

Pharmacology of TMS

Joshua C. Brown, MD, PhD

Director | Brain Stimulation Mechanisms Laboratory | McLean Hospital
Medical Director | Transcranial Magnetic Stimulation | McLean Hospital
Director of Research | Transcranial Magnetic Stimulation | McLean Hospital
Member of the Faculty | Department of Psychiatry | Harvard Medical School



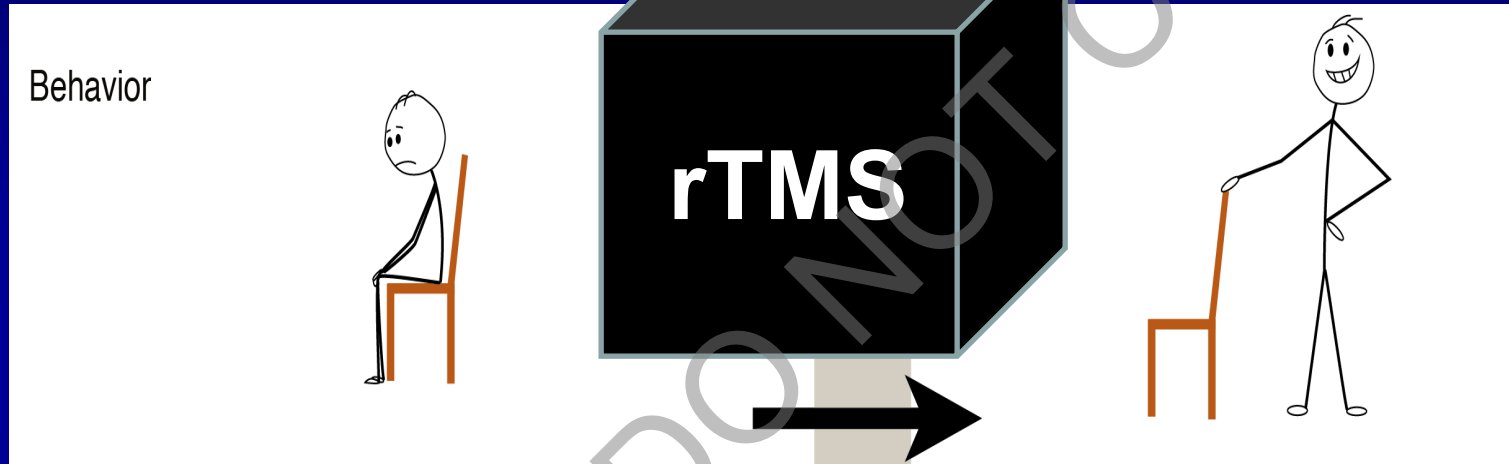
No Personal Financial Support

No Monetary Support from Industry

Generous Unrestricted Support from
Philanthropy

Disclosures





How does rTMS produce lasting therapeutic changes in the brain?

How The Brain Works

Electro

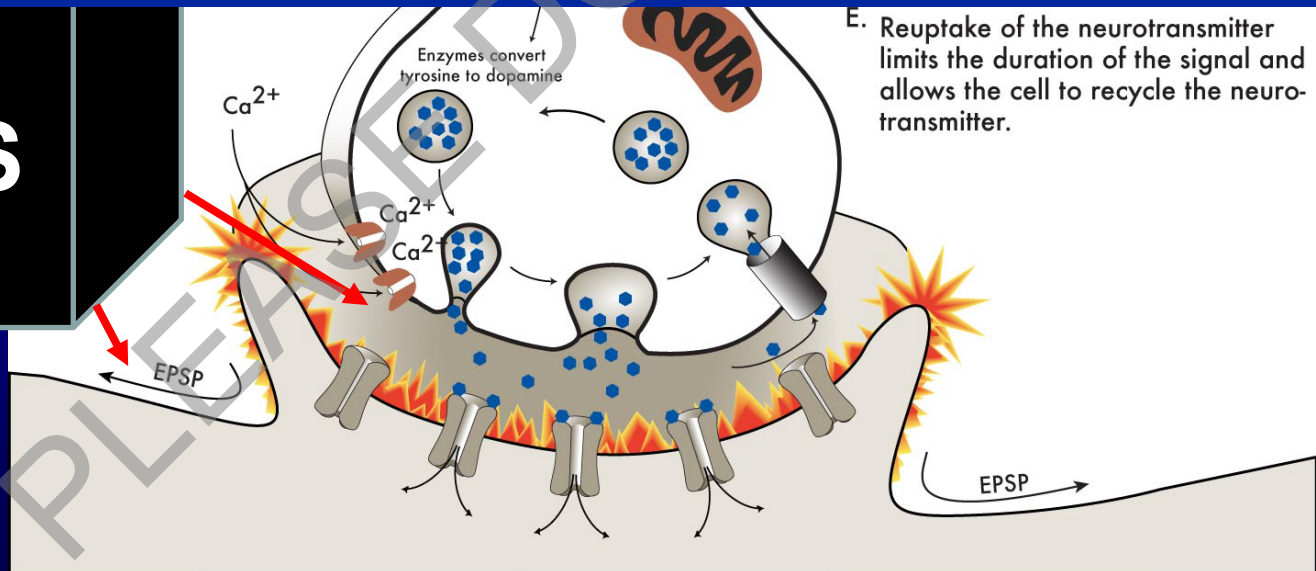
Chemical

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

rTMS

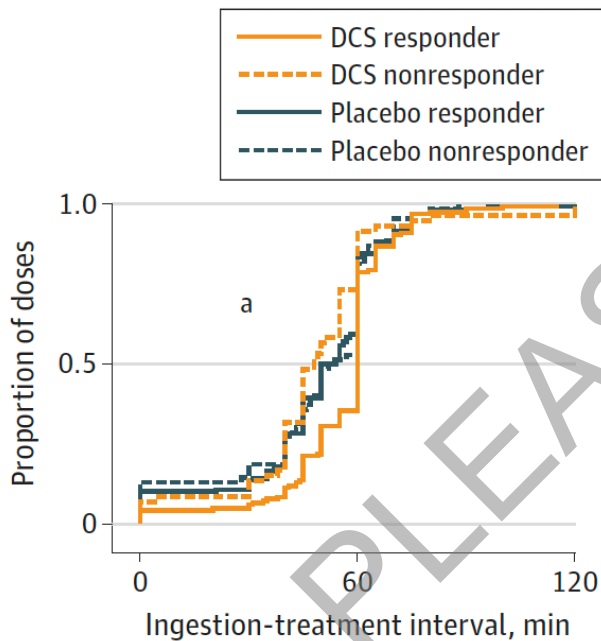


The End at the Beginning

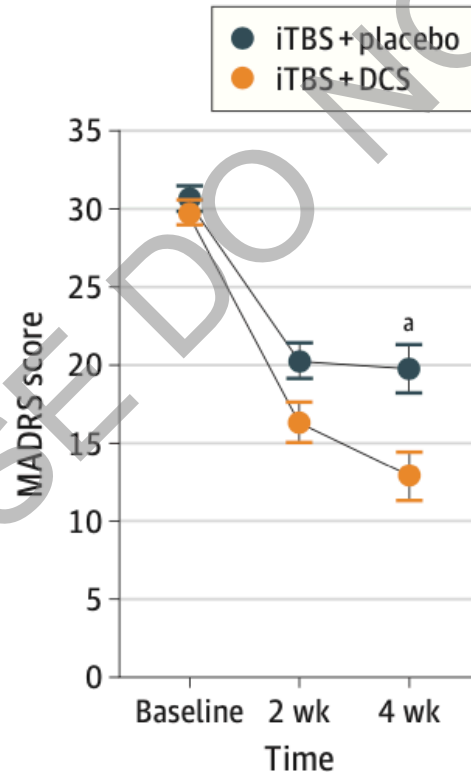


Figure 2. Clinical Outcomes in Participants Who Received Intermittent Plus Placebo and iTBS Plus D-Cycloserine (DCS)

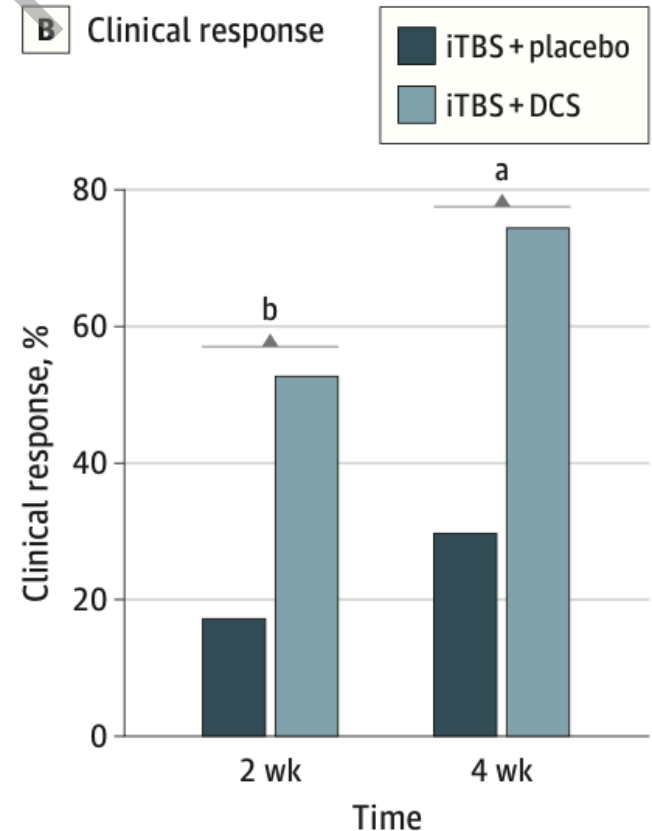
F Cumulative distribution



A MADRS score



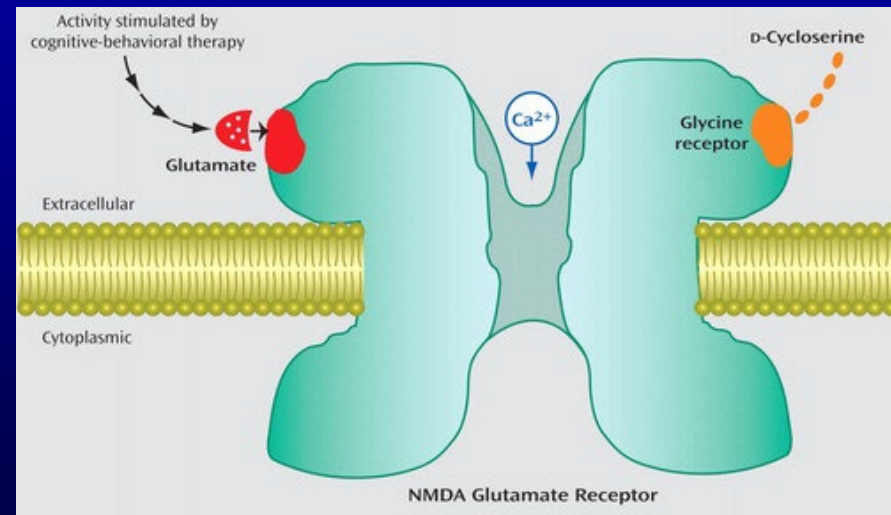
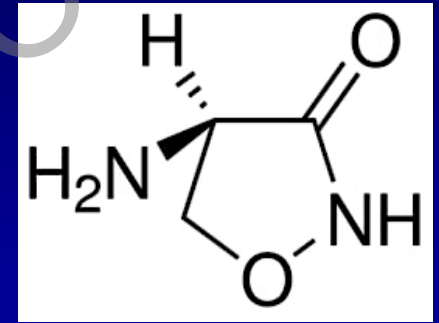
B Clinical response



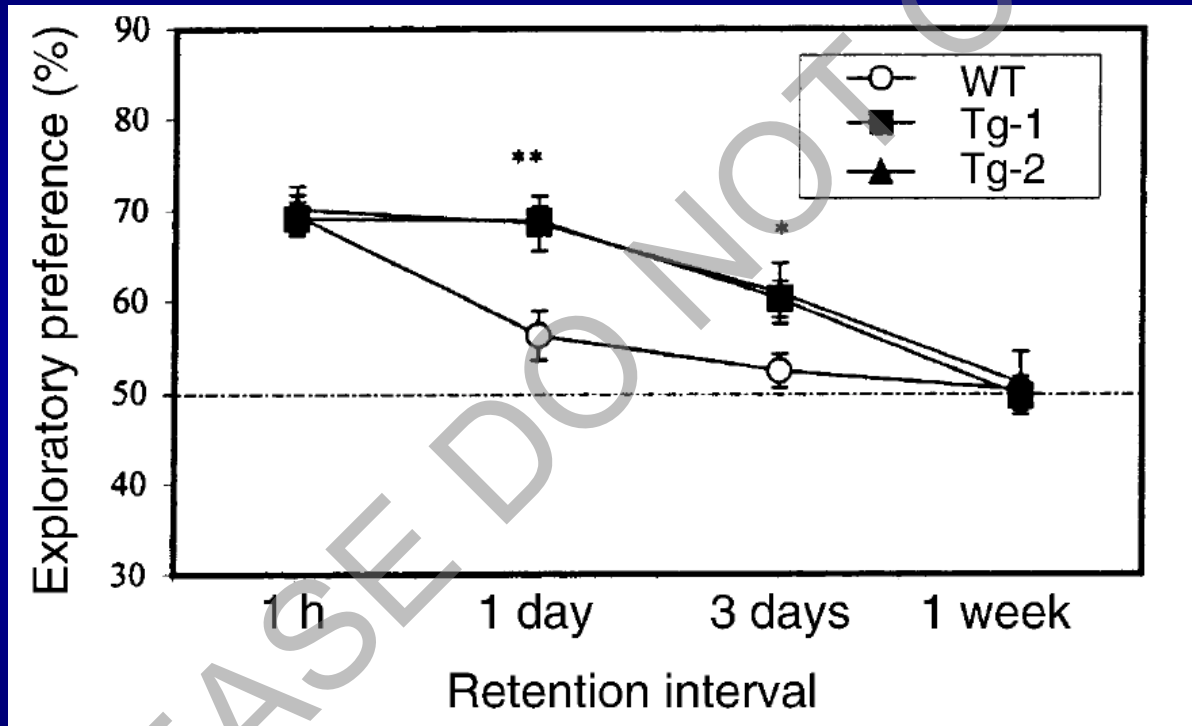
Why d-cycloserine?

- FDA-approved for Tuberculosis
- FDA-approved for Cystitis
- **NMDA receptor partial agonist**

- At low doses:
 - NMDA receptor agonist



Why the NMDA receptor?

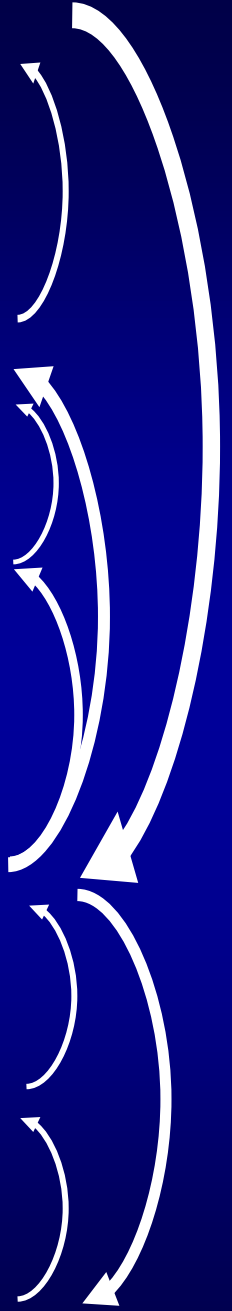
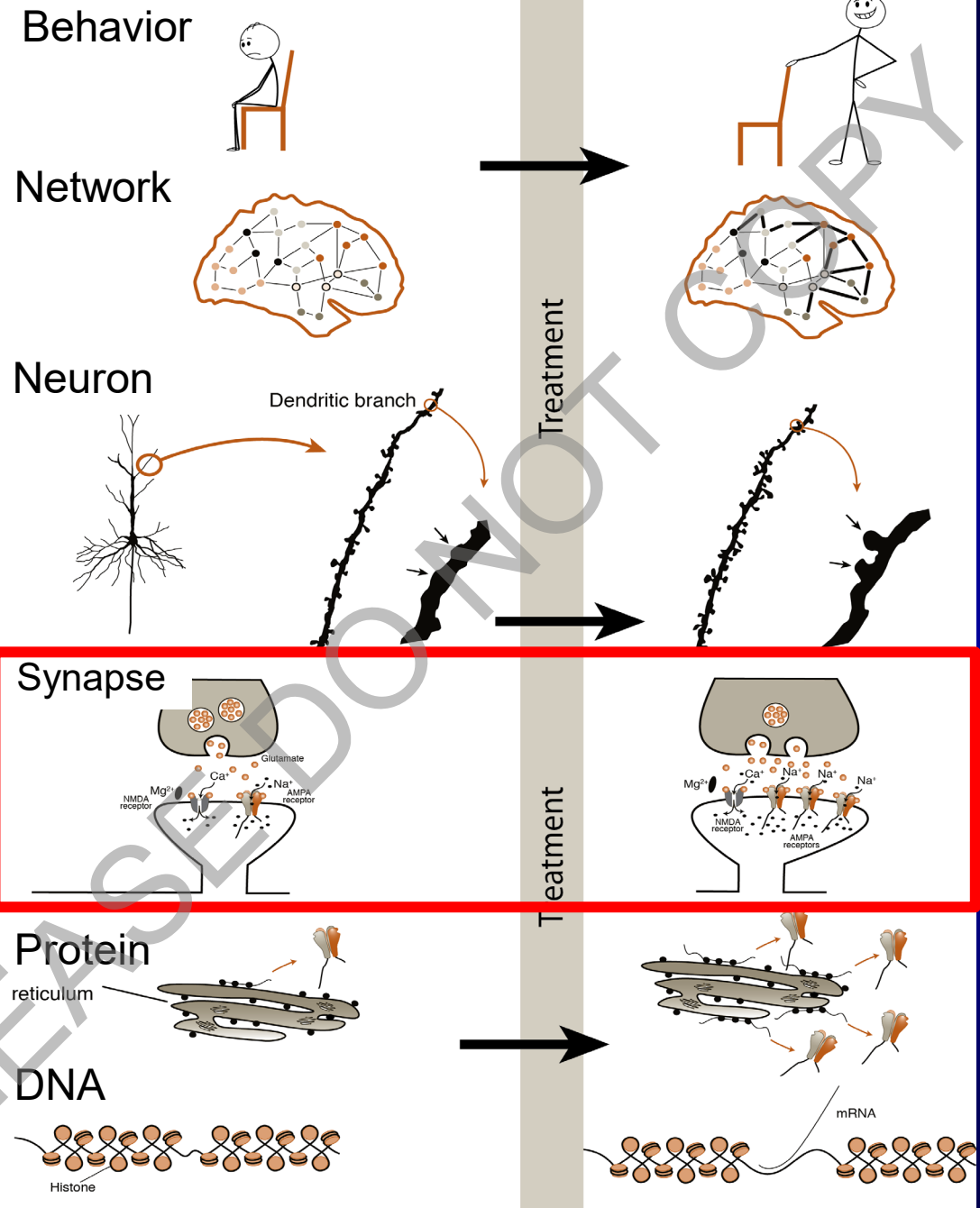


Tang et al., *Nature*, 1999

What Suberves Network and Behavioral Effects?

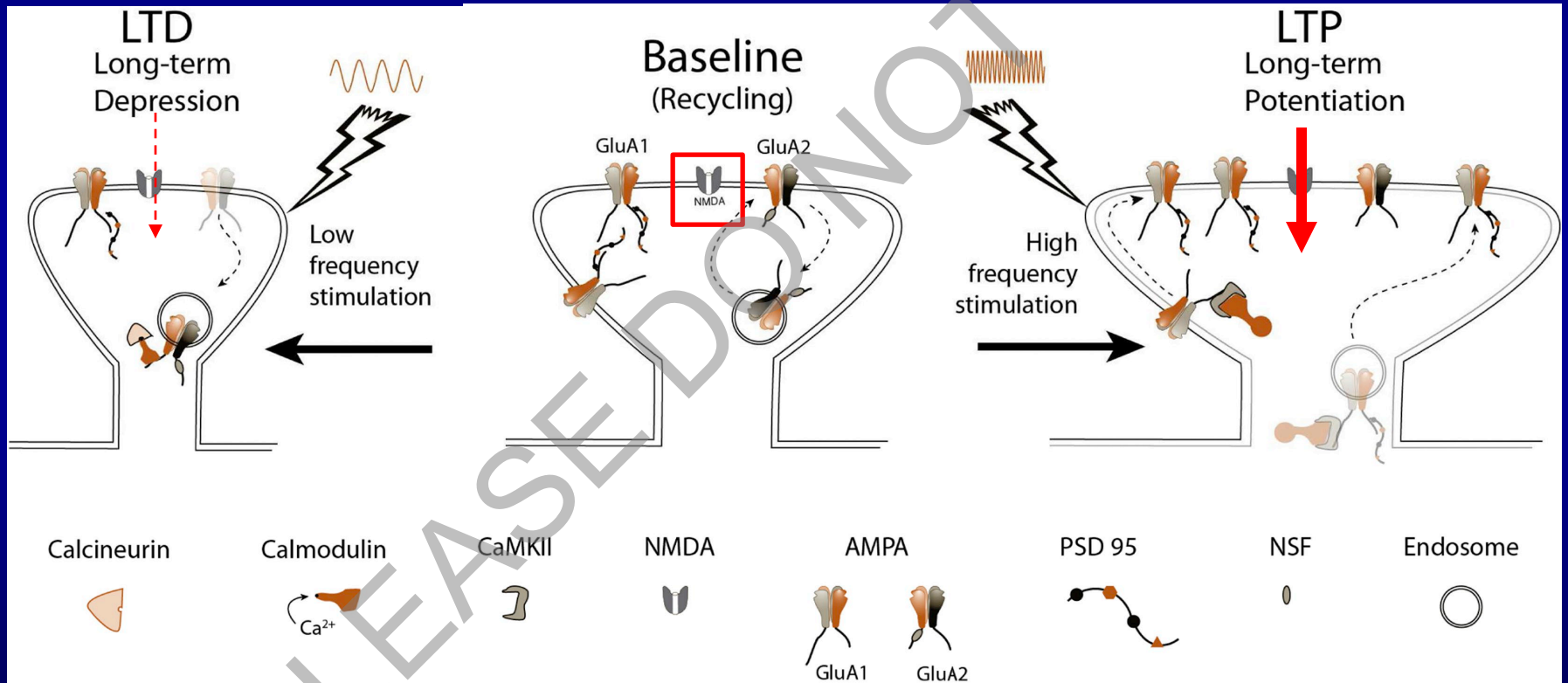
Macro

Micro



Synaptic Plasticity

critically depends on NMDA receptors

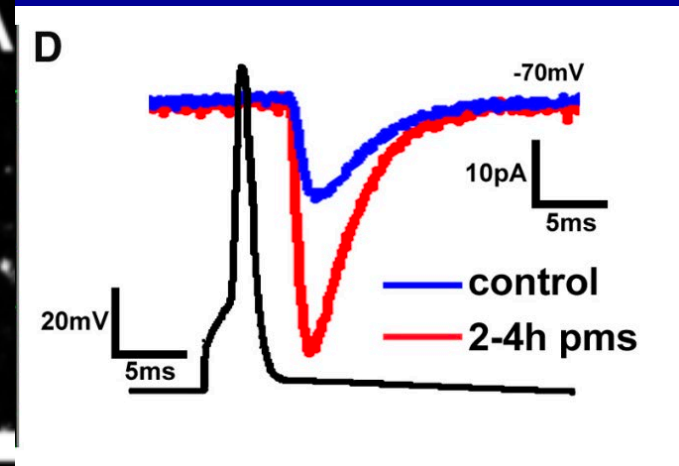
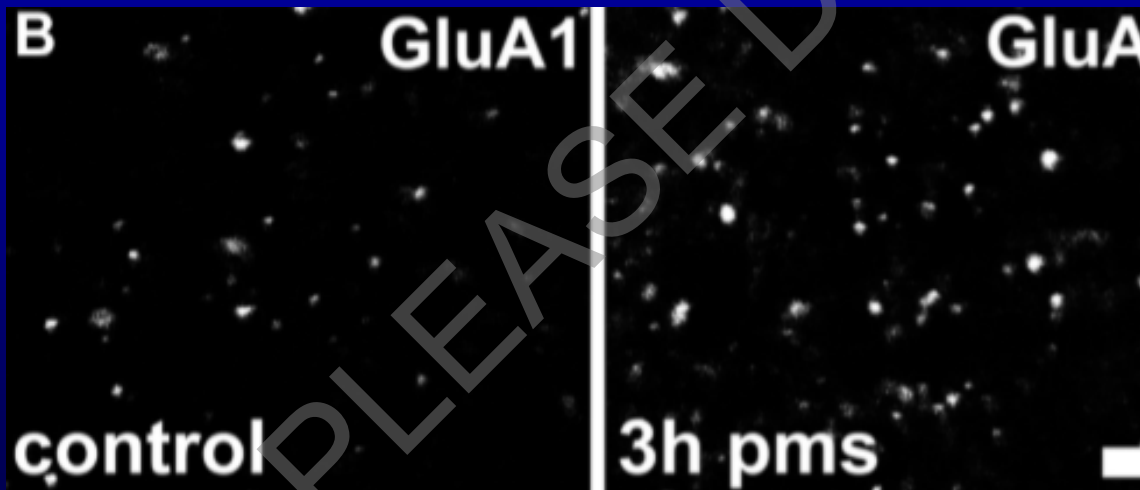
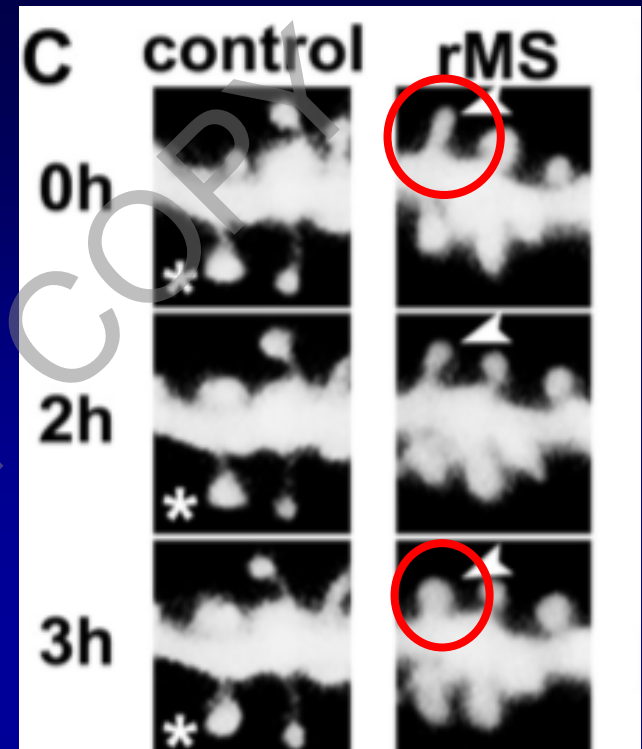
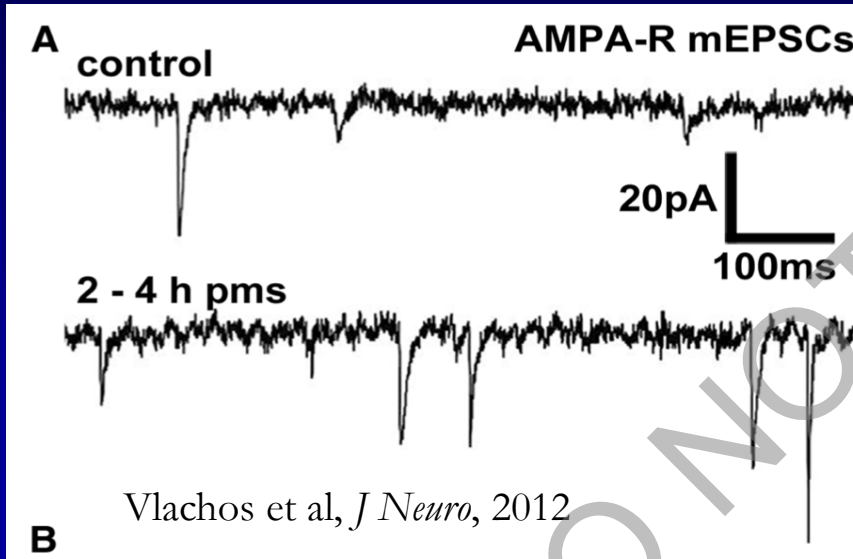


Brown, Higgins & George, *Neuromodulation*, 2022

Does TMS Work through
LTP-like Mechanisms??

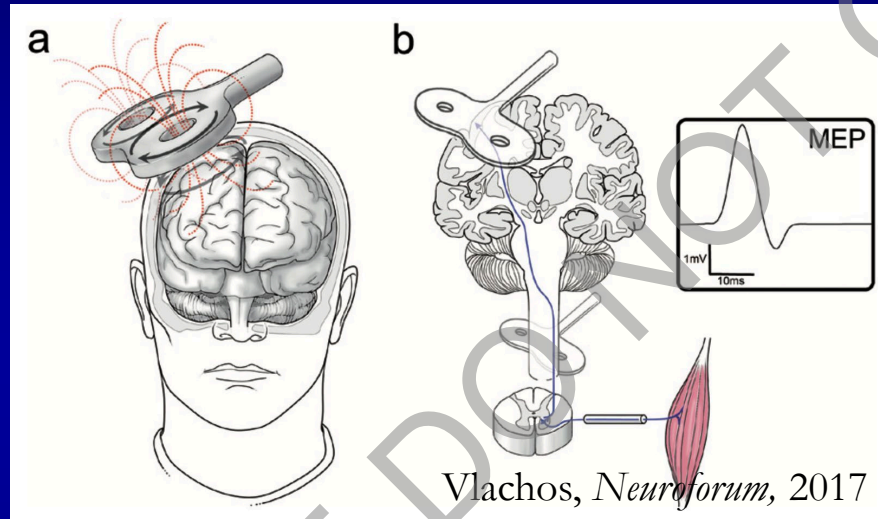
PLEASE DO NOT COPY

Does “LTP-like” = LTP?

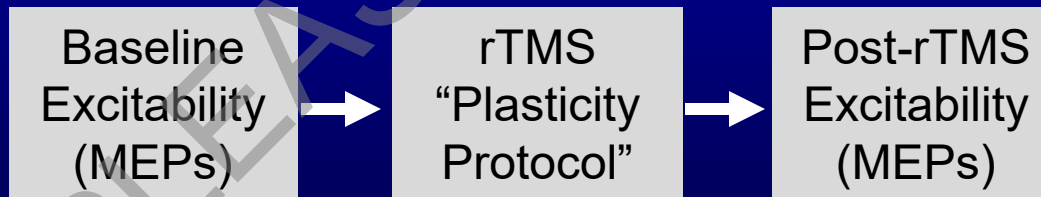


Testing plasticity in humans

Motor-Evoked Potentials



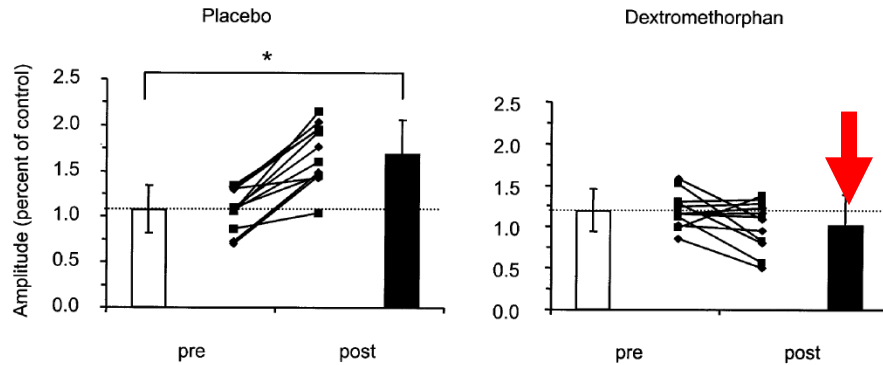
Receptor Modulation



Δ MEP =
PLASTICITY

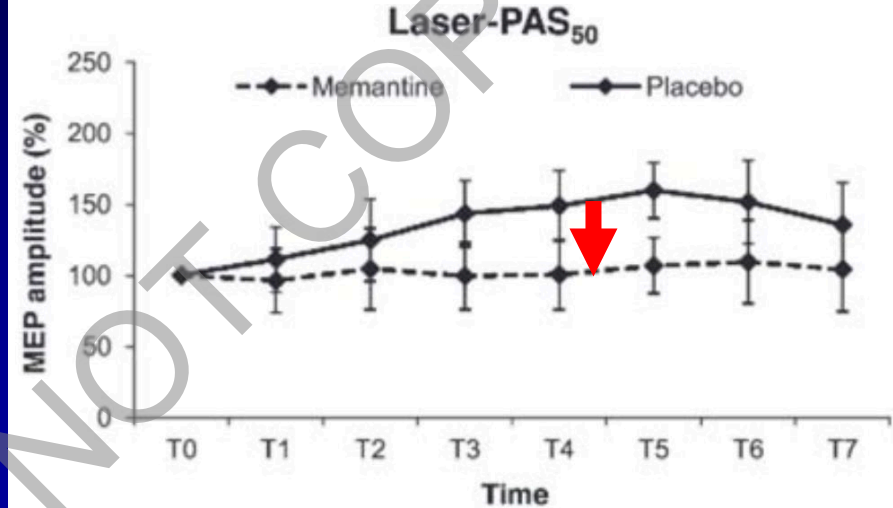
Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation

Katja Stefan *, Erwin Kunesch *, Reiner Benecke *, Leonardo G. Cohen † and Joseph Classen * ‡



Heat-Evoked Experimental Pain Induces Long-Term Potentiation-Like Plasticity in Human Primary Motor Cortex

A. Suppa¹, A. Biasiotto², D. Belvisi², L. Marsili², S. La Cesa², A. Truini², G. Cruccu² and A. Berardelli^{1,2}

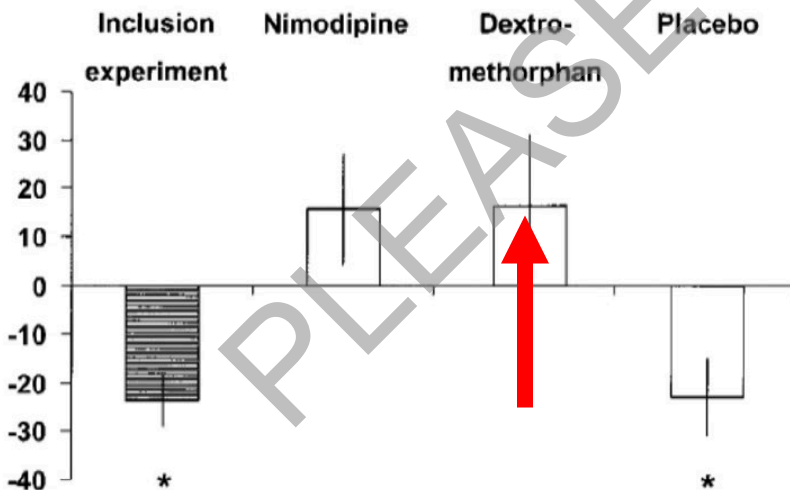


translational physiology

J Neurophysiol 89: 2339–2345, 2003.
 First published January 22, 2003; 10.1152/jn.00900.2002.

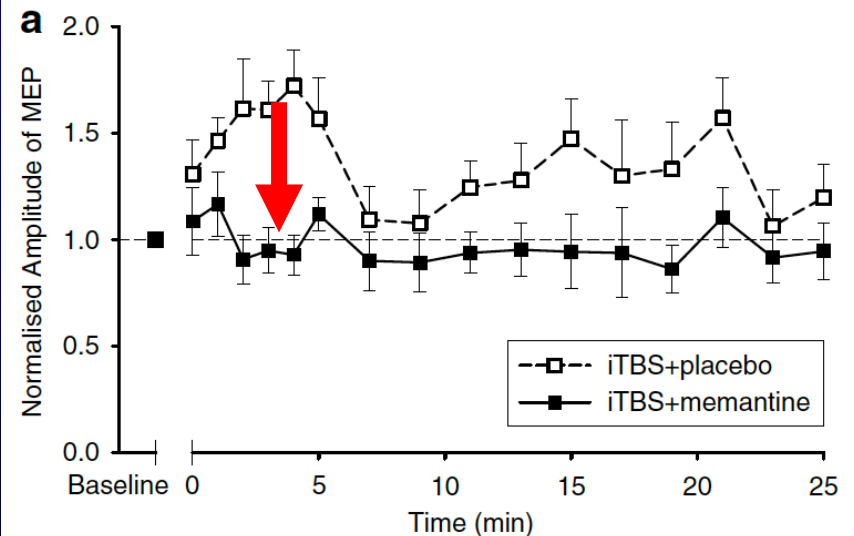
A Temporally Asymmetric Hebbian Rule Governing Plasticity in the Human Motor Cortex

Alexander Wolters,^{1,*} Friedhelm Sandbrink,^{1,*} Antje Schlottmann,¹ Erwin Kunesch,¹ Katja Stefan,¹ Leonardo G. Cohen,² Reiner Benecke,¹ and Joseph Classen^{1,3}



The after-effect of human theta burst stimulation is NMDA receptor dependent

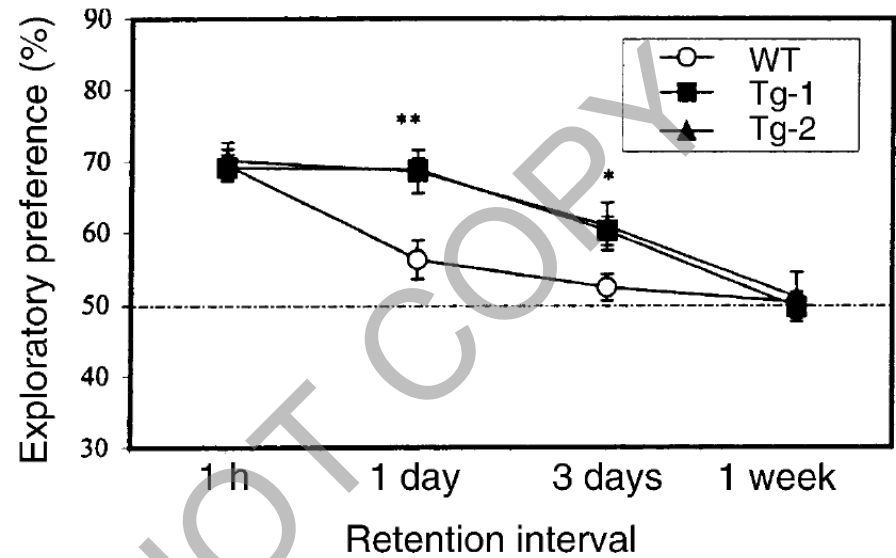
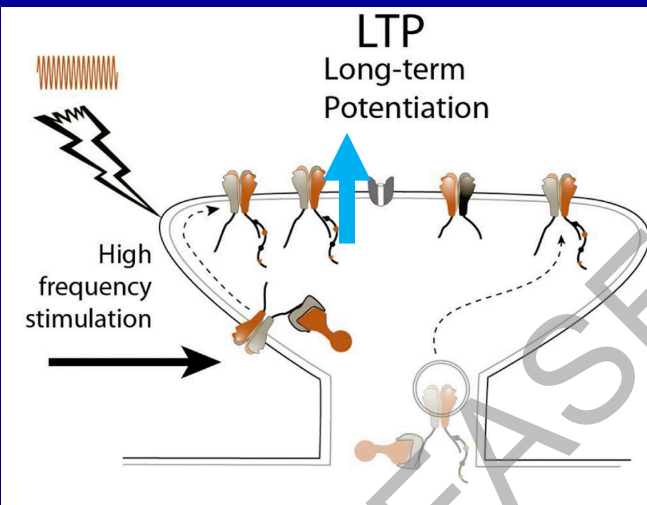
Ying-Zu Huang ^{a,*}, Rou-Shayn Chen ^a, John C Rothwell ^b, Hsin-Yi Wen



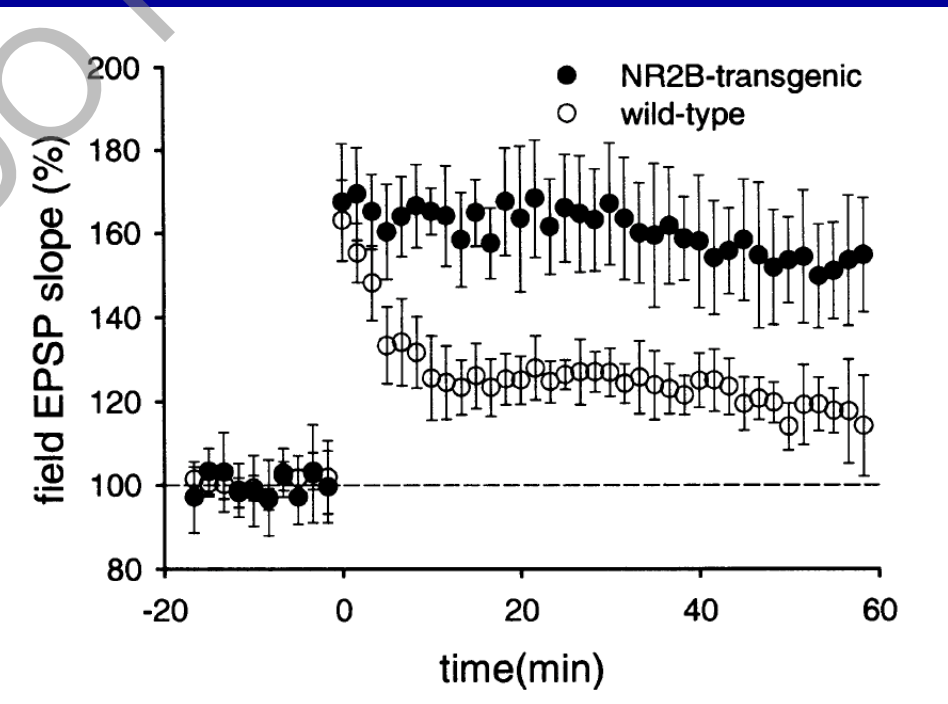
NMDAR Antagonism: Ketamine + rTMS?

- Systematic Review from Debowski et al, *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 (1 study a 2-year follow up)
 - 10-Hz x1
 - All report improvement
 - Conclusion: We don't yet know!

Are NMDARs Sufficient to Enhance TMS effects?

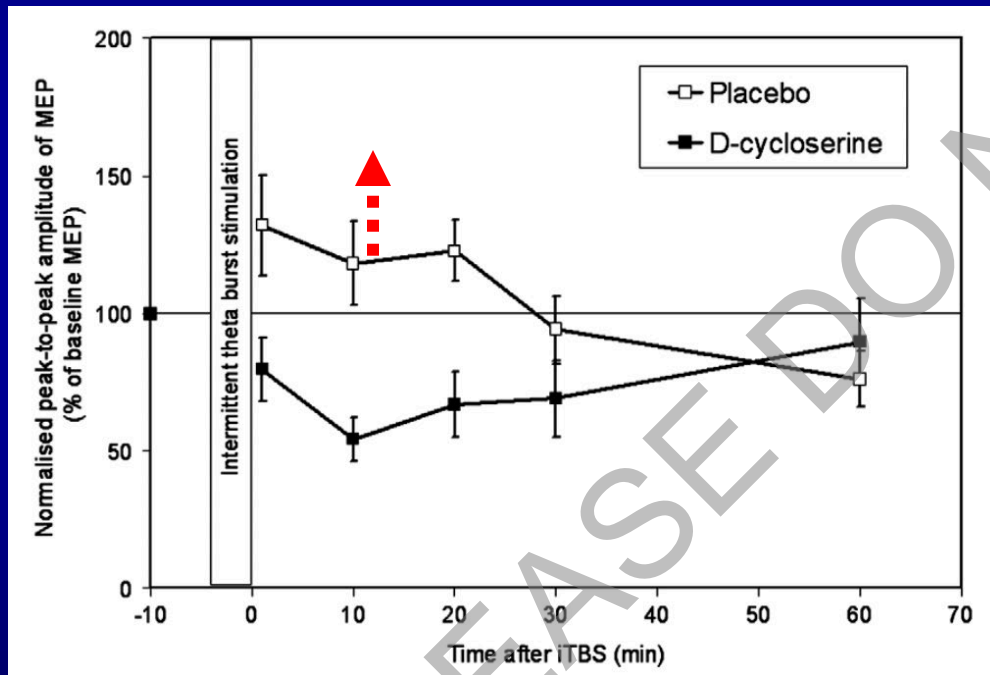


Tang et al., *Nature*, 1999

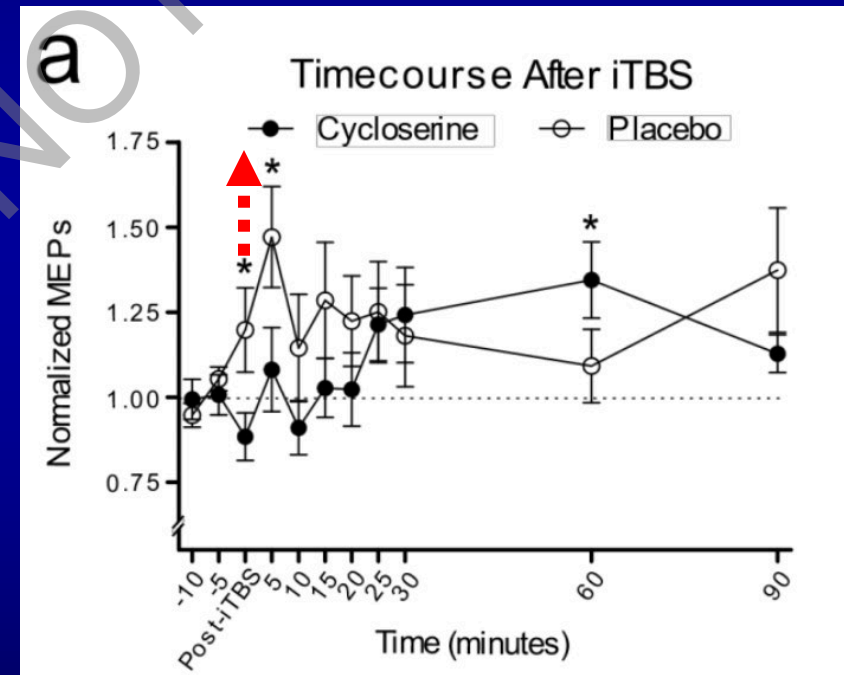


Tang et al., *Neuropharmacology*, 2001

Is NMDAR activation *sufficient* (specific) to enhance iTBS facilitation?

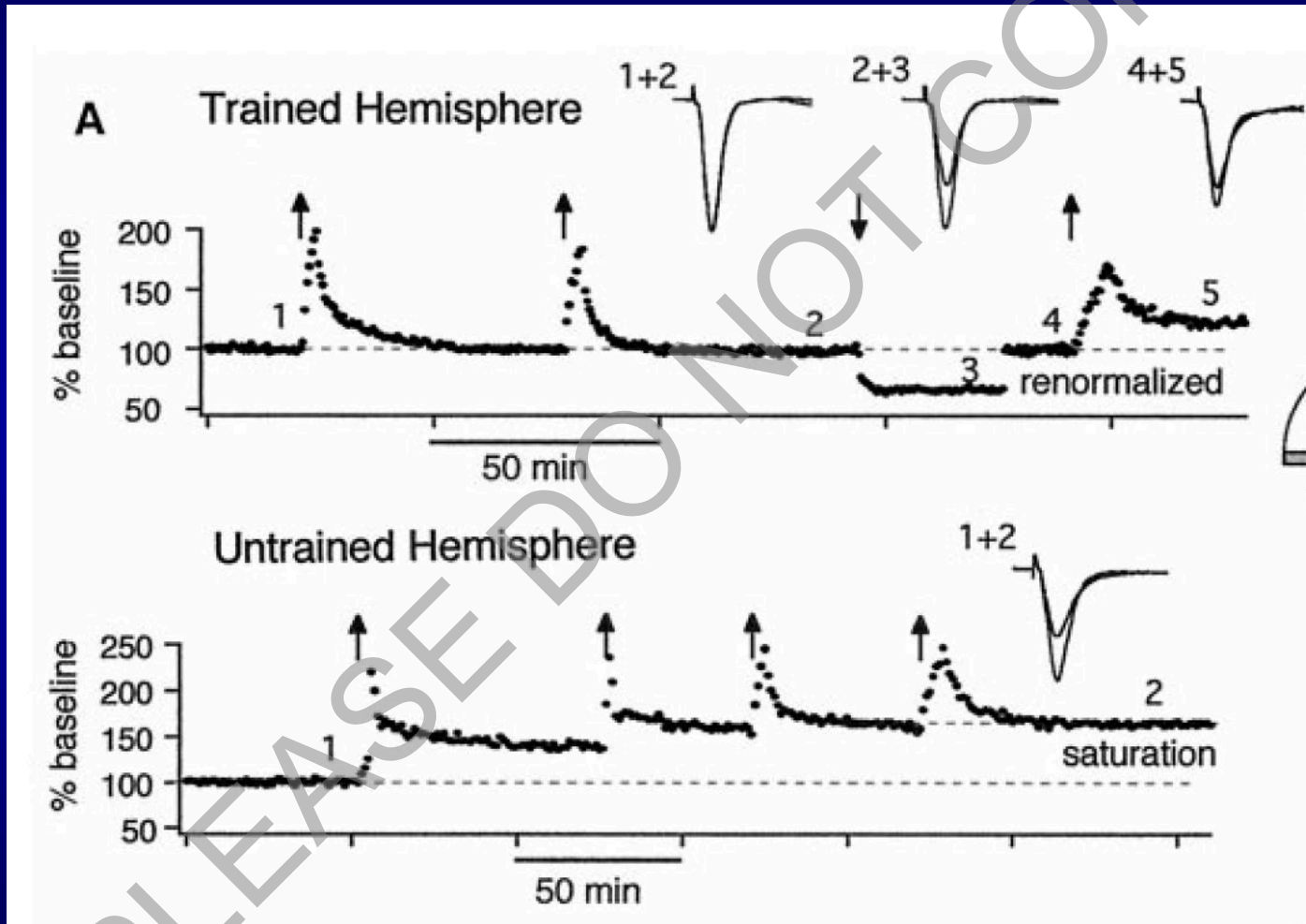


Teo et al, *Clin Neurophys*, 2007



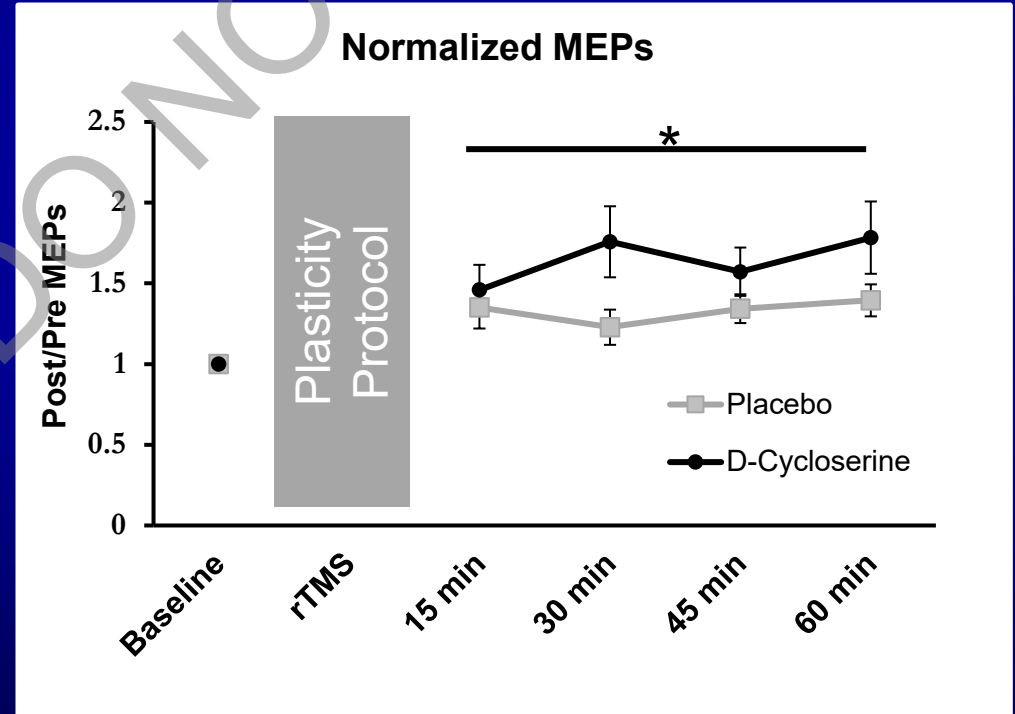
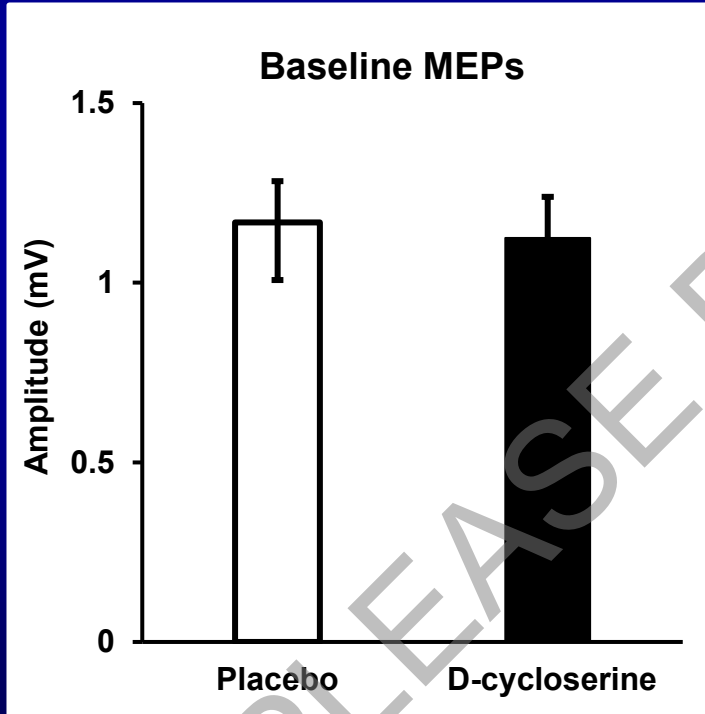
Selby et al, *Brain Stimulation*, 2019

Occlusion



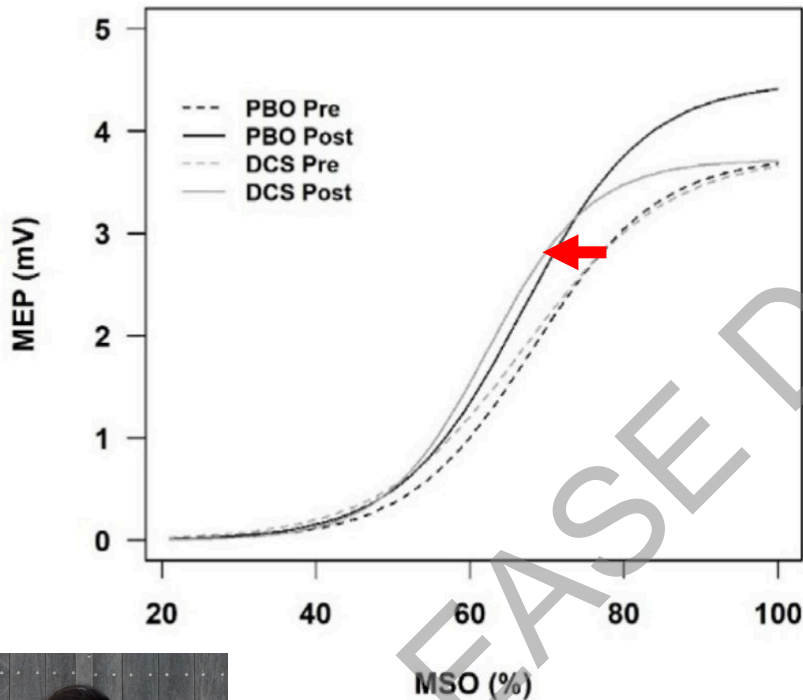
Riout-Pedotti et al, *Science*, 2000

NMDA Receptor Agonism Augments 10-Hz rTMS

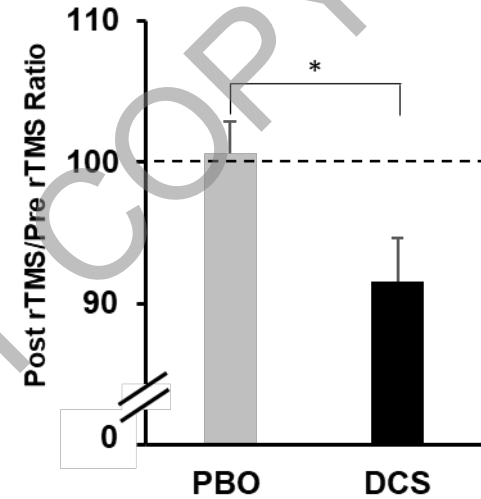


NMDA Receptor Activation Enhances Plasticity

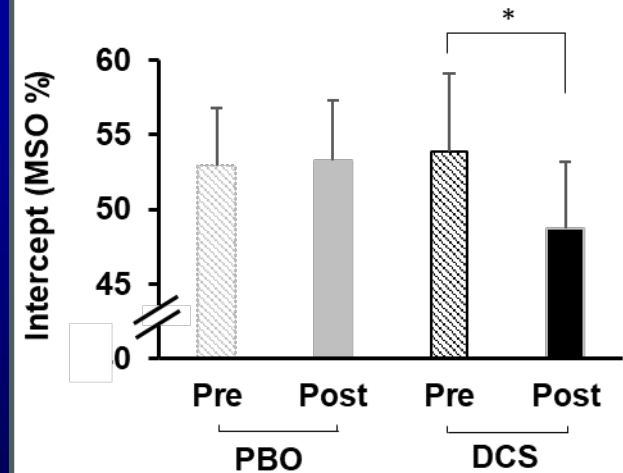
Recruitment Curves



Change in RC Intercept after rTMS



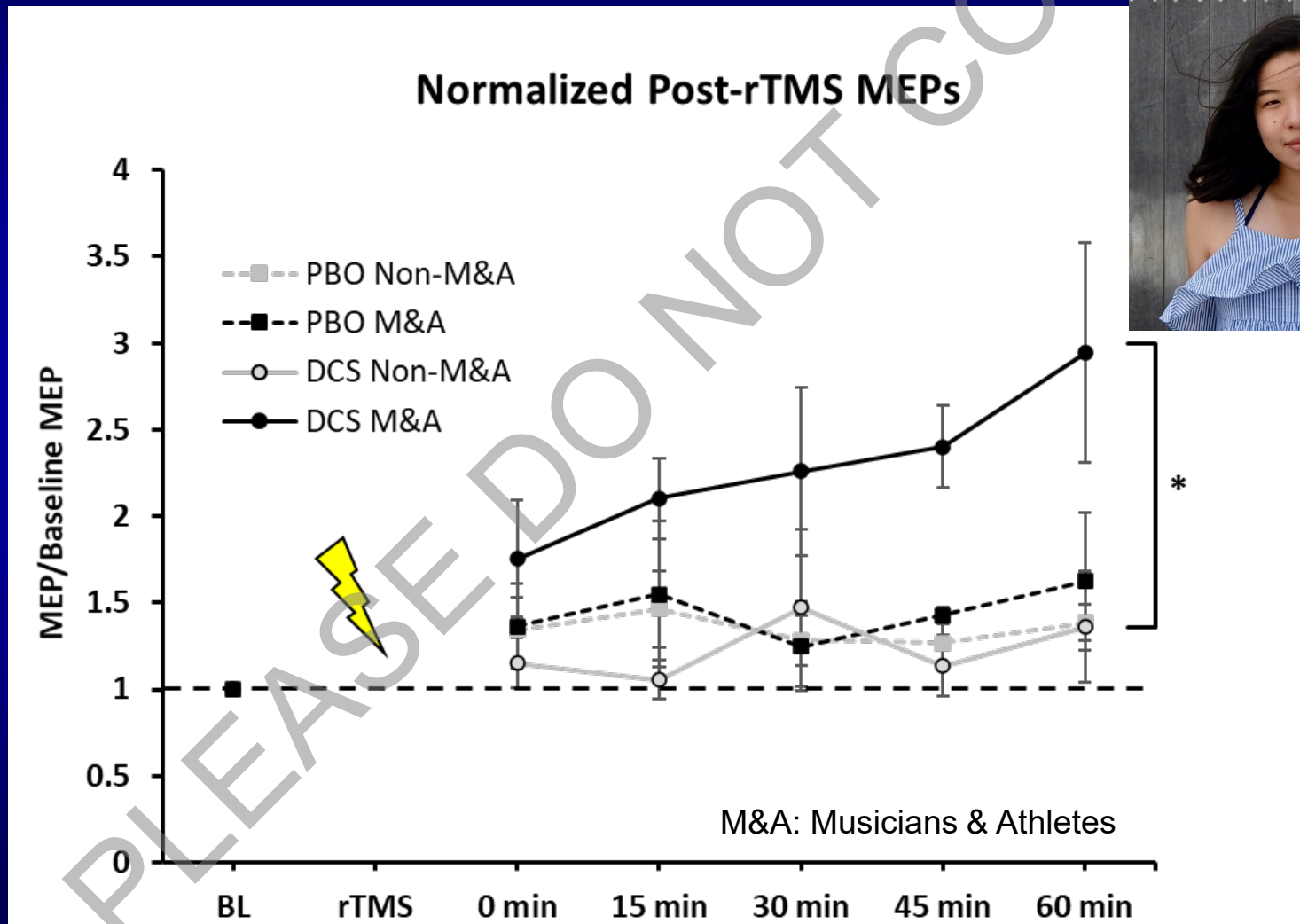
Average RC Intercepts



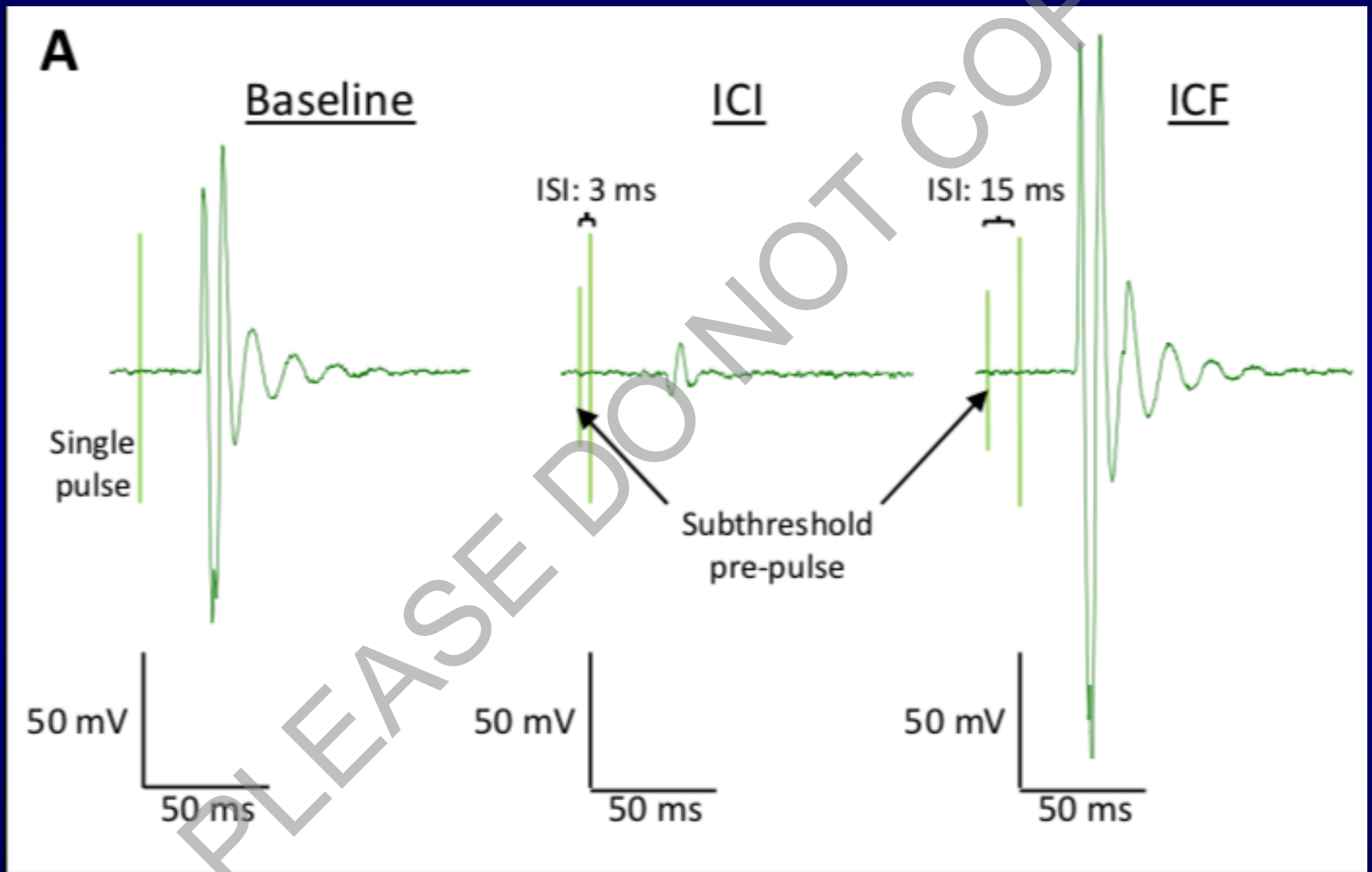
Kweon et al., *Brain Stimulation*, 2022



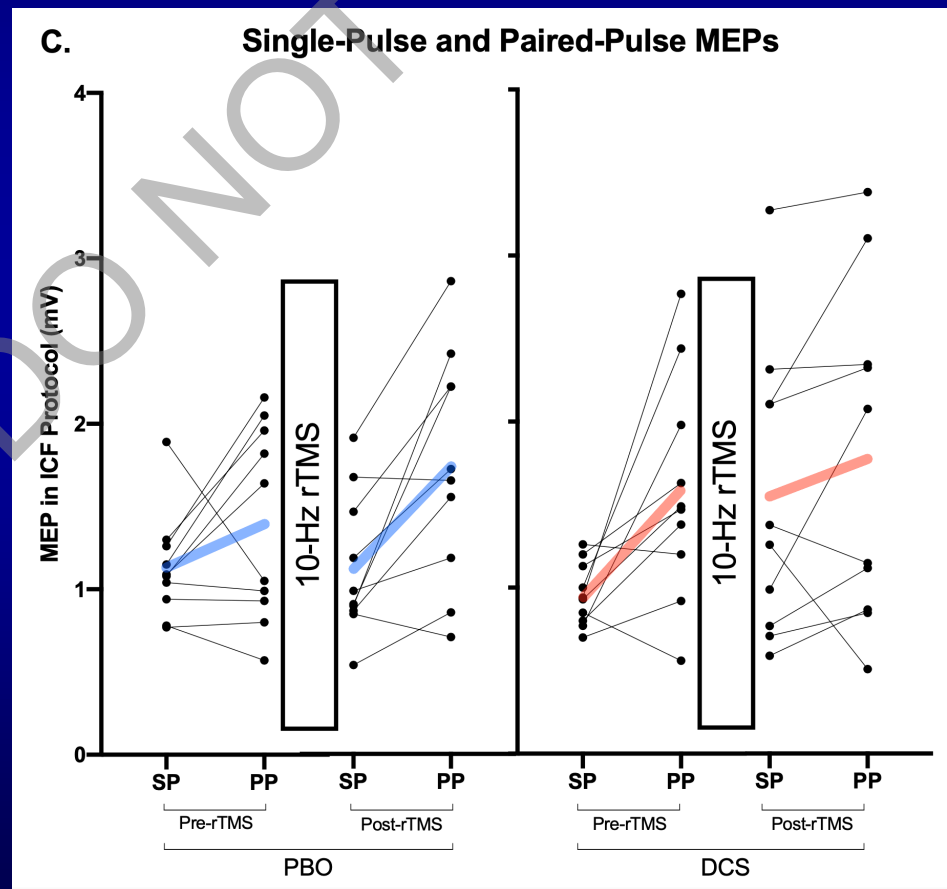
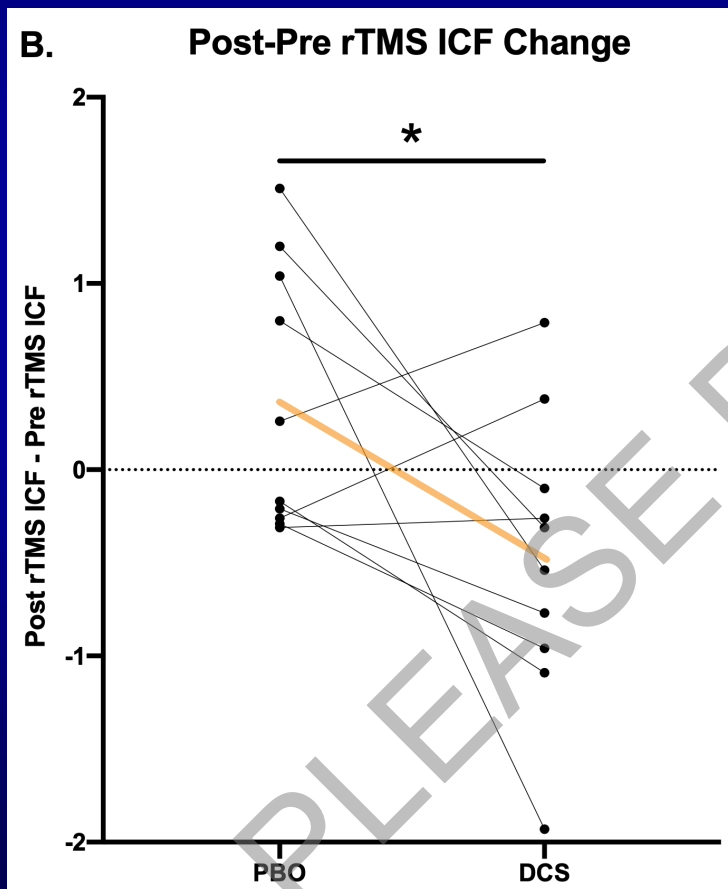
“Practice (Learning) → Enhanced Plasticity”



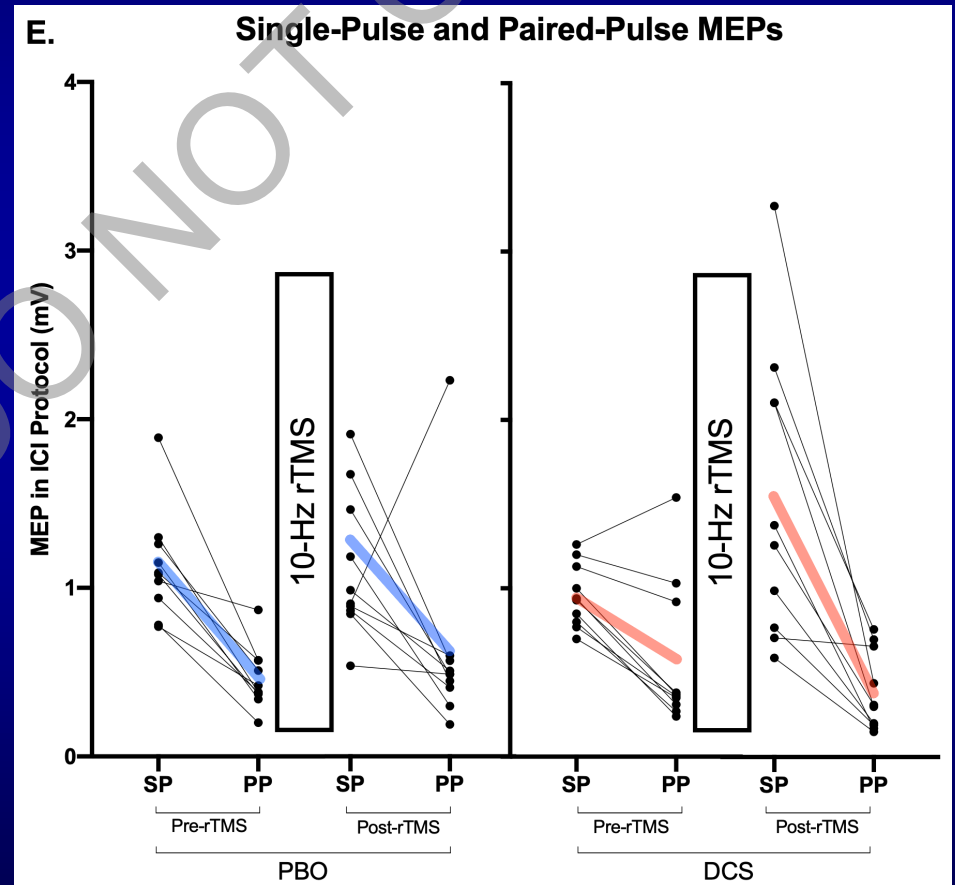
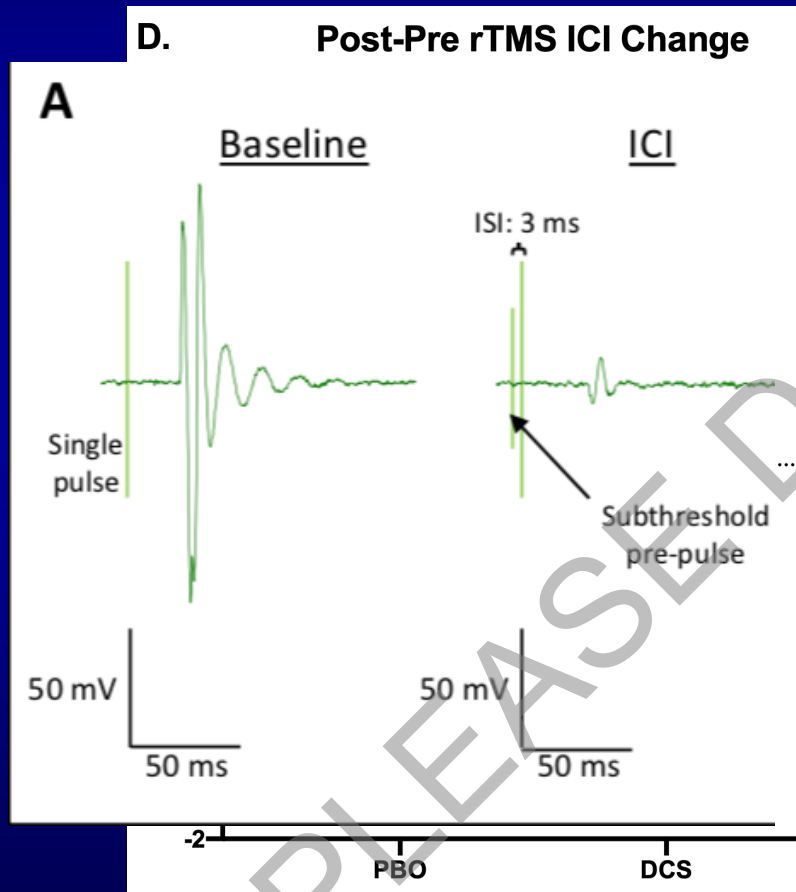
Paired-Pulse TMS



Intracortical Facilitation: LTP-like Occlusion?



Intracortical Inhibition: LTP (like)-induced homeostatic depression?

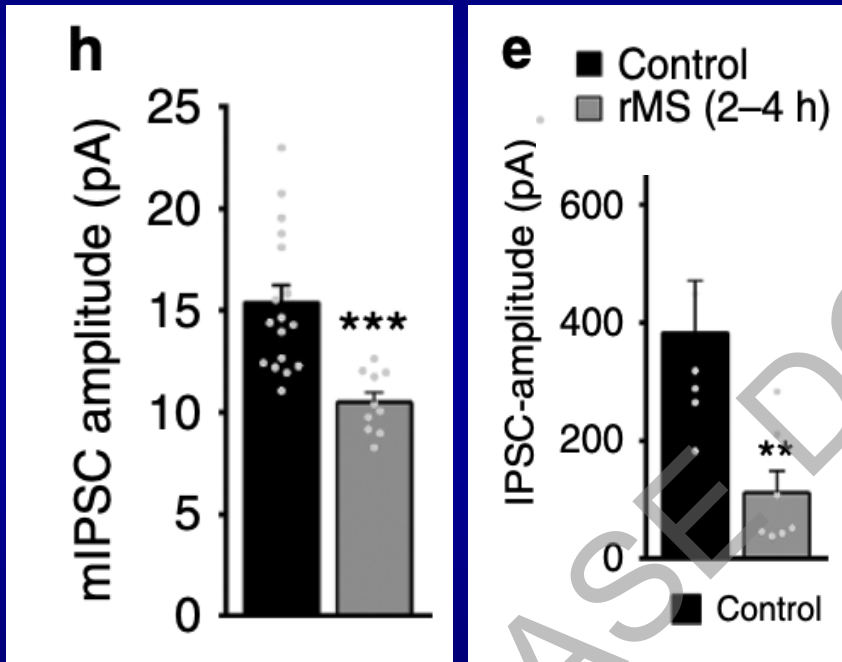


Recap

- D-cycloserine improved TMS effectiveness
- ...Through NMDA receptor activation
- ...Which is central to LTP
- So, there is evidence to suggest TMS works through LTP.
- And that's it!
- ...Or is it??

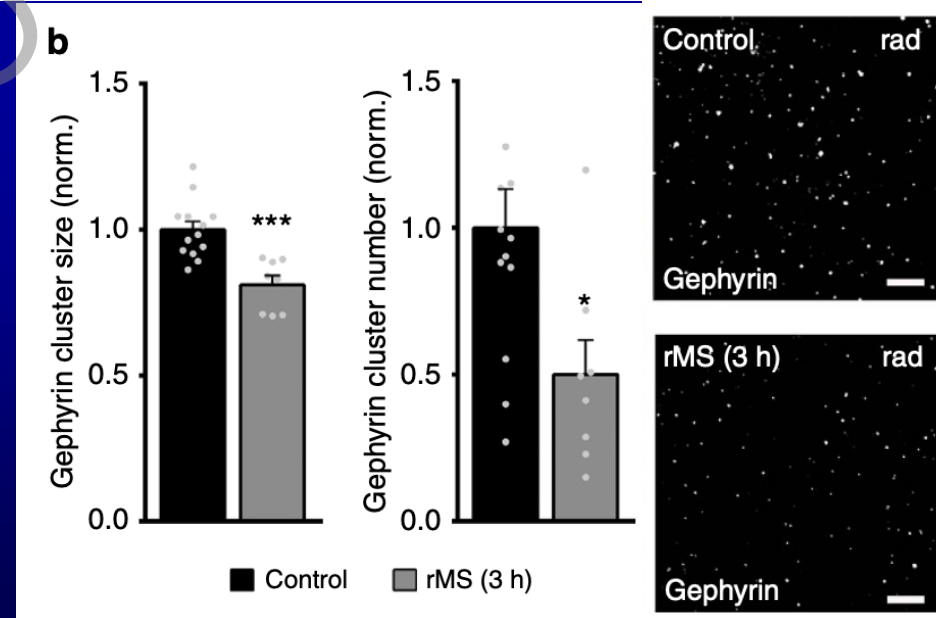
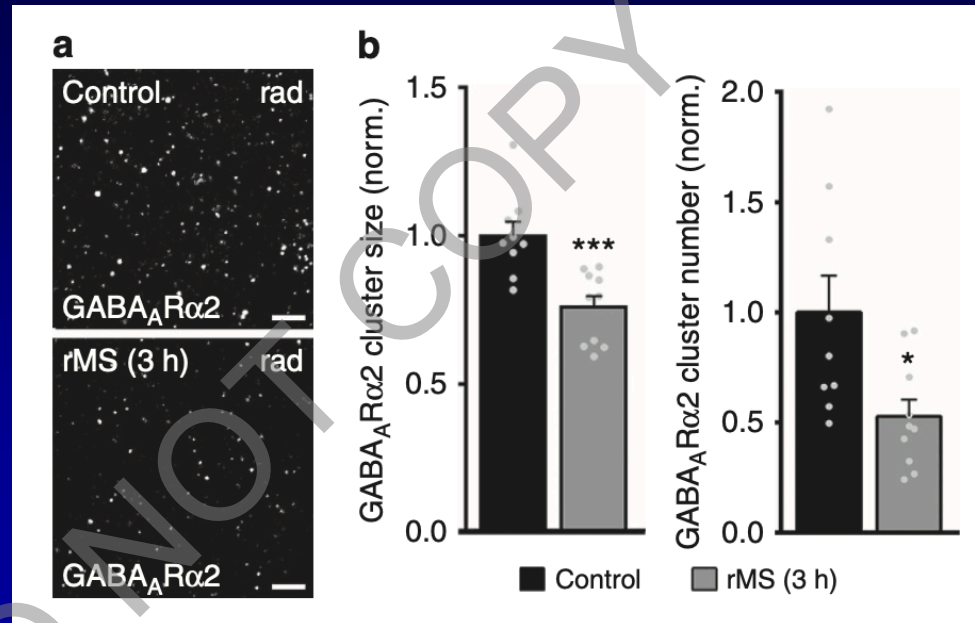
The GABA Hypothesis

1) GABAR currents decreased after rMS



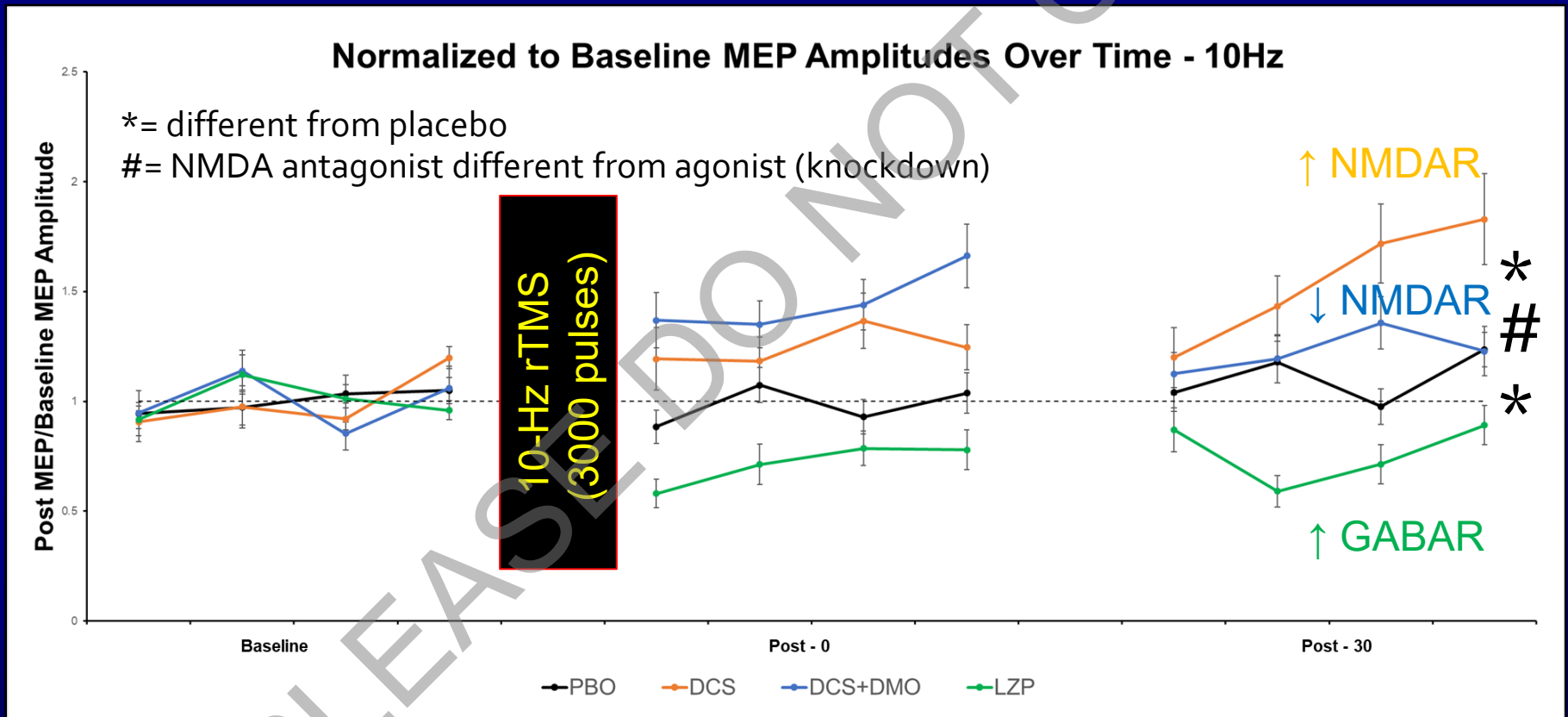
Lenz et al, *Nature Communications*, 2016

2) GABA receptors decreased after rMS



3) GABAR scaffolding proteins decreased after rMS

So...Does conventional rTMS work through NMDARs or GABARs (in healthy humans)?

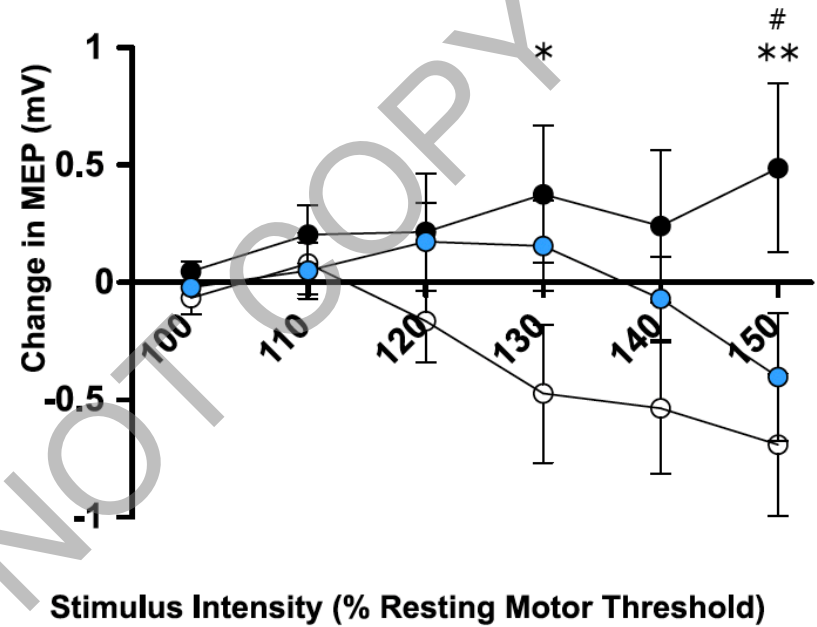


Unpublished Data in Preparation

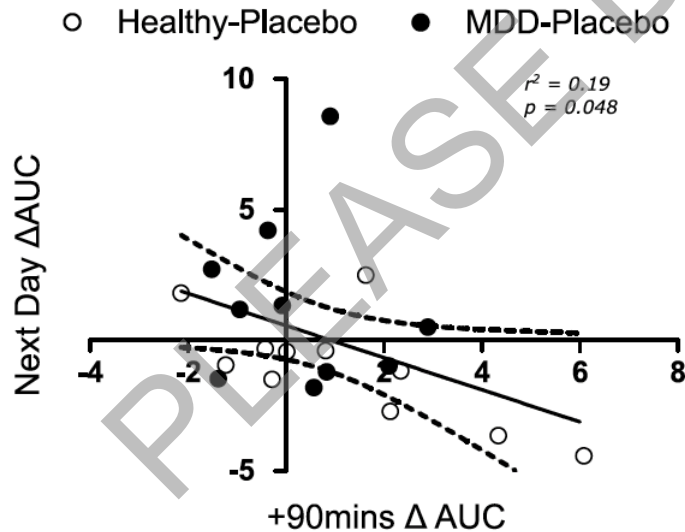
Does Healthy = MDD?

Cole et al., *Clin Neurophys*, 2021

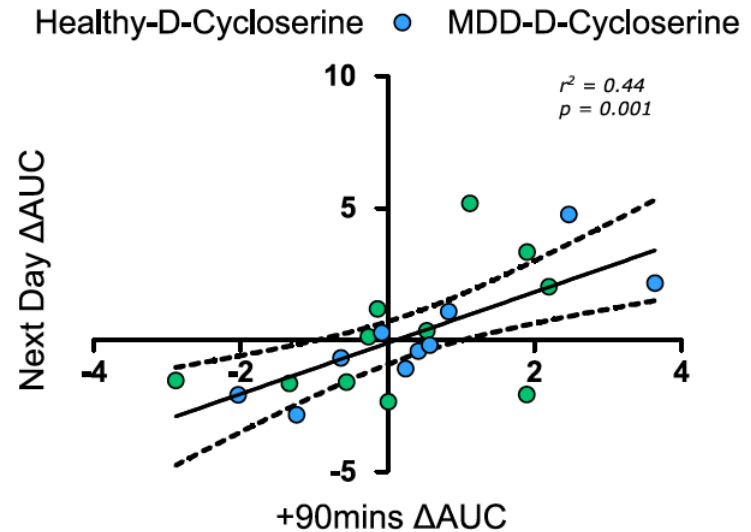
d) SRC Change from Baseline to Next Day



a) Placebo



b) D-Cycloserine



Does 10-Hz = iTBS?

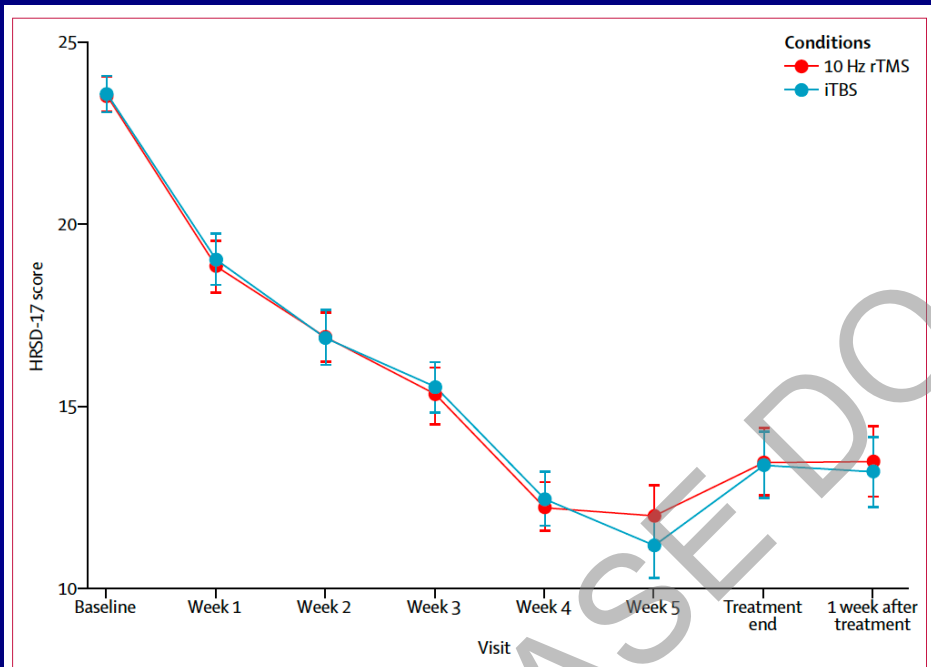
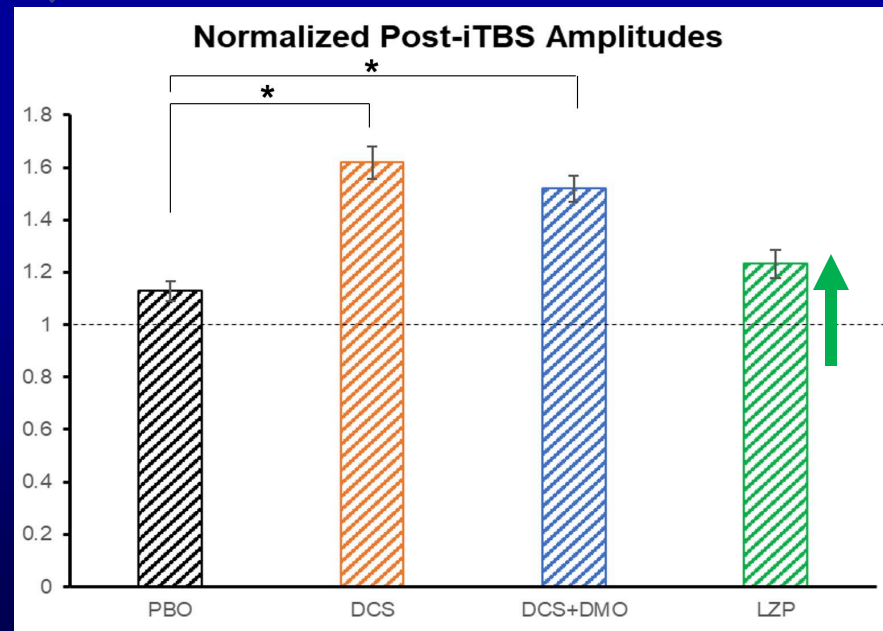
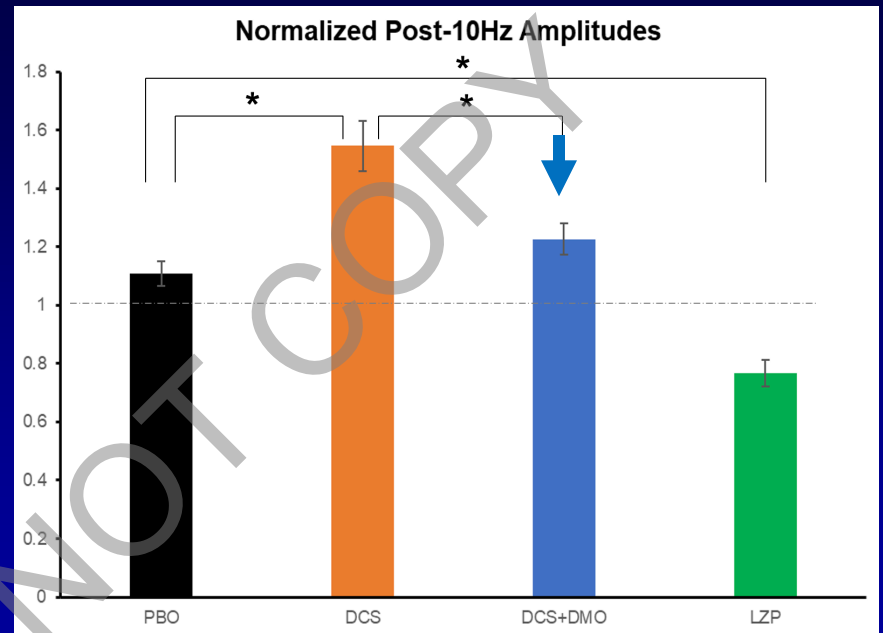


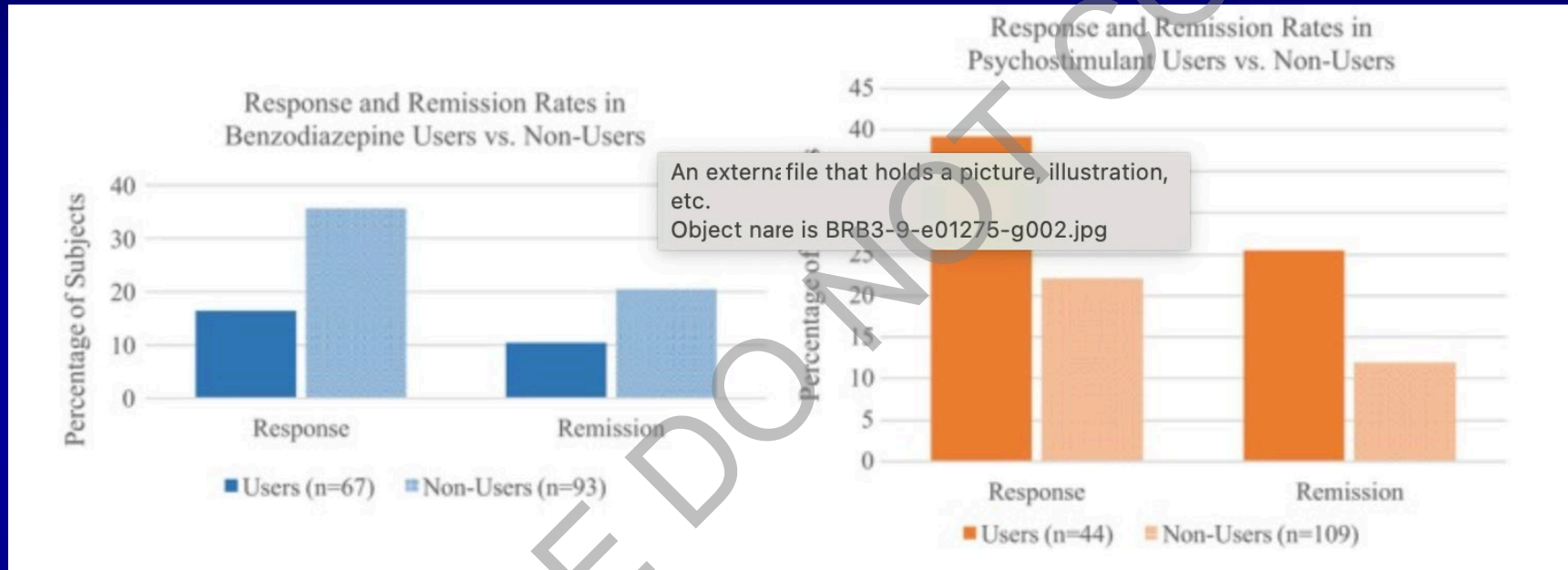
Figure 3: Change in HRSD-17 scores over time, comparing the 10 Hz rTMS and iTBS treatment groups

Blumberger et al., *Lancet*, 2018



Unpublished Data in Preparation

If GABAR were Reduced, what is Clinical Effect of GABA agonists?



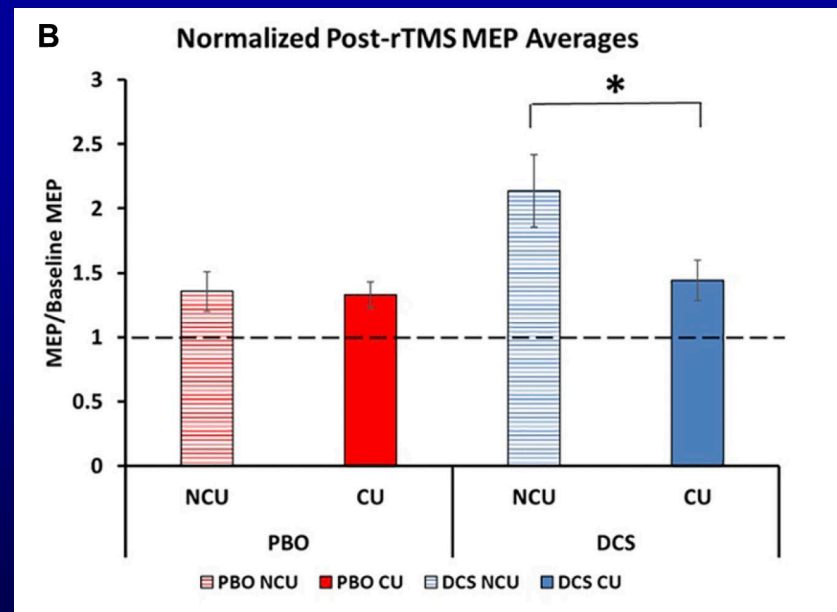
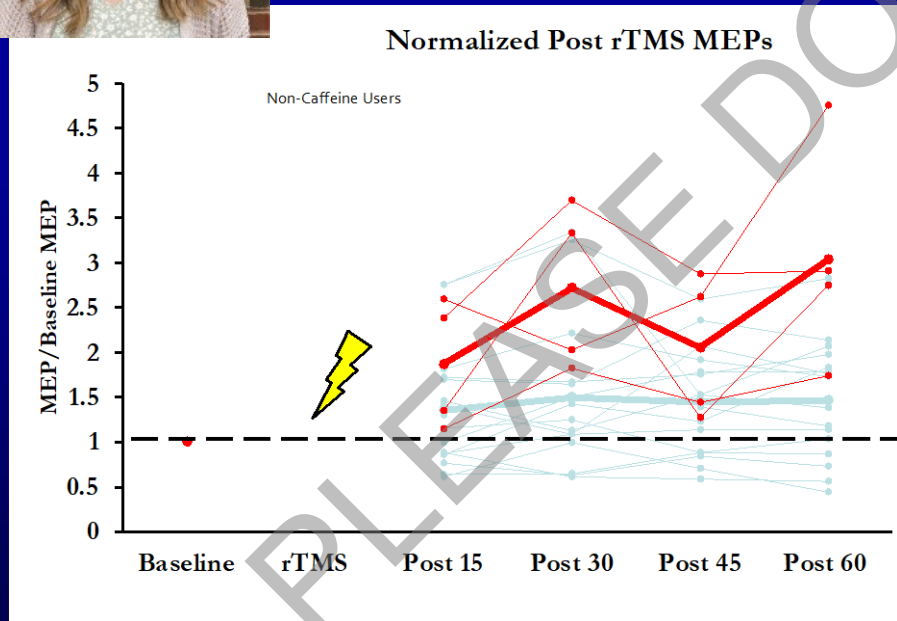
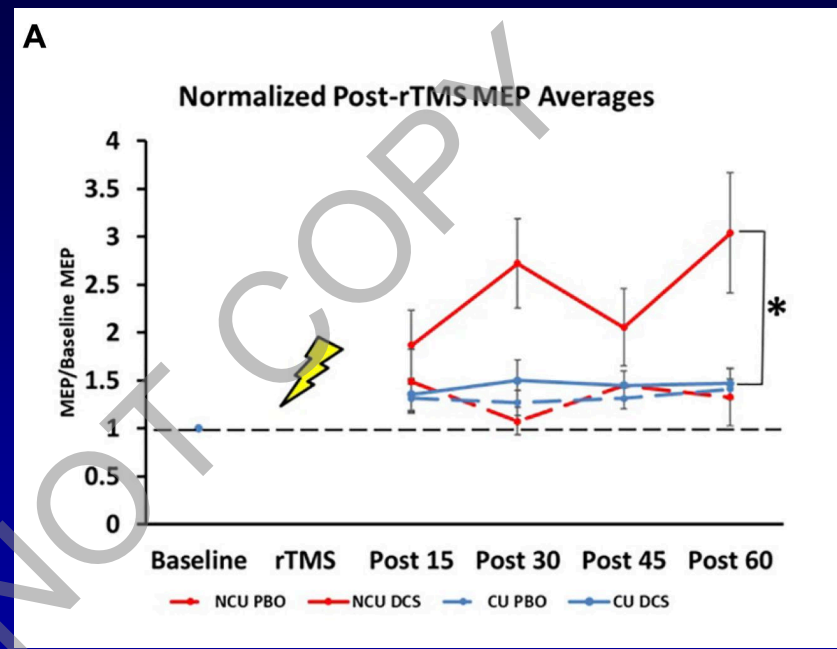
Hunter et al., *Brain Behav*, 2019

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

- More likely non-responder group,
- More likely slower trajectory group

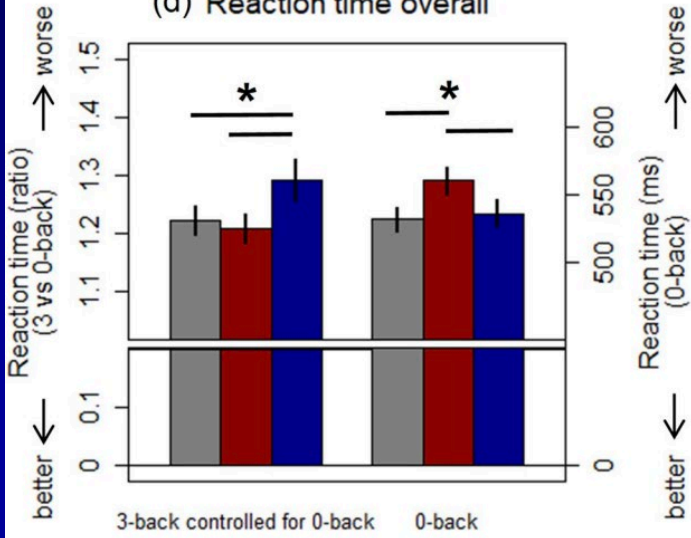
Not Supported by: Two clinical trials: 64/121 patients. (Fitzgerald, Brain Stim, 2020)

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

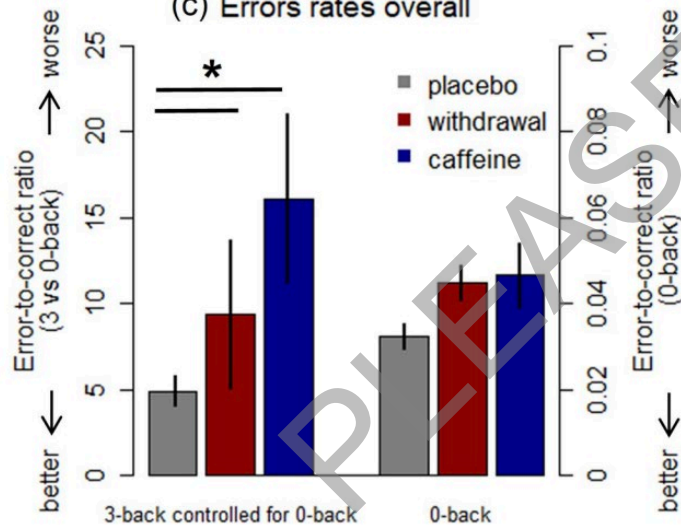


Caffeine Continued

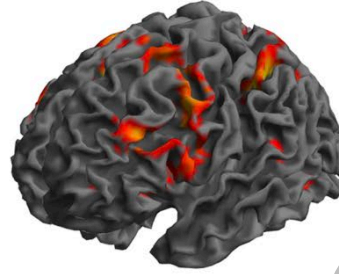
(d) Reaction time overall



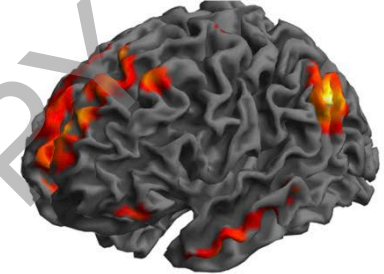
(c) Errors rates overall



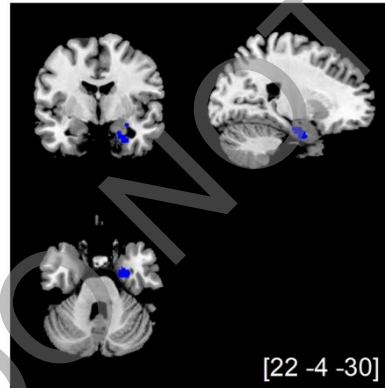
(a) 3-back > 0-back



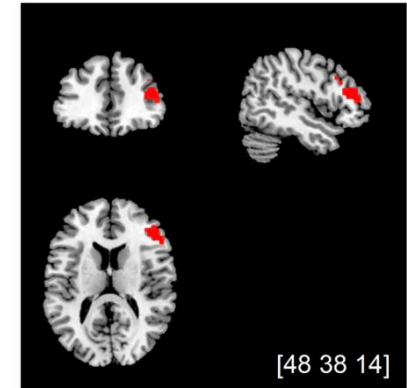
(b) 0-back > 3-back



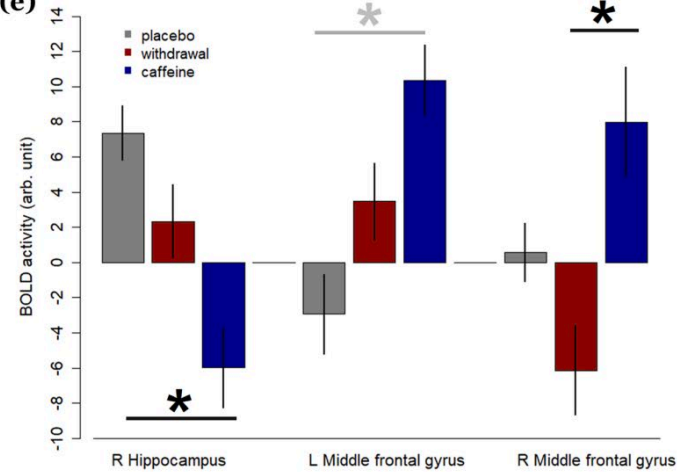
(c)



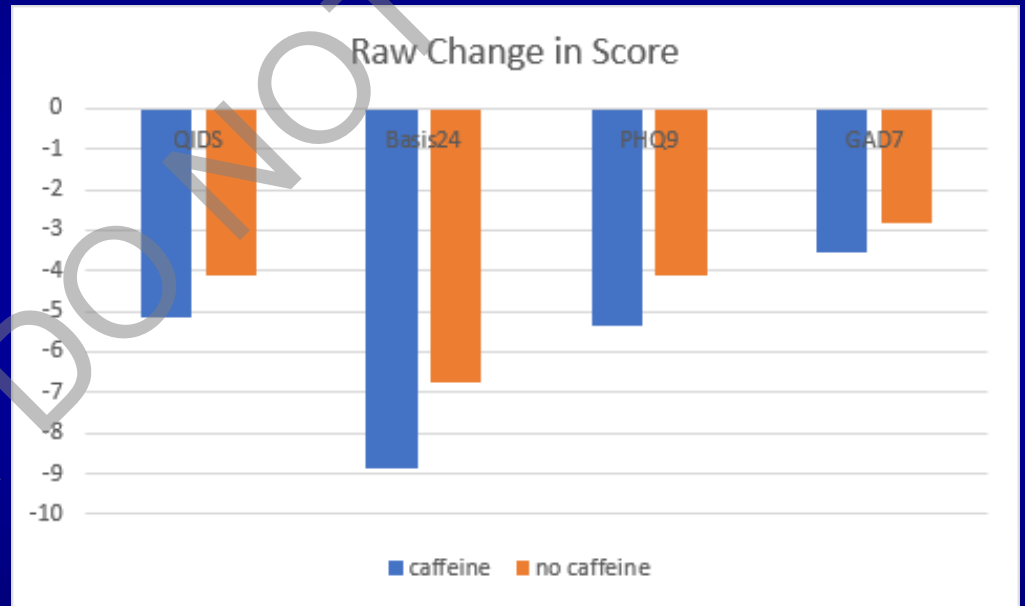
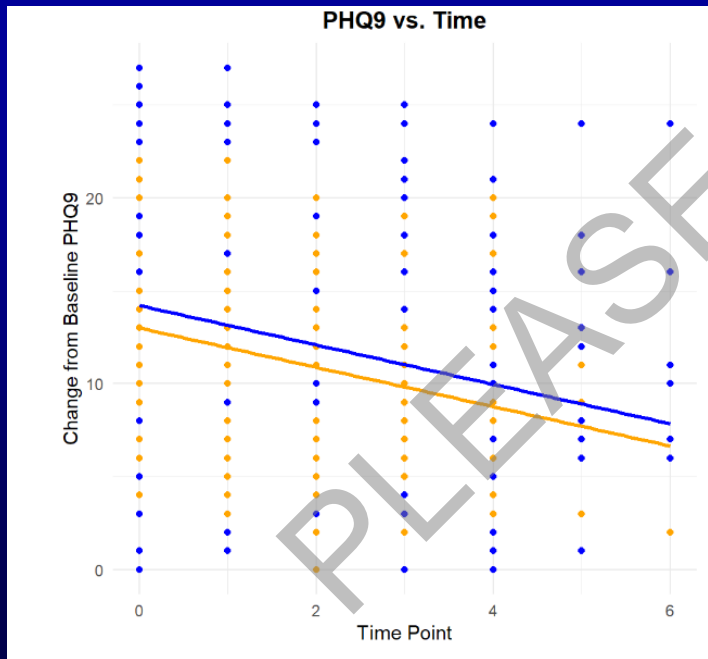
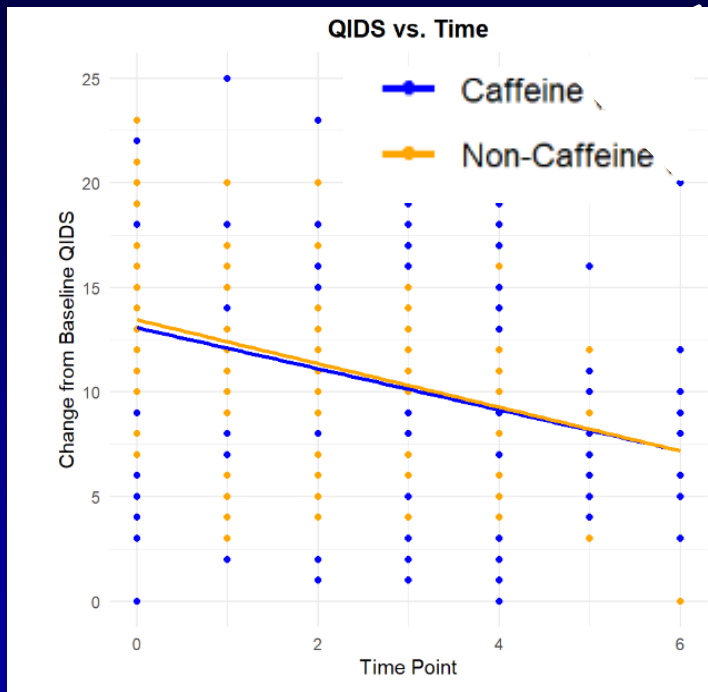
(d)



(e)



Clinical Effects of Caffeine



Unpublished Data in Preparation

Other Pharmacologic Considerations

DEPRESSION AND ANXIETY 33:746–753 (2016)

Research Article

A STUDY OF THE PATTERN OF RESPONSE TO rTMS TREATMENT IN DEPRESSION

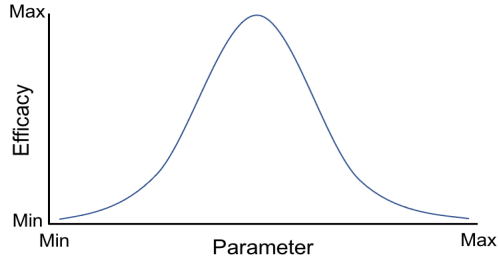
Paul B. Fitzgerald, M.B.B.S., M.P.M., Ph.D., FRANZCP,^{1*} Kate E. Hoy, B.B.N.Sc. (Hons.),
D.Psych. (Clin. Neuro.),¹ Rodney J. Anderson, B.Sc. (Hons.), G.Dip.Psych.,¹ and
Zafiris J. Daskalakis, M.D., Ph.D., FRCP (C)²

- “Concurrent antidepressant or mood stabilizer therapy was associated with a higher rate of response.”
- THC (*n* of 56, 28 THC users, 28 matched)
 - Users: 12 responders, 5 remitters
 - Matched: 16 responders, 11 remitters

Can we Enhance Accelerated TMS?

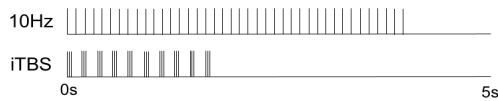
Dose-Response Curve Model

a) Inverted U-Shaped Curve

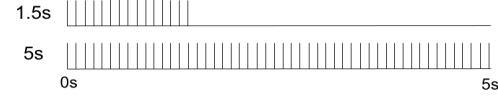


Theme 1: rTMS Parameters

b) Pulse Pattern



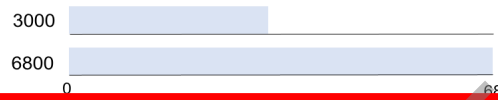
c) Train Duration



d) Intertrain Interval



e) Pulse Number- 10Hz



f) Pulse Number- iTBS



g) Sessions Per Day

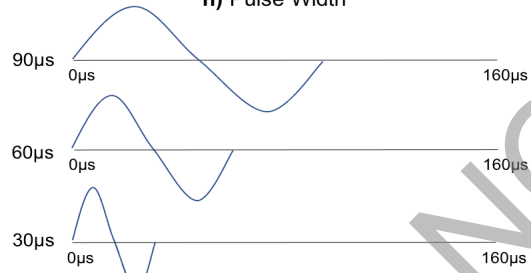
M	T	W	Th	F
1x TMS	1x TMS	1x TMS	1x TMS	1x TMS

x 6 weeks

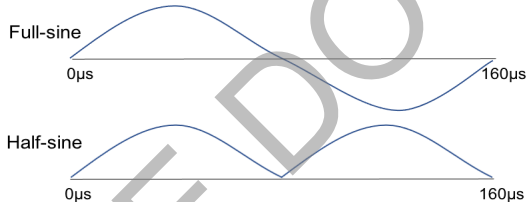
M	T	W	Th	F
10x TMS	10x TMS	10x TMS	10x TMS	10x TMS

x 1 week

h) Pulse Width



i) Pulse Shape

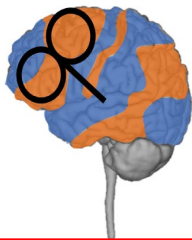


j) Frequency

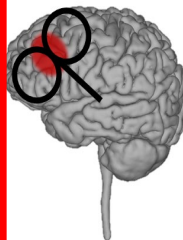


Theme 2: Personalized Targeting and Intensity

a) rsFC Targeting

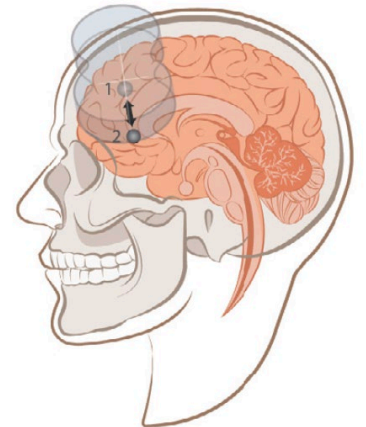


b) E-Field Dosing



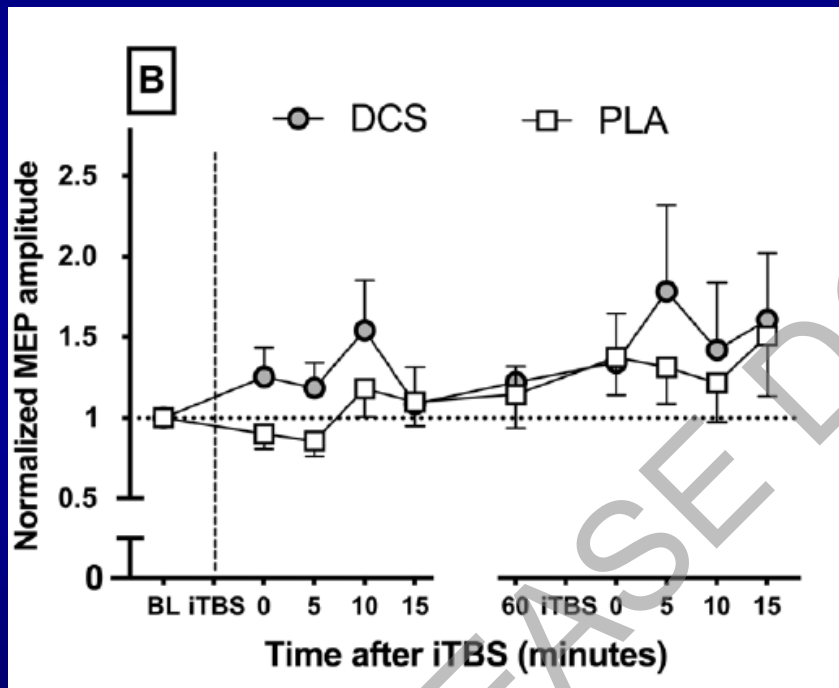
B

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
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

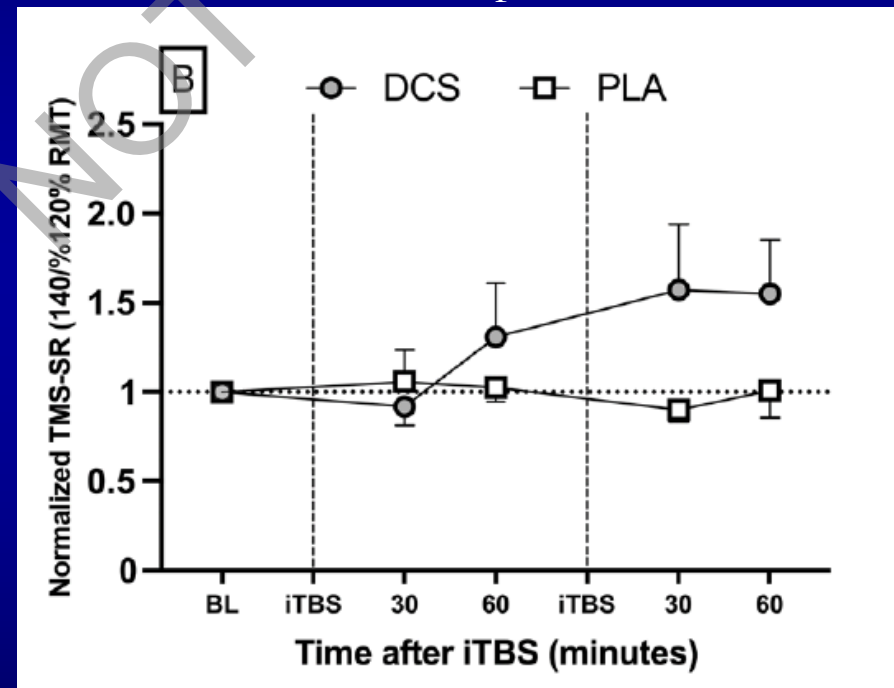


Can we Augment Accelerated TMS? (Repeated Doses)

MEPs

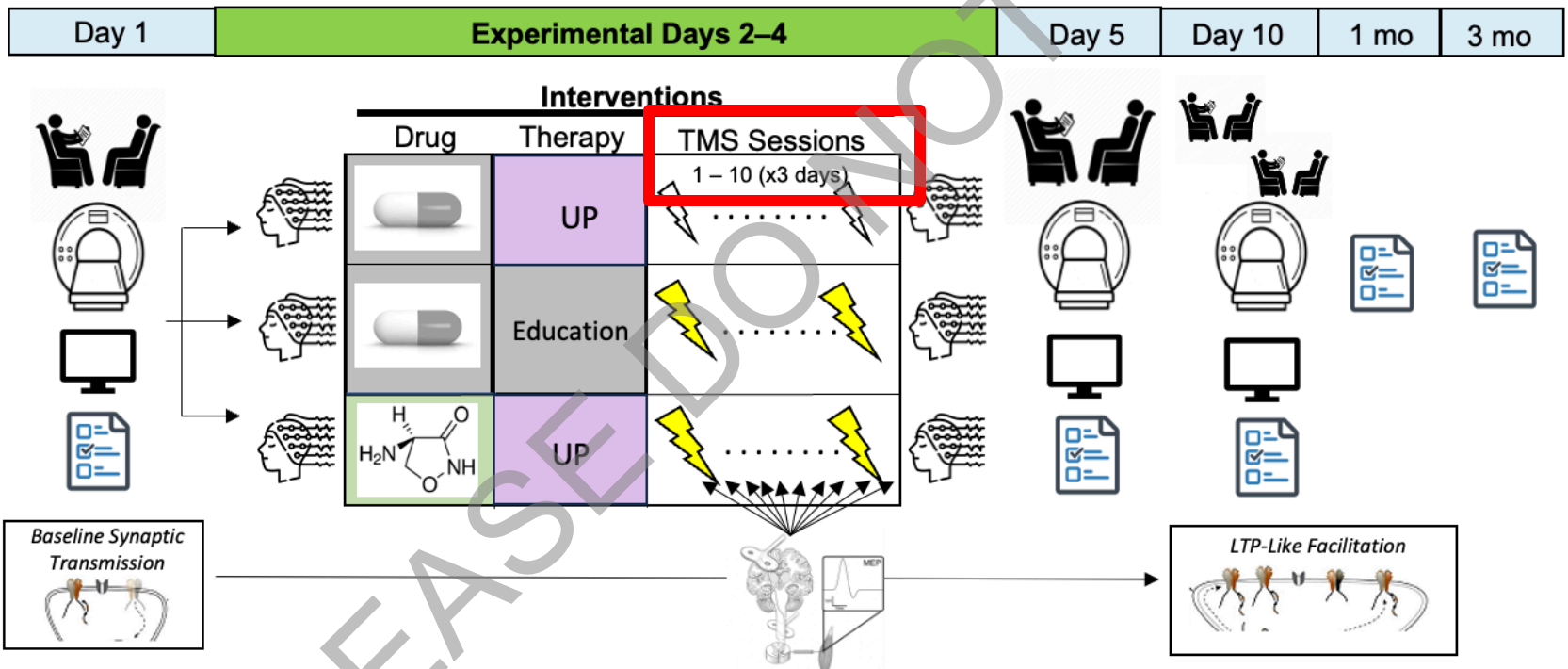


Stimulus Response Curve



Wrightson et al., *Neuropsychopharm*, 2023

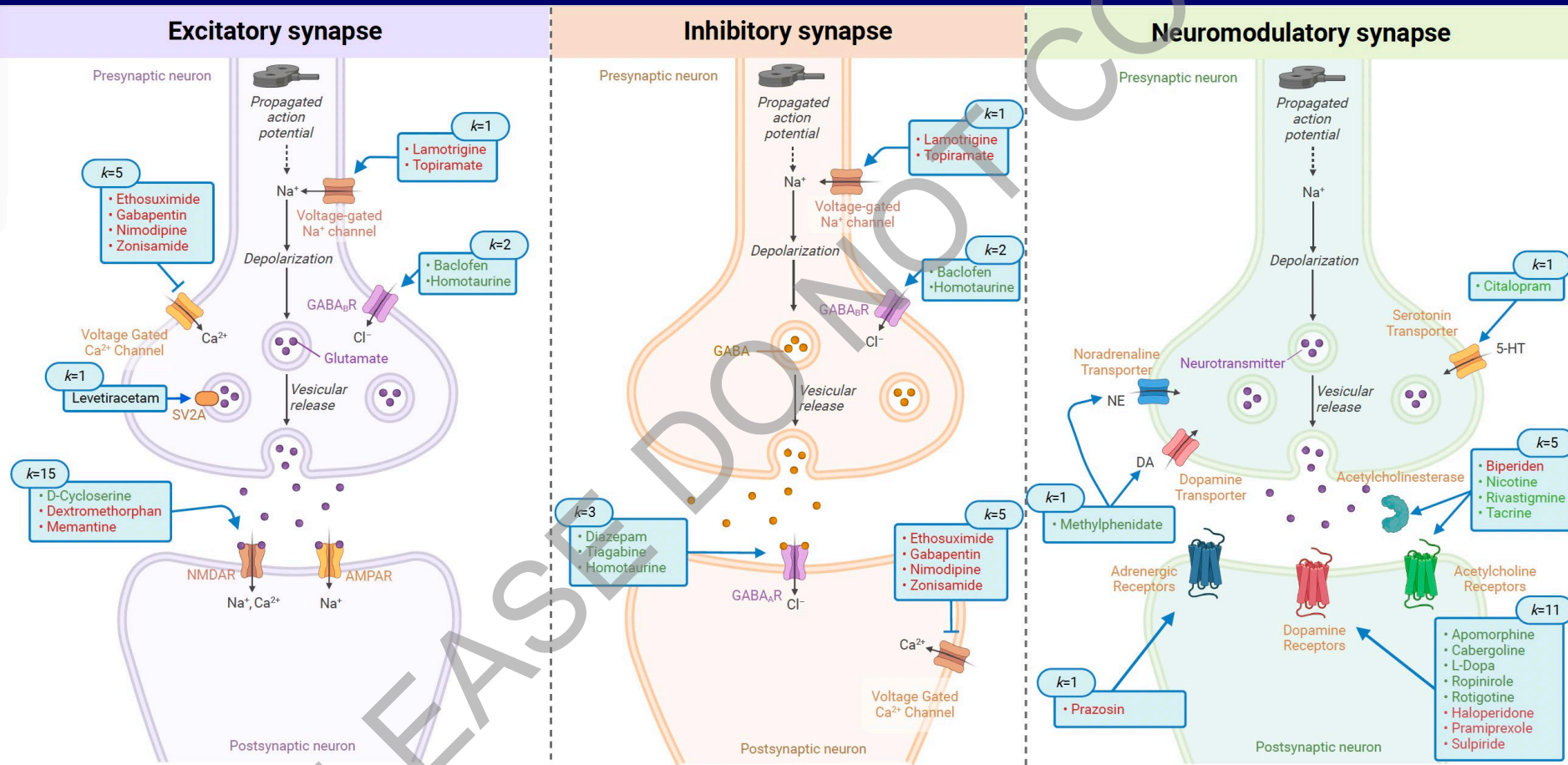
For Next Time...



2nd Recap

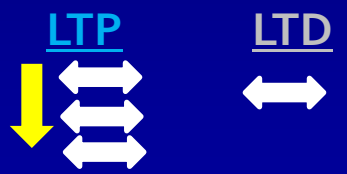
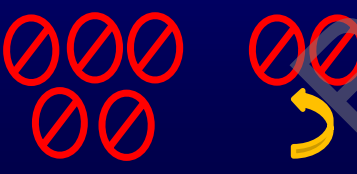
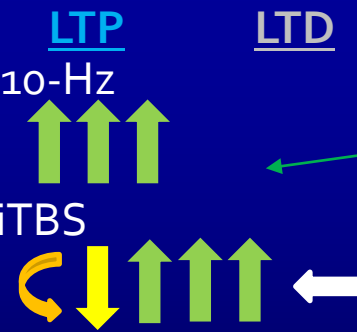
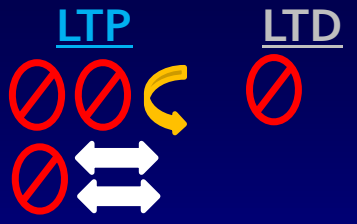
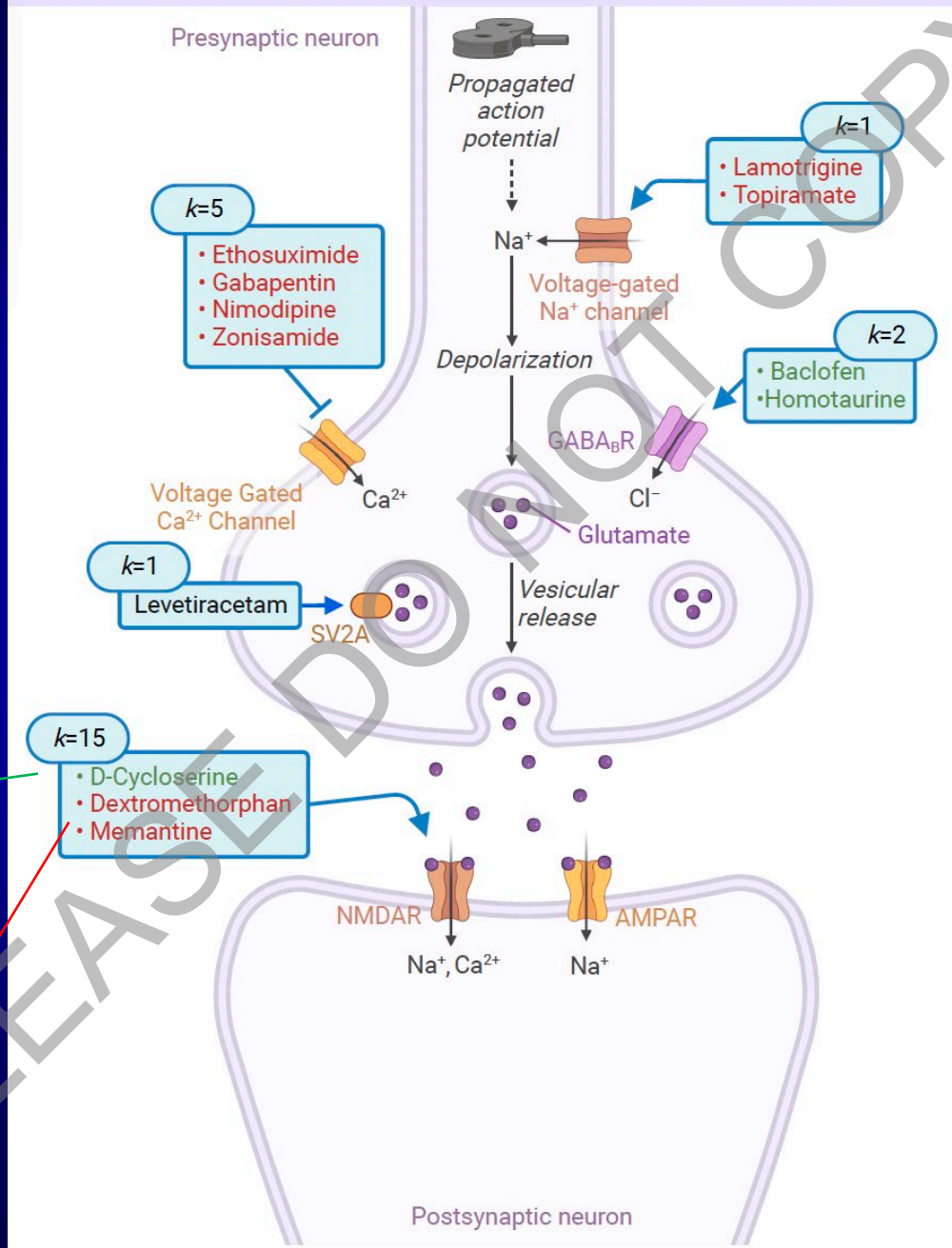
- 1st Recap: LTP, NMDA, Ketamine, Augmented TMS with d-cycloserine
- Since:
 - GABA receptor mechanism
 - Benzo's (May impair TMS effects?)
 - iTBS vs 10-Hz mechanisms (LTP-like +/- GABA)
 - Healthy controls vs MDD (MDD room to improve plasticity)
 - Stimulants including Caffeine (Impairs LTP-like, Clinical??)
 - Augmenting Accelerated TMS (Possible!)
 - Rx Meds in clinical practice (Helps)
 - THC in clinical practice (Hinders?)

What have we missed?



Sohn et al., Pharmacological enhancement of transcranial magnetic stimulation-induced synaptic plasticity: a systematic review of mechanistically informed adjuncts. *J Psychiatry Neurosci*, In Press

Excitatory synapse



Legend

Increased

Decreased

No Effect

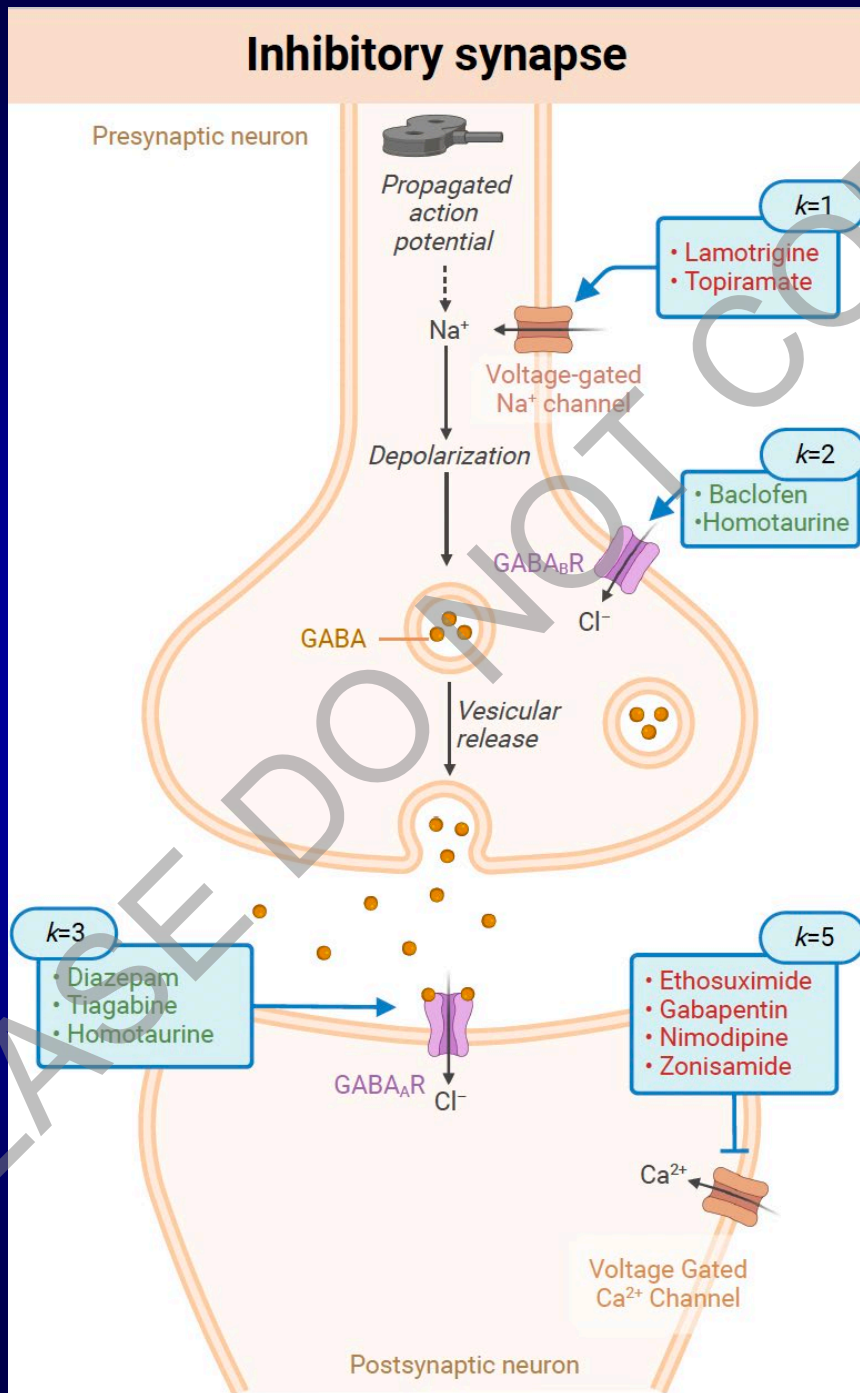
Blocked

Flipped

Inhibitory synapse

Legend

- Increased
- Decreased
- No Effect
- Blocked
- Flipped



LTP

LTD



LTP

LTD



LTP

LTD

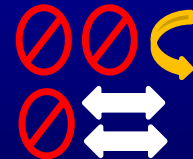


Clinical: ?






Prelim Data: ?

LTP

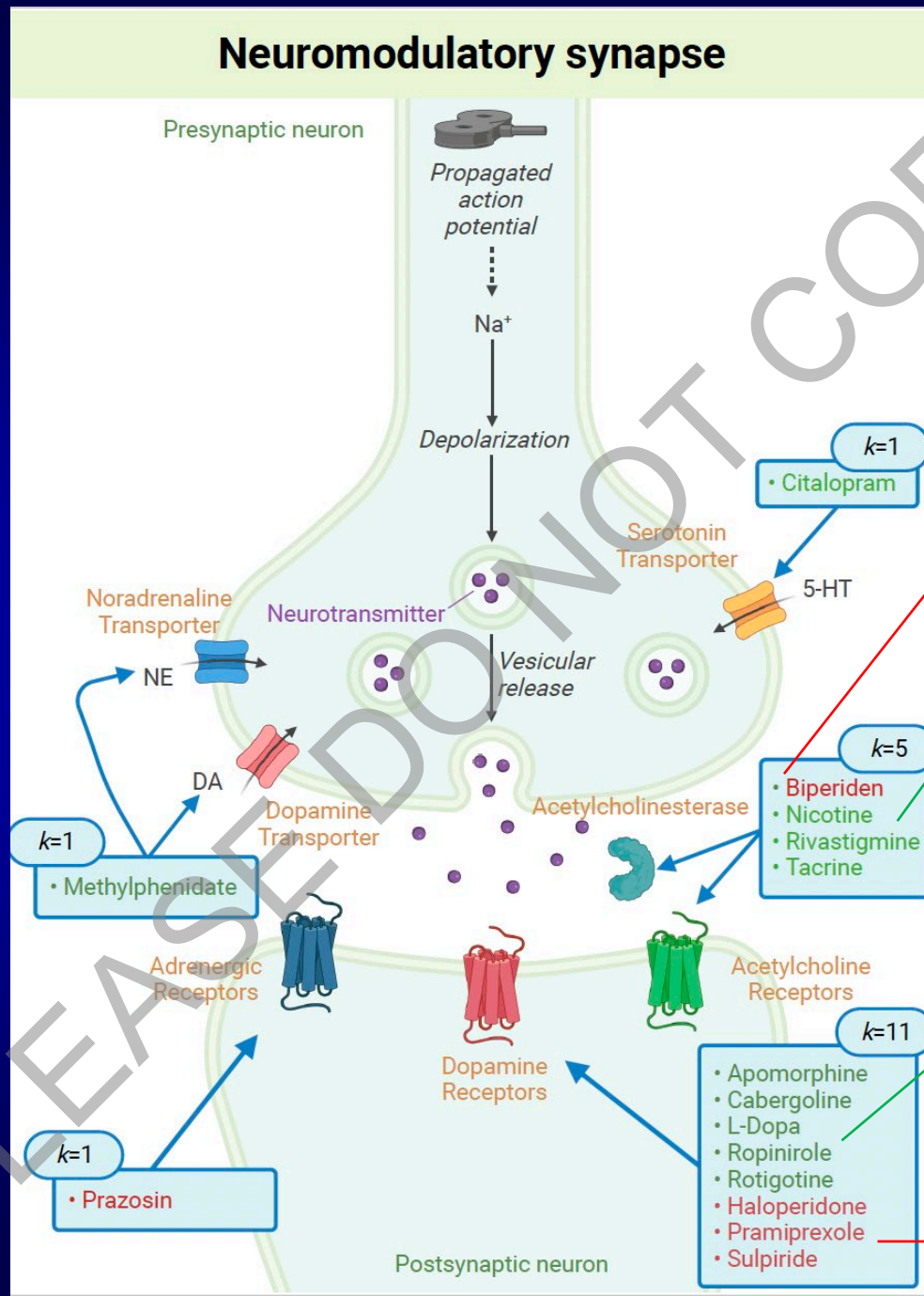
LTD



























Legend

- Increased 
- Decreased 
- No Effect 
- Blocked 
- Flipped 


Neuromodulatory synapse



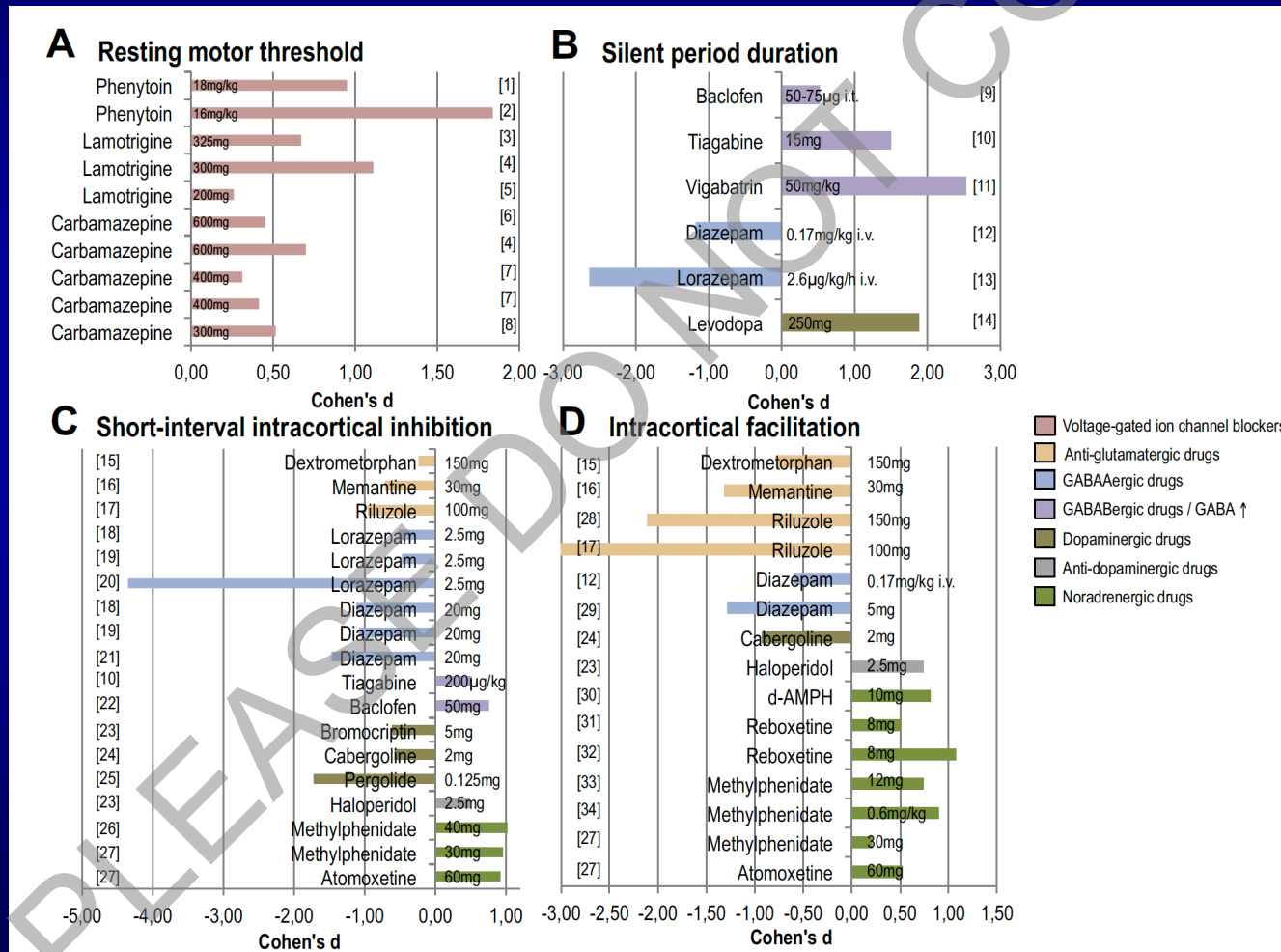
<u>LTP</u>	<u>LTD</u>
	
<u>LTP</u>	<u>LTD</u>
	
	
	
<u>LTP</u>	<u>LTD</u>
	
	
Low:	High:
	
	
	
	
	
	

LTP  LTD

Clinical: ?

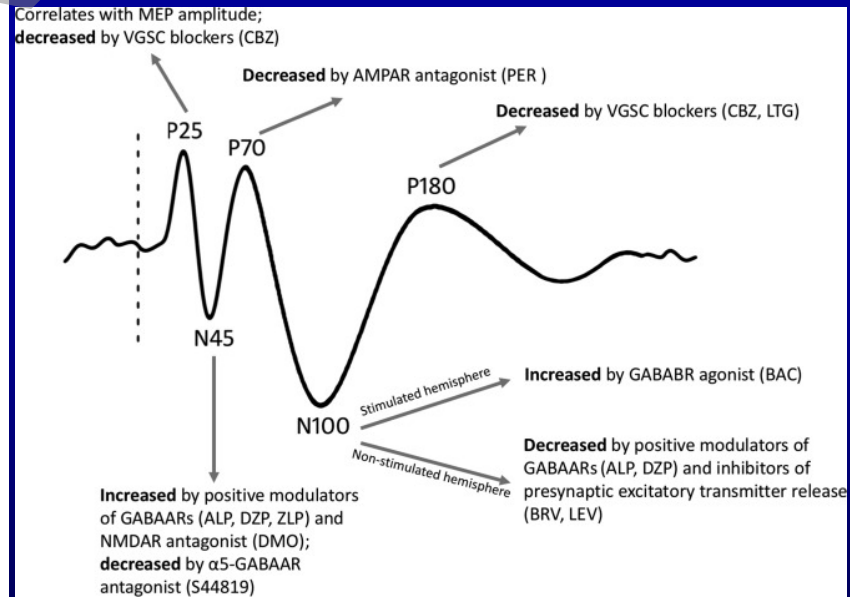
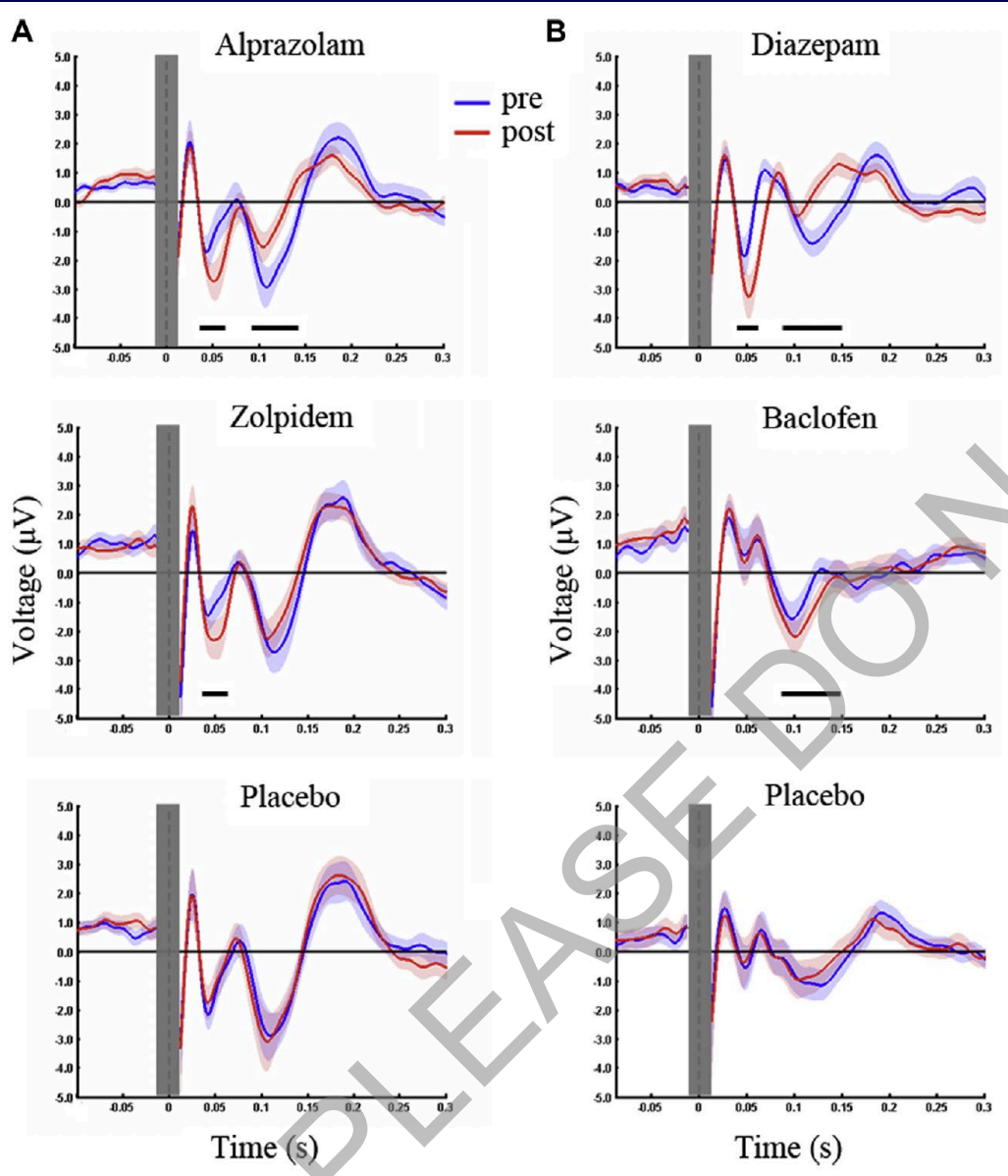
LTP  LTD

Non-(r)TMS as a Probe of Drug Effects on Brain Excitability



TMS-EEG-Pharm

(16 Studies,
None with rTMS)



Darmani & Ziemann, *Brain Stimulation*, 2019

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Collaborators:

McLean

- Kerry Ressler, MD, PhD
- Jenna Traynor, PhD
- Mark Halko, PhD
- Dan Dillon, PhD
- Brian Brennan, MD
- Gus Yip, MD
- Marc Copersino, PhD

Harvard

- Mo Shafi, MD, PhD
- Pete Fried, PhD
- Recep Ozdemir, PhD
- Tracy Barbour, MD
- Shan Siddiqi, MBBS

Collaborators:

National

- Mark George, MD
- Kevin Caulfield, PhD
- Carolina Haass-Koffler, PhD
- Linda Carpenter, MD
- Mohamed Sherif, MD, PhD
- Mohamed Sherif, MD, PhD
- Andy Fukuda, MD, PhD
- Brian Theyel, MD, PhD

International

- Andreas Vlachos, PhD
- Leo Chen, MBBS
- Alex McGirr, MD, PhD
- Andris Cerins, PhD

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Thank You!

Questions?

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