Pharmacology of TMS

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Disclosures

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How does rTMS produce lasting therapeutic changes in the brain?
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

Higgins & George, *Brain Stimulation Therapies for Clinicians*, 2019, slide adapted from Mark George
Figure 2. Clinical Outcomes in Participants Who Received Intermittent Plus Placebo and iTBS Plus D-Cycloserine (DCS)

**A** MADRS score

- iTBS + placebo
- iTBS + DCS

**B** Clinical response

- iTBS + placebo
- iTBS + DCS

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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?

![Graph showing exploratory preference (%) over retention intervals for WT, Tg-1, and Tg-2 groups.](image)

Tang et al., *Nature*, 1999
What Subserves Network and Behavioral Effects?

Brown, Higgins & George, *Neuromodulation*, 2022
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

Baseline Excitability (MEPs) → rTMS “Plasticity Protocol” → Post-rTMS Excitability (MEPs) → ∆ MEP = PLASTICITY

Vlachos, Neuroforum, 2017
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

0.0  2.5  0.0  2.5

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

Alexander Wolters,1,‡ Friedhelm Sandbrink,1,‡ Antje Schlotmann, Erwin Kunesch, Katja Stefan, Leonardo G. Cohen, Reiner Benecke, and Joseph Classen

Inclusion experiment
Nimodipine  Dextromethorphan  Placebo

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

Ying-Zu Huang*, Rou-Shayn Chen*, John C Rothwell, 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

Rioul-Pedotti et al, Science, 2000
NMDA Receptor Agonism Augments 10-Hz rTMS

Brown et al., *Brain Stimulation*, 2020

### Baseline MEPs

<table>
<thead>
<tr>
<th>Amplitude (mV)</th>
<th>Placebo</th>
<th>D-cycloserine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Normalized MEPs

<table>
<thead>
<tr>
<th>Post/Pre MEPs</th>
<th>Placebo</th>
<th>D-Cycloserine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasticity Protocol</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>rTMS</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>45 min</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

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

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

**Normalized Post-rTMS MEPs**

- PBO Non-M&A
- PBO M&A
- DCS Non-M&A
- DCS M&A

M&A: Musicians & Athletes

Kweon et al., *Front Neural Circuits*, 2023
Paired-Pulse TMS

- **Baseline**
- **ICI** (Inter Stimulus Interval: 3 ms)
- **ICF** (Inter Stimulus Interval: 15 ms)

**Single pulse**

- 50 mV
- 50 ms
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??
1) GABAR currents decreased after rMS

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)?

![Normalized to Baseline MEP Amplitudes Over Time - 10Hz](image)

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

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

$r^2 = 0.44$
$p = 0.001$

**d) SRC Change from Baseline to Next Day**

Stimulus Intensity (% Resting Motor Threshold)
Does 10-Hz = iTBS?

Blumberger et al., *Lancet*, 2018
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?

Vigne et al, *Front Psych*, 2023
Caffeine
Continued

(d) Reaction time overall

(e) BOLD activity (arb. units)

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?

**Theme 1: rTMS Parameters**

- **a) Inverted U-Shaped Curve**
- **b) Pulse Pattern**
- **c) Train Duration**
- **d) Intertrain Interval**
- **e) Pulse Number- 10Hz**
- **f) Pulse Number- iTBS**

**Theme 2: Personalized Targeting and Intensity**

- **a) rsFC Targeting**
- **b) E-Field Dosing**

**g) Sessions Per Day**

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>T</th>
<th>W</th>
<th>Th</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1x TMS</strong></td>
<td>1x TMS</td>
<td>1x TMS</td>
<td>1x TMS</td>
<td>1x TMS</td>
<td></td>
</tr>
<tr>
<td><strong>10x TMS</strong></td>
<td>10x TMS</td>
<td>10x TMS</td>
<td>10x TMS</td>
<td>10x TMS</td>
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</tr>
</tbody>
</table>

**h) Pulse Width**

<table>
<thead>
<tr>
<th></th>
<th>0μs</th>
<th>60μs</th>
<th>90μs</th>
<th>160μs</th>
</tr>
</thead>
</table>

**i) Pulse Shape**

- Full-sine
- Half-sine

**j) Frequency**

<table>
<thead>
<tr>
<th></th>
<th>1Hz</th>
<th>5Hz</th>
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</table>

**B**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
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</thead>
<tbody>
<tr>
<td>ITBS 1800</td>
<td>ITBS 1800</td>
<td>ITBS 1800</td>
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<td>ITBS 1800</td>
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<tr>
<td>50 minute ISI</td>
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<td>50 minute ISI</td>
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</table>

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

MEPs

Stimulus Response Curve

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>
</tr>
</thead>
</table>

**Interventions**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapy</th>
<th>TMS Sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>UP</td>
<td></td>
<td>1 – 10 (x3 days)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Ziemann et al., Clin Neurophys, 2015

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### A. Resting motor threshold

<table>
<thead>
<tr>
<th>Drug</th>
<th>Resting Motor Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytin</td>
<td>1000 µg/kg</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>1500 µg/kg</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>325 µg/kg</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>600 µg/kg</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>400 µg/kg</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>300 µg/kg</td>
</tr>
</tbody>
</table>

### B. Silent period duration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration (µs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen</td>
<td>50 ± 15</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>20 ± 10</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>50 ± 10</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.17 ± 0.05 mg i.v.</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>10 ± 2.6 µg/kg i.v.</td>
</tr>
<tr>
<td>Levodopa</td>
<td>250 ± 80 mg</td>
</tr>
</tbody>
</table>

### C. Short-interval intracortical inhibition

<table>
<thead>
<tr>
<th>Drug</th>
<th>Short-interval Intracortical Inhibition (µA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextromethorphan</td>
<td>150 µg/kg</td>
</tr>
<tr>
<td>Memantine</td>
<td>300 µg/kg</td>
</tr>
<tr>
<td>Riluzole</td>
<td>100 µg/kg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>200 µg/kg</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>500 µg/kg</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>5 mg</td>
</tr>
<tr>
<td>Carbogline</td>
<td>2 mg</td>
</tr>
<tr>
<td>Periosteol</td>
<td>0.125 mg</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>20 mg</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>400 mg</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>300 mg</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>600 µg/kg</td>
</tr>
</tbody>
</table>

### D. Intracortical facilitation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intracortical Facilitation (µA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextromethorphan</td>
<td>150 µg/kg</td>
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</tr>
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<td>200 ± 80 mg</td>
</tr>
<tr>
<td>Carbogline</td>
<td>2 mg</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>20 mg</td>
</tr>
<tr>
<td>d-AMPH</td>
<td>10 mg</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>8 mg</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>8 mg</td>
</tr>
<tr>
<td>Methyphenidate</td>
<td>10 mg</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>600 mg</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>600 µg/kg</td>
</tr>
</tbody>
</table>

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Voltage-gated ion channel blockers
- Anti-glutamatergic drugs
- GABAergic drugs
- GABAergic drugs / GABAergic drugs
- Dopaminergic drugs
- Anti dopaminergic drugs
- Noradrenergic drugs
TMS-EEG-Pharm

(16 Studies, None with rTMS)

Ziemann et al., Clin Neurophys, 2015

Darmani & Ziemann, Brain Stimulation, 2019
Sincere THANKS to:

The McLean TMS Clinical Staff

The Brain Stimulation Mechanisms Laboratory (brainstimlab.mclean.harvard.edu)

Collaborators: McLean
- Kerry Ressler, MD, PhD
- Jenna Traynor, PhD
- Mark Halko, PhD
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- Gus Yip, MD
- Marc Copersino, PhD

Collaborators: National
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- 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

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

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Questions?