Harvard TMS Course

Pharmacology and TMS

Joshua C. Brown, MD, PhD

Medical Director | Transcranial Magnetic Stimulation | McLean Hospital

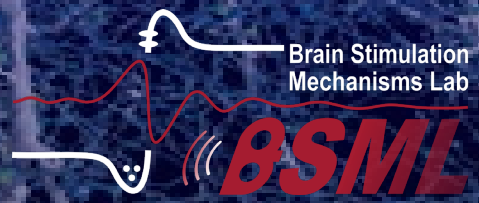
Director of Research | Transcranial Magnetic Stimulation | McLean Hospital

Director | Brain Stimulation Mechanisms Laboratory | McLean Hospital

Assistant Professor | Department of Psychiatry | Harvard Medical School

President-Elect | Clinical TMS Society

Editor-in-Chief | *Transcranial Magnetic Stimulation*



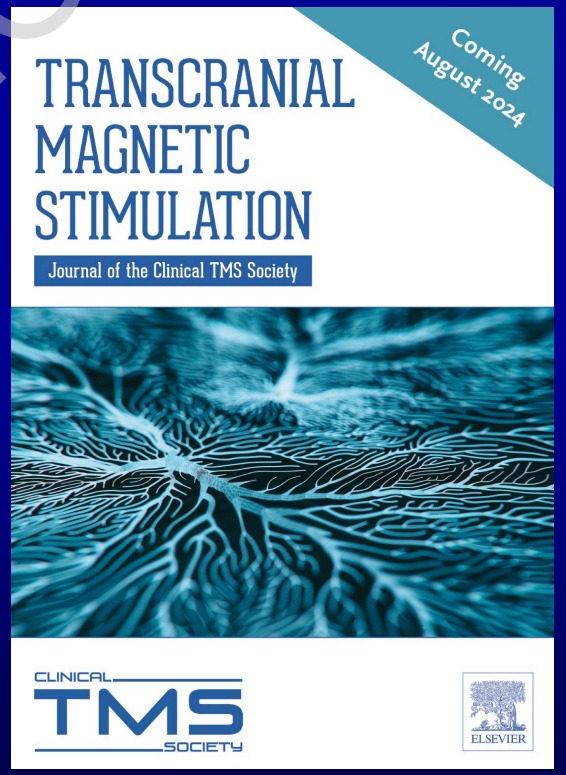
Disclosures

Research support from:

- Cindy & Paul Gamble Fund
- Marlene Zuckerman Fund

Financial support from:

- Editorial Stipend from Elsevier
- Speaking Honoraria



*50% off in 2025

Objectives

1. Recognize the brain is an electrochemical organ.
2. Understand the putative mechanisms of repetitive rTMS.
3. Appreciate how leveraging these mechanisms can enhance rTMS efficacy.
4. Understand the real-world effects of medications on rTMS effectiveness.
   - Know mediator vs modulator
   - Understand chronic effects (including homeostatic plasticity)

How The Brain Works

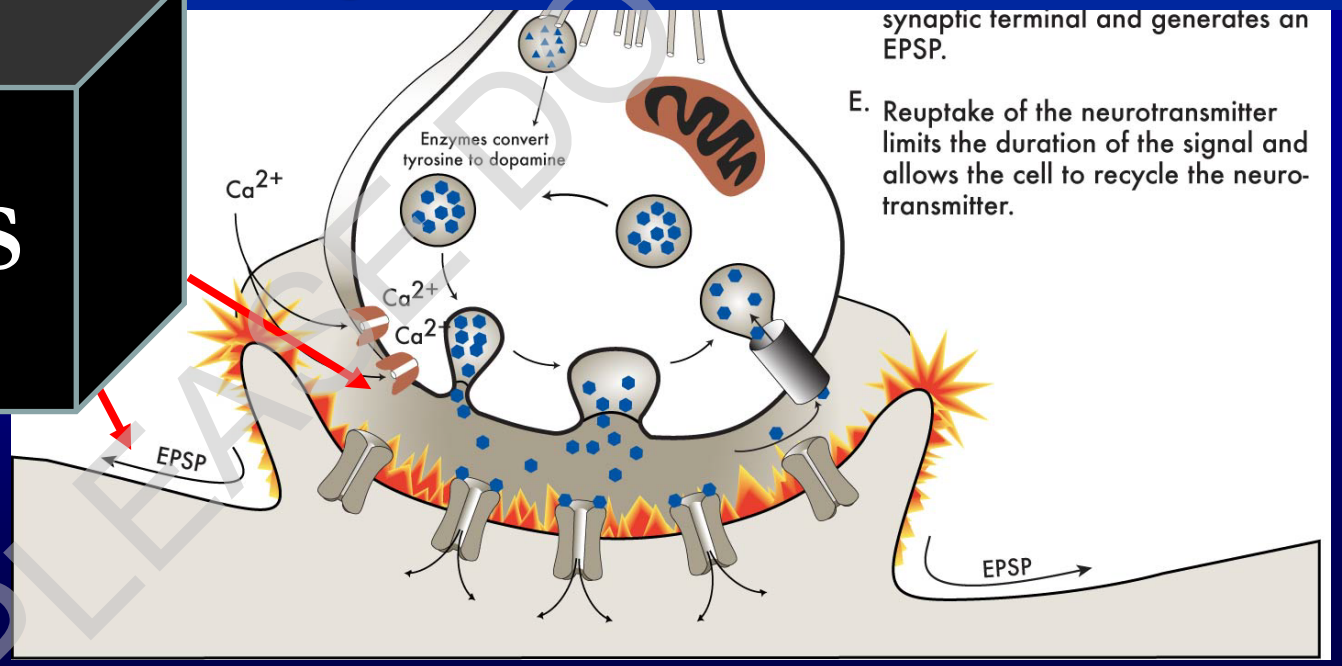
Electro Chemical

The Brain is an Electrochemical Organ

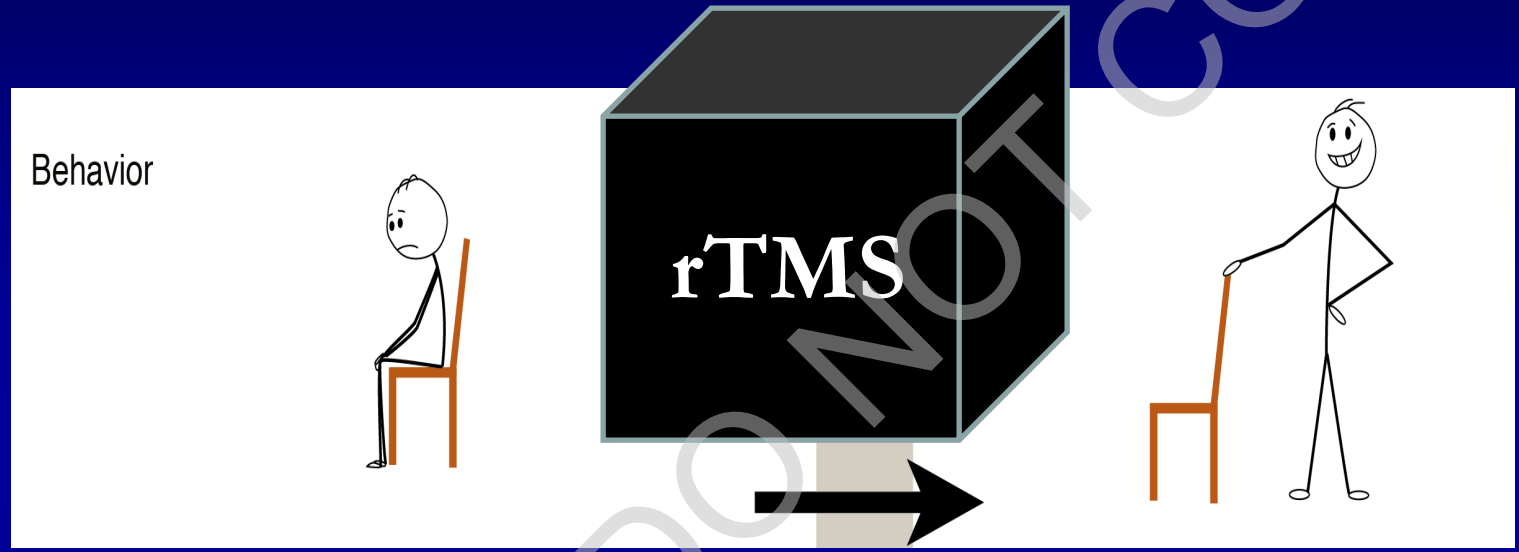
Electricity is the Currency of the Brain

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

rTMS

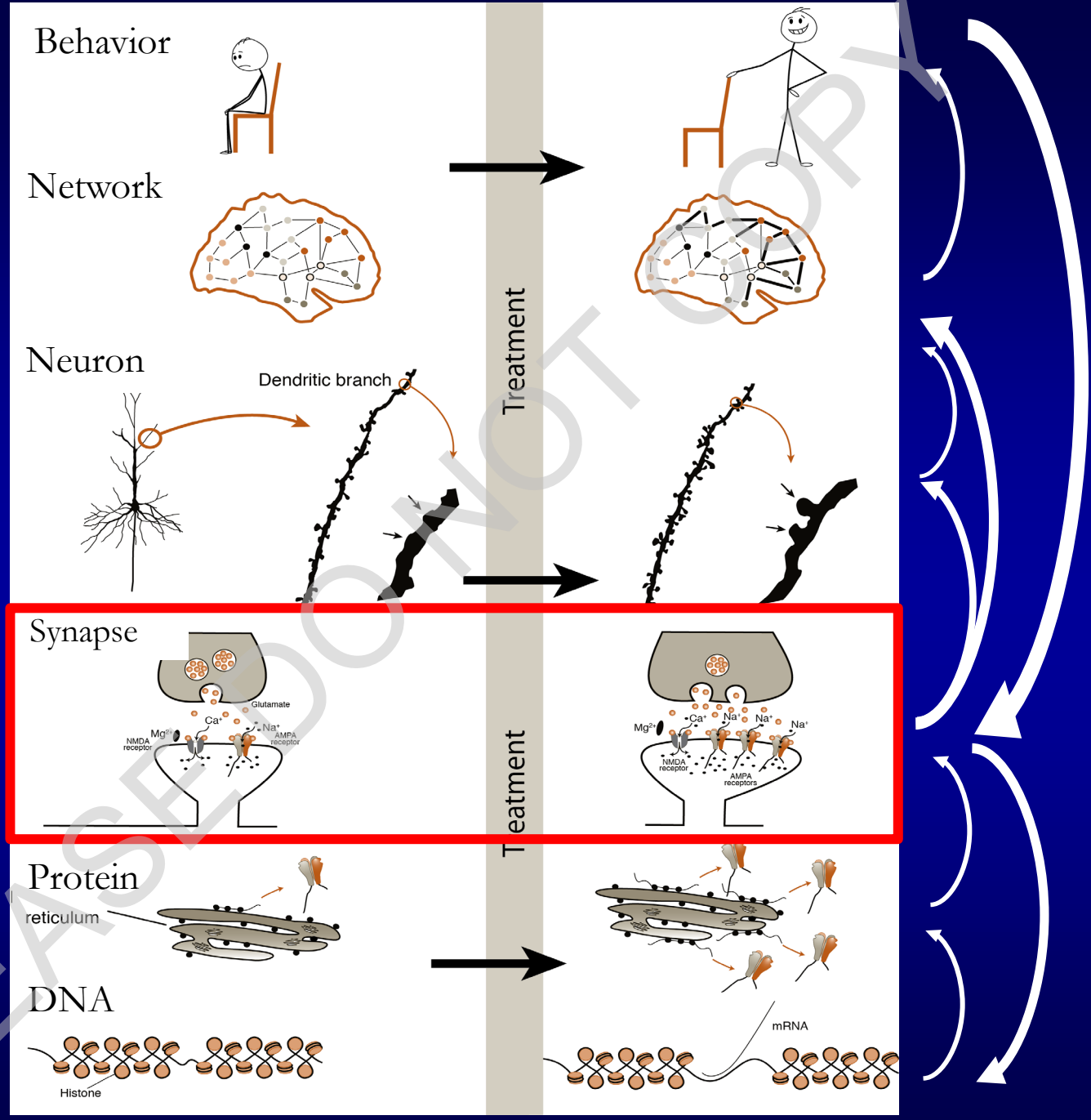


Higgins & George, *Brain Stimulation Therapies for Clinicians*, 2019, slide adapted from Mark George



How does rTMS produce lasting therapeutic changes in the brain?

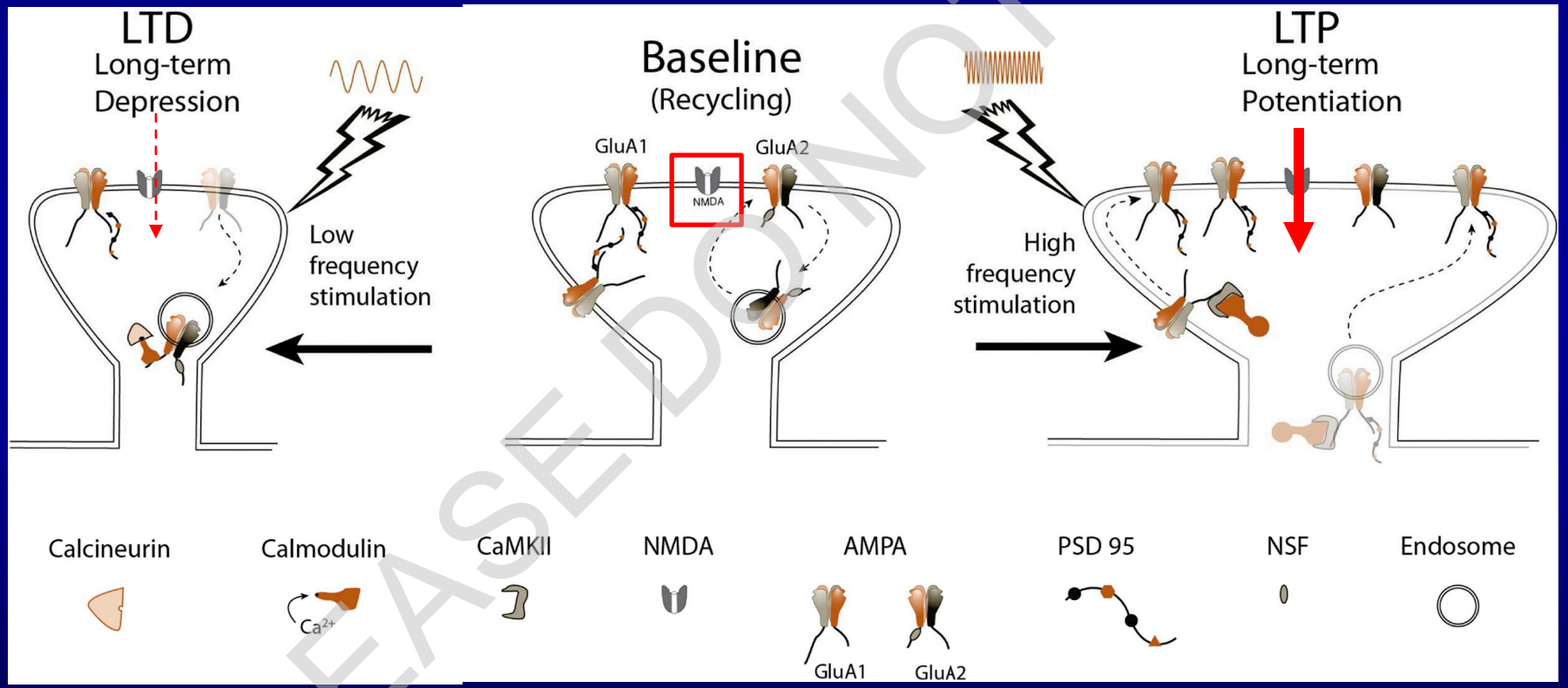
What Underlies
(aka causes?)
Network and Behavioral Effects?



Brown, Higgins & George, *Neuromodulation*, 2022

Synaptic Plasticity

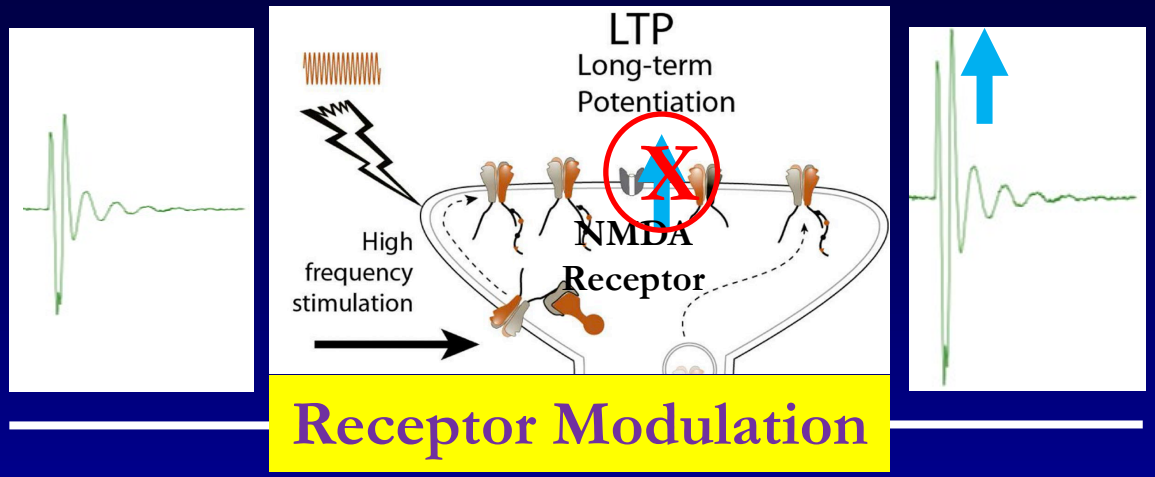
critically depends on NMDA receptors



Brown et al, *Neuromodulation*, 2022

Vlachos, *J Neuro*, 2012

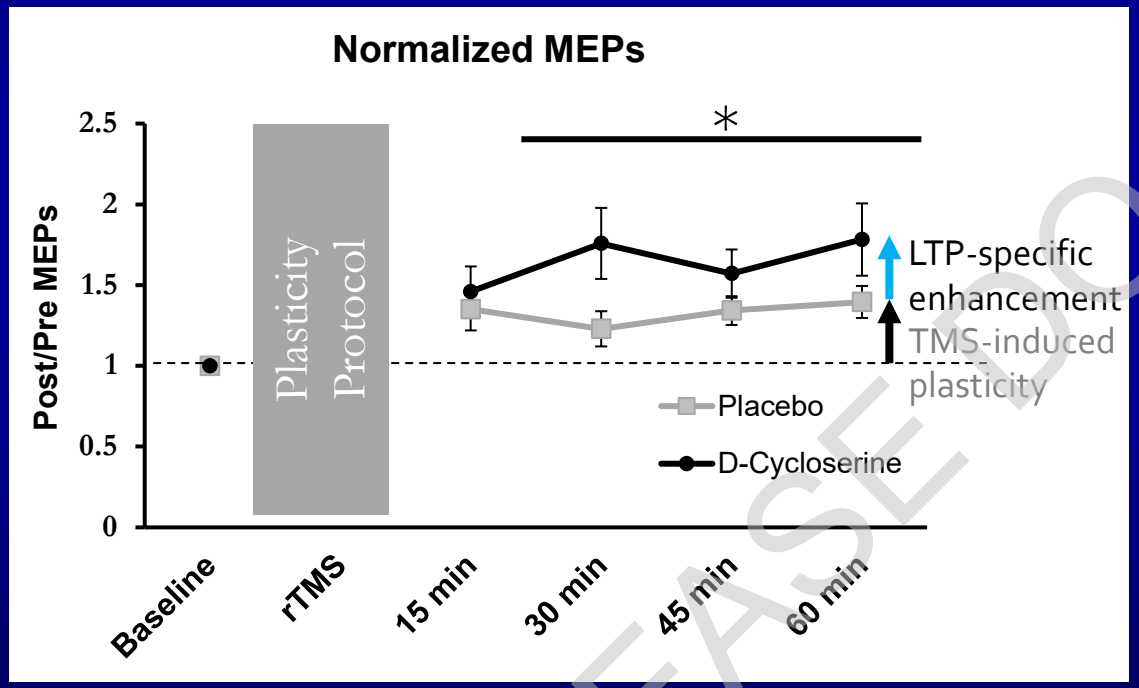
Huang, Clin Neurophys, 2007



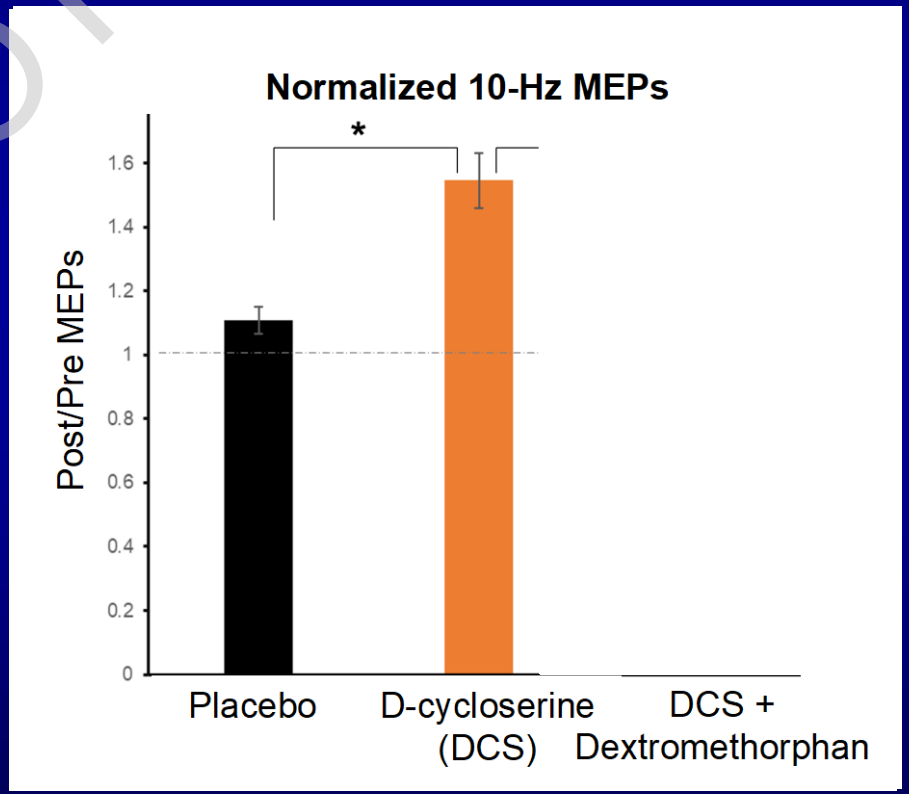
Receptor Modulation

Clinical TMS Protocol:

- 3000 pulses
- 4 sec on/26 sec off

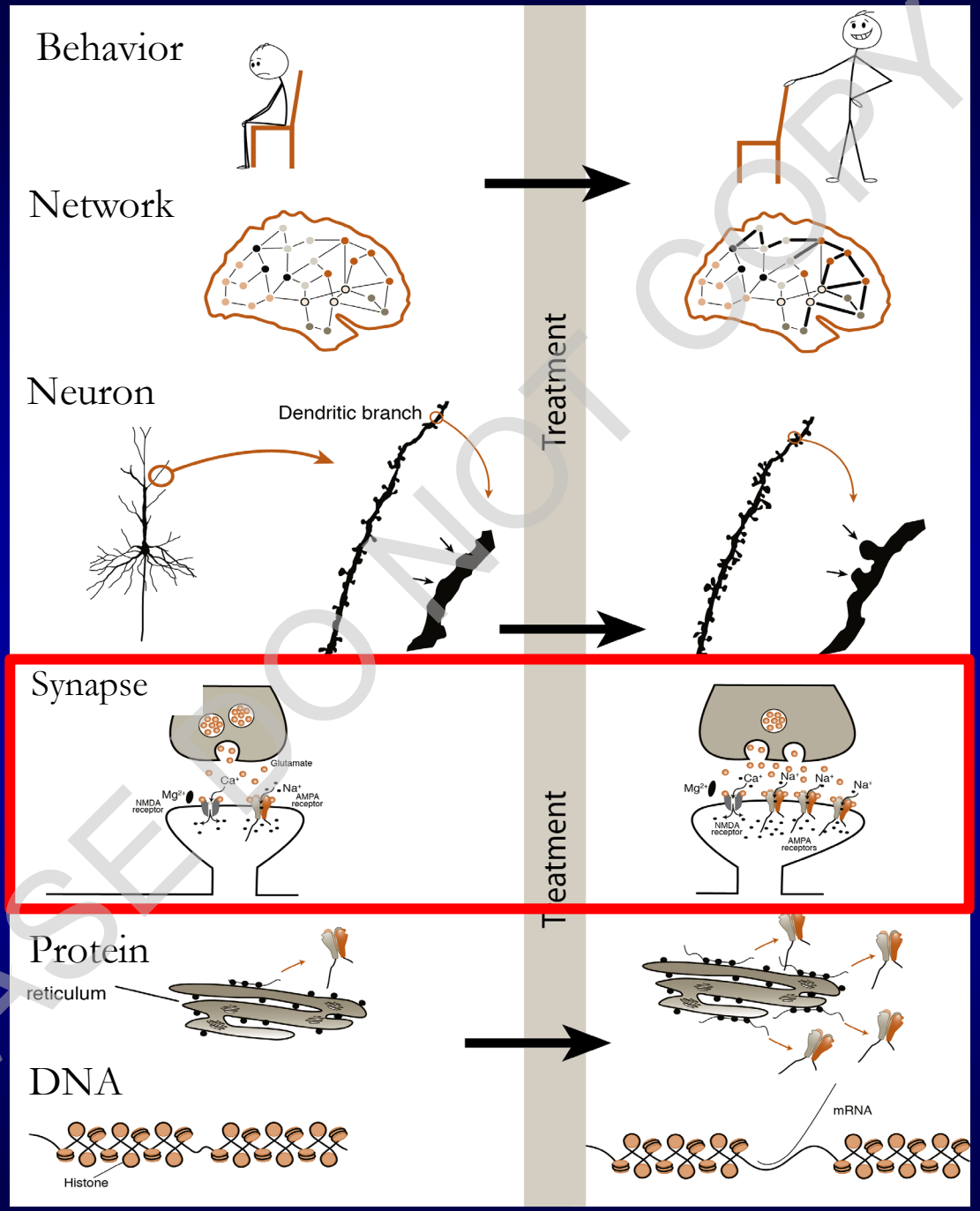


Brown et al., *Brain Stimulation*, 2020



NMDAR Activation Enhances rTMS Physiology

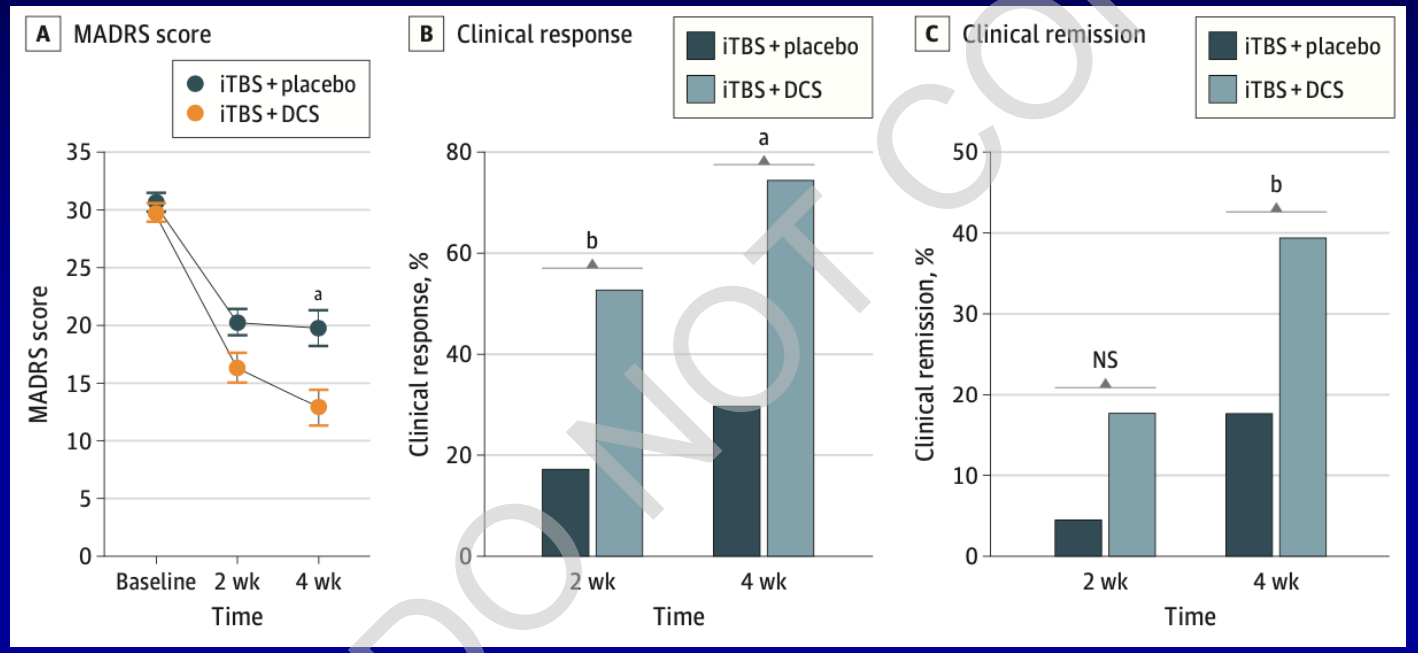
Does this Translate to Clinical Improvements?

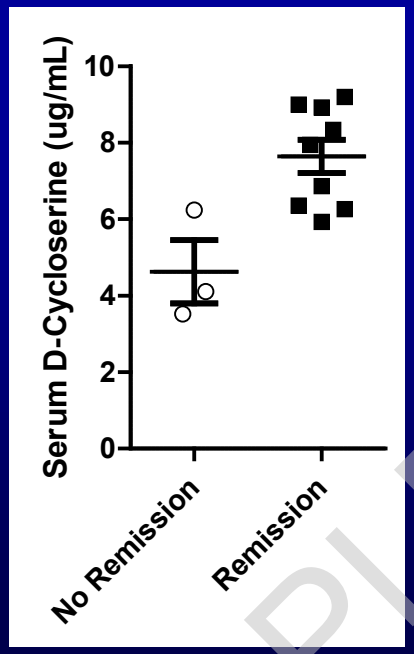


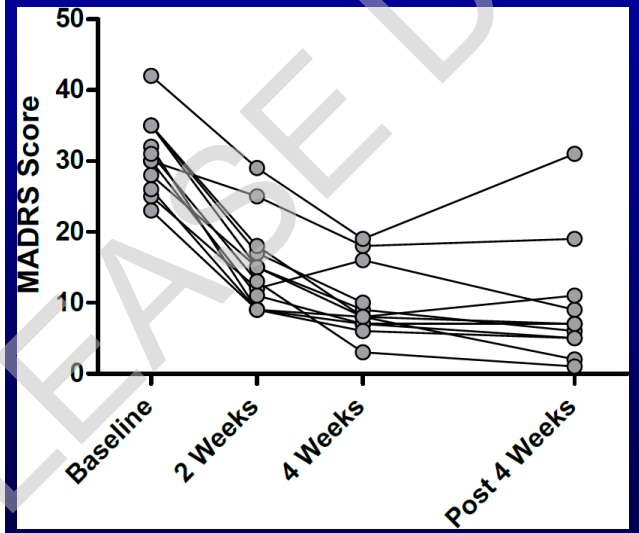
Brown, Higgins & George, *Neuromodulation*, 2022

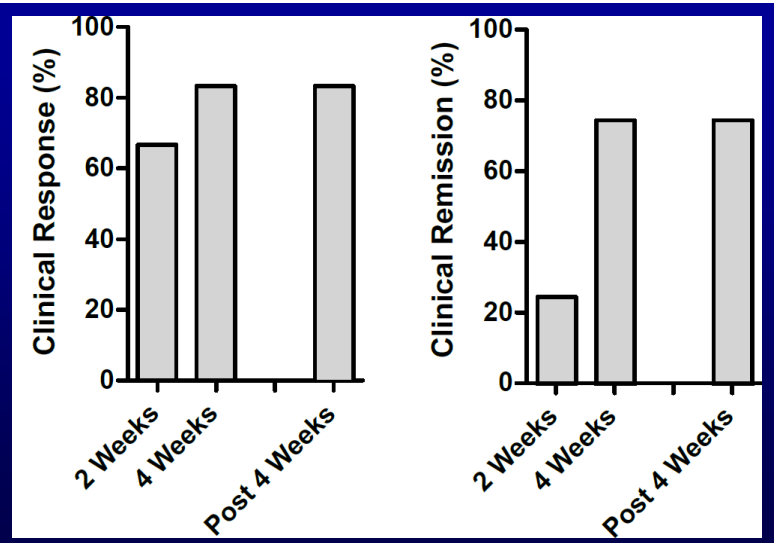
Leveraging the Mechanism of TMS to Improve Clinical Efficacy

Cole et al., *JAMA Psych*, 2022



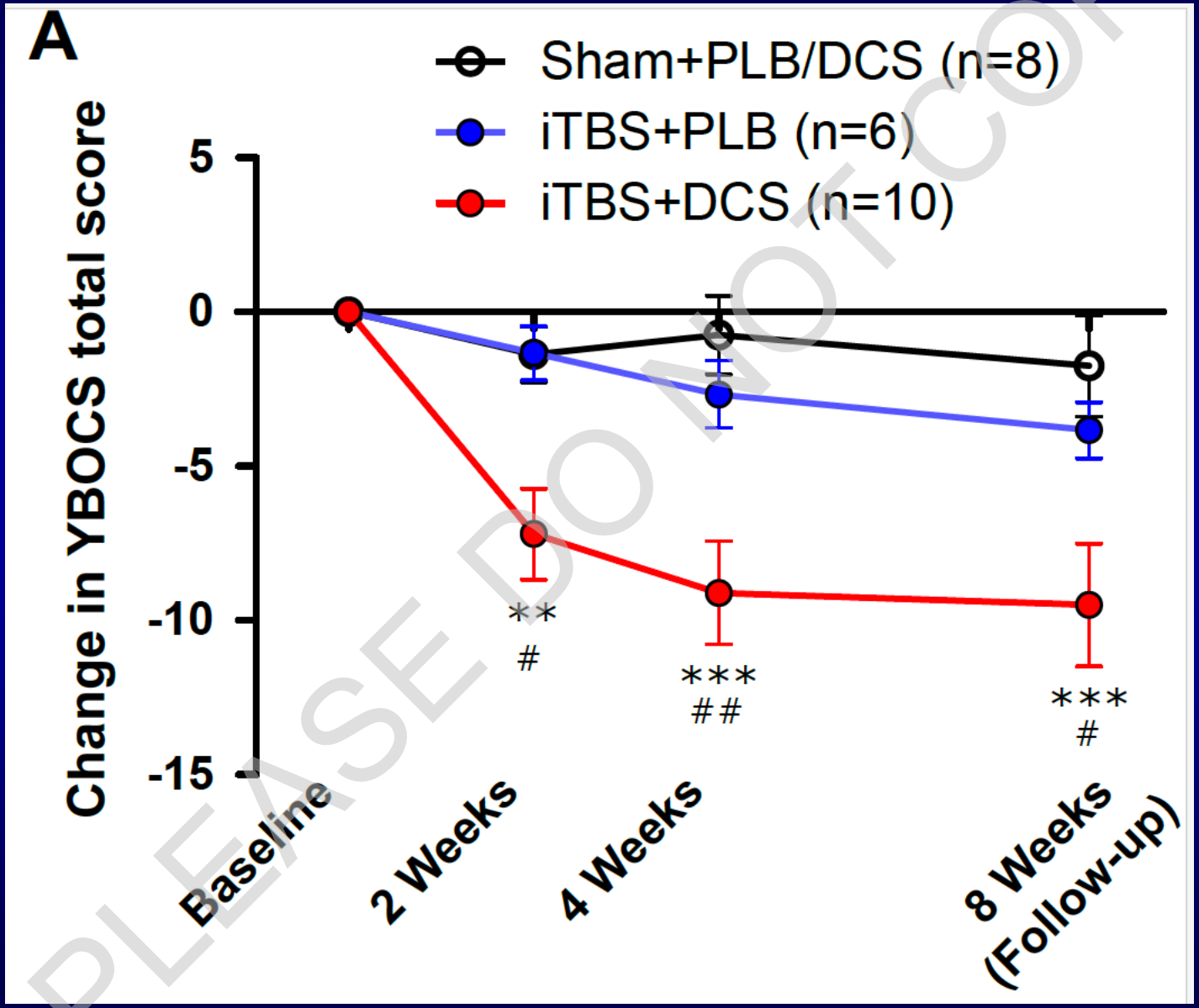






*Unpublished data from Alex McGirr laboratory @ University of Calgary, shared with permission

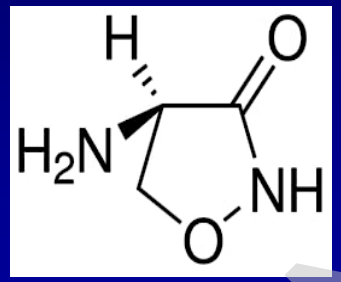
Transdiagnostic Augmentation?



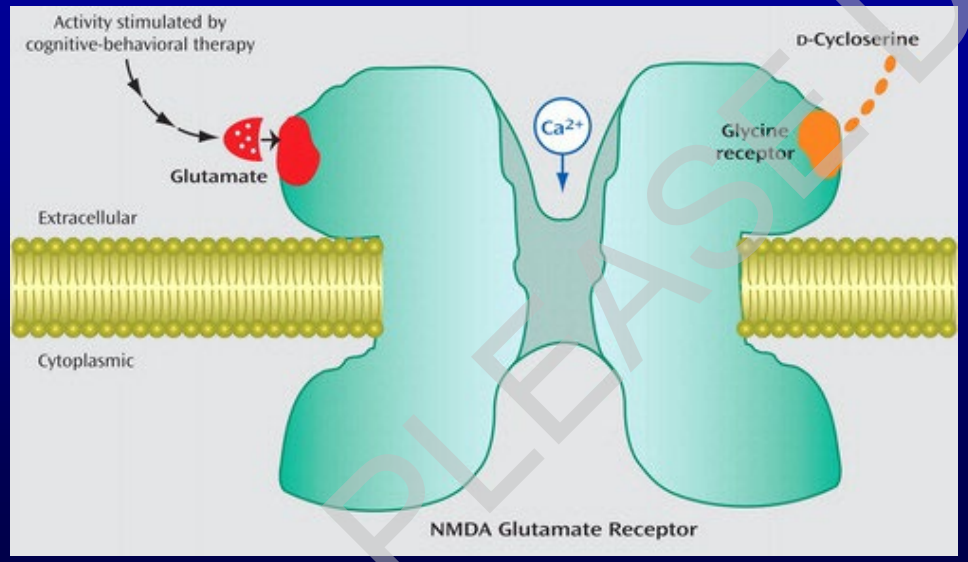
*Unpublished data from Alex McGirr laboratory @ University of Calgary, shared with permission

Why d-cycloserine?

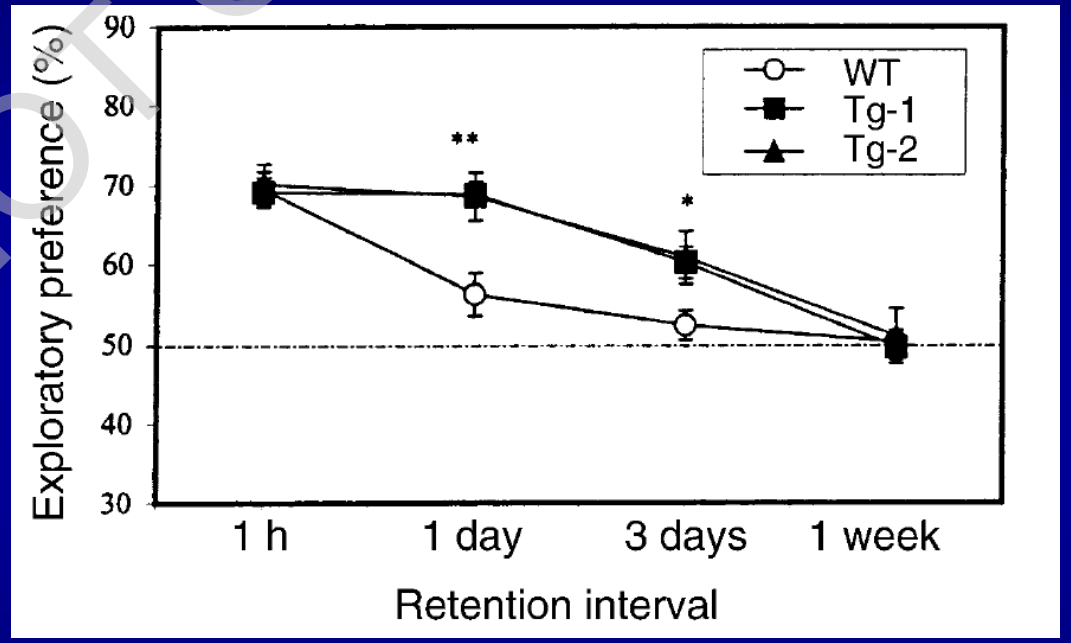
- FDA-approved for Tuberculosis
- FDA-approved for Cystitis



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

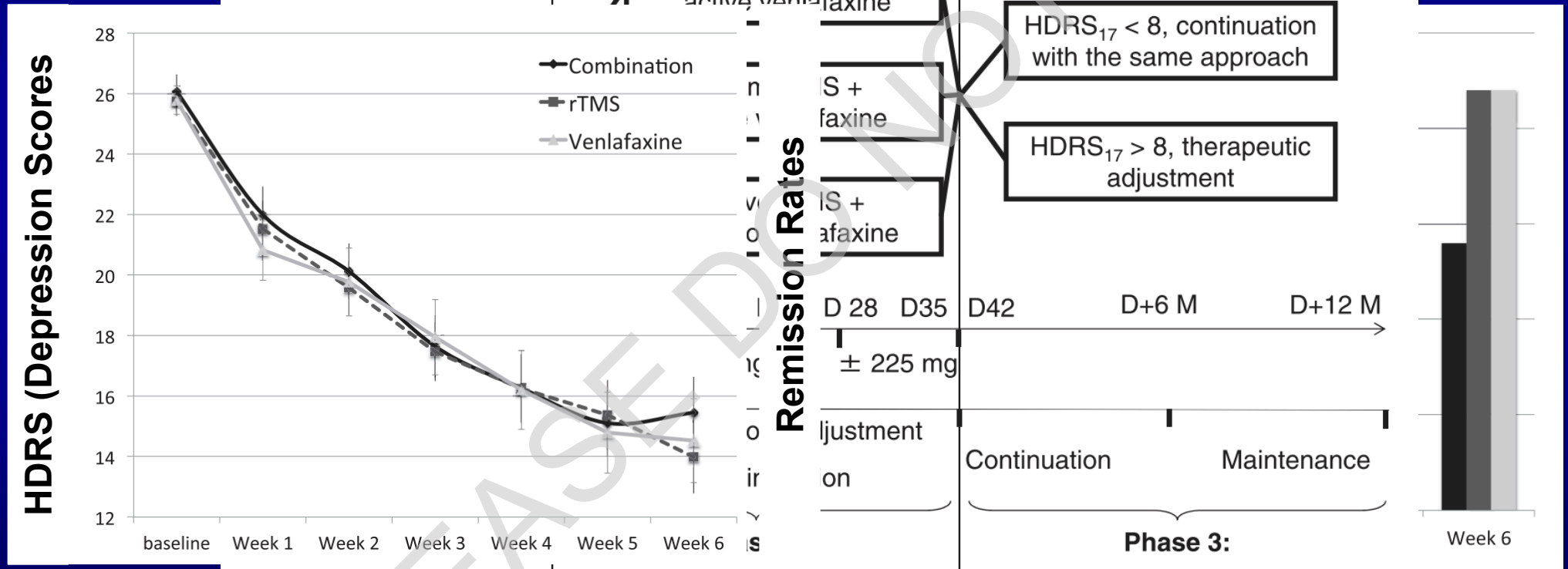


Why the NMDA receptor?



Tang et al., *Nature*, 1999

If NMDAR makes TMS better, what about an antidepressant?

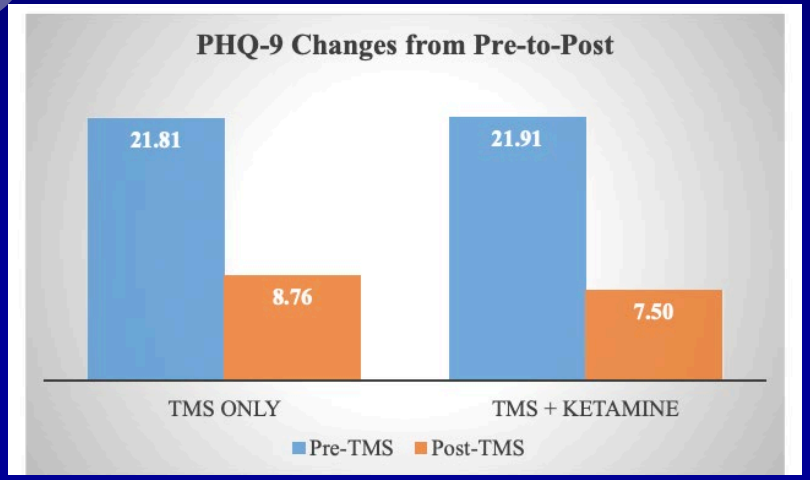


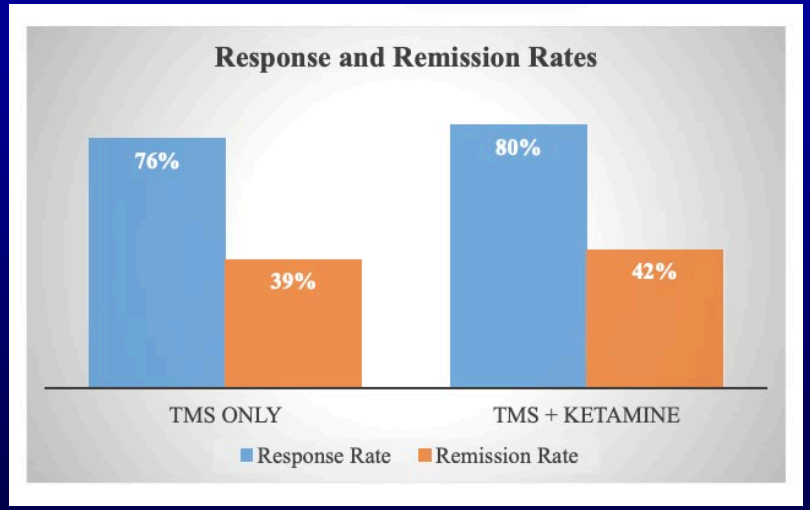
Brunelin et al., *Brain Stim*, 2014

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
    - Conclusion: We don't yet know!
    - *Update…

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



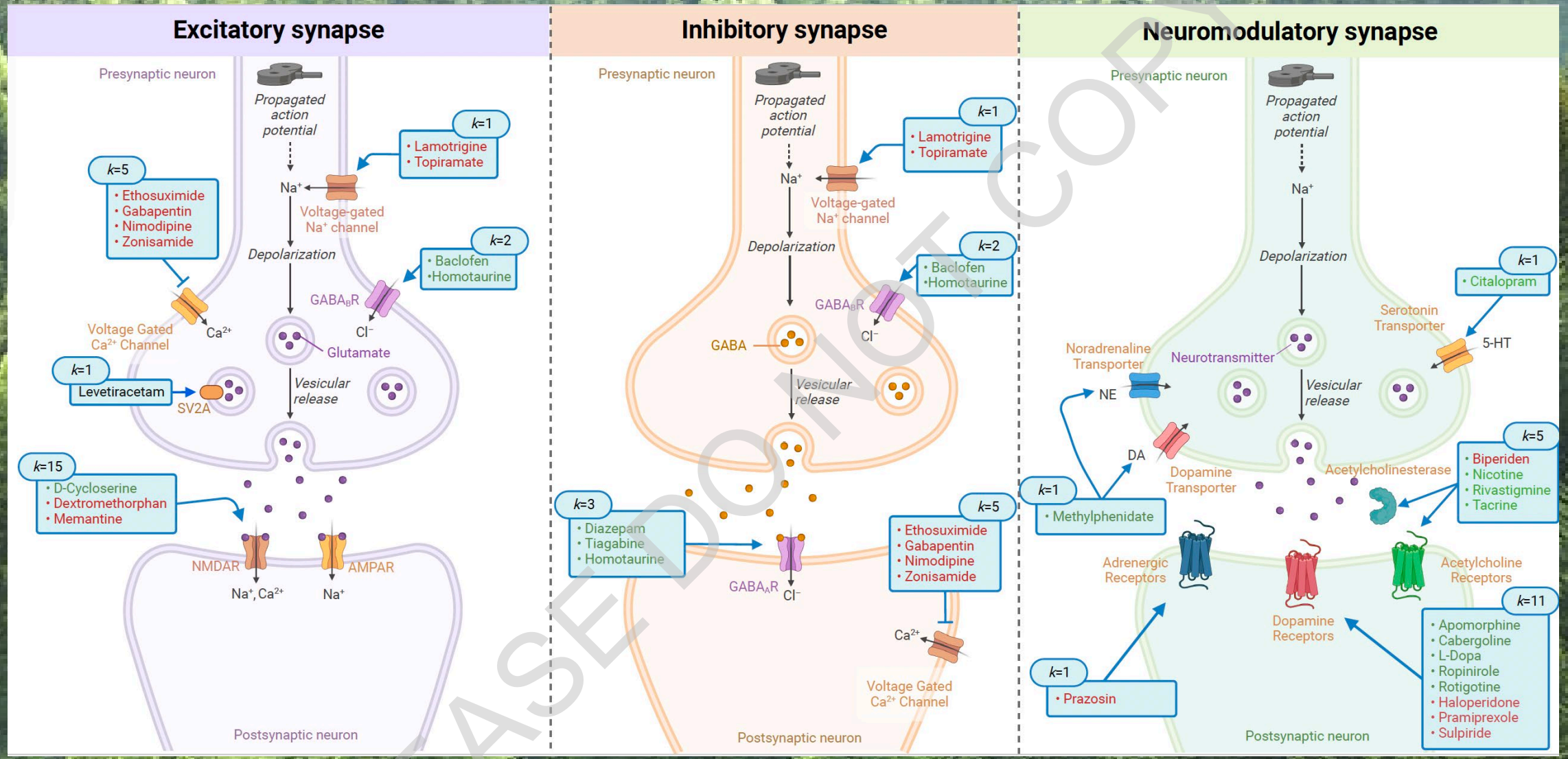


Shanok et al., *Psychopharm*, 2024

Recap

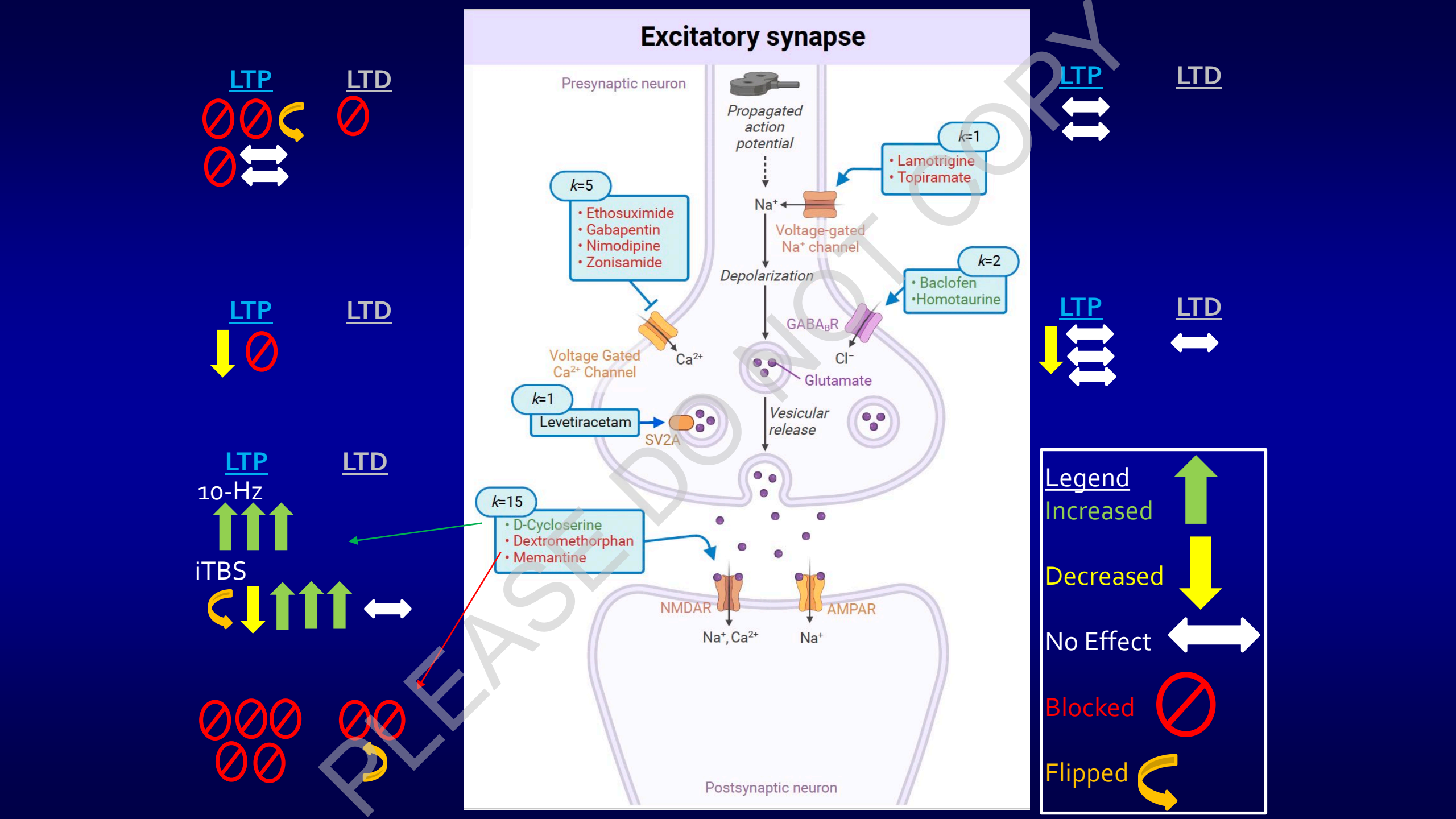
- NMDAR agonist, d-cycloserine, enhances TMS effectiveness
  - …Through NMDA receptor activation
  - …Which is central to LTP
  - …suggests TMS works through LTP.
  - May be Trandiagnostic!
- Neither SNRI (venlafaxine) nor ketamine helped TMS.

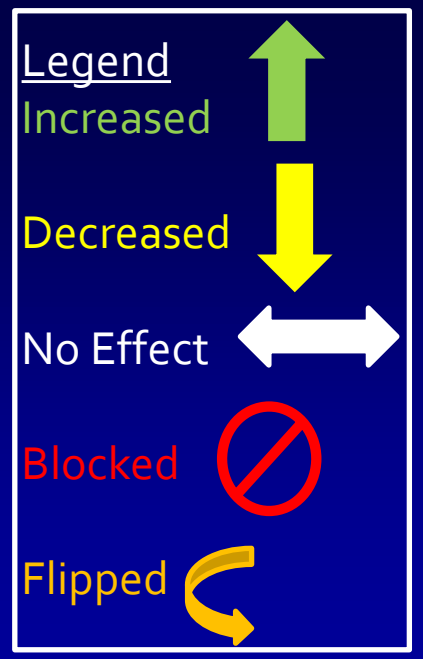
- Any other augmentation candidates??

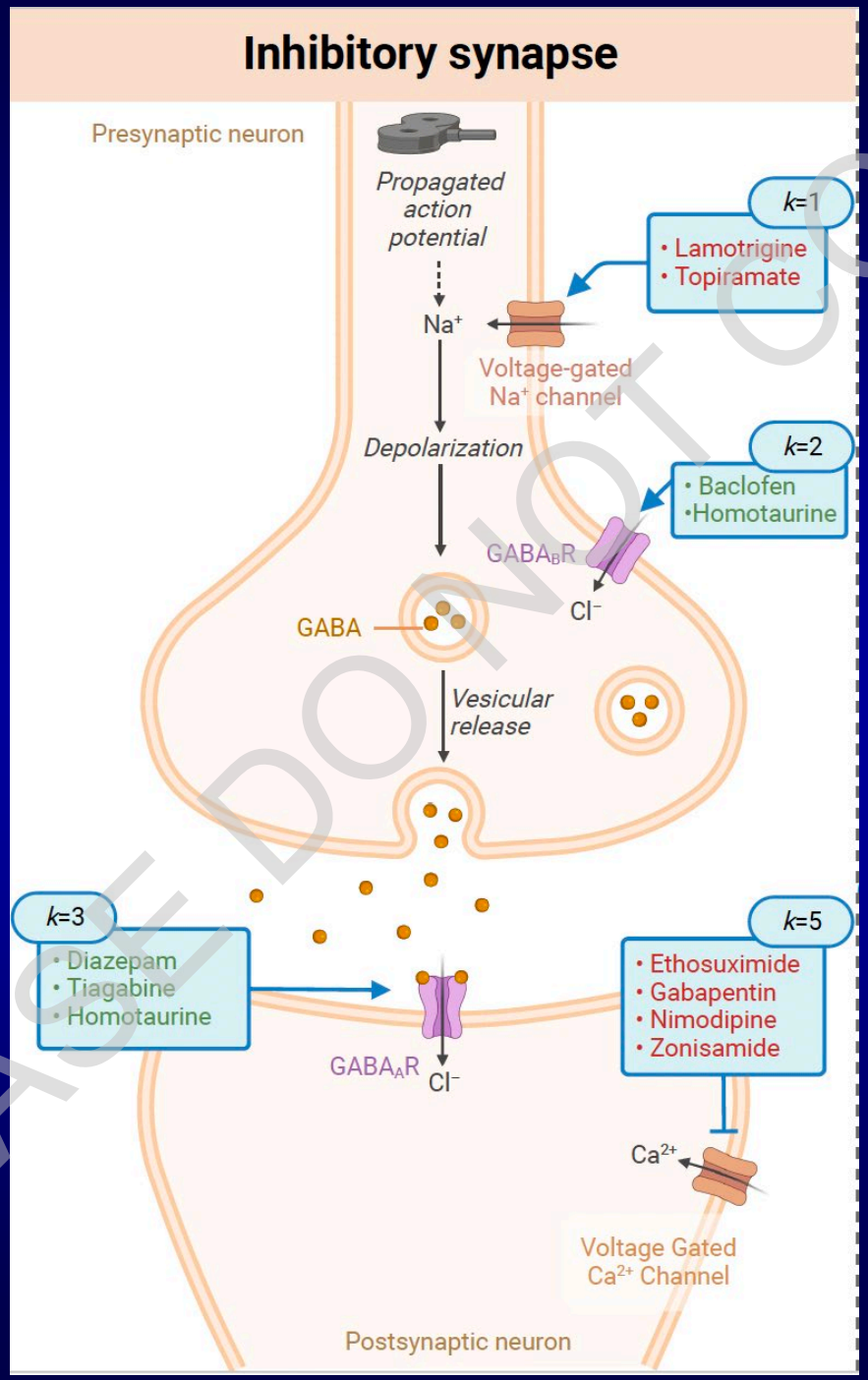


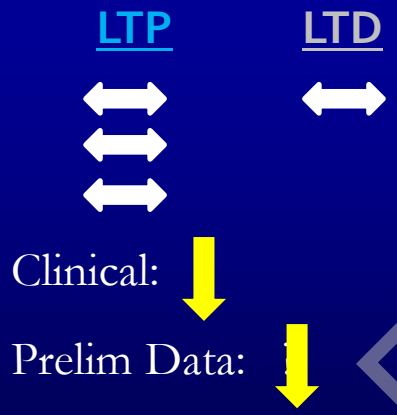
Sohn et al., *J Psychiatry Neurosci*, 2024

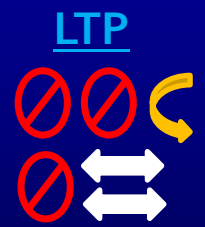
Survey of Pharmacologic Enhancement





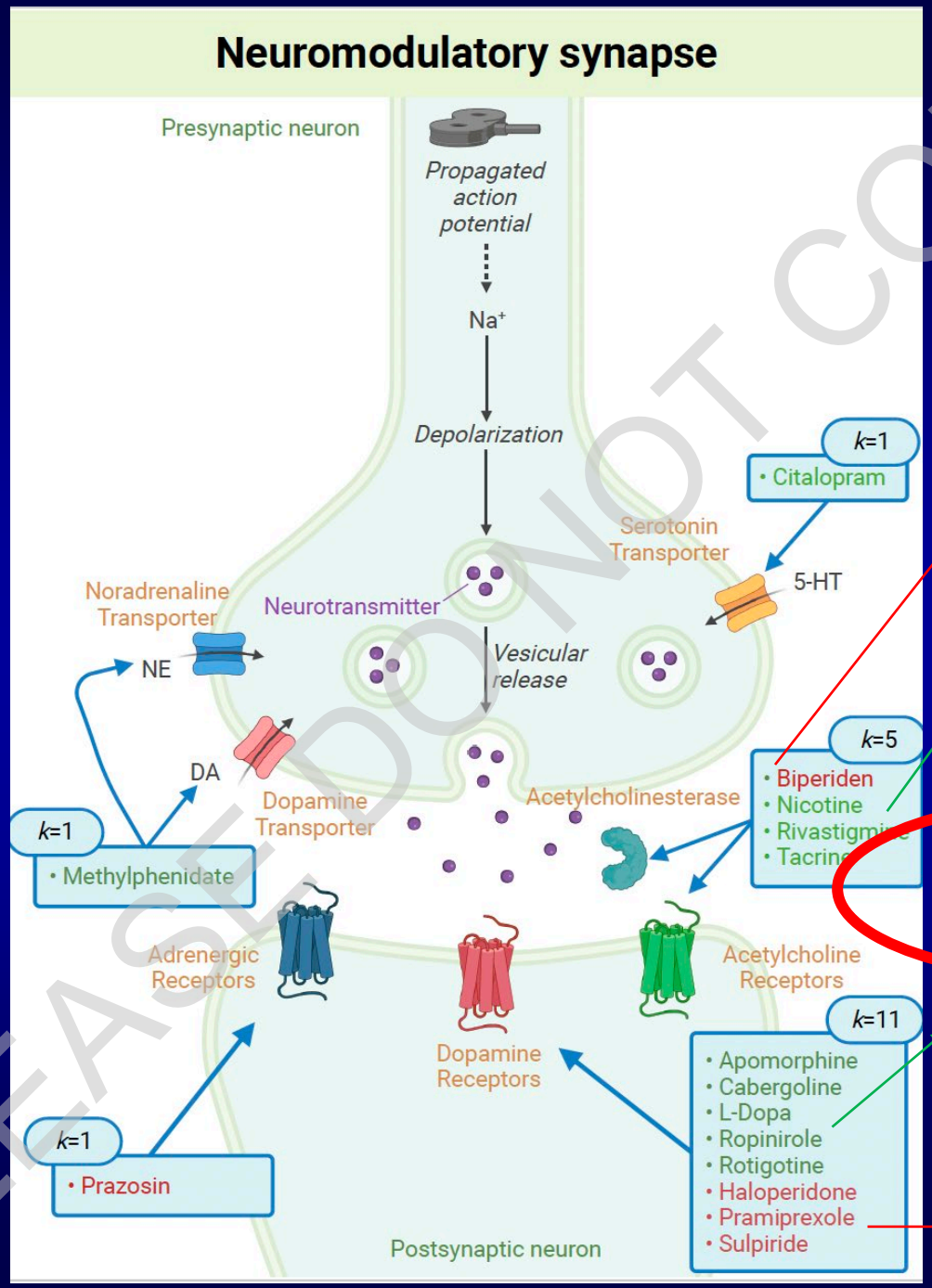






Legend
Increased
Decreased
No Effect
Blocked
Flipped

Neuromodulatory synapse



LTP LTD

LTP LTD

LTP LTD

LTP LTD

LTP LTD

Clinical:

LTP LTD

Low: High:

RCT → Naturalistic

All studies except those pointed out: Active vs. Sham TMS + Drug (No comparison for drug)

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*

TMS + MEDICATIONS									
Authors (year)	**Sample**	**Type of trial**	**Control condition**	**Stimulation protocol**	**# of sessions**	**Treatment combined with TMS**	**Outcome measures**	**% score change**	**Main finding**
Conca, et al. (2000)[32]	12	Open-label	N/A	Fp1, Fp2, F3, F4; Cz, T3, T4; P3, P4, 500 pulses	10 rTMS sessions	Citalopram, 20 mg/day (optional increase to 40 mg/day after 1 week) and trazodone, 150 mg/day (optional increase to 250 mg/day after 1 week), lorazepam allowed (1-4 mg/day)	HAM-D24	66.7% responders (HAM-D ≥ 50% reduction)	Significant reductions
Huang, et al. (2012)[31]	28 active rTMS + citalopram 28 sham rTMS + citalopram	Randomized, controlled, double-blind	Sham TMS (coil angled differently)	10 Hz over left dlPFC at 90% MT, 20 trains of 4 seconds, ITI 56 seconds, 800 pulses	10 rTMS sessions	Citalopram, 20 mg/day or 40 mg/day if necessary	HAM-D17 MADRS	Active TMS + citalopram: HAM-D17 - 32.4% dec MADRS - 32.3% dec Sham TMS + citalopram: HAM-D17 - 22.5% dec MADRS - 22.3% dec	Combination superior; Also accelerated symptom reduction at 2 weeks into treatment
Garcia-Toro, et al. (2001a)[33]	11 active rTMS + sertraline 11 sham rTMS + sertraline	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	Sertraline, minimum of 50 mg/day and 93% took benzodiazepines	HAM-D BDI	Active rTMS + medication: HAM-D - 38.2% dec BDI - 28.1% dec Sham rTMS + medication: HAM-D - 34.3% dec BDI - 8.2% dec	Combination not superior
Wang, et al. (2017)[34]	22 active rTMS + paroxetine 21 sham rTMS + paroxetine	Randomized, controlled, double-blind	Sham coil	10 Hz over left dlPFC at 80% MT, 40 trains of 2 seconds, ITI 28 seconds, 800 pulses	20 rTMS sessions	Paroxetine, 10-40 mg/day	HAM-D24	Active rTMS + medication: 83.2% dec Sham rTMS + medication: 81% dec	Combination accelerated symptom reduction at 1 week into treatment but no group differences at end of treatment

Eche, et al. (2012)[35]	6 10 Hz rTMS + venlafaxine 8 1 Hz rTMS + venlafaxine	Randomized, controlled	N/A	10 Hz over left dlPFC at 100% MT, 40 trains of 5 seconds, ITI 30 seconds, 2000 pulses or 1 Hz to right dlPFC at 100% MT, 2 trains of 60 seconds, 120 pulses	20 rTMS sessions	Venlafaxine, 150 mg/day	MADRS	1 Hz: 51.3% dec 10 Hz: 53% dec	Both combinations reduced symptoms
Brunelin, et al. (2014)[36]	54 active rTMS + placebo venlafaxine 51 sham rTMS + venlafaxine 55 active rTMS + venlafaxine	Randomized, controlled	Sham rTMS (sham coil and TENS stimulator over FP2 and F8) and placebo venlafaxine	1 Hz over dlPFC at 120% MT, 6 trains of 60 seconds, ITI 20 seconds	Up to 42 rTMS sessions	Venlafaxine, 150 or 225 mg/day	HAM-D17	% responders (<8 on HAM-D) Active rTMS + placebo venlafaxine: 41% responders Sham rTMS + venlafaxine: 43% responders Active rTMS + venlafaxine: 28% responders	Combination inferior
Haesebaert, et al. (2016 [follow-up to Brunelin, et al.])[37]	25 rTMS responders 22 venlafaxine responders 19 rTMS + venlafaxine responders	Randomized, controlled	rTMS or venlafaxine only	1 Hz over 6 cm anterior to motor cortex hot spot at 120% MT, 6 trains of 60 seconds, ITI 30 seconds, 360 pulses	34 rTMS sessions	Venlafaxine, 150 or 225 mg/day	HAM-D17	Rate of patients who did not relapse at endpoint (HAM-D < 15) rTMS only: 40% Medication only: 45.1% rTMS + medication: 36.9%	Combination had similar relapse rates as rTMS only and venlafaxine only
Rossini, et al. (2005)[38]	50 active rTMS + medication 49 sham rTMS + medication	Double-blind, randomized, controlled	Sham TMS (coil angled differently)	15 Hz over left dlPFC at 100% MT, 30 trains of 2 seconds, ITI 28 seconds, 900 pulses	10 rTMS sessions	Venlafaxine, 225 mg/day, sertraline, 150 mg/day, or escitalopram, 15 mg/day	HAM-D	Active rTMS + medication: 27.9% dec Sham rTMS + medication: 18.3% dec	All 3 combinations accelerated reduction in symptoms
Herwig, et al. (2007)[39]	60 active rTMS + medication and/or therapy 61 sham rTMS + medication and/or therapy	Randomized, controlled	Sham rTMS (coil placed 5 cm lateral to left dlPFC and angled)	10 Hz over left dlPFC at 110% MT, 100 trains of 2 seconds, ITI 8 seconds, 2000 pulses	15 rTMS sessions	Either no medication, venlafaxine minimum of 75 mg/day, or mirtazapine minimum of 15 mg/day (<1.5 mg lorazepam allowed), ongoing psychotherapy allowed	BDI HAM-D21 MADRS	Active rTMS + medication and/or therapy: BDI - 39.3% dec HAM-D - 43% dec MADRS - 38.4% dec Sham rTMS + medication and/or therapy: BDI - 32.4% dec HAM-D - 38.2% dec MADRS - 38.5% dec	No statistically significant group differences
Ullrich, et al. (2012)[40]	22 30 Hz rTMS + medication 21 1 Hz rTMS + medication	Randomized, controlled	N/A	30 Hz over left dlPFC at 110% MT, 20 trains of 3 seconds, ITI 57 seconds, 1800 pulses or 1 Hz over left dlPFC at 110% MT, 11 trains of 90 seconds, ITI 30 seconds, 990 pulses	15 rTMS sessions	Stable dose of ongoing venlafaxine or mirtazapine (lithium, lorazepam < 1.5 mg/day and antipsychotics allowed)	HAM-D BDI	30 Hz rTMS + medication: HAM-D - 23.9% dec BDI - 19.7% dec 1 Hz rTMS + medication: HAM-D - 13.8% dec BDI - 18.3% dec	Both combinations reduced symptoms

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)			80% MT, 120 trains of 10 seconds, ITI 2 seconds, 1200 pulses				ated from graph rTMS + medication: D17 ~ 46% dec S ~57% dec TMS + medication: D17 ~ 47% dec S~59% dec Sham rTMS + medication: HAM-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

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:	Significant reduction in symptoms

"Concurrent antidepressant or mood stabilizer therapy was associated with a higher rate of response."

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

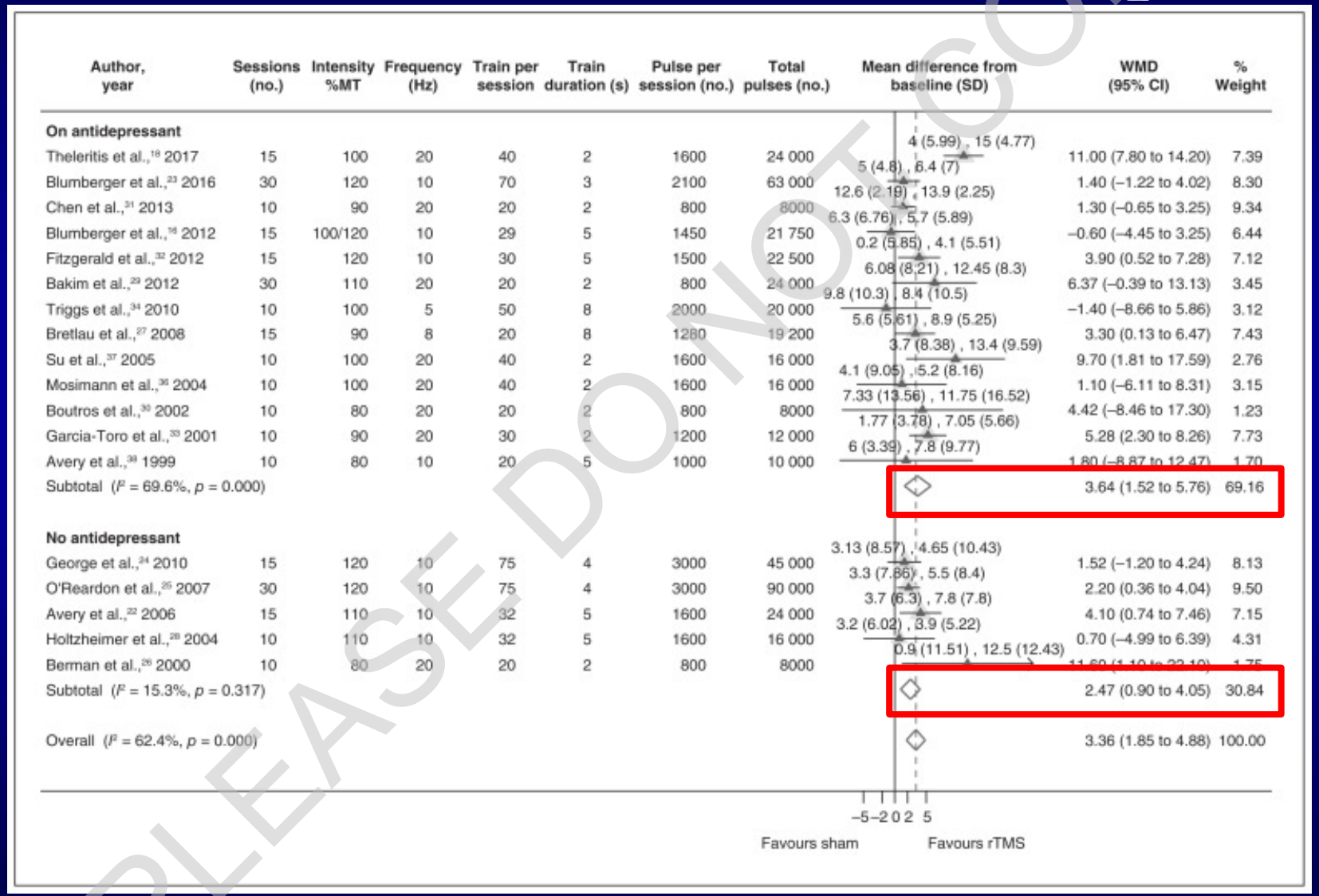
TMS + MEDICATIONS									
Herwig, et al. (2003)[53]	13 active rTMS + medication 12 sham rTMS + medication	Double-blind, randomized, sham-controlled	Same parameters but over midline at the parieto-occipital transition at 90% MT	15 Hz over right or left dlPFC at 110% MT, 30 trains of 2 seconds, ITI 4 seconds, 3000 pulses	10 rTMS sessions	Stable dose of ongoing medications	BDI HAM-D MADRS	Active rTMS + medication: BDI - 73.4% dec HAM-D - 68.7% dec MADRS - 66.4% dec Sham rTMS + medication: BDI - 9.3% dec HAM-D - 2.2% dec MADRS - 3.1% inc	Combination superior
Mosimann, et al. (2004)[54]	15 active rTMS + medication 9 sham rTMS + medication	Randomized, controlled	Sham rTMS (coil angled differently)	20 Hz over left dlPFC at 100% MT, 40 trains of 2 seconds, ITI 28 seconds, 1600 pulses	10 rTMS sessions	Stable dose of ongoing medications	HAM-D21 BDI-21	Active rTMS + medication: HAM-D21 - 18.3% dec BDI-21 - 18.7% dec Sham rTMS + medication: HAM-D21 - 16.7% dec BDI-21 - 16.7% dec	Combination not superior
Garcia-Toro, et al. (2006)[51]	10 active rTMS to prefrontal cortex + medication 10 active rTMS to SPECT-identified target + medication 10 sham rTMS + medication	Randomized, controlled, double-blind	Sham TMS (coil angled differently)	20 Hz to left PFC, 30 trains of 2 seconds and 1 Hz to right PFC, 30 trains of 60 seconds at 110% MT, ITI 20-25 seconds, 3000 pulses SPECT: Same as above except to either right or left PFC or right or left temporoparietal areas	10 rTMS sessions	Stable dose of ongoing medications	HAM-D	Active rTMS + medication: 23.51% dec Active rTMS + SPECT + medication: 32.4% dec Sham rTMS + medication: 5.6% dec	Combination superior, TMS based on SPECT to temporoparietal area not beneficial
Ray, et al. (2011)[48]	20 active rTMS + ongoing medications 20 sham rTMS + ongoing medications	Randomized, controlled	Sham rTMS (coil angled differently)	10 Hz over right dlPFC at 90% MT, 20 trains of 6 seconds, ITI 24 seconds, 1200 pulses	10 rTMS sessions	Stable dose of ongoing medications	HAM-D	Active rTMS + medications: 84.7% dec Sham rTMS + medications: 33.3% dec	Combination superior
Berlim, et al. (2011)[62]	15	Open-label	N/A	10 Hz over left dlPFC at 120% MT, 75 trains of 4 seconds, ITI 26 seconds, 3000 pulses	20 rTMS sessions	Stable dose of ongoing medications	HAM-D IDS-SR	HAM-D - 15.4% dec IDS-SR - 20.3% dec	Significant reductions in symptoms
Charnsil, et al. (2012)[61]	9	Open-label	N/A	10 Hz over left dlPFC at 100% MT, 25 trains of 5 seconds, 1250 pulses	10 rTMS sessions	Stable dose of ongoing medications	HAM-D	% responders (<8 on HAM-D): 78%	Significant response

Table 1

Continued

TMS + MEDICATIONS									
Prasser, et al. (2015)[49]	17 TMS + medication 20 TBS + medication 17 sham TMS + medication	Randomized, controlled	Sham rTMS (sham coil with TBS protocol)	TMS: 1 Hz over right dlPFC or 10 Hz over left dlPFC at 110% MT, 1000 pulses TBS: continuous TBS over right dlPFC or intermittent TBS over left dlPFC at 80% MT, 1200 pulses	15 rTMS sessions	Stable dose of ongoing medications	HAM-D	*Estimated from graph rTMS + medication: ~ 43.6% dec TBS + medication: ~ 50.8% dec Sham TMS + medication: ~ 29.6% dec	Combination superior, tendency toward better outcomes for TBS + medication group at follow-up
Iznak, et al. (2015)[59]	20	Open-label	N/A	20 Hz over left dlPFC at 60-80% MT, 40 trains, ITI 14 seconds, 1600 pulses	10 rTMS sessions	Stable dose of ongoing medications	HAM-D17	62.5% dec	Significant reduction in symptoms
Qiao, et al. (2020)[60]	114	Open-label	N/A	10 Hz over left dlPFC or 1 HZ to right dlPFC at 120% MT, 80 trains of 30 pulses, ITI 12 seconds, 2400 pulses	10-20 rTMS sessions	Stable dose of ongoing medications	HAM-D	61.5% dec	Significant reduction in symptoms

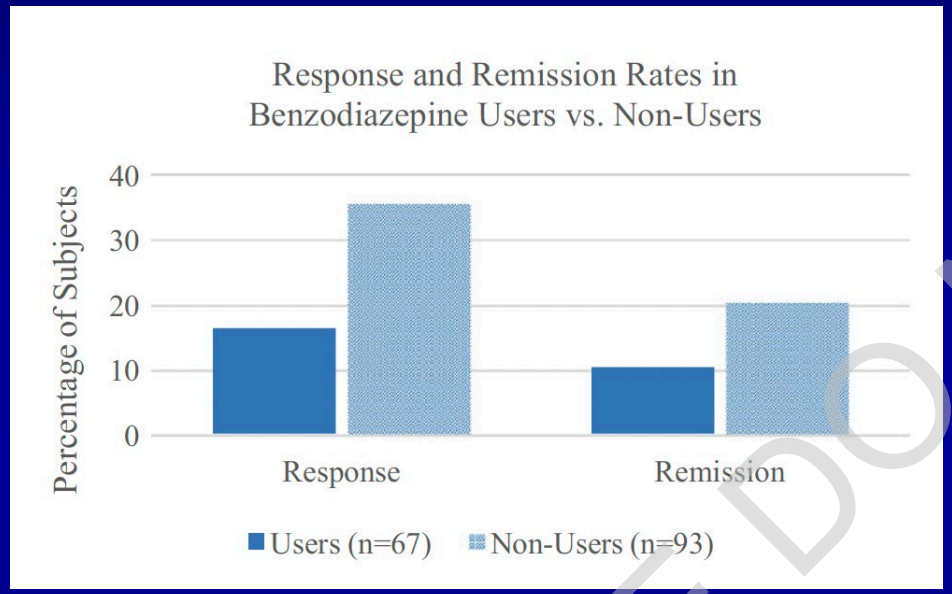
TMS may be better with Meds (Depression)

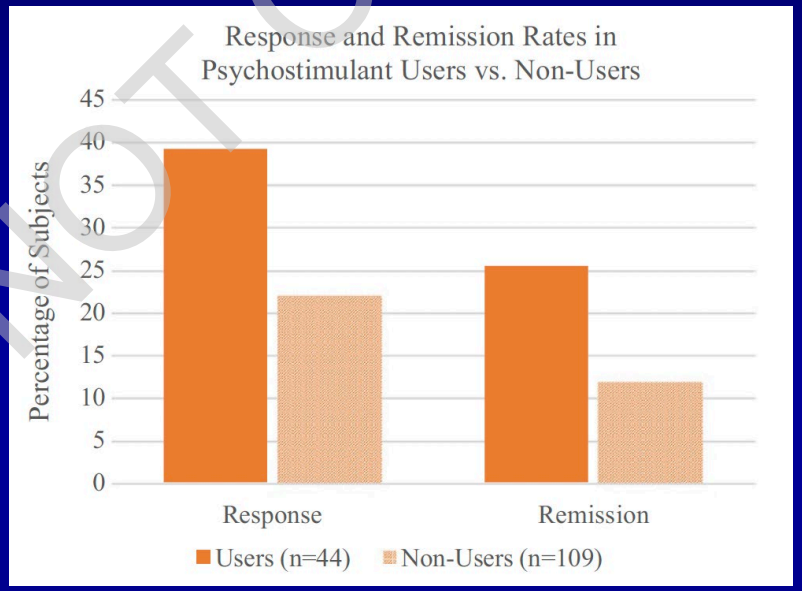


Author, year	Sessions (no.)	Intensity %MT	Frequency (Hz)	Train per session	Train duration (s)	Pulse per session (no.)	Total pulses (no.)	Mean difference from baseline (SD)	WMD (95% CI)	% Weight
On antidepressant										
Theleritis et al.,[18] 2017	15	100	20	40	2	1600	24 000	4 (5.99) , 15 (4.77)	11.00 (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)	5.60 (–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

"Didn't I hear that benzo's impair and stimulants help TMS?





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?

Other Pharmacologic Considerations

Clinical Neurophysiology 126 (2015) 1847–1868

Contents lists available at ScienceDirect

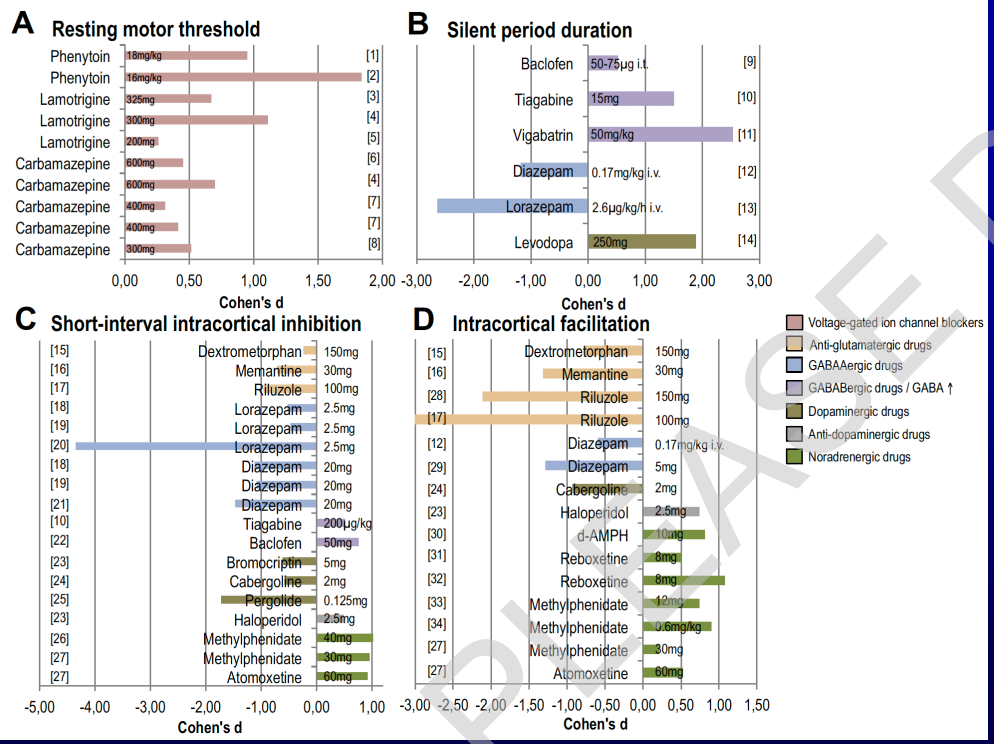
Clinical Neurophysiology

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

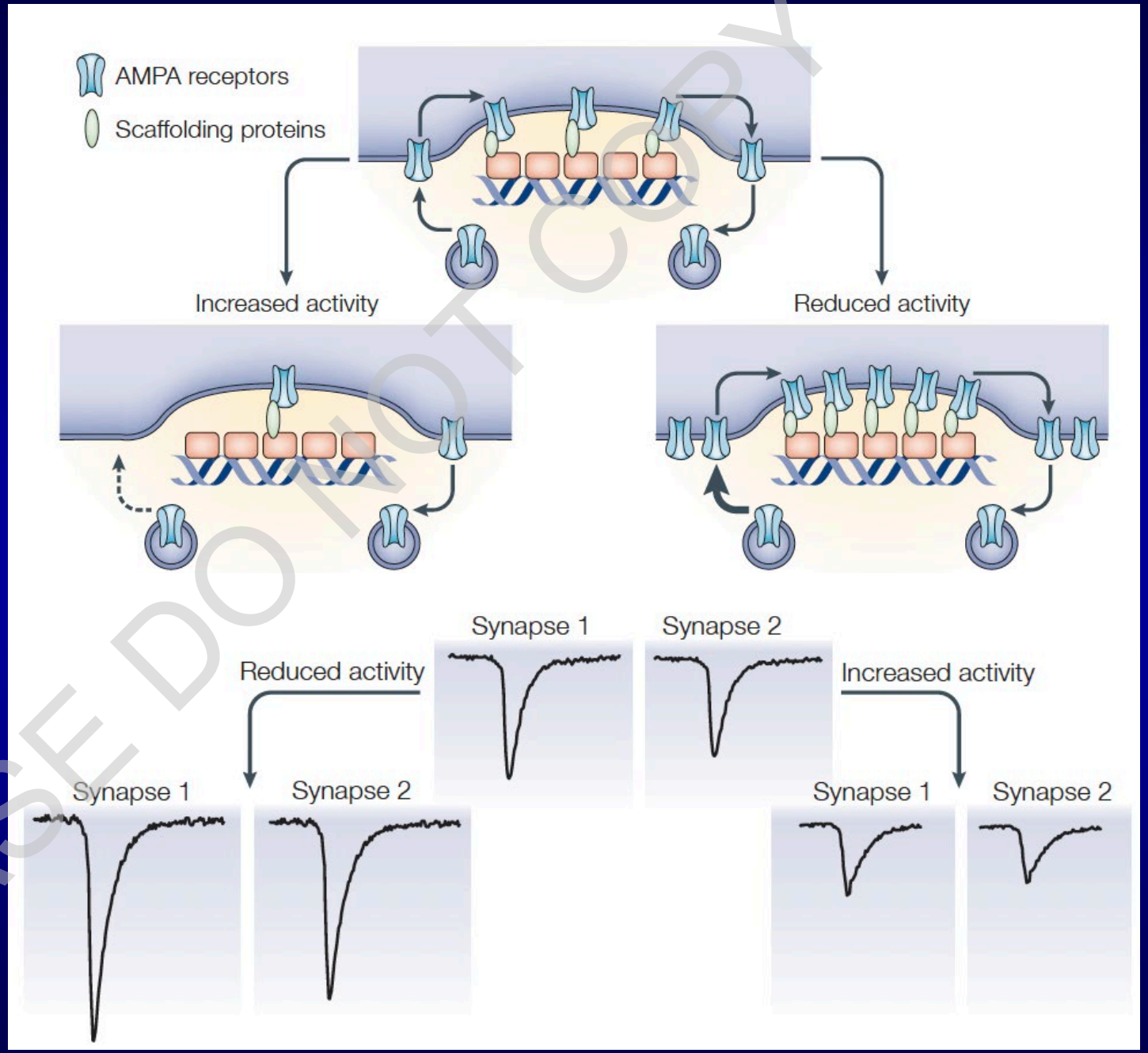
ORIGINAL PAPER

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]

A Final but Critical Consideration:

Homeostatic Plasticity



Turrigiano et al., *Nature Reviews Neuroscience*, 2004

Summary of Rx-Pharmacologic Augmentation

- 2 RCTs:
  - 1 with SNRI
  - 1 with NMDAR agonist
- 5 Retrospective comparisons:
  - Antipsychotics and Benzo's (x2) (may) impair
  - Stimulants (may) enhance (x2)
- Non-controlled and open-label: People seem to do well with meds + TMS (no surprise)
- What level of evidence do we need to change practice??

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*

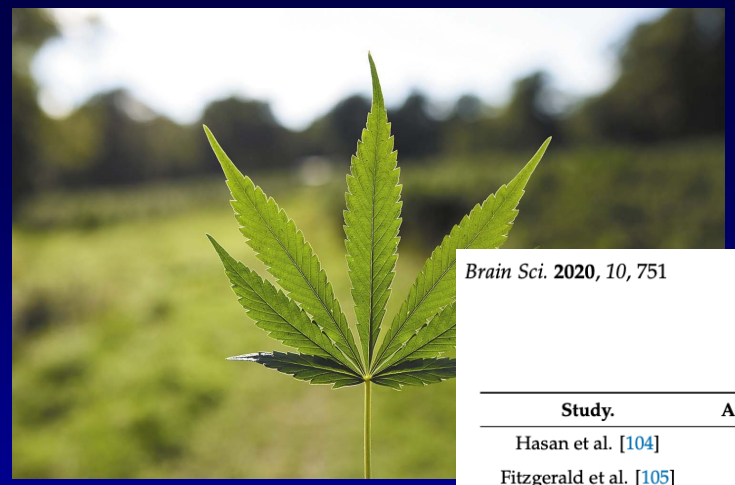


Table 2. Effects of cannabis on TMS measures.

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

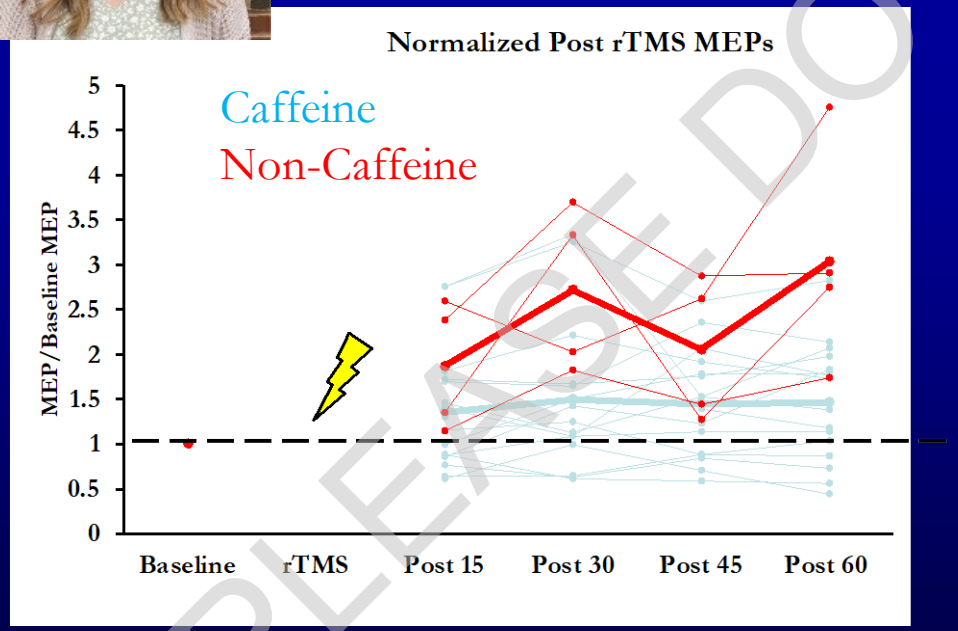
Matched: 16/28 responders, 11/28 remitters

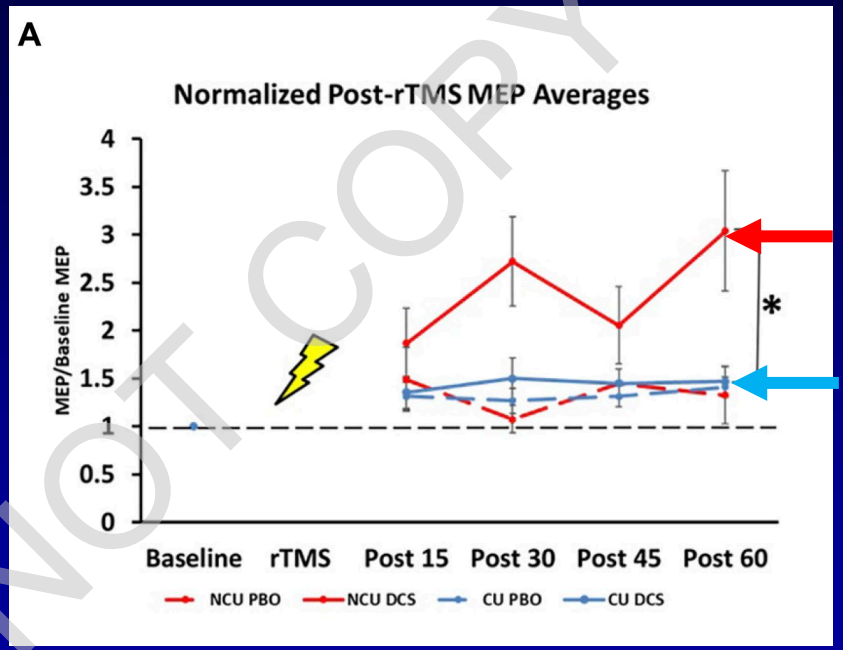
6 cases (Confusion, Psychosis, Sensory Changes, Panic)

-DePamphilis, *Brain Stimulation,* 2024

How about our Drug of Choice?

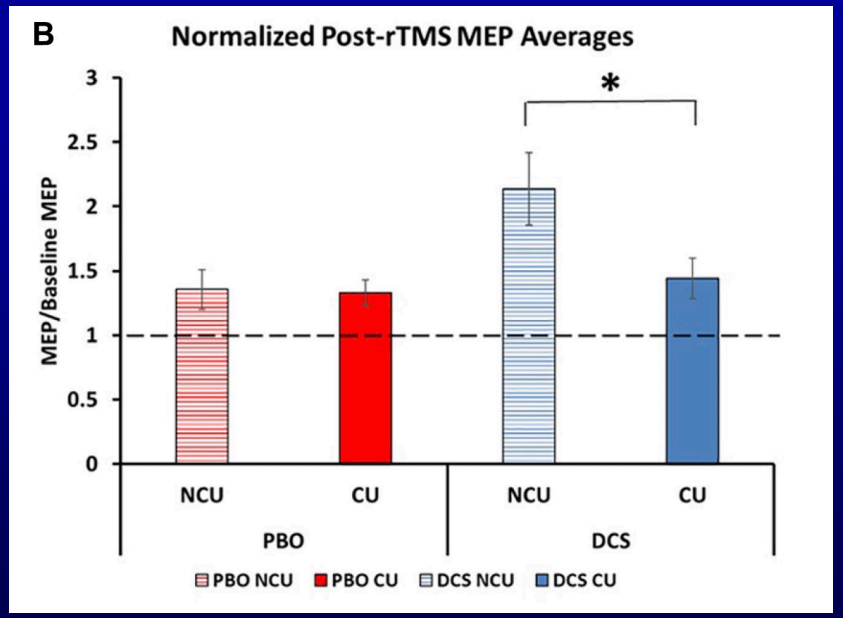
How Does the Most Common Stimulant (Caffeine) Effect TMS?





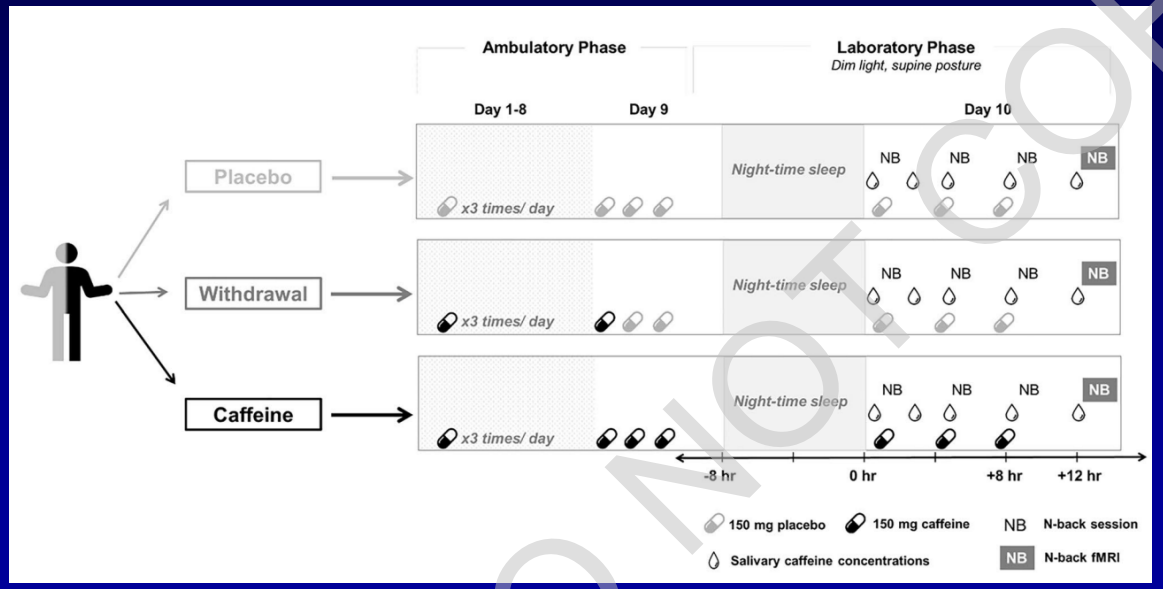
Caffeine-Free

Caffeine

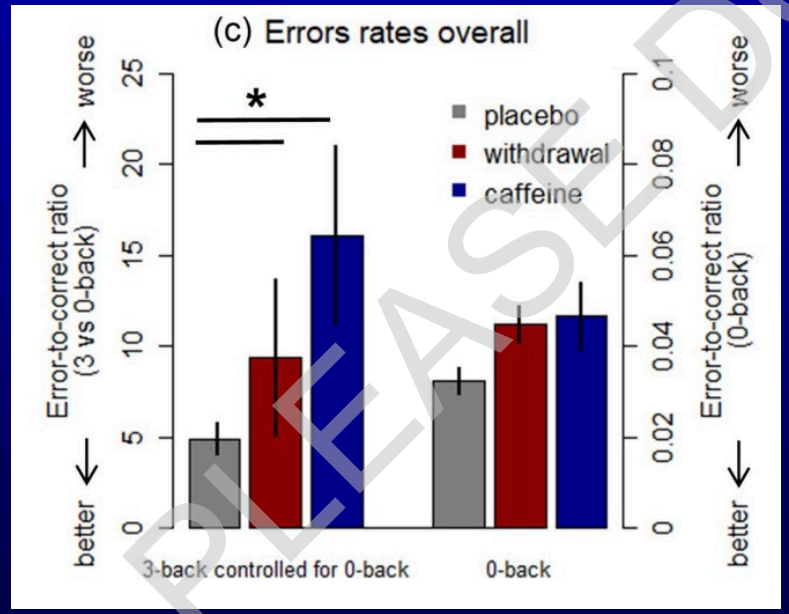


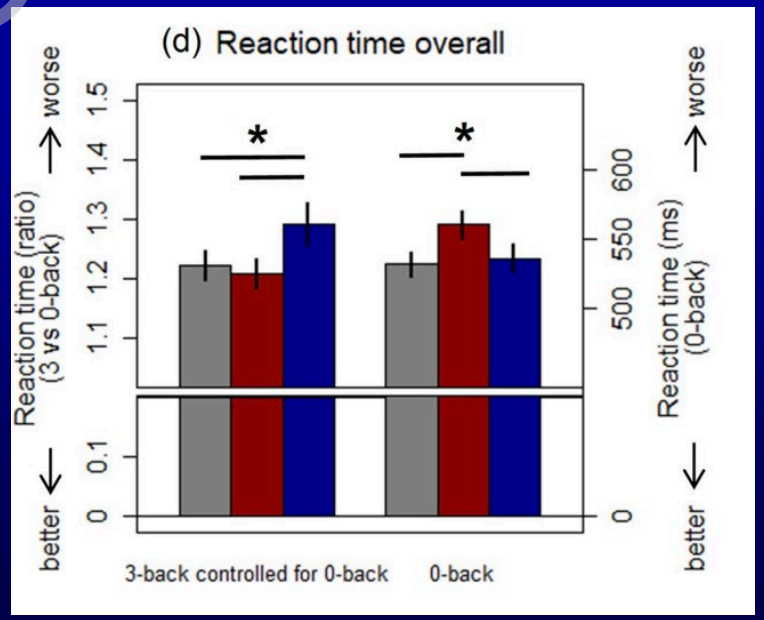
Vigne et al, *Front Psych*, 2023

BUT…Doesn't Caffeine Make Us Smarter?

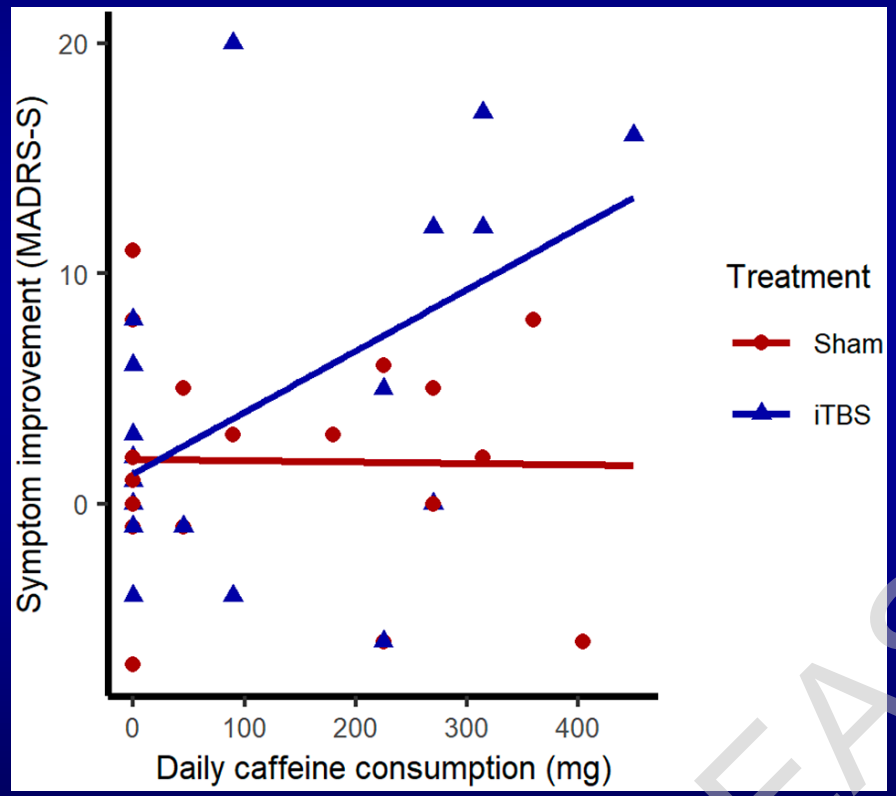


Lin et al, *Sci Reports*, 2023

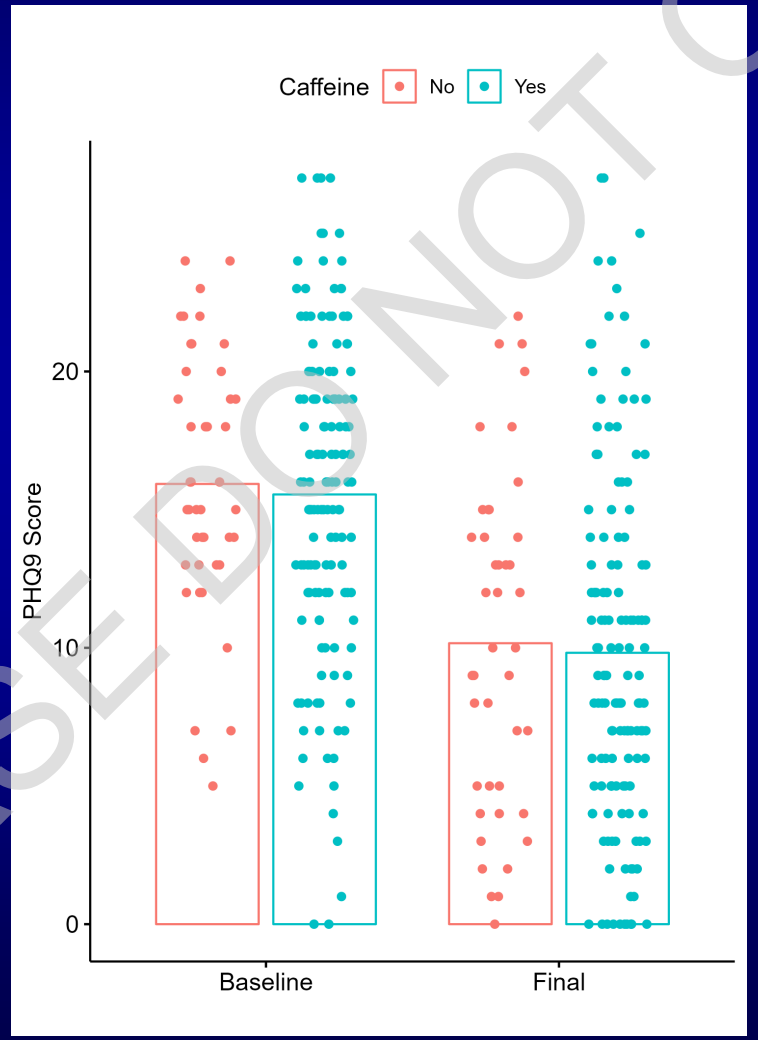




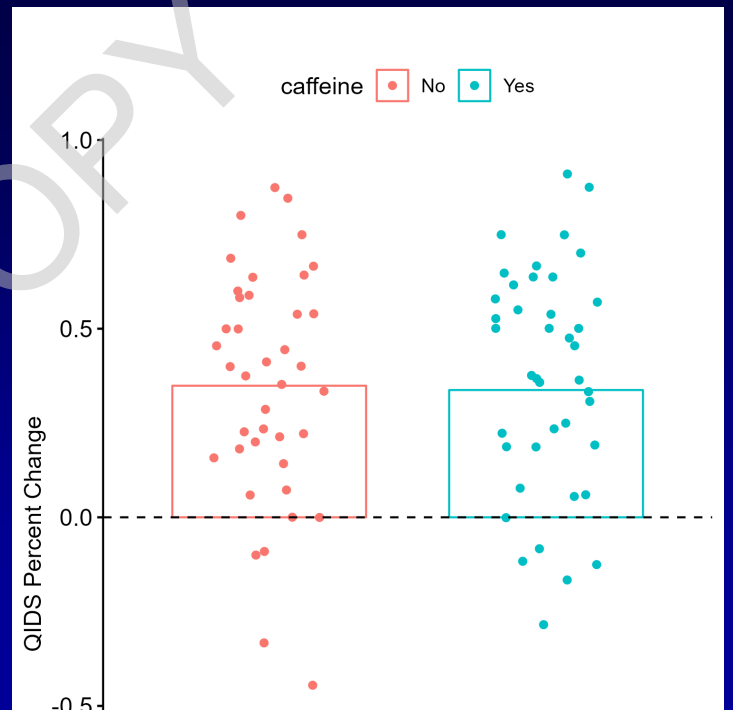
So, should we tell people not to use caffeine during TMS??

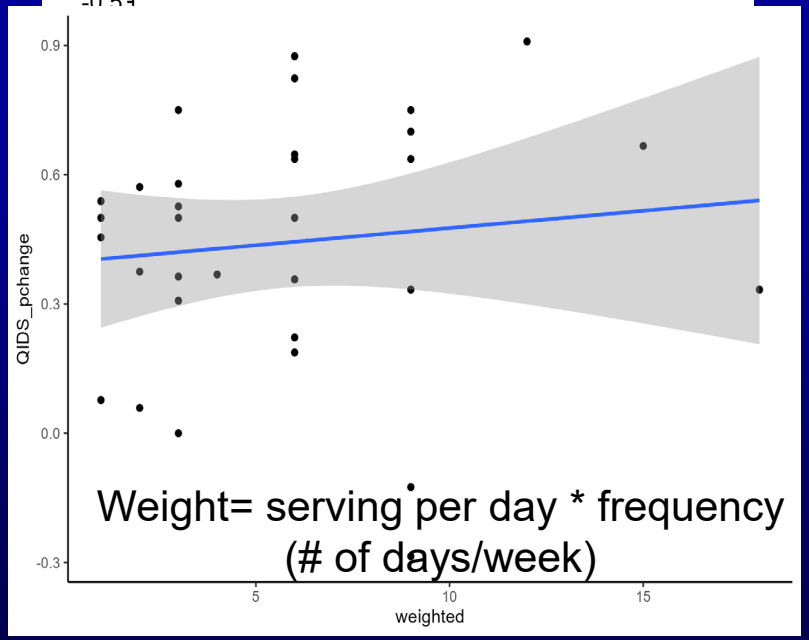


Frick et al, *Psychopharm*, 2021



Unpublished data



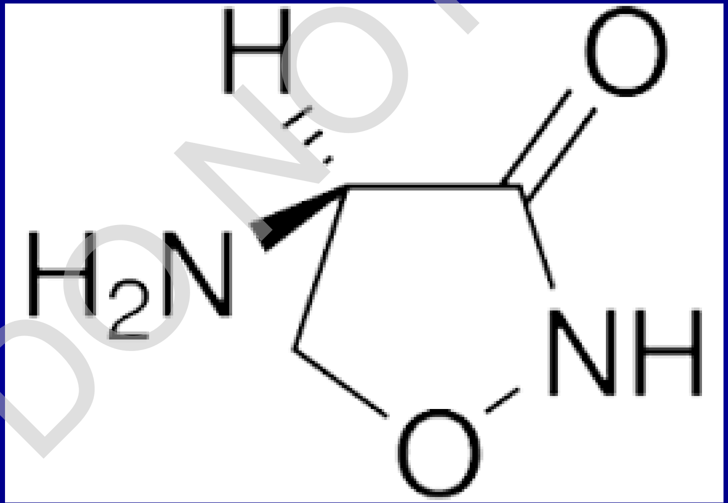


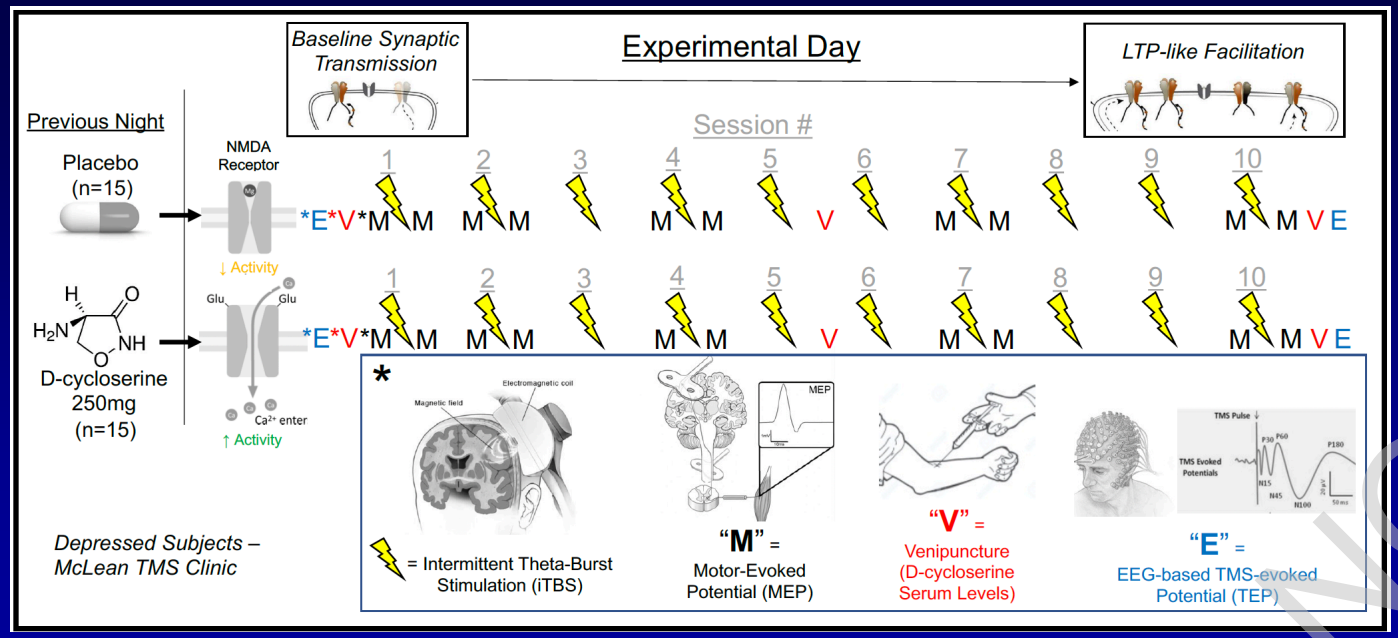
To the Future!

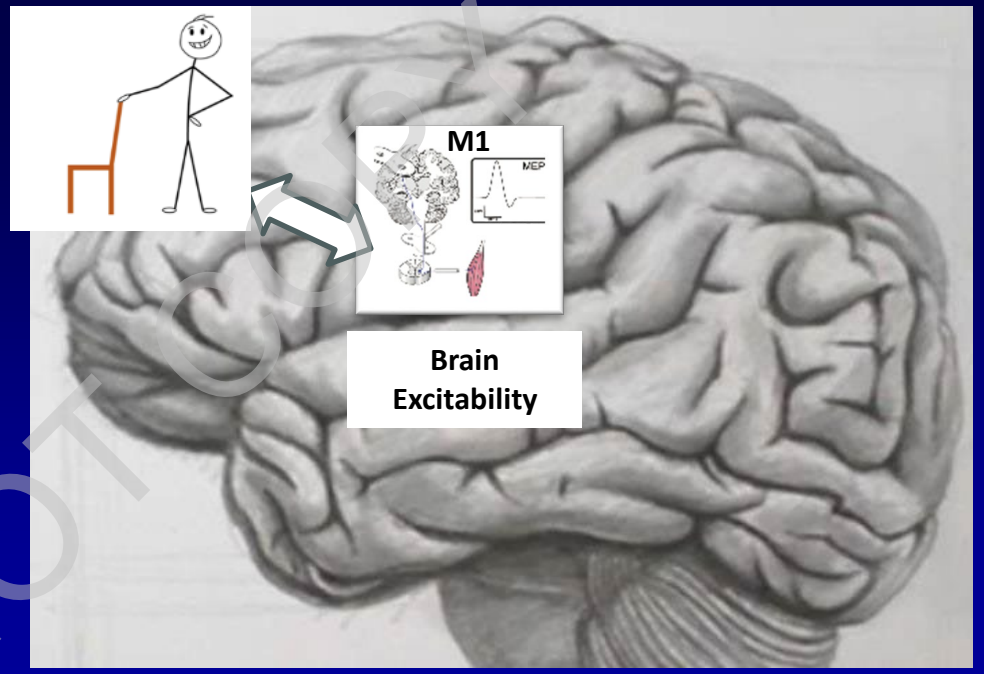
Can Accelerated TMS be Augmented?

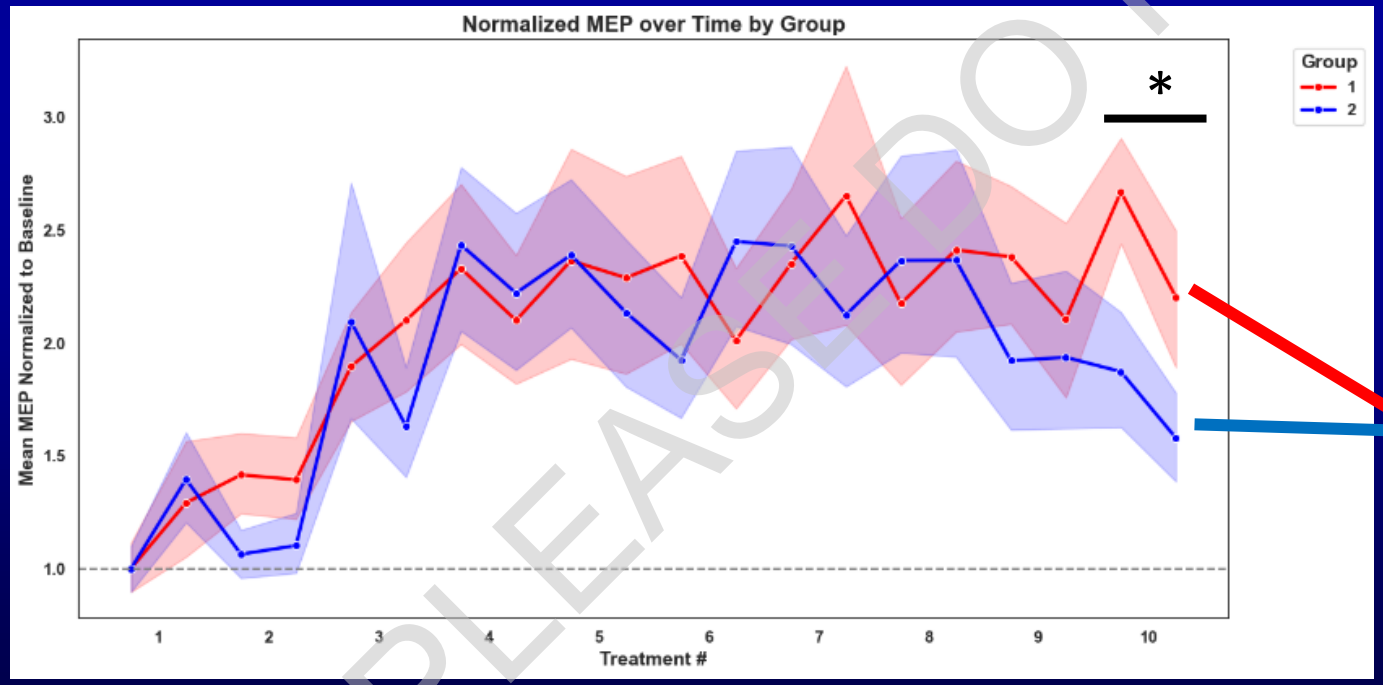
Day 1	Day 2	Day 3	Day 4	Day 5
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI

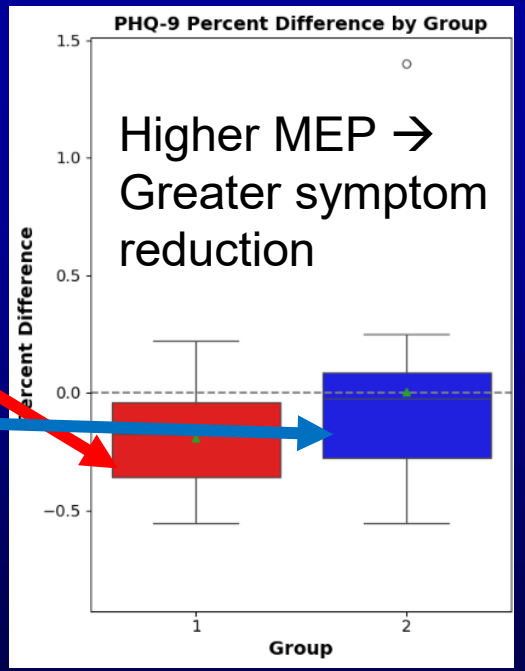
Cole et al., 2021







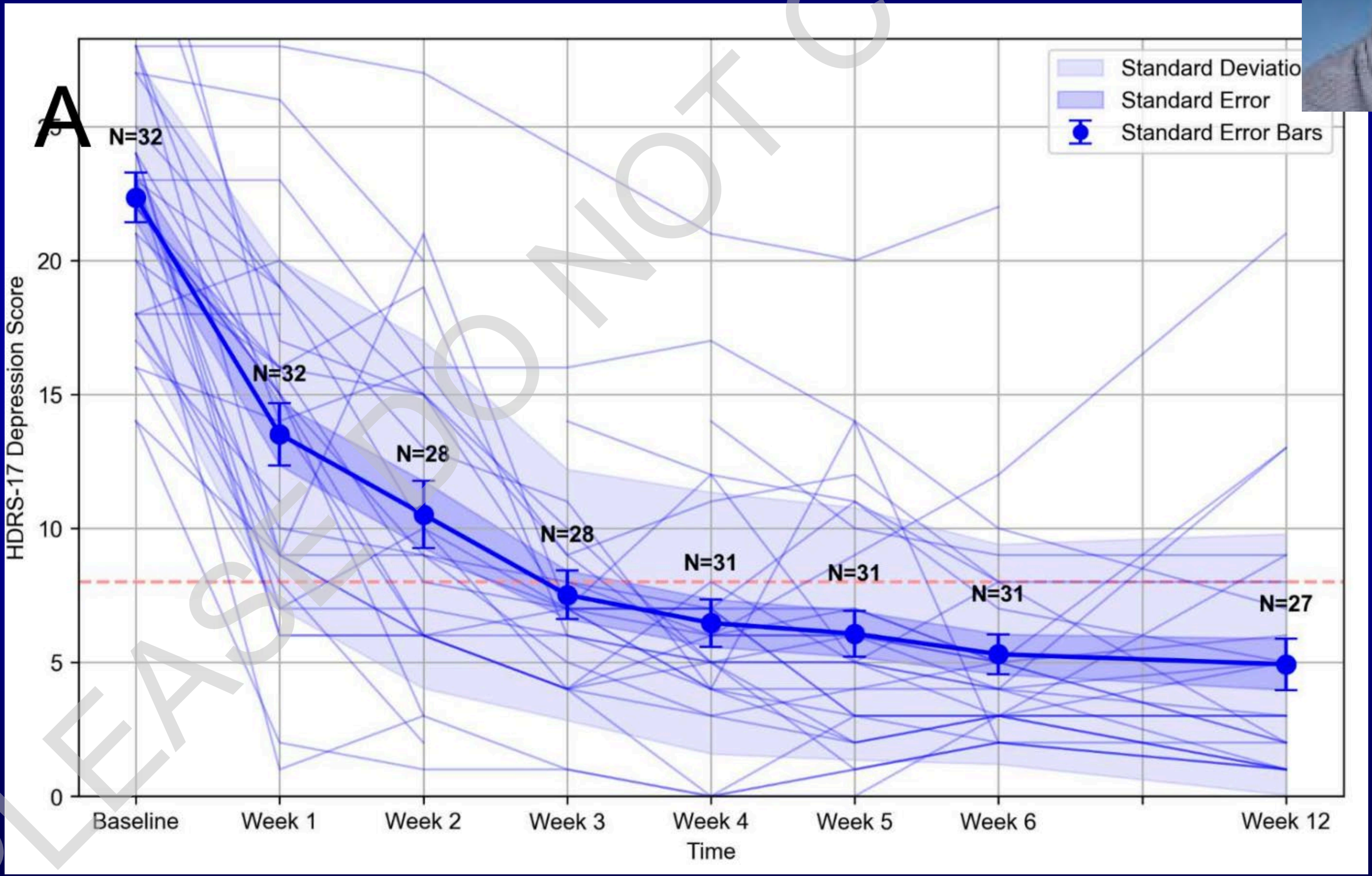


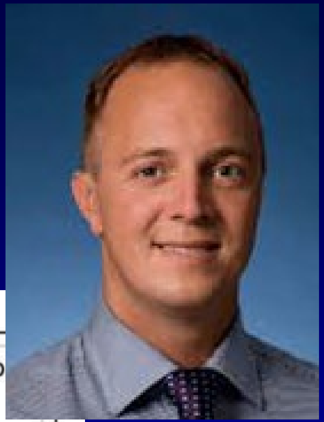


(Blinded) Red group has higher MEPs at end of day – corresponds with greater clinical improvement

"One-D"

Day 1
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI
iTBS 600
25 minute ISI





Vaughn et al, *Res Sq*, 2024

Take Home Points – TMS & Pharmacology

- NOTHING has level of evidence to recommend widespread implementation
- NMDAR agonism (d-cycloserine) has RCT and open-label and physiology data suggesting benefit (Only RCT)…this is close.
- Antidepressants and mood stabilizers seem to help overall TMS response (nothing prospective)
- Ketamine, SNRI = no benefit when added to TMS.
- 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?