Pharmacology of TMS

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Disclosures

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How does rTMS produce lasting therapeutic changes in the brain?
How The Brain Works

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
The End at the Beginning

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

- MADRS score
- Clinical response

Cumulative distribution

Proportion of doses

DCS responder
DCS nonresponder
Placebo responder
Placebo nonresponder

Ingestion-treatment interval, min

0 60 120

MADRS score

Baseline 2 wk 4 wk

Clinical response, %

0 20 40 60 80

2 wk 4 wk

Cole et al., JAMA Psych, 2022
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 Subserves Network and Behavioral Effects?
Synaptic Plasticity critically depends on NMDA receptors

Brown, Higgins & George, *Neuromodulation*, 2022
Does TMS Work through LTP-like Mechanisms??
Does “LTP-like” = LTP?

Testing plasticity in humans

*Motor-Evoked Potentials*

Vlachos, *Neuroforum*, 2017

Baseline Excitability (MEPs) → rTMS “Plasticity Protocol” → Post-rTMS Excitability (MEPs)

$\Delta \text{ MEP} = \text{PLASTICITY}$
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‡

Placebo

Dextromethorphan

Amplitude (percent of control)

pre post

pre post

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

A. Suppa1, A. Biasiotta2, D. Belvisi2, L. Marsili2, S. La Cascia2, A. Truini2, G. Cruccu2 and A. Berardelli1,2

Laser-PAS50

MME amplitude (%)

T0 T1 T2 T3 T4 T5 T6 T7

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

Inclusion Nimodipine Dextromethorphan Placebo

Normalised Amplitude of MEP

-40 -30 -20 -10 0 10 20 30 40

Baseline 0 5 10 15 20 25

Time (min)
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

NMDA Receptor Agonism Augments 10-Hz rTMS

Brown et al., Brain Stimulation, 2020
NMDA Receptor Activation Enhances Plasticity

Kweon et al., *Brain Stimulation*, 2022
“Practice (Learning) → Enhanced Plasticity”

M&A: Musicians & Athletes

Kweon et al., *Front Neural Circuits*, 2023
Paired-Pulse TMS
Intracortical Facilitation: LTP-like Occlusion?

Brown et al, *Brain Stimulation*, 2021
Intracortical Inhibition: LTP (like)-induced homeostatic depression?

Brown et al, *Brain Stimulation*, 2021
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

2) GABA receptors decreased after rMS

3) GABAR scaffolding proteins decreased after rMS

Lenz et al, *Nature Communications*, 2016
So…Does conventional rTMS work through NMDARs or GABARs (in healthy humans)?

Normalized to Baseline MEP Amplitudes Over Time - 10Hz

*= different from placebo
# = NMDA antagonist different from agonist (knockdown)

↑ NMDAR

↓ NMDAR

↑ GABAR

Unpublished Data in Preparation
Does Healthy = MDD?

Cole et al., *Clin Neurophys*, 2021

**a) Placebo**
- Healthy-Placebo
- MDD-Placebo

- $r^2 = 0.19$
- $p = 0.048$

**b) D-Cycloserine**
- Healthy-D-Cycloserine
- MDD-D-Cycloserine

- $r^2 = 0.44$
- $p = 0.001$
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 the **Clinical Effect** of GABA agonists?

**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)

Hunter et al., *Brain Behav*, 2019
How Does the Most Common Stimulant (Caffeine) Effect TMS?

Vigne et al, Front Psych, 2023
Caffeine
Continued

(d) Reaction time overall

(a) 3-back > 0-back

(b) o-back > 3-back

(c) Errors rates overall

(e)

Lin et al, Sci Rep, 2023
Clinical Effects of Caffeine

Unpublished Data in Preparation
Other Pharmacologic Considerations

“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**

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<tr>
<th>M</th>
<th>T</th>
<th>W</th>
<th>Th</th>
<th>F</th>
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<tr>
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x 6 weeks

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x 1 week

**h) Pulse Width**
- 90µs
- 60µs
- 30µs

**i) Pulse Shape**
- Full-sine
- Half-sine

**j) Frequency**
- 1Hz
- 5Hz

**Theme 2: Personalized Targeting and Intensity**
- a) rsFC Targeting
- b) E-Field Dosing

Caulfield & Brown, *Front. Psych*, 2022
Can we Augment Accelerated TMS?
(Repeated Doses)

Wrightson et al., *Neuropsychopharm*, 2023

![MEPs](image1)

![Stimulus Response Curve](image2)

Wrightson et al., *Neuropsychopharm*, 2023
For Next Time...

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Experimental Days 2–4</th>
<th>Day 5</th>
<th>Day 10</th>
<th>1 mo</th>
<th>3 mo</th>
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**Interventions**

- **Drug**
  - UP
- **Therapy**
  - Education
  - UP
- **TMS Sessions**
  - 1 – 10 (x3 days)

**Baseline Synaptic Transmission**

**LTP-Like Facilitation**
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?

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

Ziemann et al., Clin Neurophys, 2015
TMS-EEG-Pharm

(16 Studies, None with rTMS)

Ziemann et al., Clin Neurophys, 2015

Darmani & Ziemann, Brain Stimulation, 2019
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PLEASE DO NOT COPY
Thank You!

Questions?