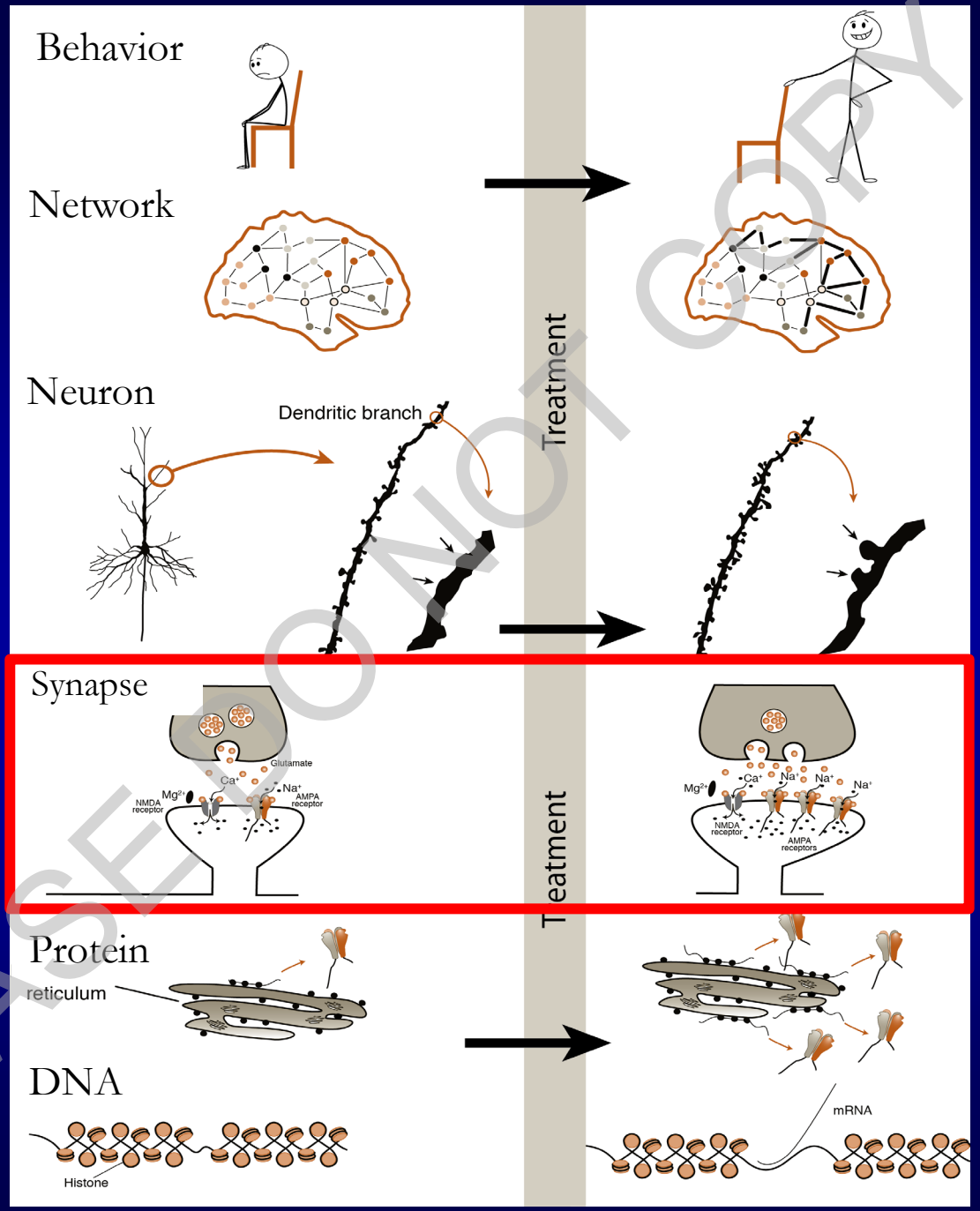
Does iTBS and 10-Hz work in the same way?

- DCS enhances 10-Hz > iTBS:
  - Partial occlusion?
- 10-Hz more inhibited by iTBS:
  - iTBS removes GABARs?
  - iTBS LTP compensates?



Ganesh et al., *TMS*, 2025

Does this Translate to Clinical Improvements?



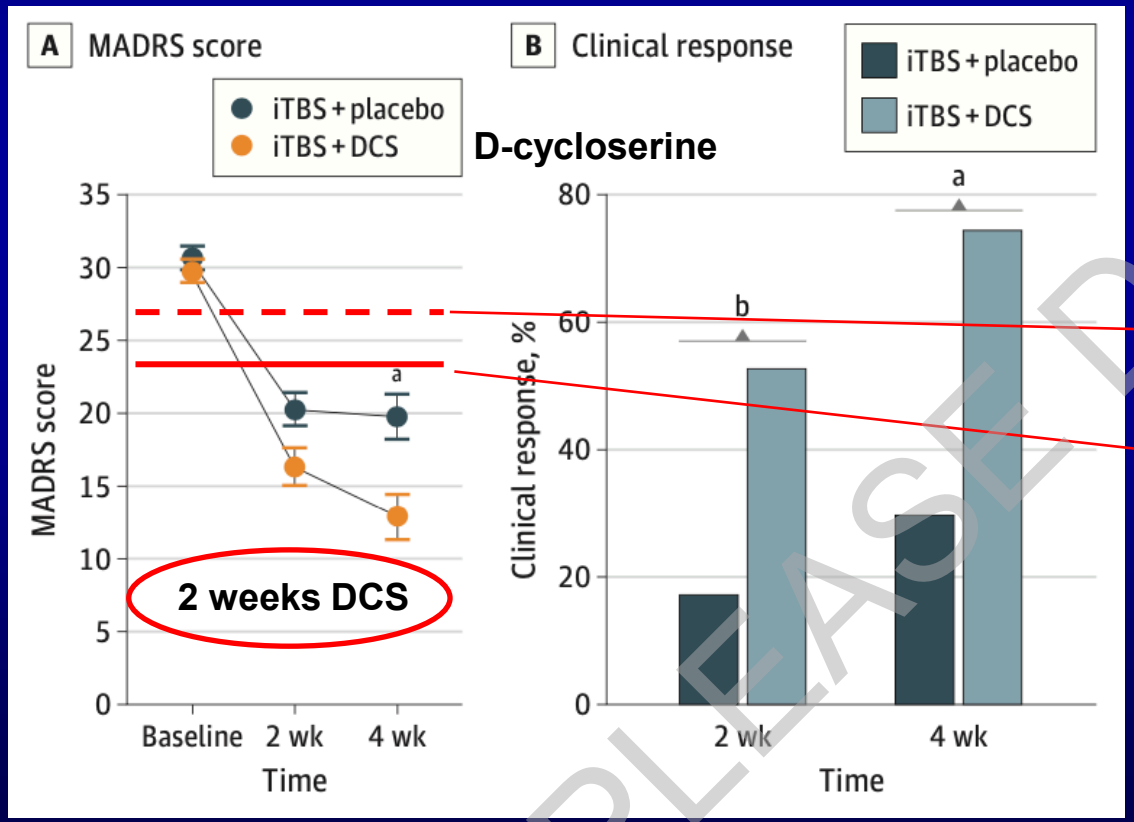
Brown, Higgins & George, *Neuromodulation*, 2022

iTBS
600 pulses
80%
5/50Hz, 2/8 sec
Beam F3

What does Synaptic Plasticity have to do with Clinical TMS?

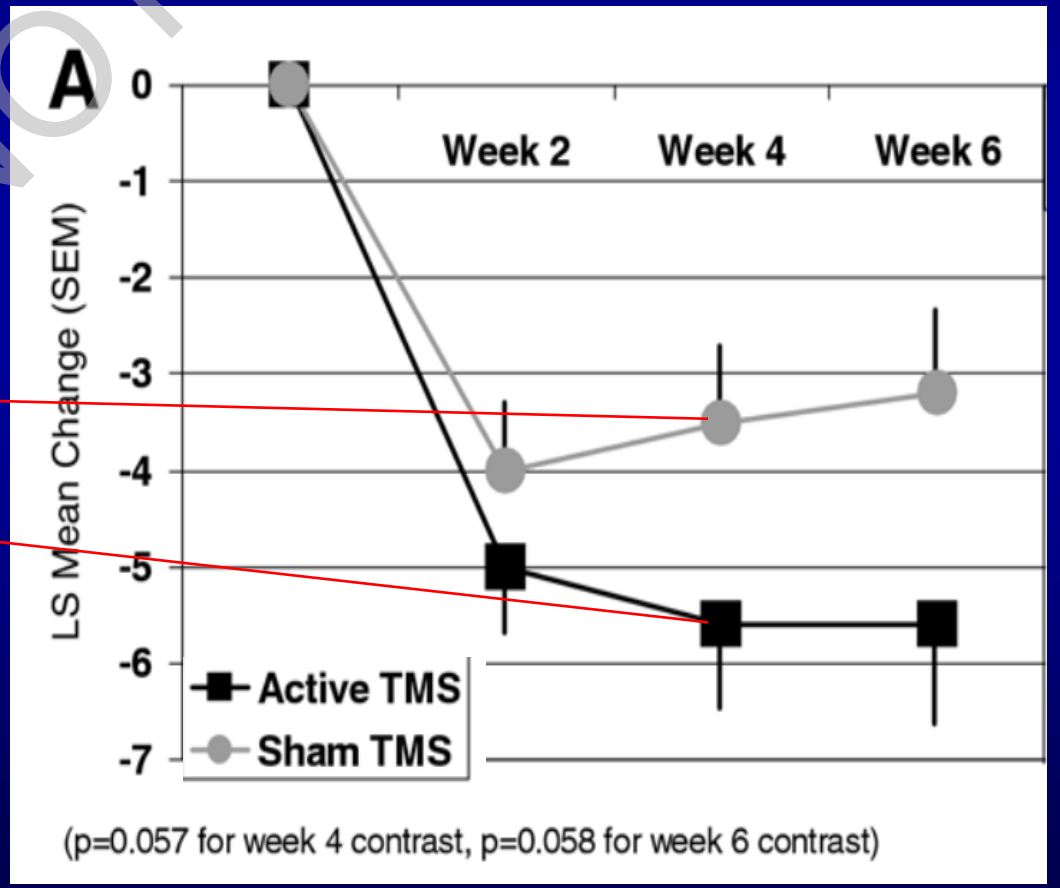
Boosting Synaptic Plasticity Improves Clinical TMS Efficacy

10-Hz
3000 pulses
120%
4/26 sec duty cycle
5cm targeting



Cole et al., *JAMA Psych*, 2022

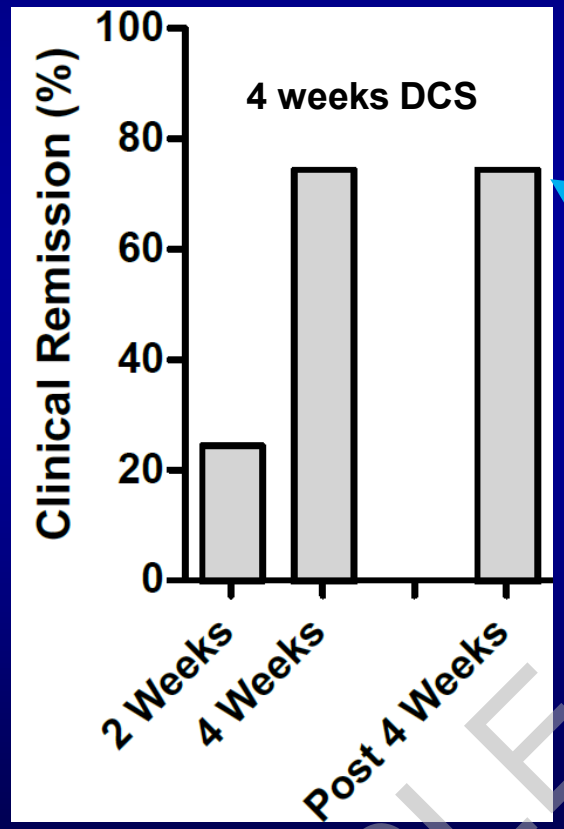
Pivotal TMS Trial



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

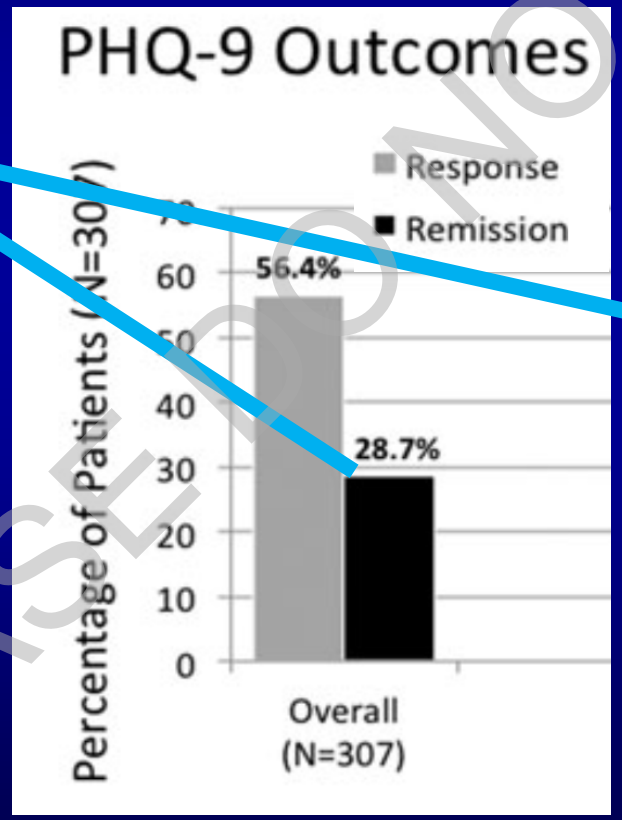
What does Synaptic Plasticity have to do with Clinical TMS? (Naturalistic)

4 weeks:
75% Remission



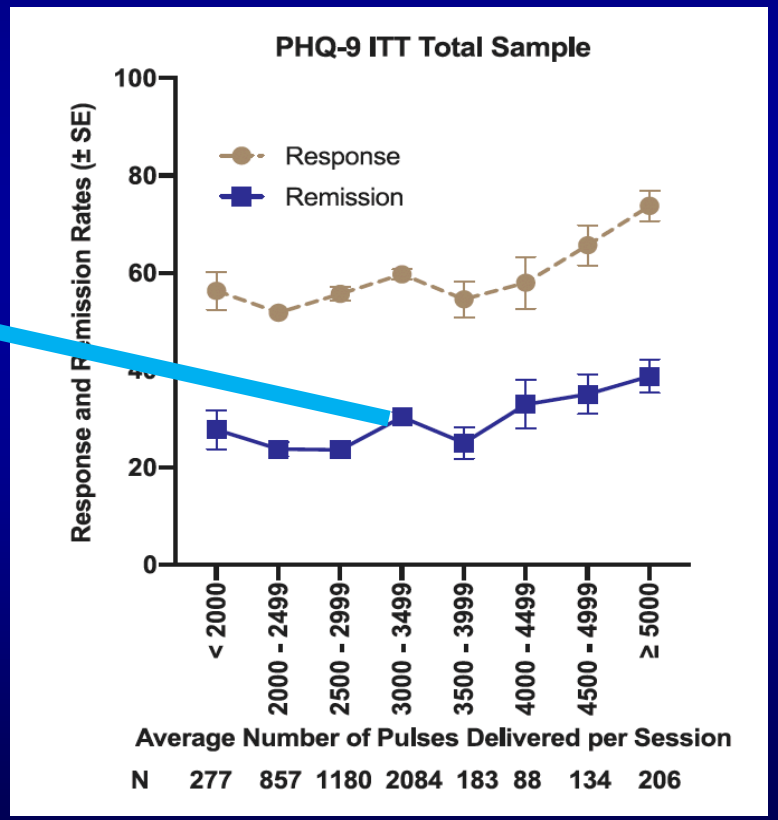
DeMayo et al., *J Affect Dis*, 2025

6+ weeks:
29% Remission



Carpenter et al., *Depress Anxiety*, 2012

6+ weeks:
~30% Remission



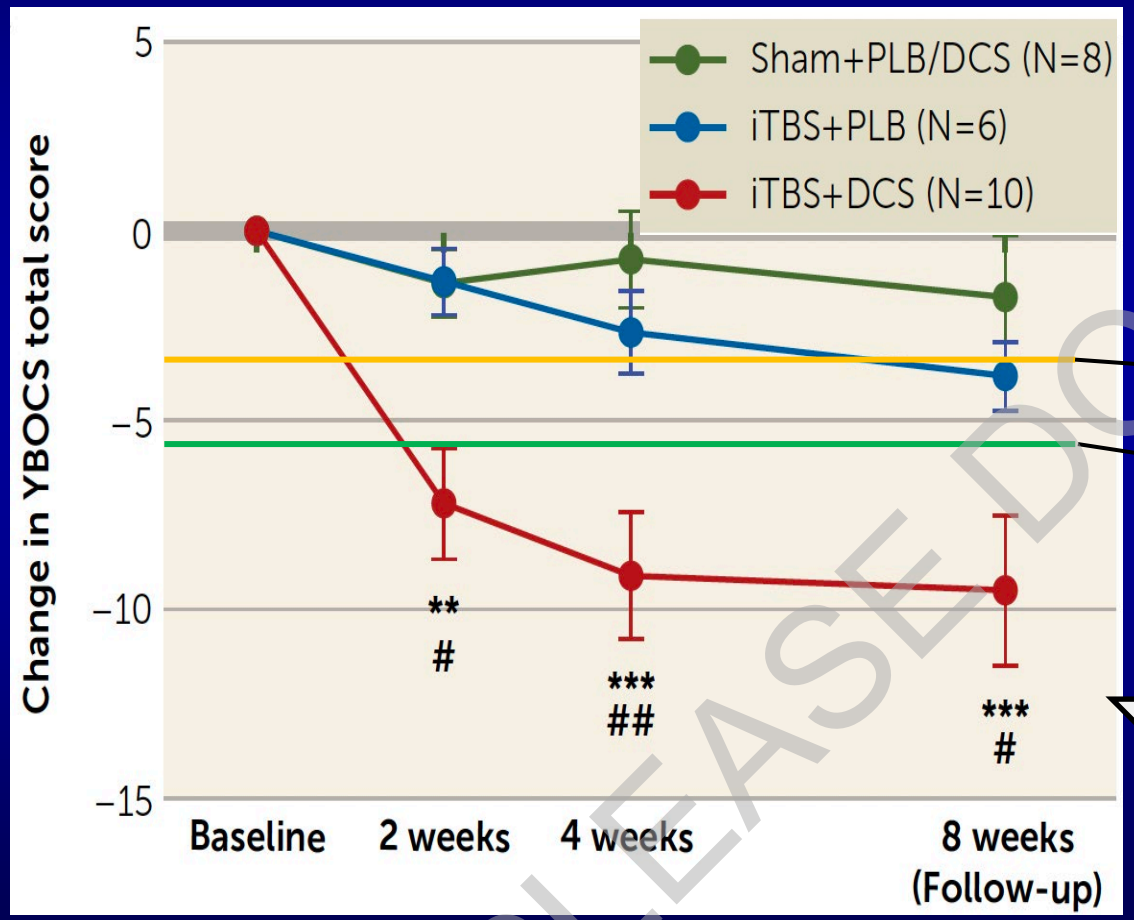
Sackeim et al., *J Affect Dis*, 2020

What does Synaptic Plasticity have to do with Clinical TMS? For OCD

YBOCS Δ: 8

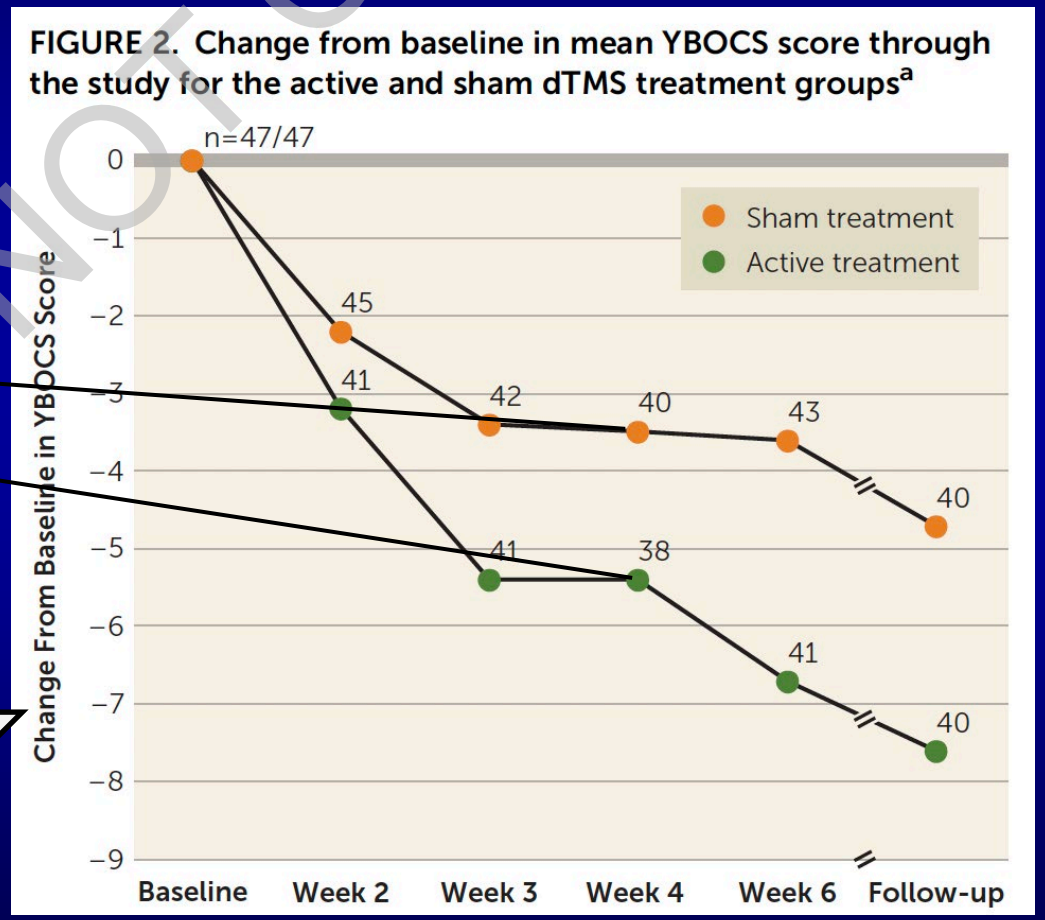
DCS v Active Δ: 6

YBOCS Δ: 2



McGirr et al., *AJP*, 2025

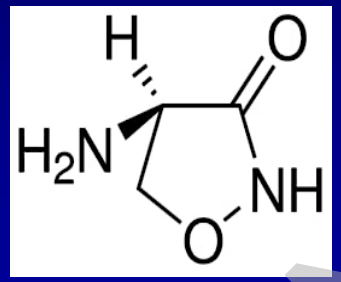
Improvement



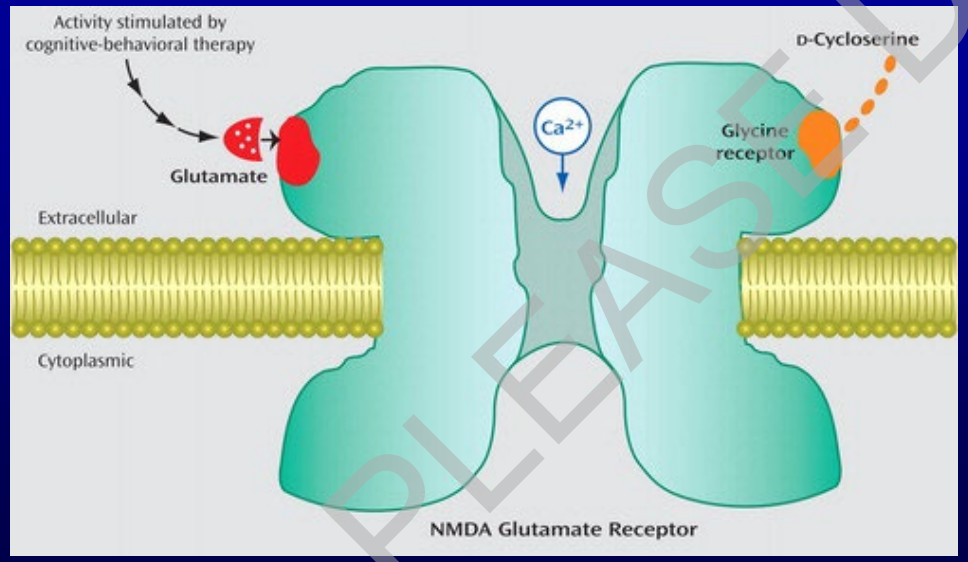
Carmi et al., *AJP*, 2018

Why d-cycloserine?

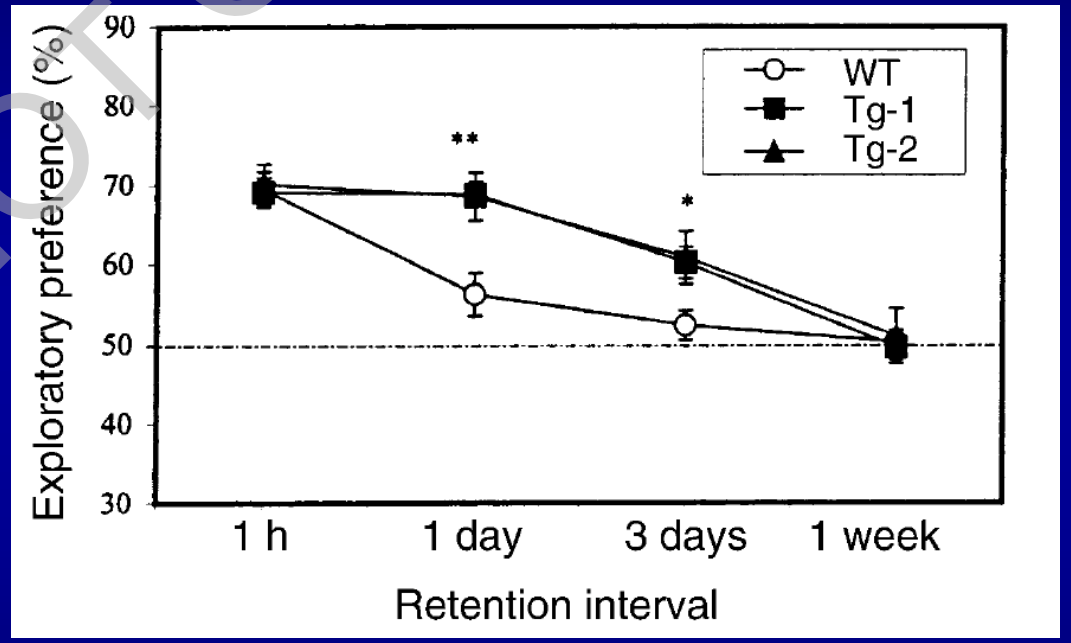
- FDA-approved for Tuberculosis
- FDA-approved for Cystitis



- NMDA receptor partial agonist (when <250mg) (Review: Schade et al., *Int J Neuropsychopharm*, 2016)

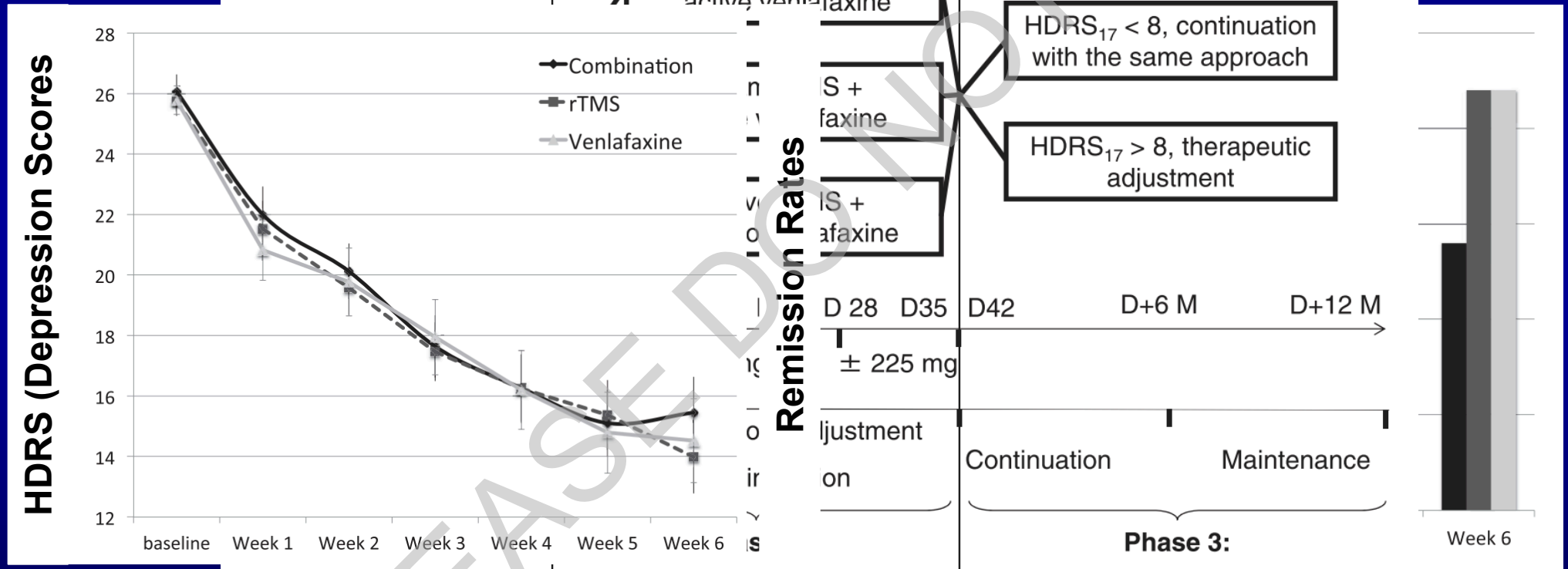


Why the NMDA receptor?



Tang et al., *Nature*, 1999

If NMDAR makes TMS better, what about an antidepressant?

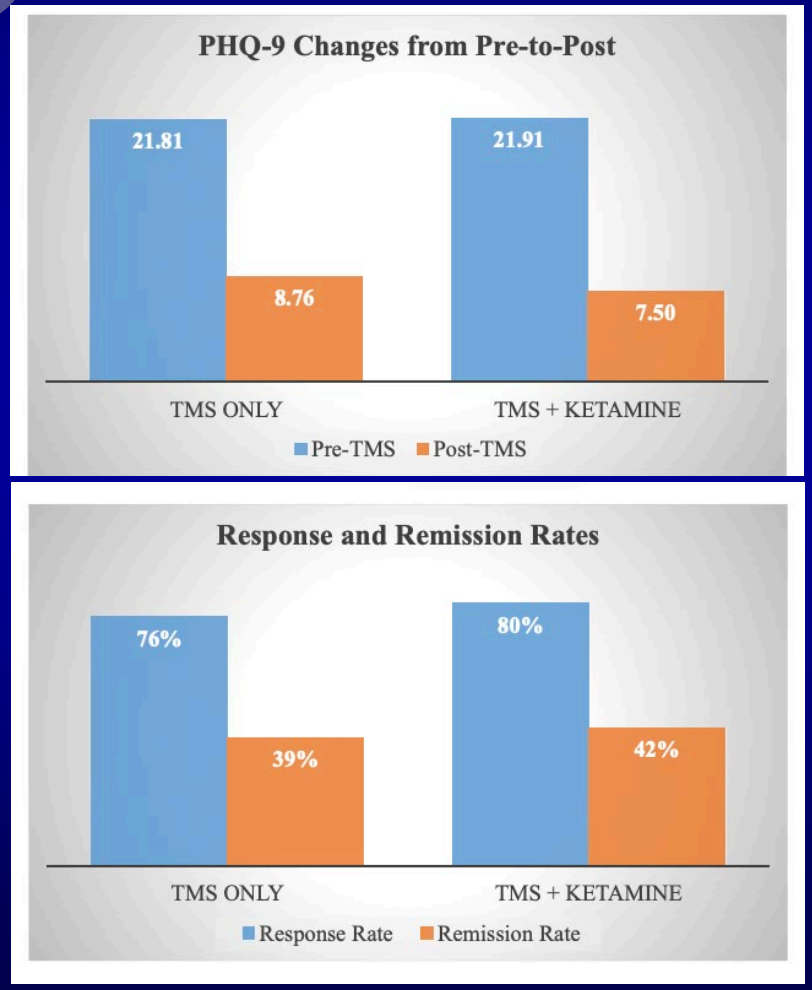


Brunelin et al., *Brain Stim*, 2014

NMDA?? What about (Ketamine) + rTMS?

- Systematic Review (Debowska, *Front Neurosci*, 2023):
  - No Prospective Studies!
  - 11 studies reported
    - *n* of 1 Case studies: 7
    - 4 retrospective studies: total *n* of 53
      - 1-Hz x2 studies (short-term and 2-year follow up)
      - 10-Hz x1 study
      - All report improvement
      - 1 comparative study

36 TMS (H-coil) +/- 6 IV ketamine treatments

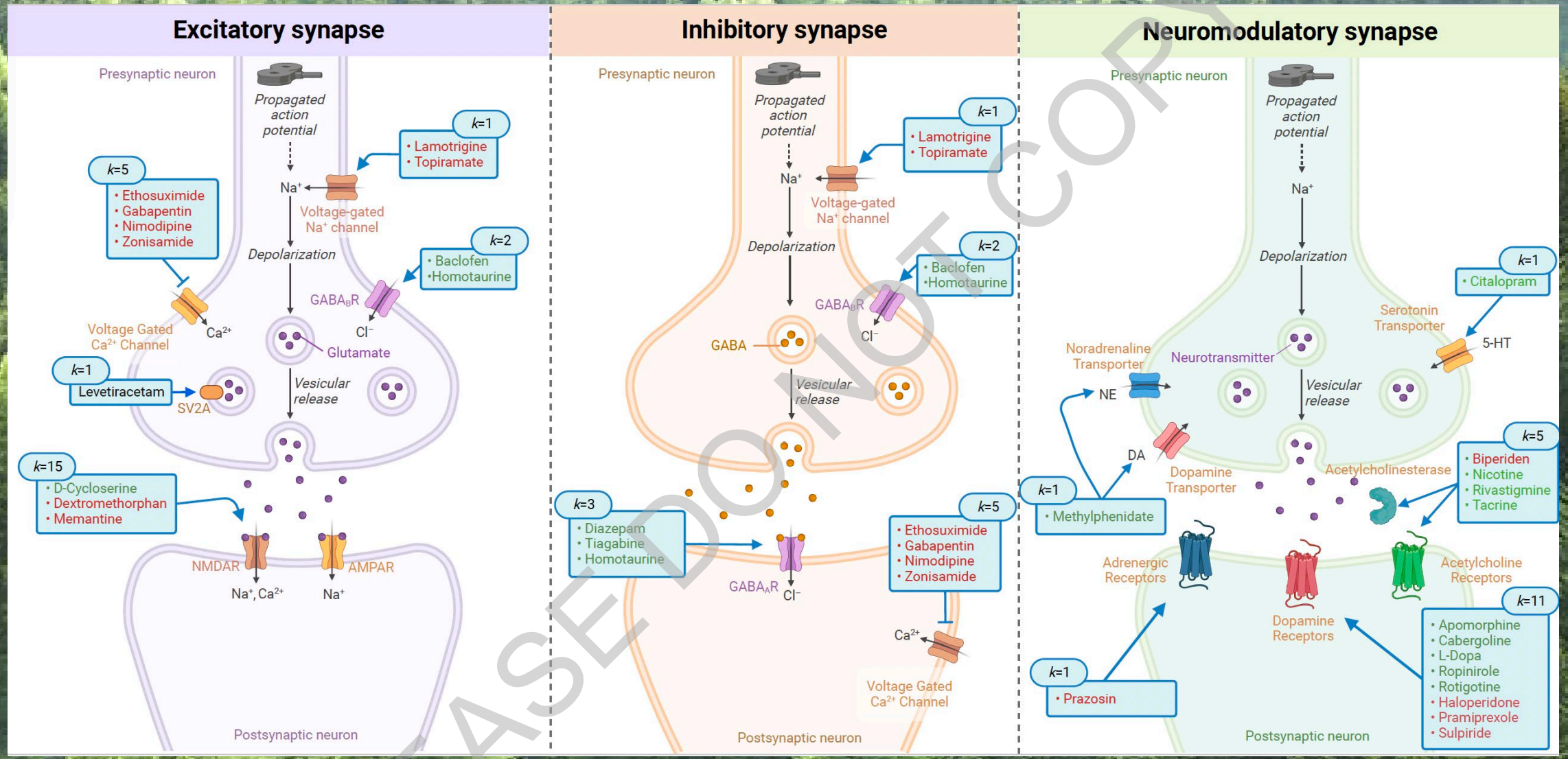


Shanok et al., *Psychopharm*, 2024

Recap

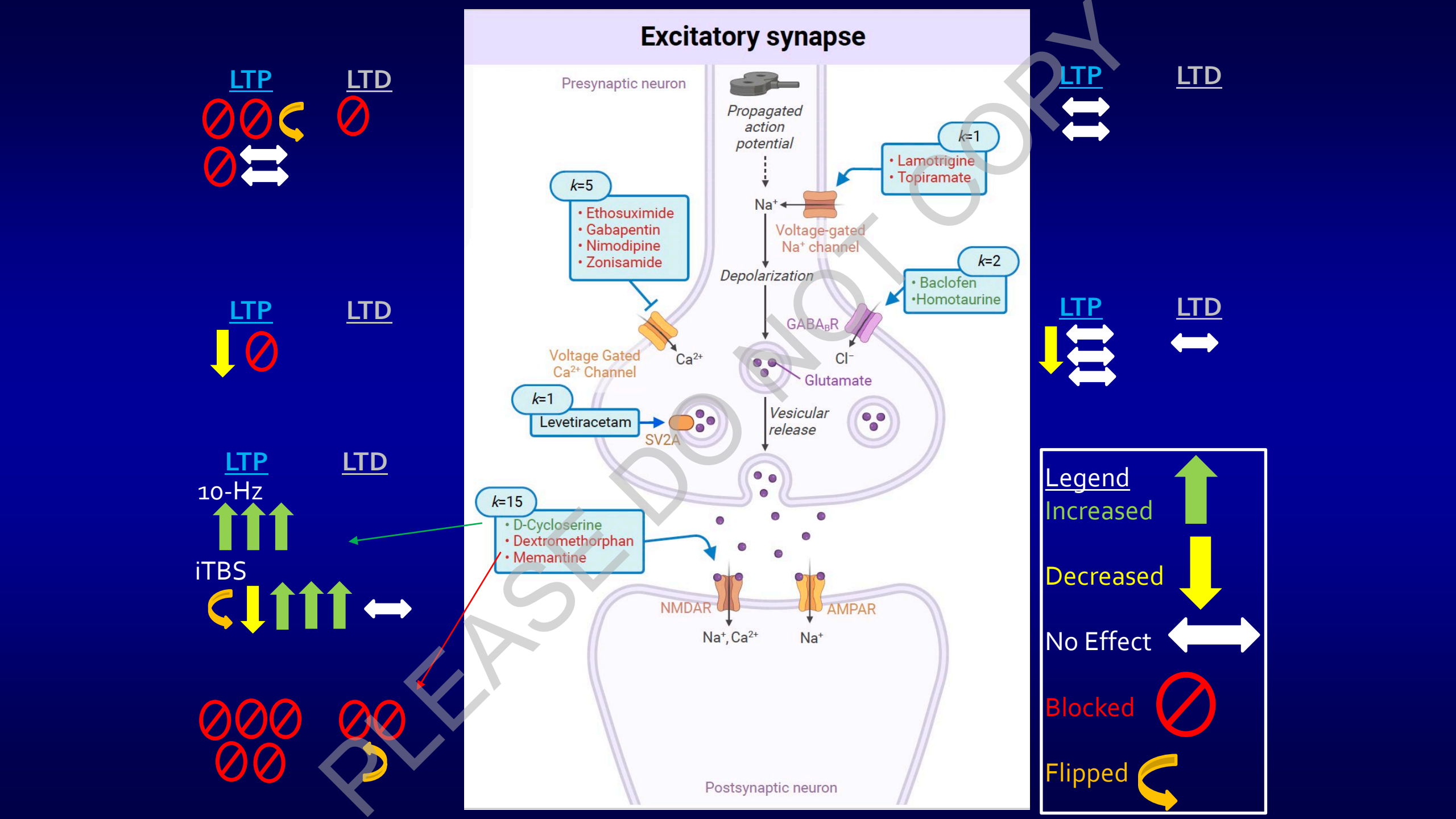
- NMDAR agonist, d-cycloserine, enhances TMS effectiveness
  - …Through NMDA receptor activation
  - …Which is central to LTP
  - …suggests TMS works through LTP.
  - May be Trandiagnostic!
- Neither SNRI (venlafaxine) nor ketamine helped TMS.

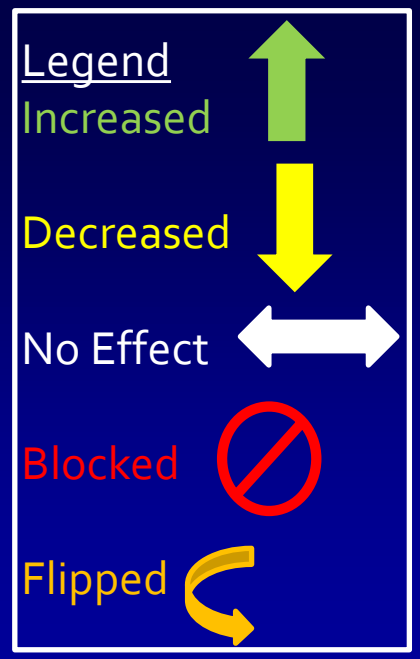
- Any other augmentation candidates??

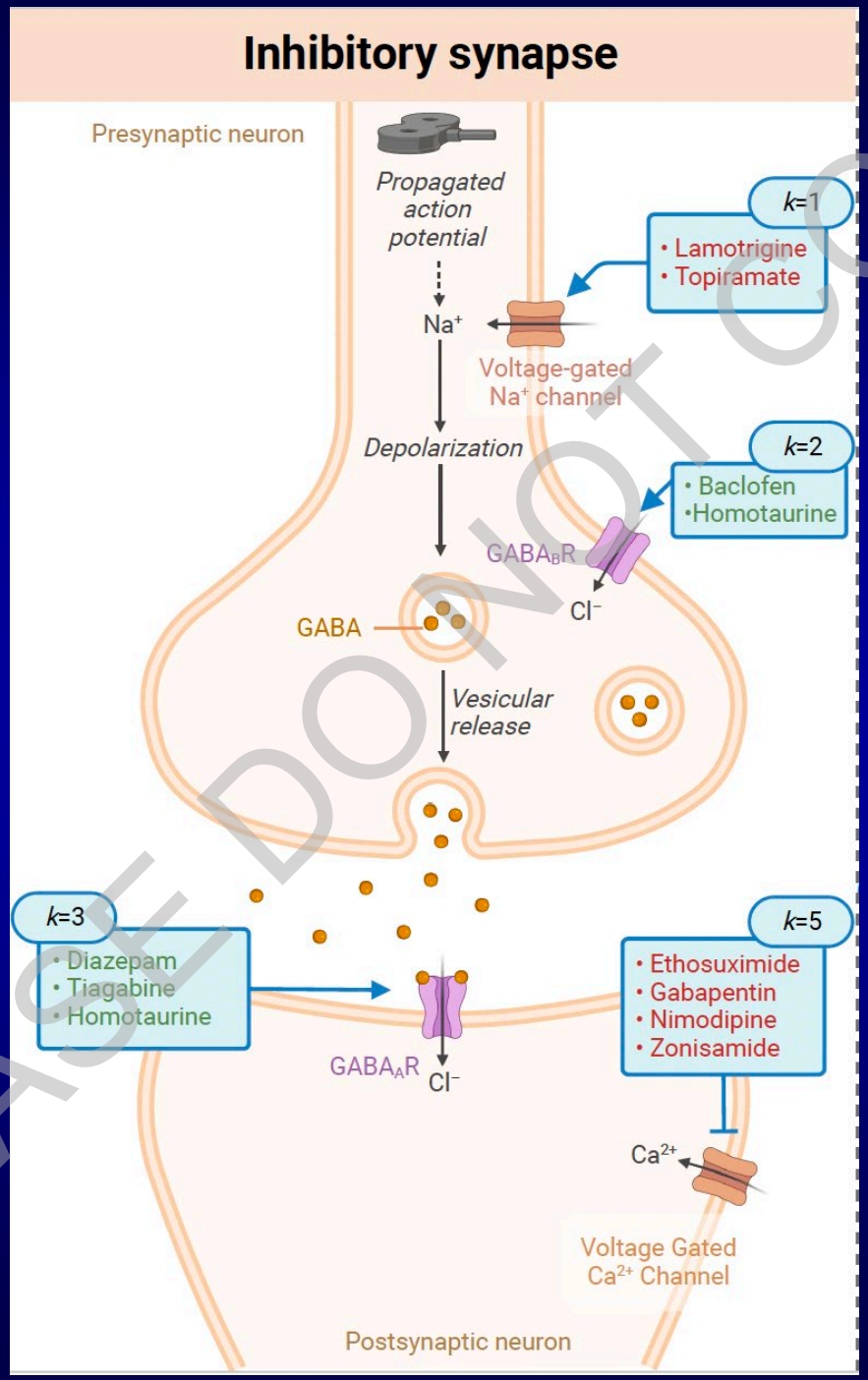


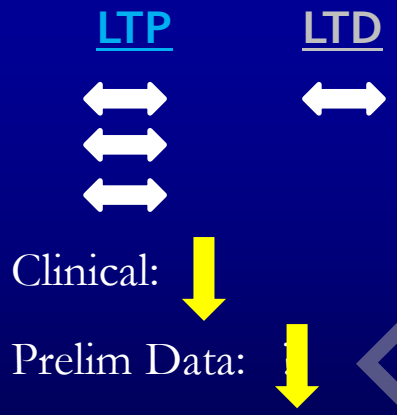
Sohn et al., *J Psychiatry Neurosci*, 2024

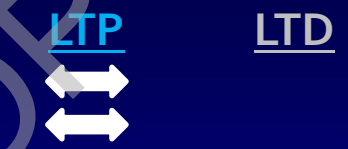
Survey of Pharmacologic Enhancement

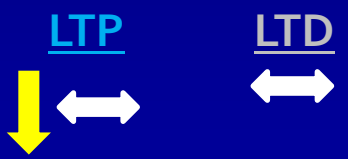

LTP
LTD
LTP
LTD
LTP
LTD
LTP
LTD
10-Hz
iTBS
LTP
LTD
LTP
LTD
Excitatory synapse
Presynaptic neuron
Propagated action potential
k=1
• Lamotrigine
• Topiramate
k=5
• Ethosuximide
• Gabapentin
• Nimodipine
• Zonisamide
Na+
Voltage-gated Na+ channel
Depolarization
k=2
• Baclofen
•Homotaurine
GABA$_B$R
Voltage Gated Ca2+ Channel
Ca2+
Cl−
Glutamate
k=1
Levetiracetam
SV2A
Vesicular release
k=15
• D-Cycloserine
• Dextromethorphan
• Memantine
NMDAR
AMPAR
Na+, Ca2+
Na+
Postsynaptic neuron
Legend
Increased
Decreased
No Effect
Blocked
Flipped
PLEASE DO NOT COPY

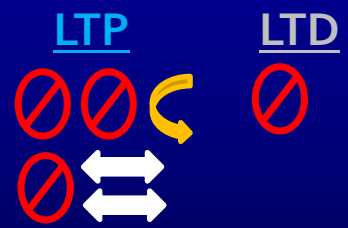






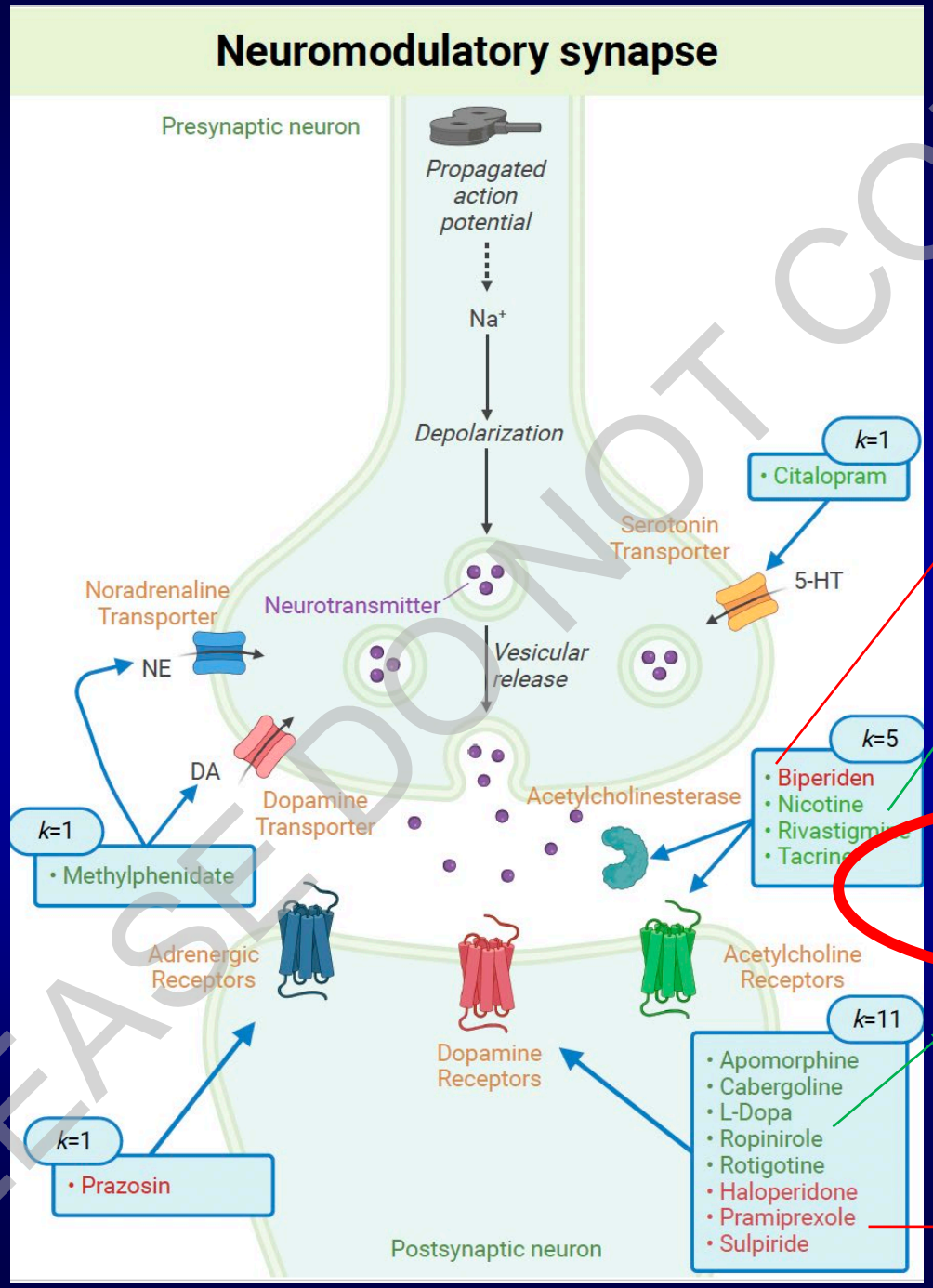






Legend
Increased
Decreased
No Effect
Blocked
Flipped

Neuromodulatory synapse



LTP LTD

LTP LTD

LTP LTD

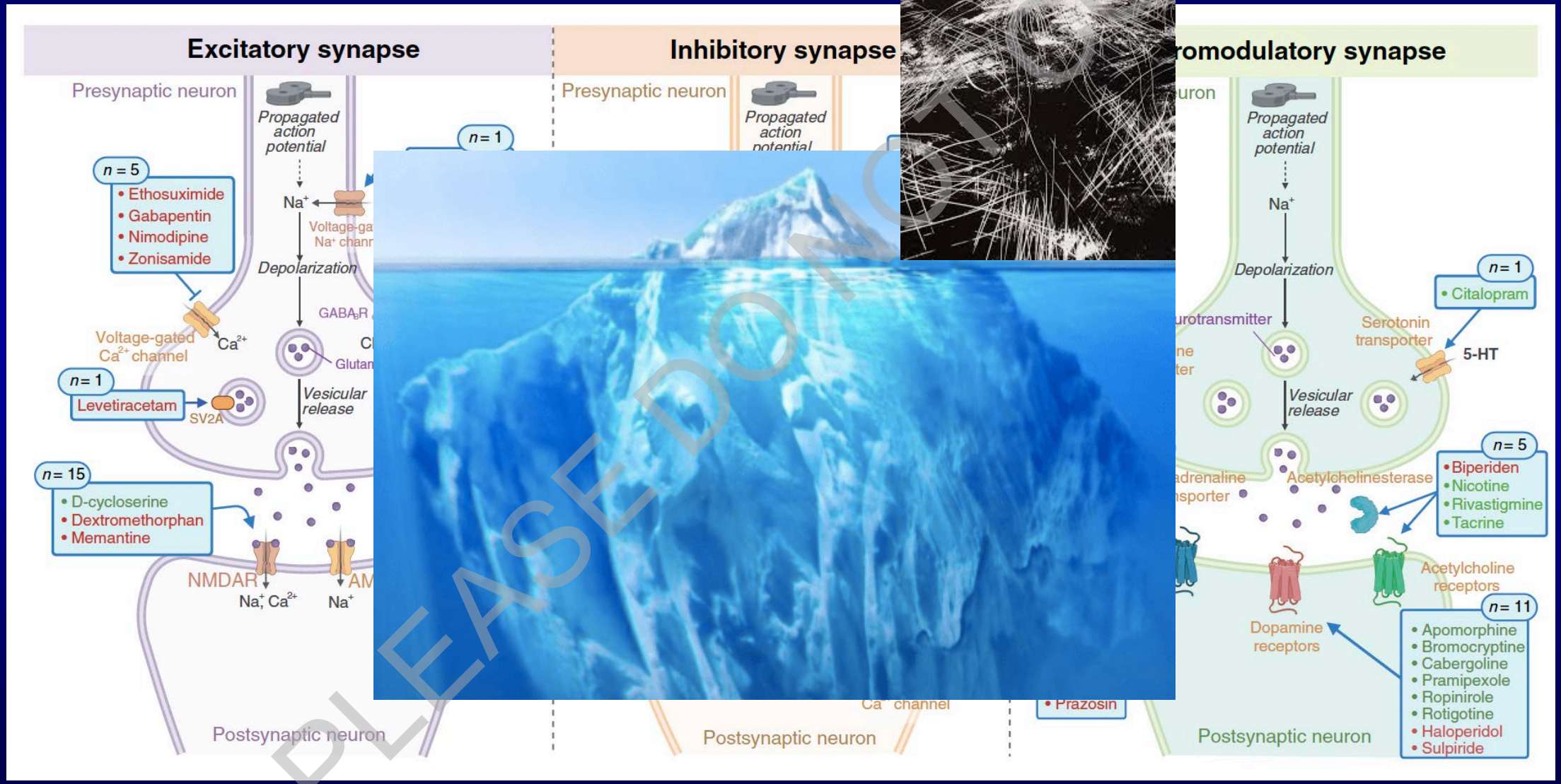
LTP LTD

LTP LTD

Clinical:

Low: High:

Where are we Headed?

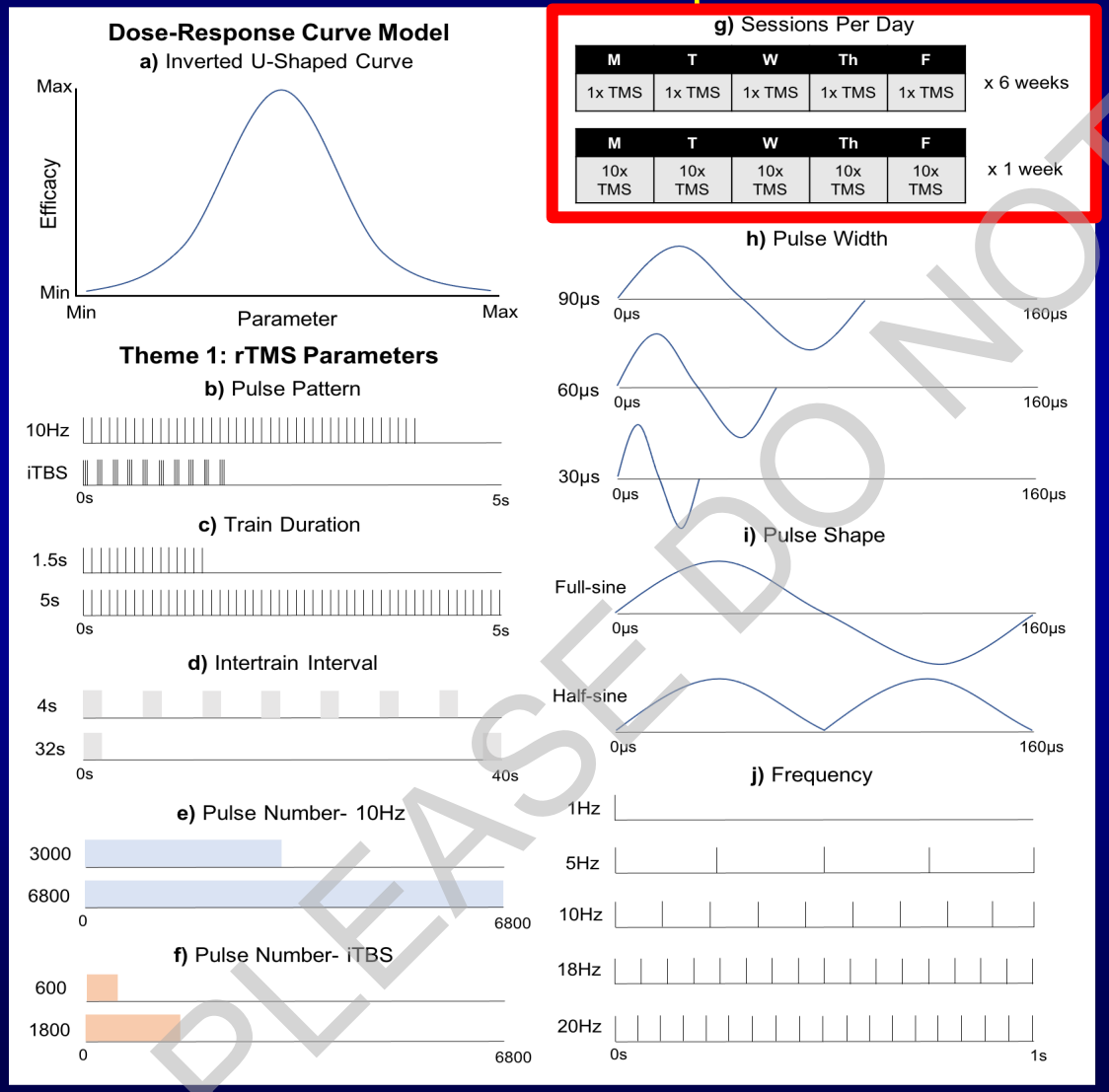


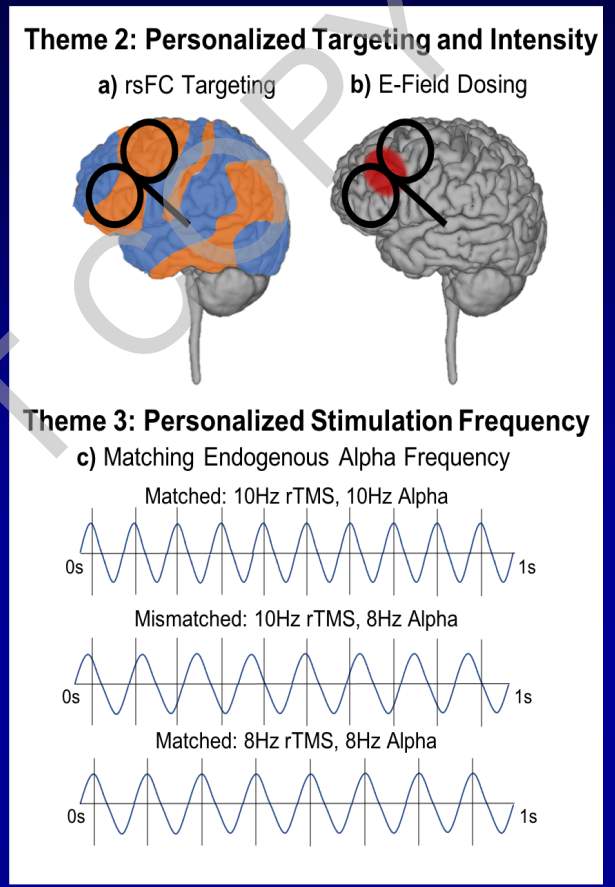
To the Future!

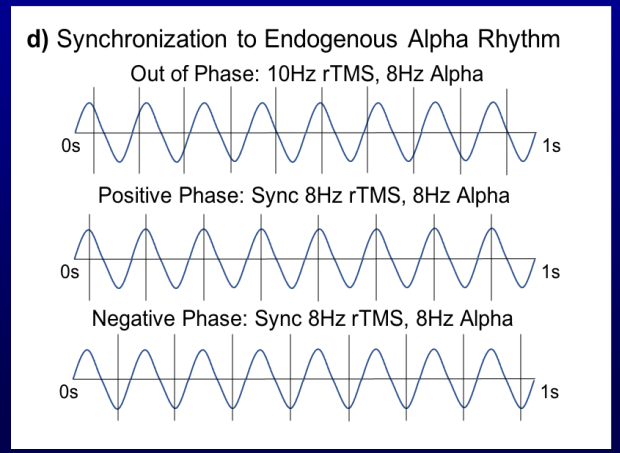
Potential

The ~~Problem~~ of TMS'

Infinite Parameter Space







Caulfield & Brown, *Front. Psych,* 2022

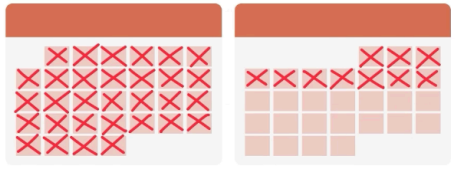
Accelerated TMS

Mass General Brigham McLean

HARVARD MEDICAL SCHOOL

Consultation — 6+ Weeks

Approximately 1-week for insurance approval — Daily treatments



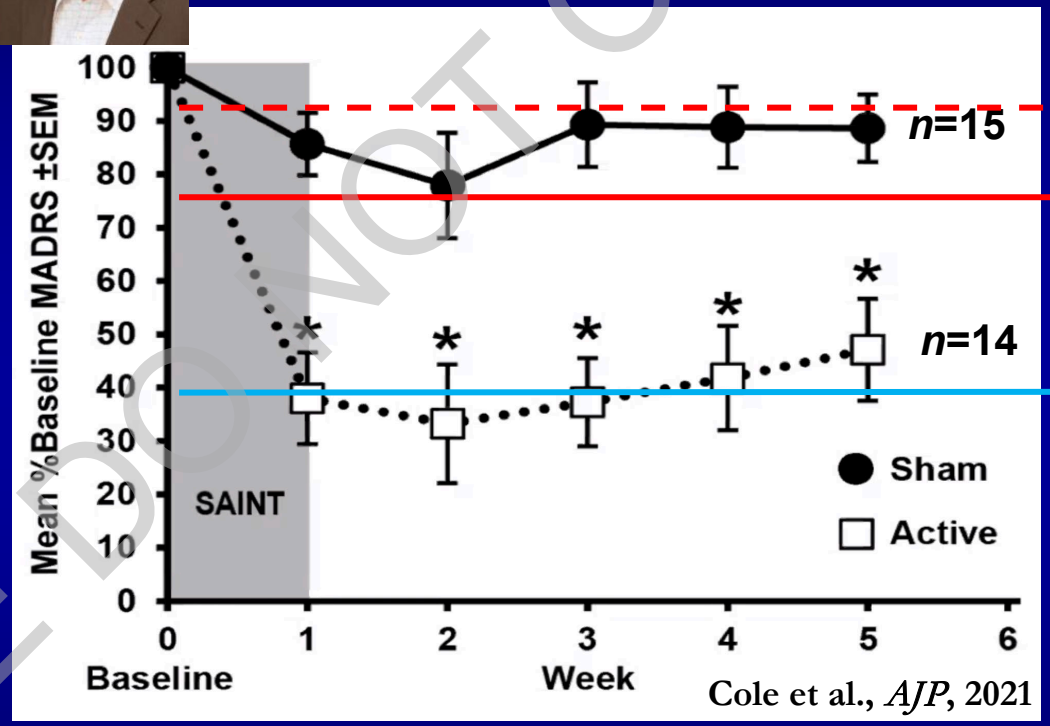
Mass General Brigham McLean

HARVARD MEDICAL SCHOOL

Consultation — 6+ Weeks — OR — Up to 5 days

Approximately 1-week for insurance approval — Daily treatments — Up to 10 treatments per day

Day 1	Day 2	Day 3	Day 4	Day 5
TMS session	TMS session	TMS session	TMS session	TMS session
TMS session	TMS session	TMS session	TMS session	TMS session
TMS session	TMS session	TMS session	TMS session	TMS session
TMS session	TMS session	TMS session	TMS session	TMS session
TMS session	TMS session	TMS session	TMS session	TMS session
TMS session	TMS session	TMS session	TMS session	TMS session
TMS session	TMS session	TMS session	TMS session	TMS session
TMS session	TMS session	TMS session	TMS session	TMS session
TMS session	TMS session	TMS session	TMS session	TMS session
TMS session	TMS session	TMS session	TMS session	TMS session



Cole et al., *AJP*, 2021

Sham in Pivotal Trial

Active in Pivotal Trial (20-30 sessions)

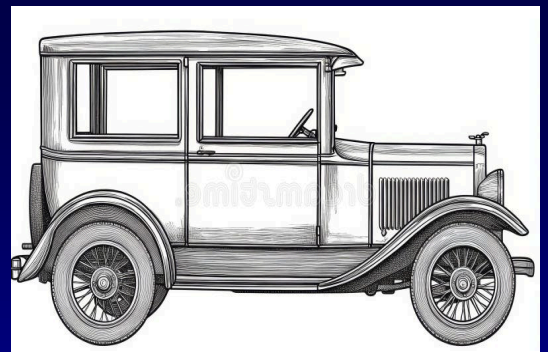
(50 sessions)

71% Response Rate (57% Remission)

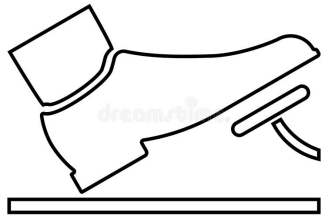
69% Response Rate (46% Remission)

Open-label: 70% Response Rate (*n*=20)

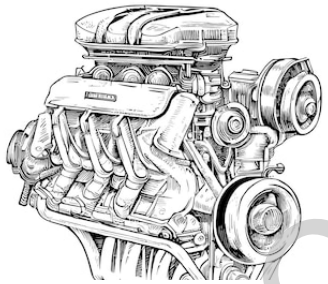
(Comparable to Response rates to 50 daily sessions)



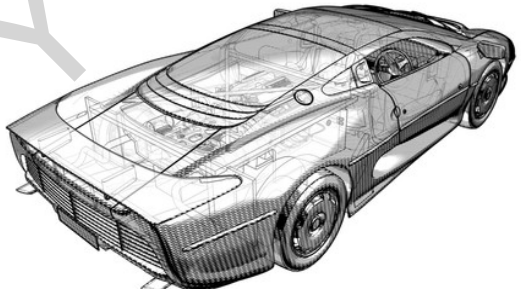
TMS



aTMS

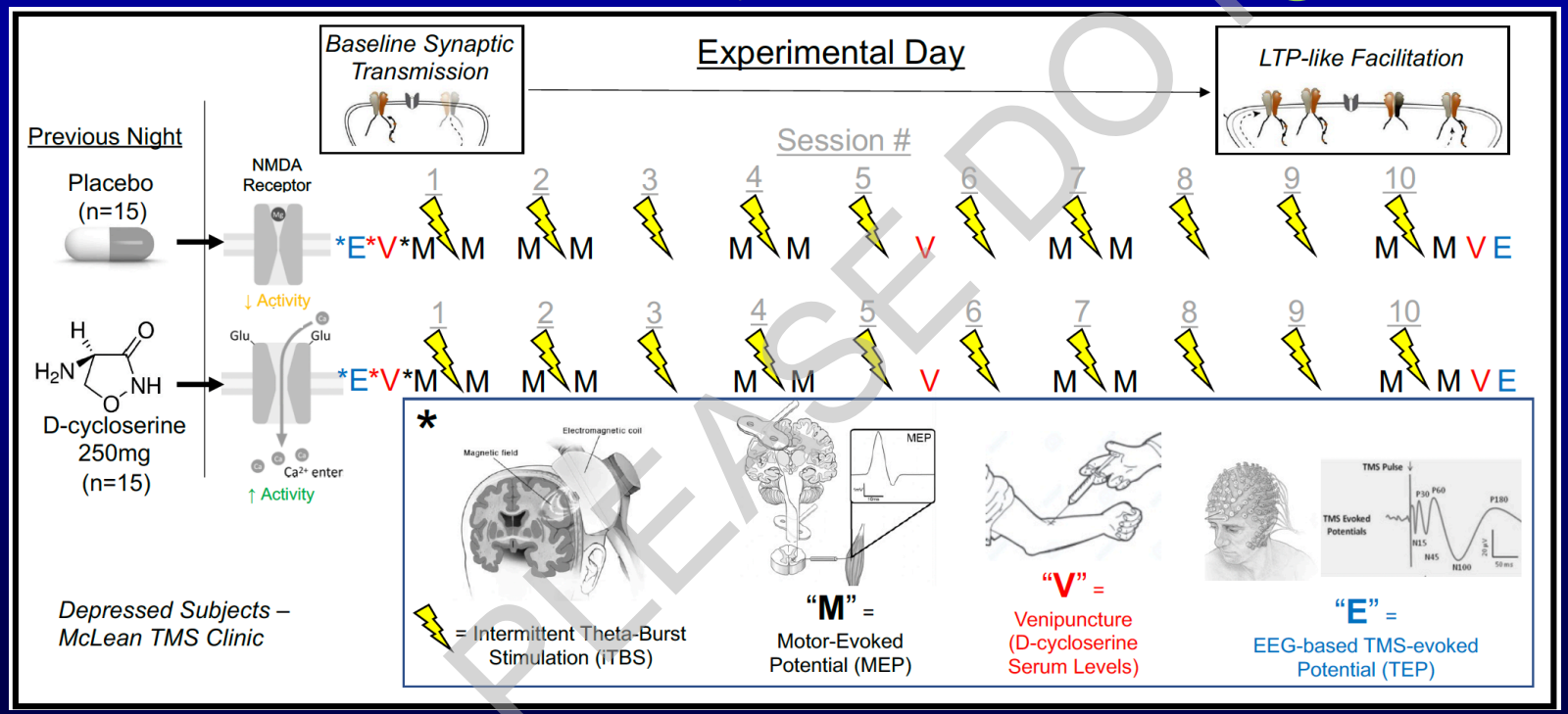


TMS mechanisms



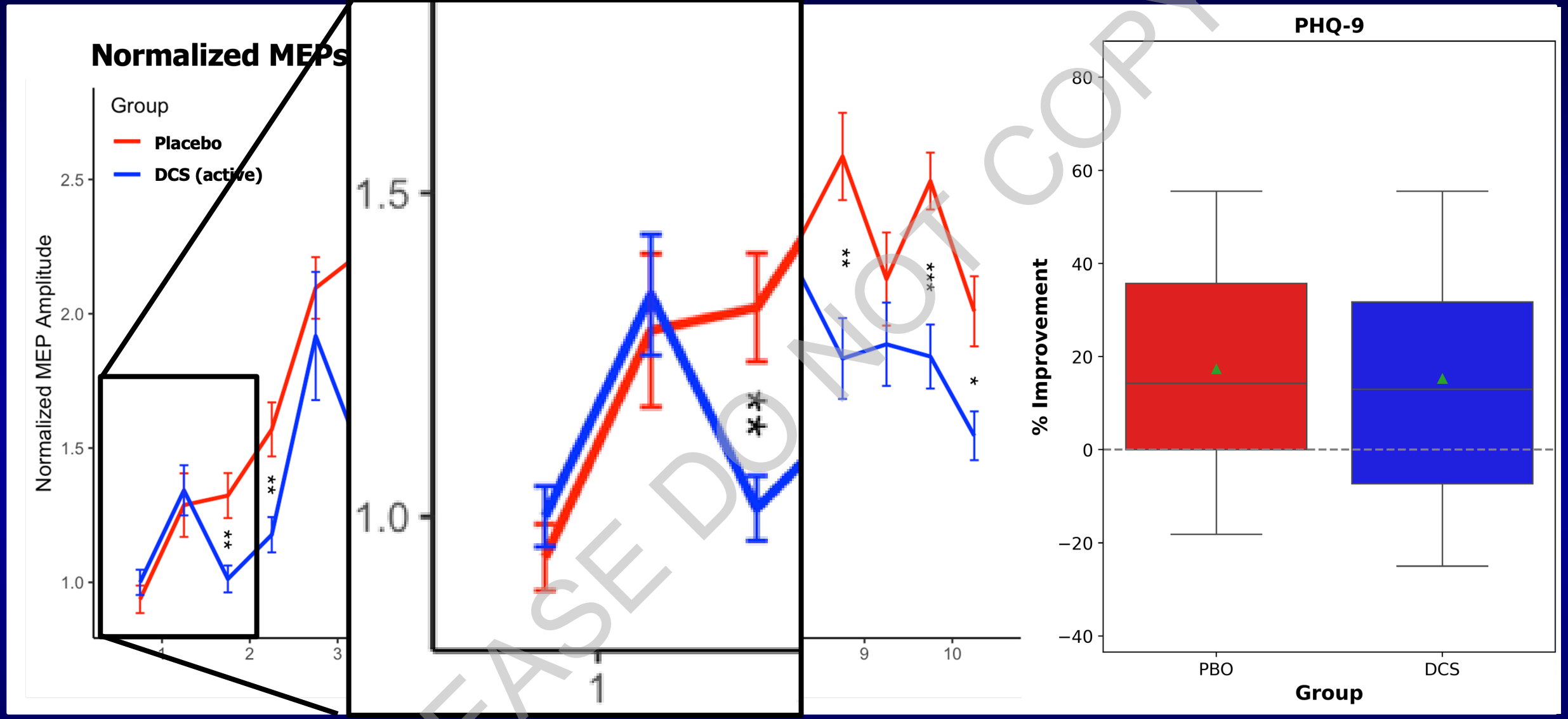
TMS mechanisms clinically applied

What if we Combined the Rapid action of Accelerated TMS with the Enhanced Efficiency of Mechanism-guided Augmentation of TMS?



Hypothesis:

Null Hypothesis:



D-cycloserine had lower MEPs than Placebo

D-cycloserine did NOT improve clinical response

Day 1
iTBS 600
25 minute ISI
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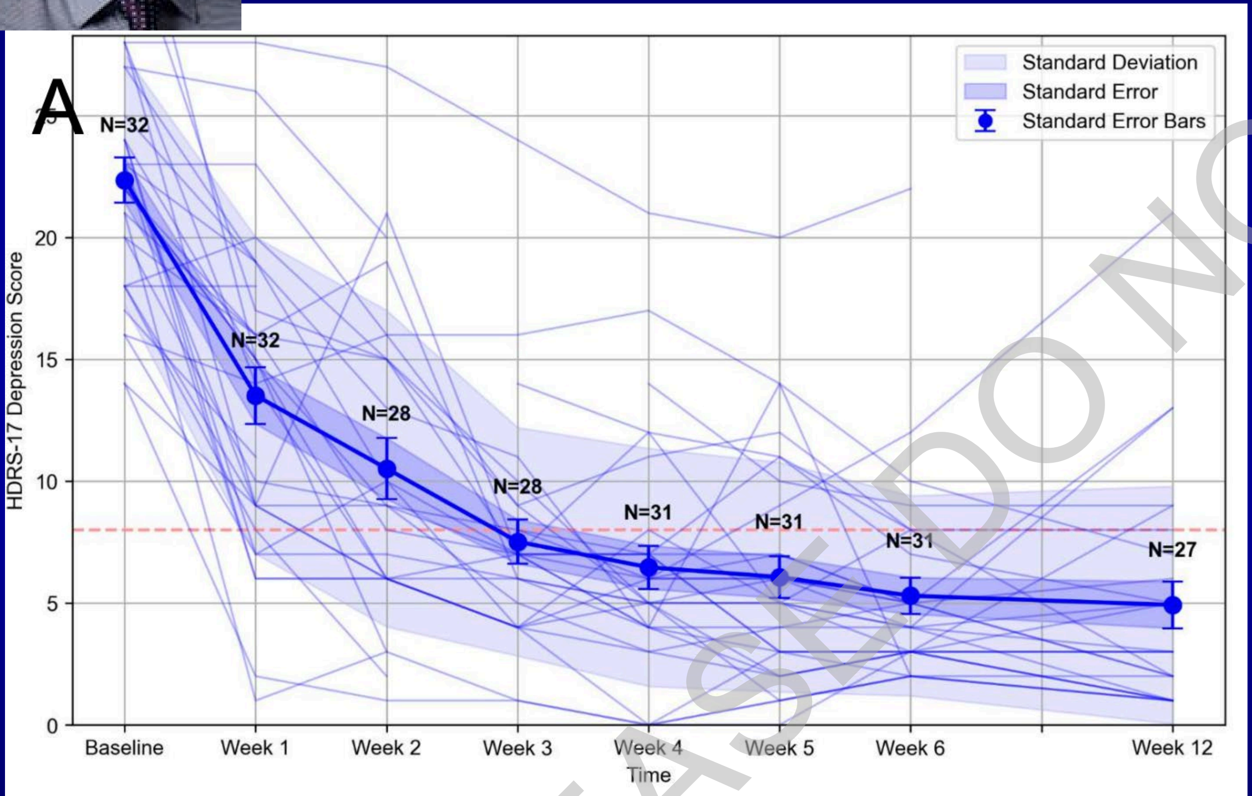
In the meantime…



Vaughn et al, *TMS* 2025

80-90% remission rates @ 3 months –
After 1 day of treatment

What Happened?

- One key difference:
  1800 pulses vs 600 pulses
- 600 v 900 pulses: more pulses= more robust plasticity
- Only weak LTP protocols enhanced by DCS (Vestring 2024) = Occlusion
- Our DARPA-funded 3-day study 1800 pulses w/ similar effects

Take Home Points – TMS & Pharmacology

- Daily TMS with D-cycloserine: Not yet FDA-cleared: NMDAR agonism (d-cycloserine) has RCT and open-label and physiology data suggesting benefit (Only RCT)
- One-day accelerated TMS with D-cycloserine: Naturalistic Case Series
- Controlled trials: Ketamine, SNRI = no benefit when added to TMS.
- Naturalistic Observations:
  - Antidepressants and mood stabilizers seem to help overall TMS response (nothing prospective)
  - Stimulants (incl caffeine) could help TMS (nothing prospective)
  - Benzos could impair TMS (nothing prospective)
  - Marijuana could be harmful with TMS
  - Augmenting Accelerated TMS (Possible!)

Thank You!

Questions?