# Combining TMS with Psychotherapy for Treating Depression and OCD

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NIMH

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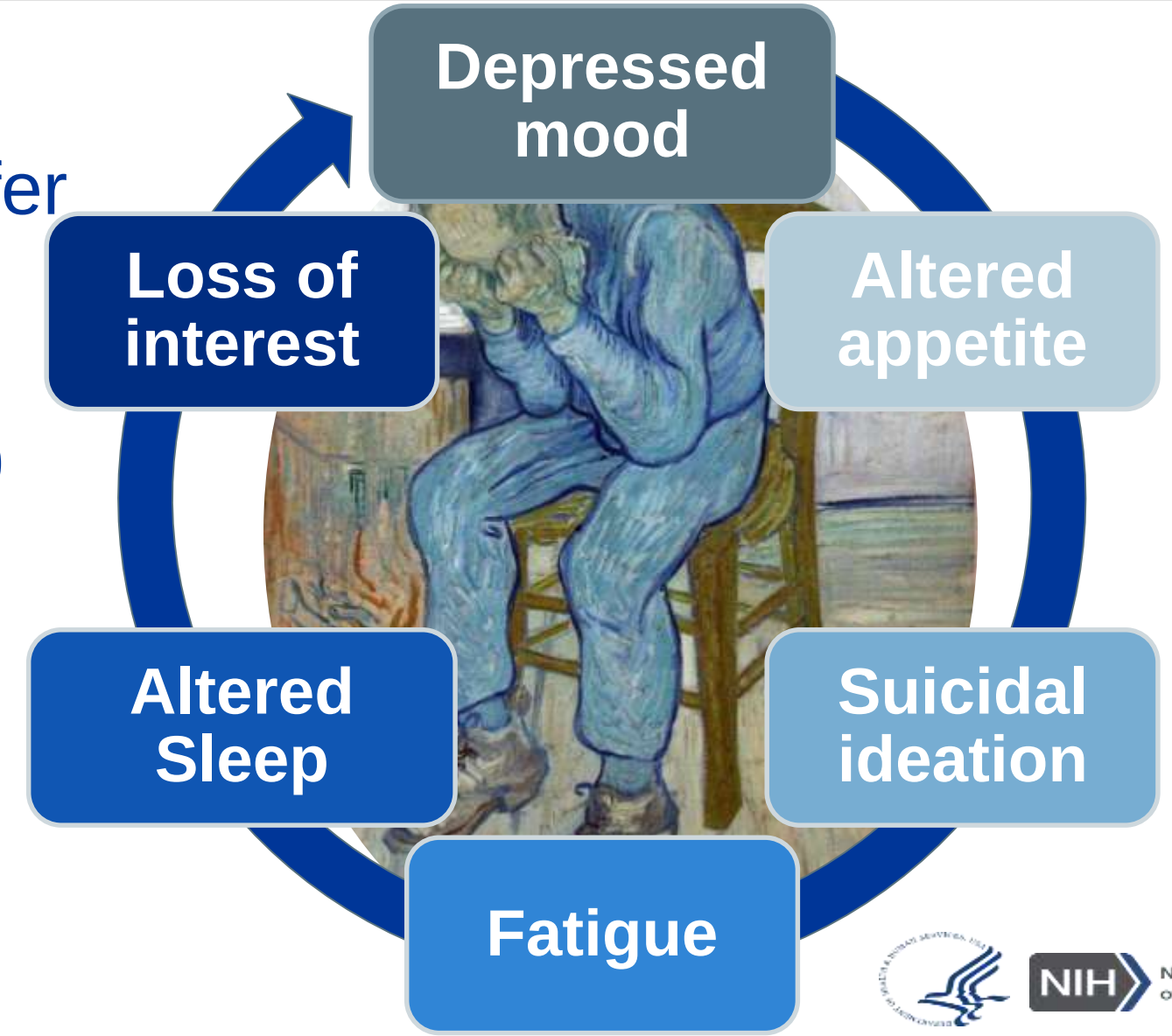
# Take Home Points

- Depression and OCD can be disabling and current treatments are not effective for everyone
- Transcranial Magnetic Stimulation (TMS) is a new tool for treating depression and OCD
- TMS effects are state-dependent
- Combining elements of psychotherapy with TMS may improve outcomes by leveraging the state-dependency of TMS effects

# Depression

- Symptoms include:
- Over 300 million suffer from depression worldwide (World Health Organization)




Fried, 2017

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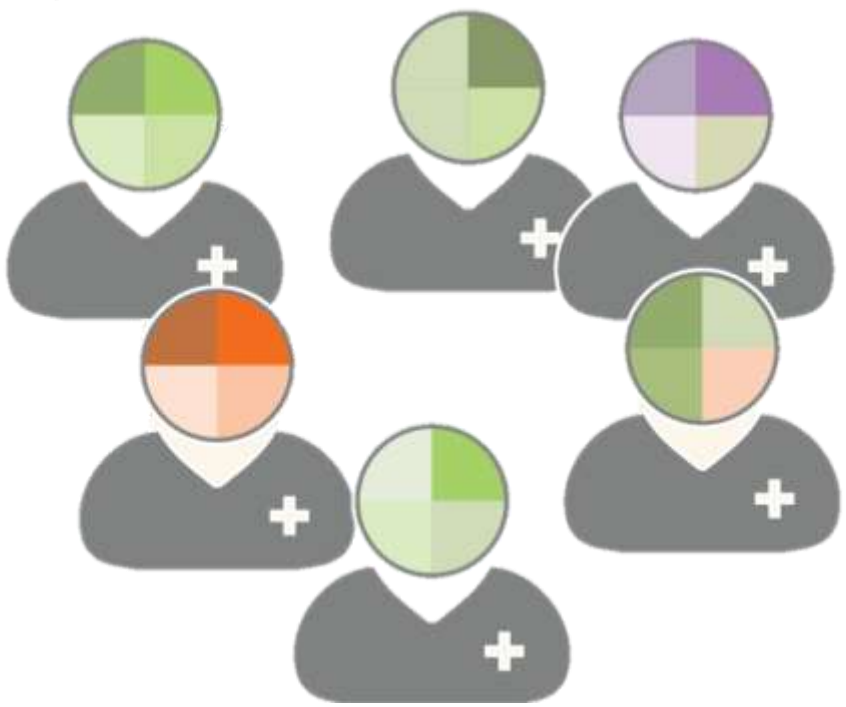
# Heterogeneity of Depression



- The nature of depression differs across individuals
- Need for precise, individualized treatments

Zhi-De Deng, PhD
Drysdale et al., 2017; Williams 2016

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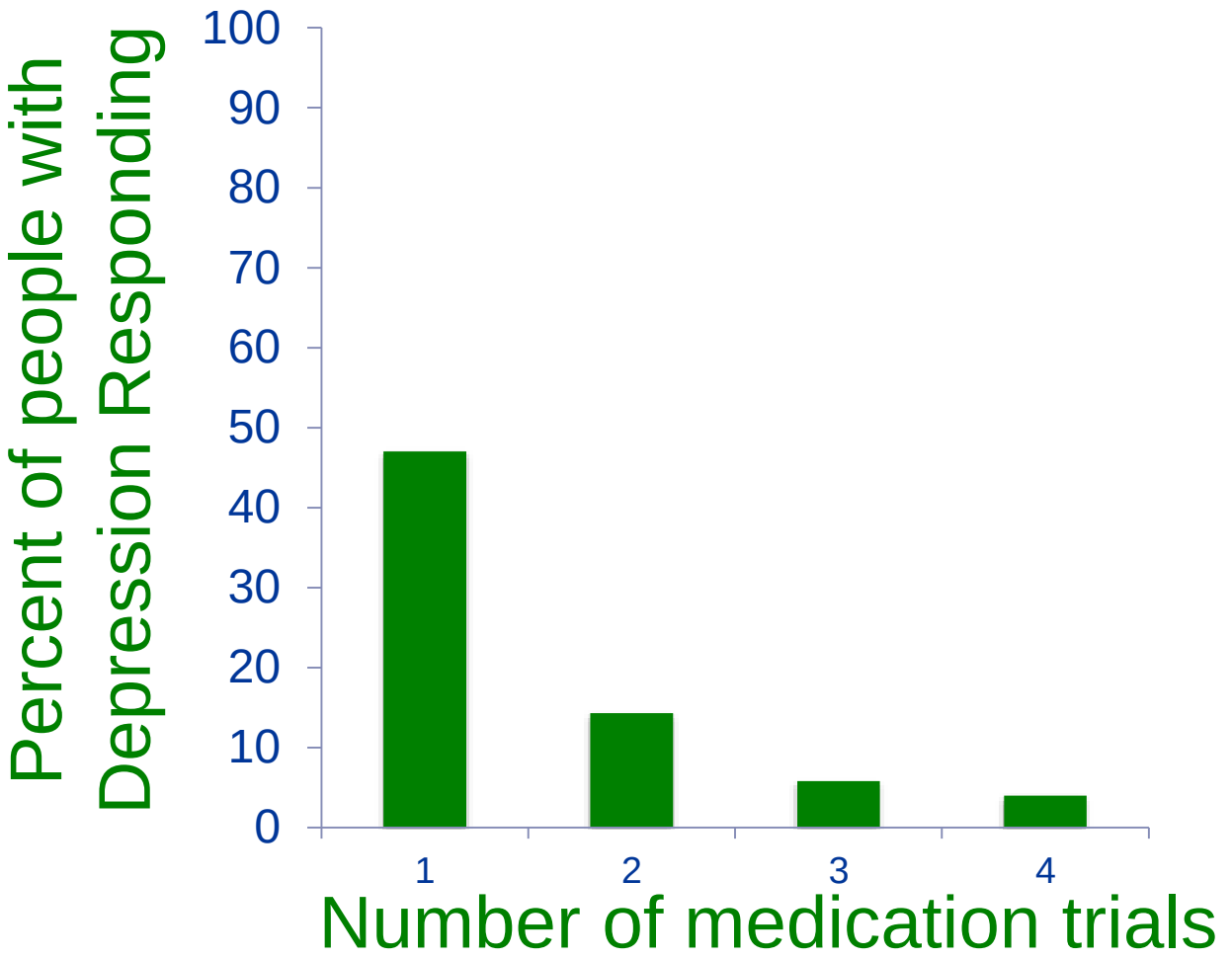
# Treatment Resistant Depression (TRD)

- Majority do not respond to first-line treatments
- Diminishing returns from medication switches




STAR-D Trial; Trivedi et al., 2006; Warden et al., 2007

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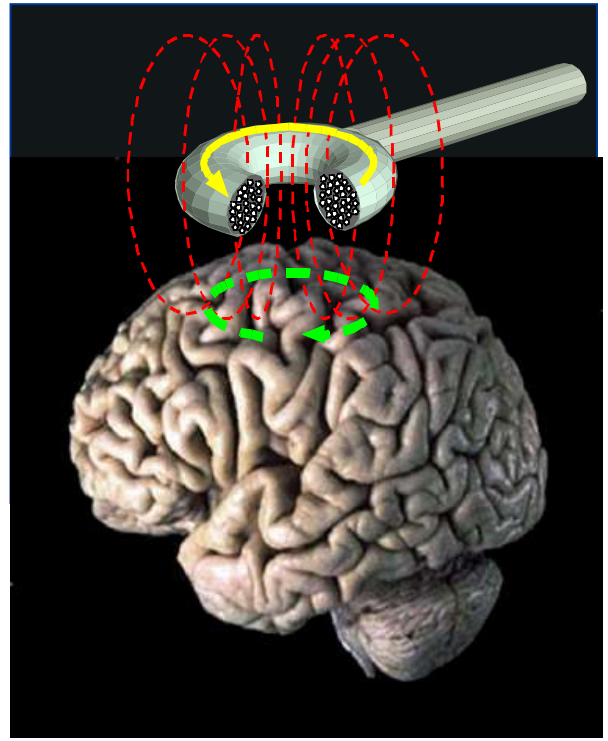
# Depression Treatments

- Psychotherapy
- Pharmacology
- Brain Stimulation
  - Electroconvulsive Therapy (ECT)
  - Transcranial magnetic Stimulation (TMS)

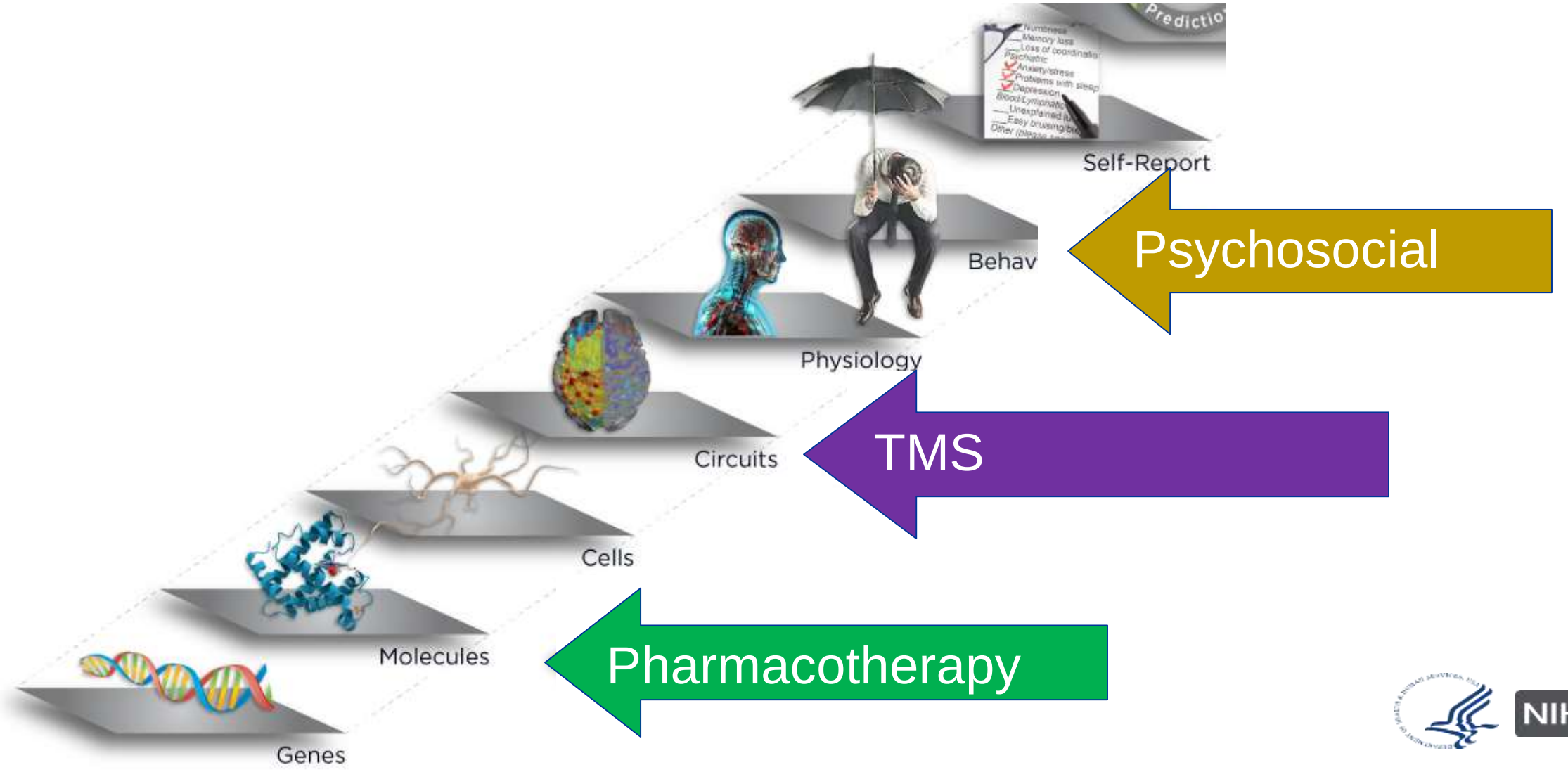
# Transcranial Magnetic Stimulation (TMS)

- Noninvasive
  - Uses magnetic fields
- Neuromodulation
  - Stimulates circuits
- Neuroscience tool
  - Test brain-behavior relationships
- Treatment tool
  - FDA cleared for depression and OCD



# Promise of TMS

- Complementary to Pharmacological and Psychosocial Interventions

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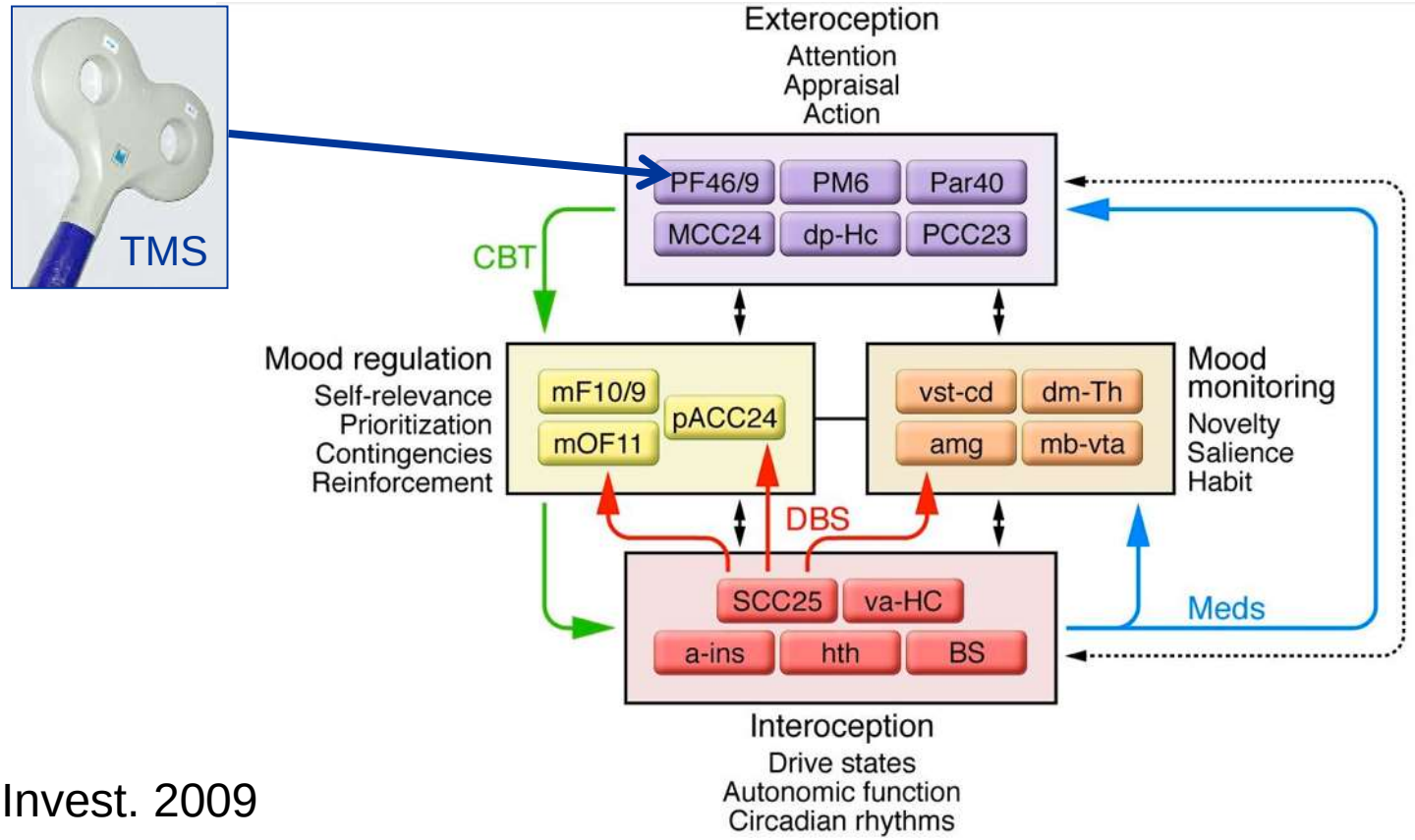
# Promise of Brain Stimulation

- Complementary to Pharmacological and Psychosocial Interventions
- Translates knowledge of circuitry into therapeutic targets




Mayberg. J Clin Invest. 2009

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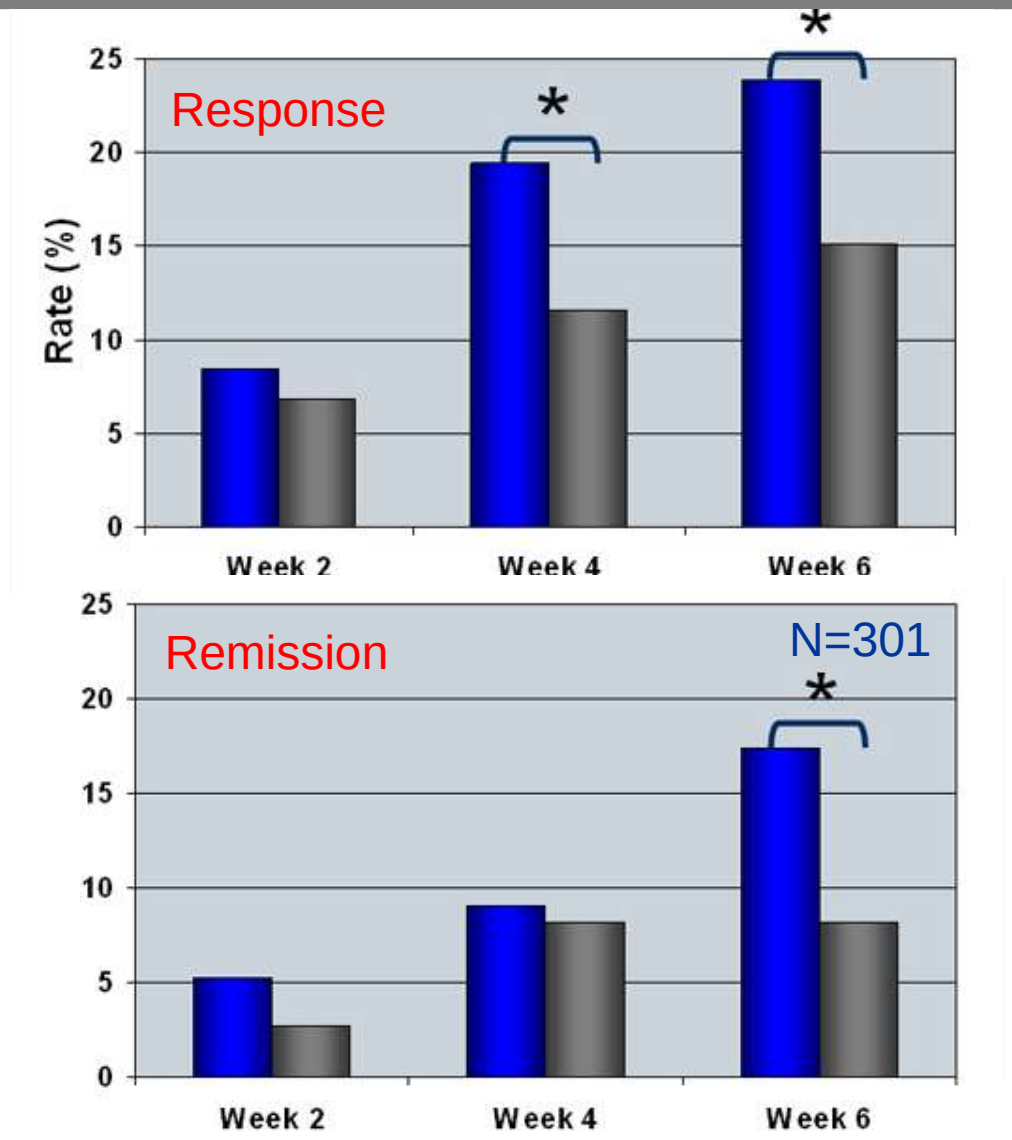
# TMS: Antidepressant Efficacy




- NIH replication
- Sample
  - Unipolar depression (n=190)
  - Baseline HRSD=26
  - 1.5 meds failures
  - Episode length 1-2 years
- Response Rate
  - 15% active, 5% sham
- Remission Rate
  - 14% active, 5% sham

O'Reardon et al. Biol Psychiatry 2007

George, Lisanby, Avery, McDonald et al. Arch Gen Psychiatry. 2010

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# TMS Dose

## Space

**Spiral Galaxy M83 .**
Credit: NASA, ESA, and the Hubble Heritage Team

# TMS Dose

Space

**Spiral Galaxy M83 .**
Credit: NASA, ESA, and the Hubble Heritage Team

Time

**The Persistence of Memory – Salvador Dali**

Context

# TMS Dose

## Space


## Time


## Context

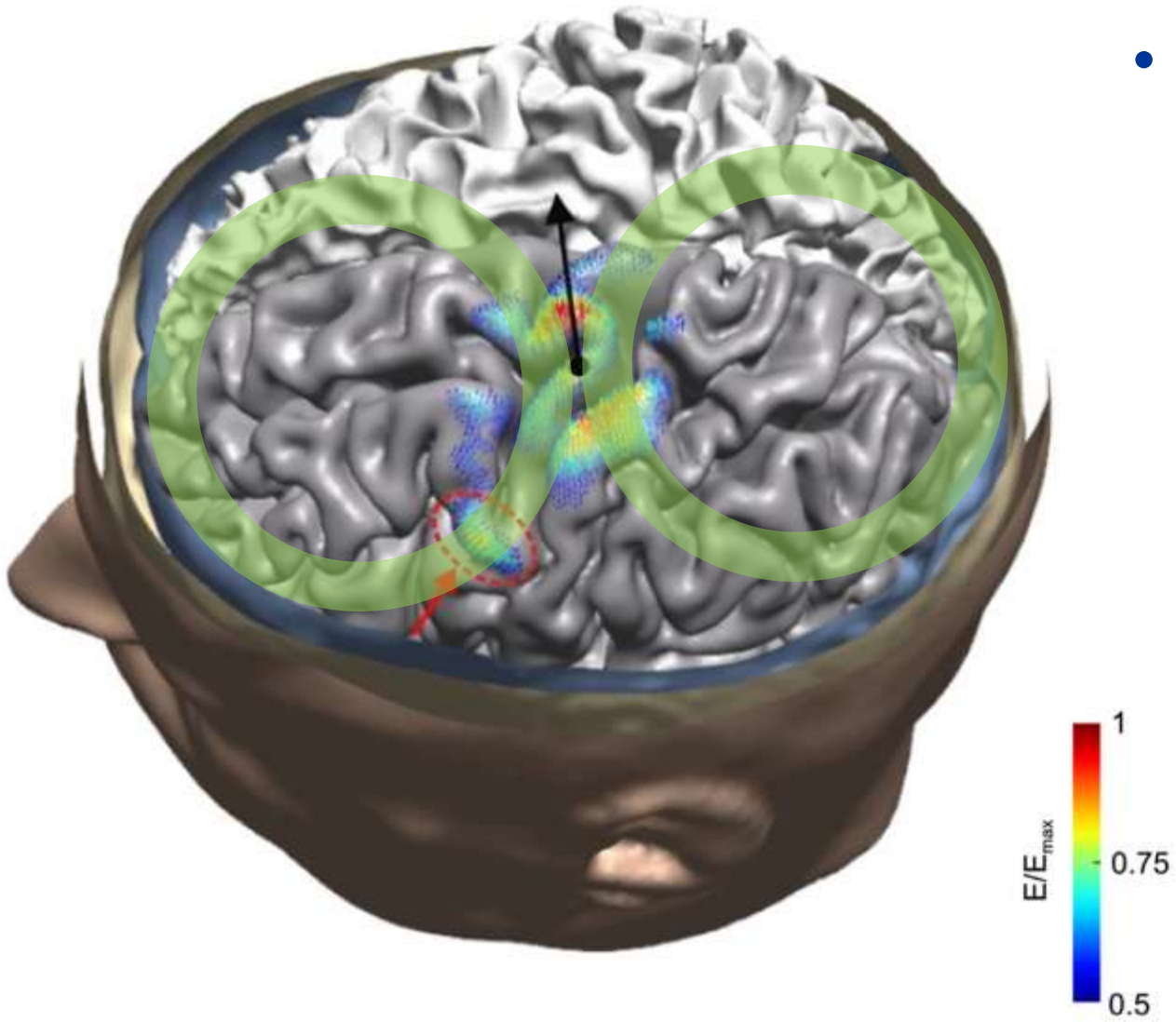
# TMS Dose

## Where


## When


## How

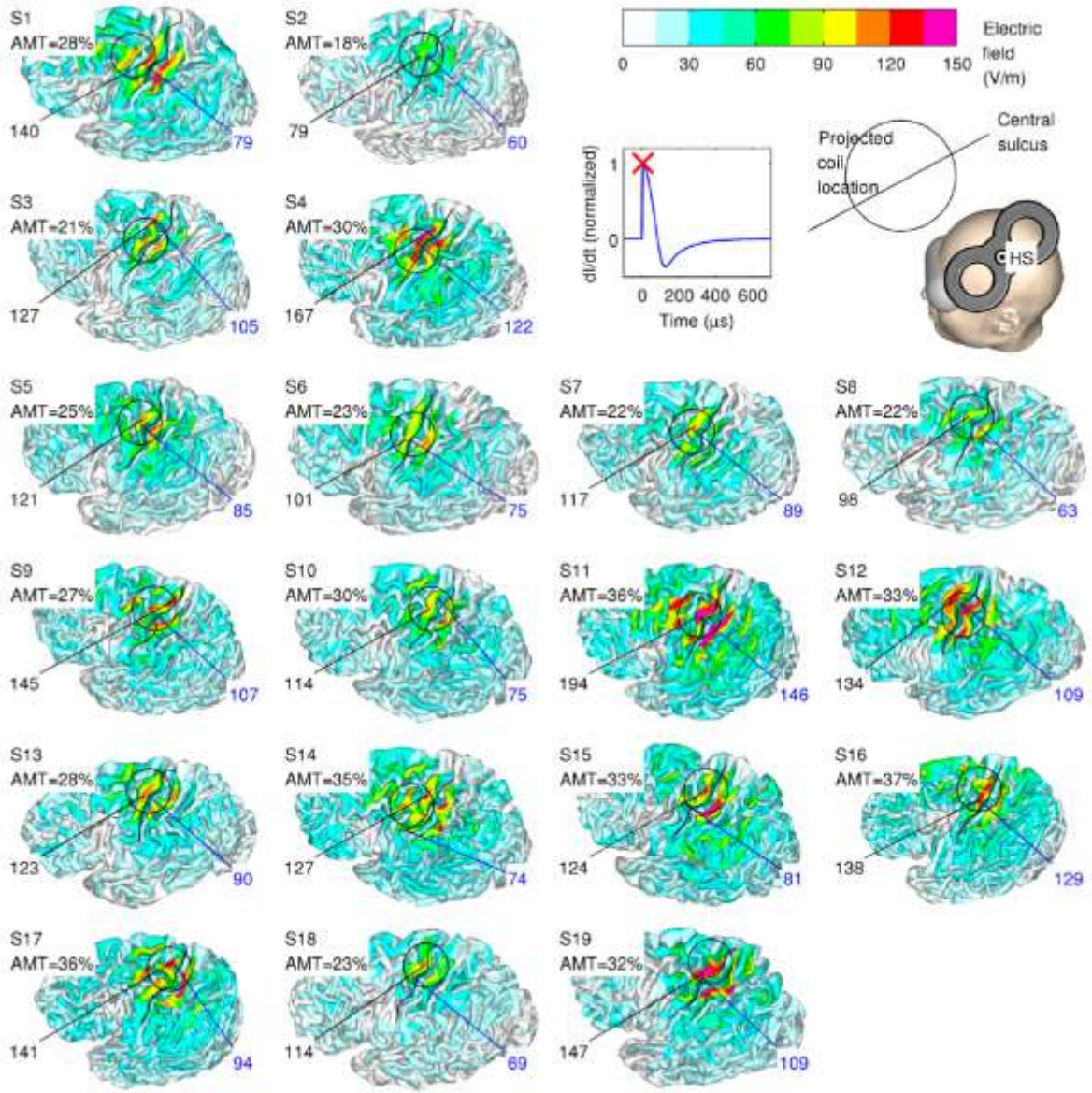
# TMS Dose: Spatial Targeting




- E-field affected by
  - Shape, size, placement of TMS coil
  - Amplitude of current pulses
  - Hair thickness
  - Scalp-to-cortex distance
  - Head shape
  - Cortical folding

[Thielscher et al, NeuroImage 2011]

# TMS Dose: Spatial Targeting




- E-field affected by
- Highly variable across individuals

Laakso et al, Brain Stimul 2018

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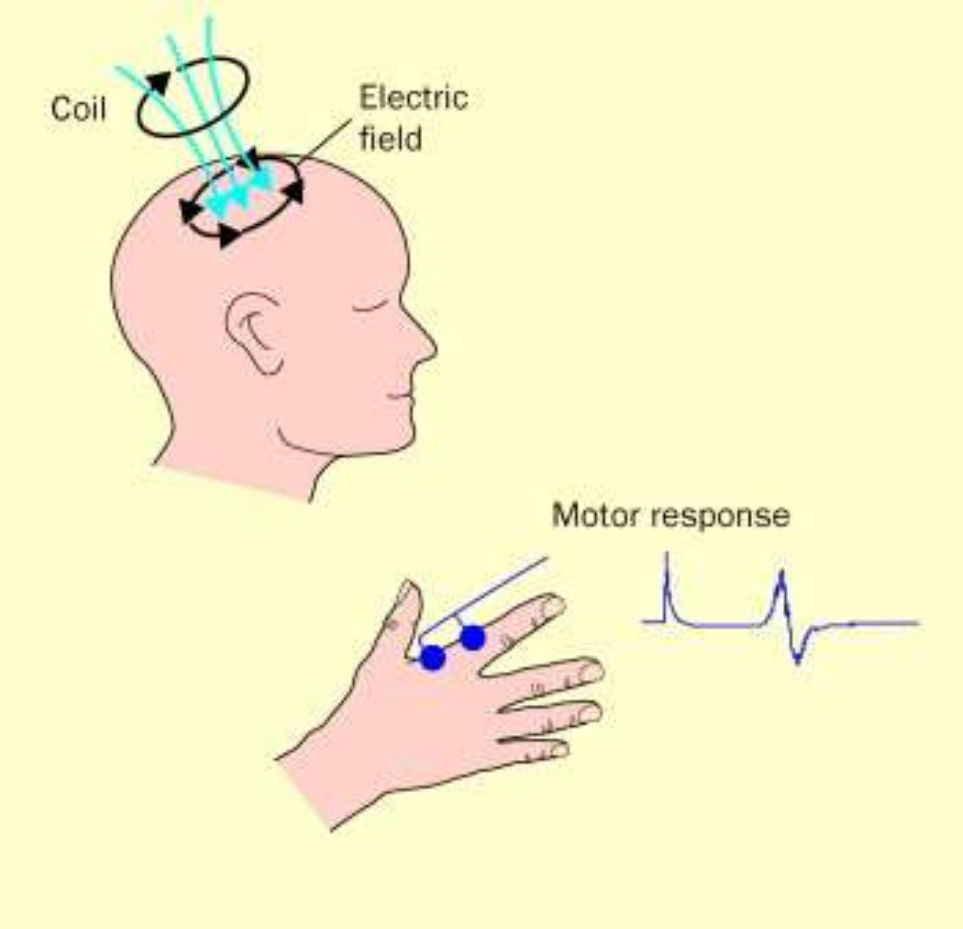
# TMS Dose: Spatial Targeting


- E-field affected by
- Highly variable across individuals
- Can be improved with image-guidance and neuronavigation

# TMS Dose: Context

- TMS effects are state dependent
  - Muscle tone

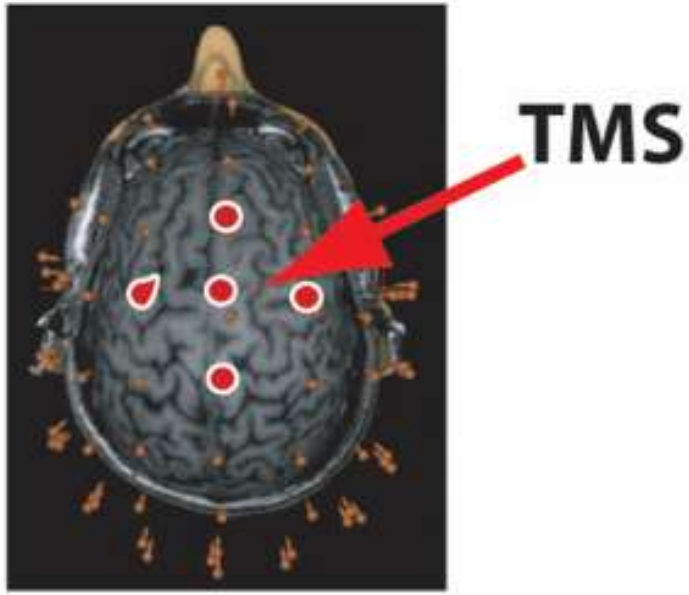




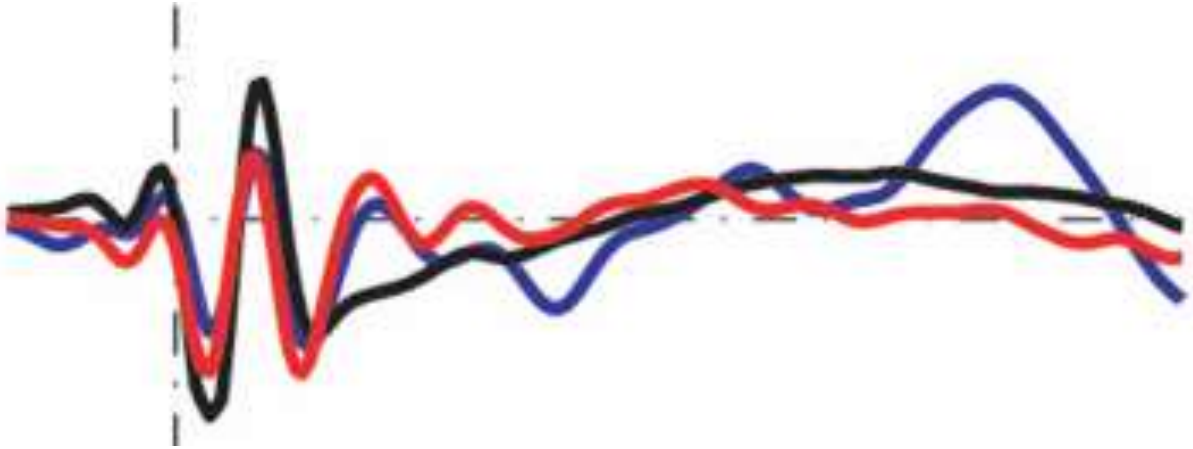
Resting

# TMS Dose: Context

- TMS effects are state dependent
  - Muscle tone
  - Sleep / Wake




TMS-Evoked Potential




Massimini et al. Cogn Neurosci 2011

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# TMS Dose: Context

- TMS effects are state dependent
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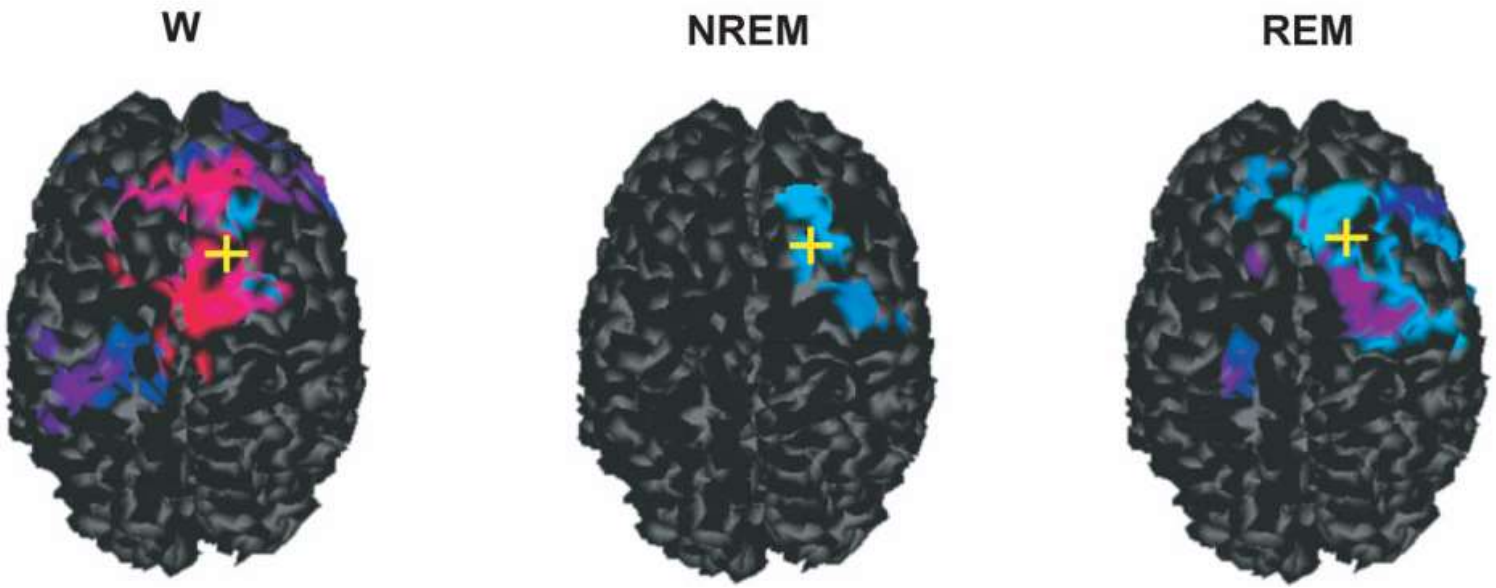
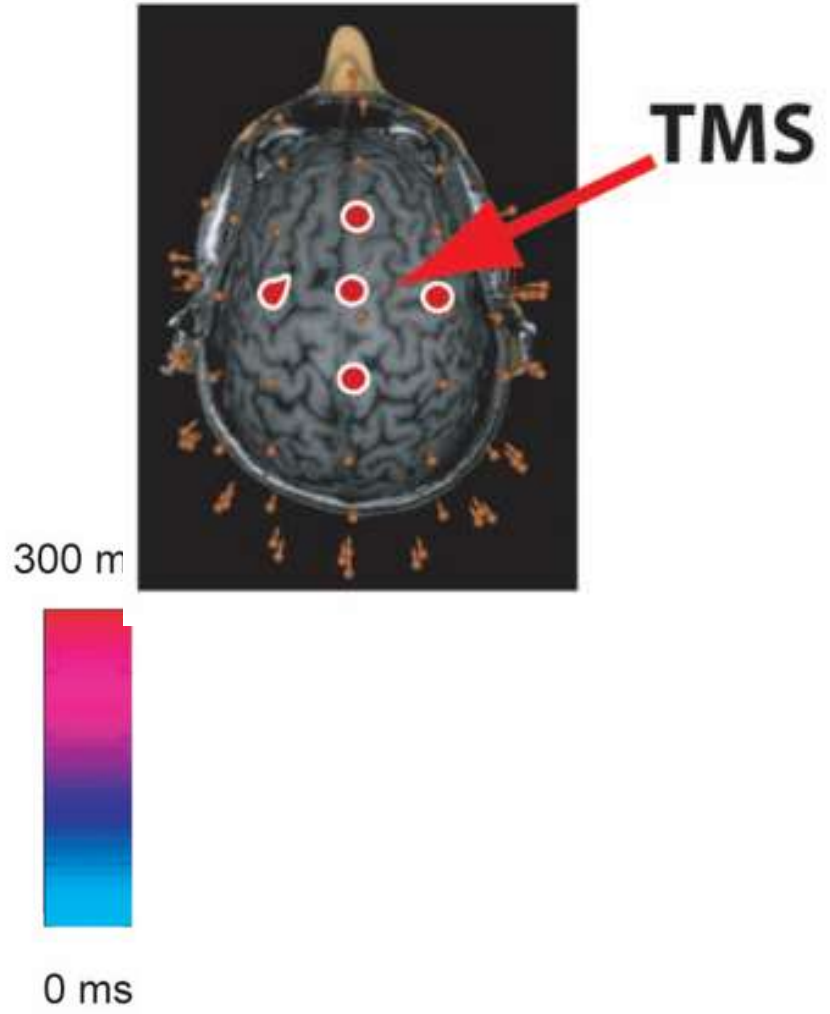


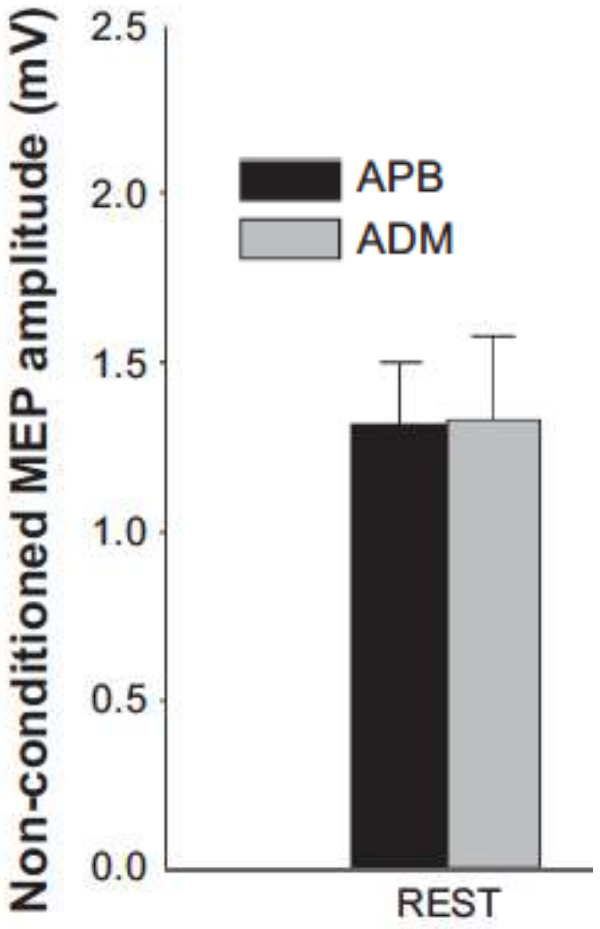




Massimini et al. Cogn Neurosci 2011

# TMS Dose: Context

- TMS effects are state dependent
- Brain state can be controlled by
  - Instruction

Motor Imagery (MI) Instruction:
"stop contracting your thumb and just imagine the feel and sensation of the contraction"




Chong & Stinear J Neurophysiol 2017

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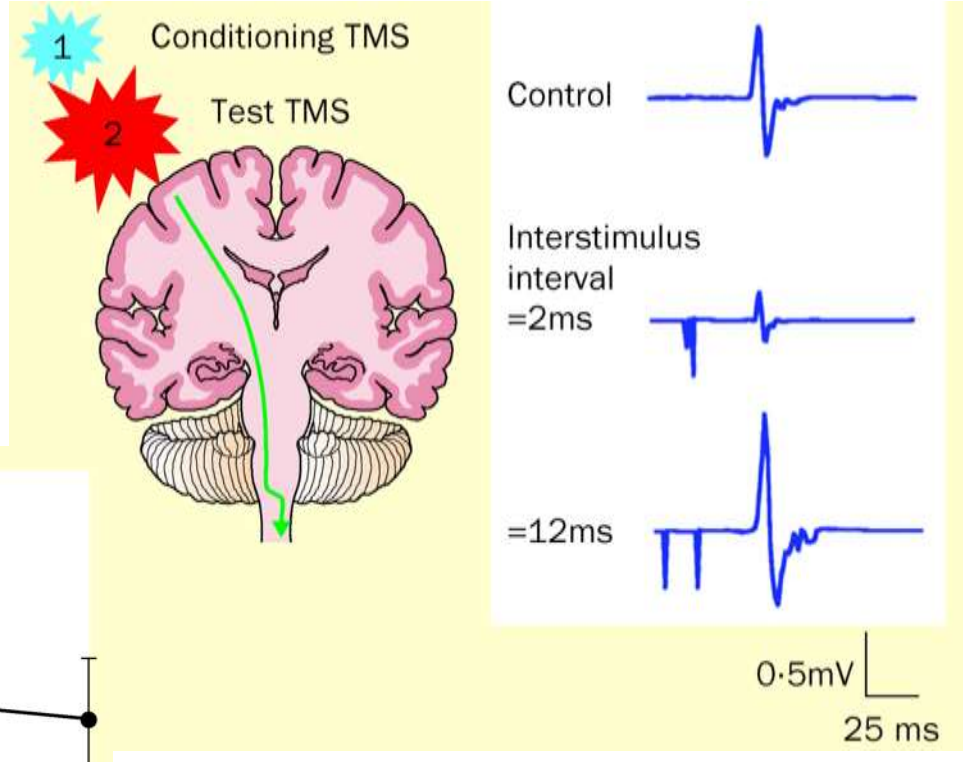
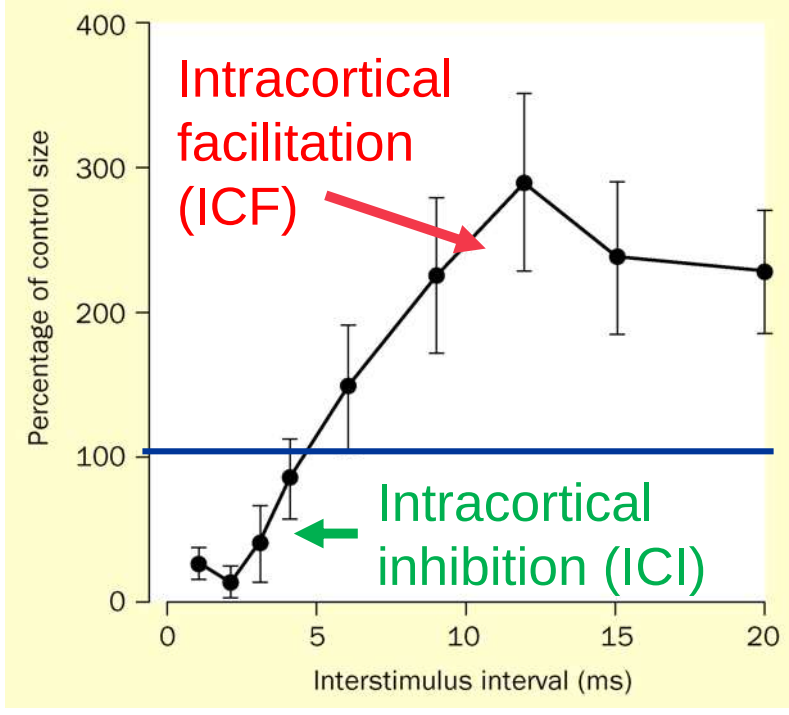
# TMS Dose: Context

- TMS effects are state dependent
- Brain state can be controlled by
  - Instruction
  - Stimulation
    - Paired Pulse TMS

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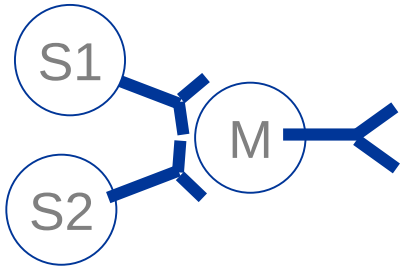
# TMS Dose: Context

- TMS effects are state dependent
- Brain state can be controlled by
  - Instruction
  - Stimulation
    - Paired Pulse TMS
    - Paired Associative Stimulation (PAS)

Synaptic coincidence:
Hebbian plasticity

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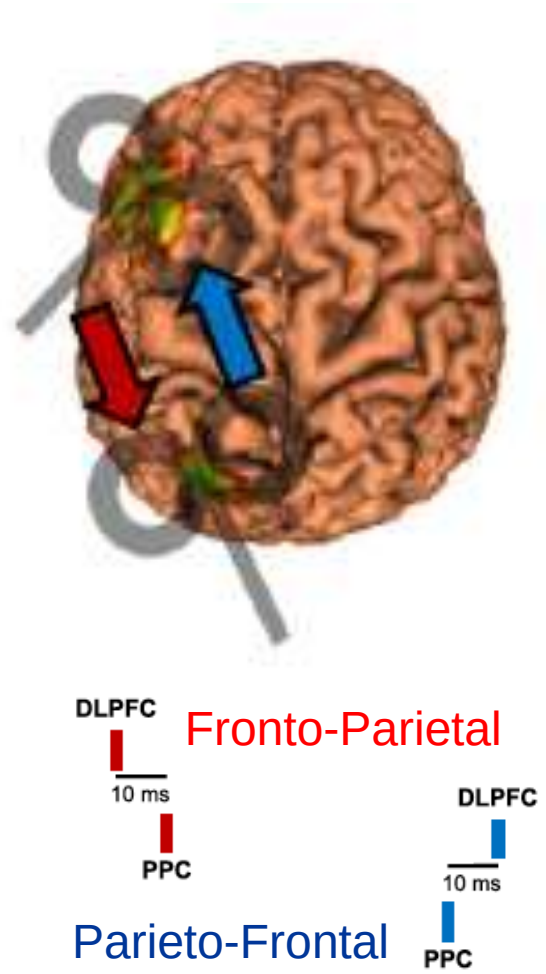
# TMS Dose: Context

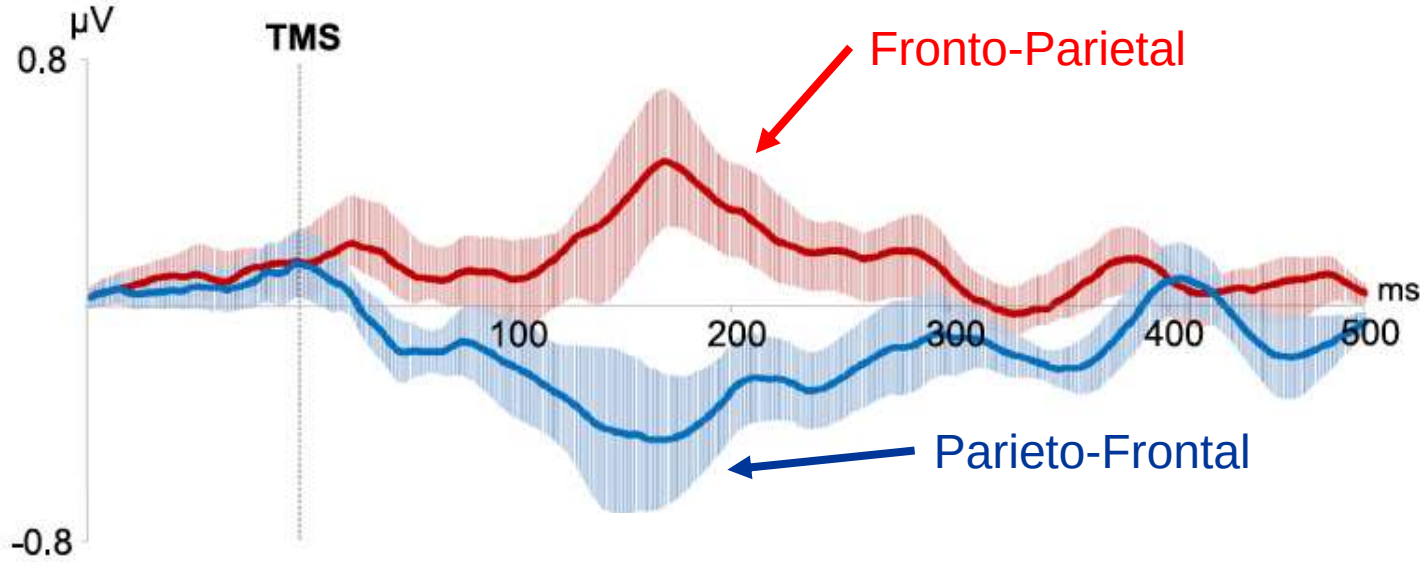
- TMS effects are state dependent
- Brain state can be controlled by
  - Instruction
  - Stimulation
    - Paired Pulse TMS
    - Paired Associative Stimulation (PAS)
    - 2-Coil Paired Associative Stimulation (PAS)

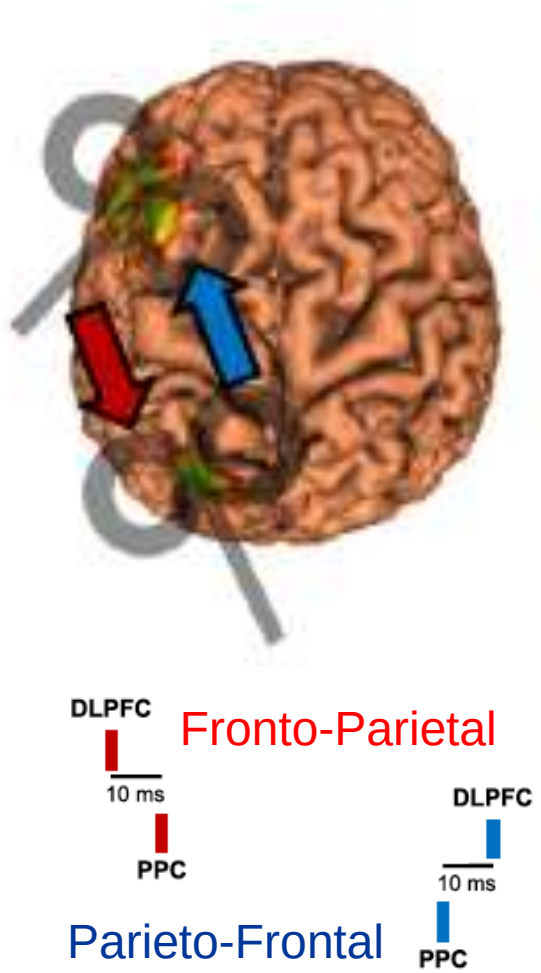



Casula et al. NeuroImage 2016;143:204

# TMS Dose: Context

- TMS effects are state dependent
- Brain state can be controlled by
  - Instruction
  - Stimulation




Casula et al. NeuroImage 2016;143:204

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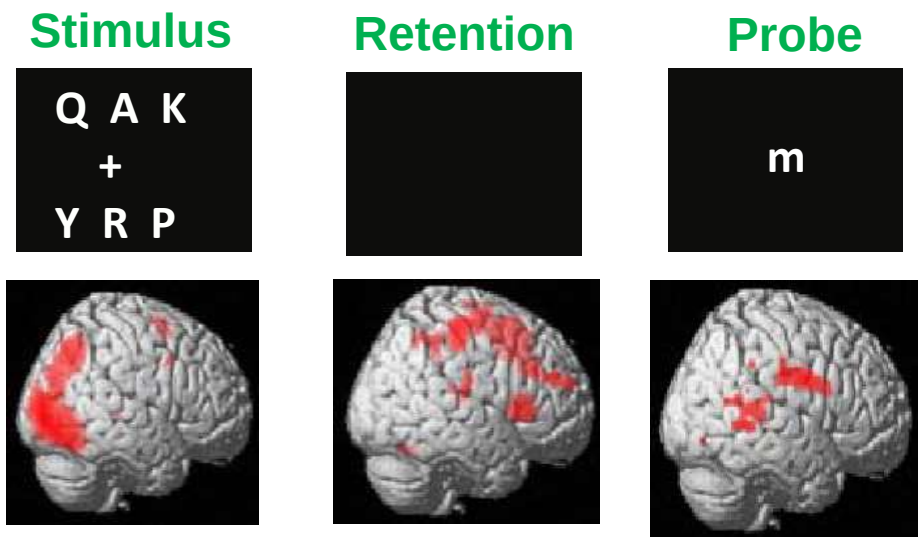
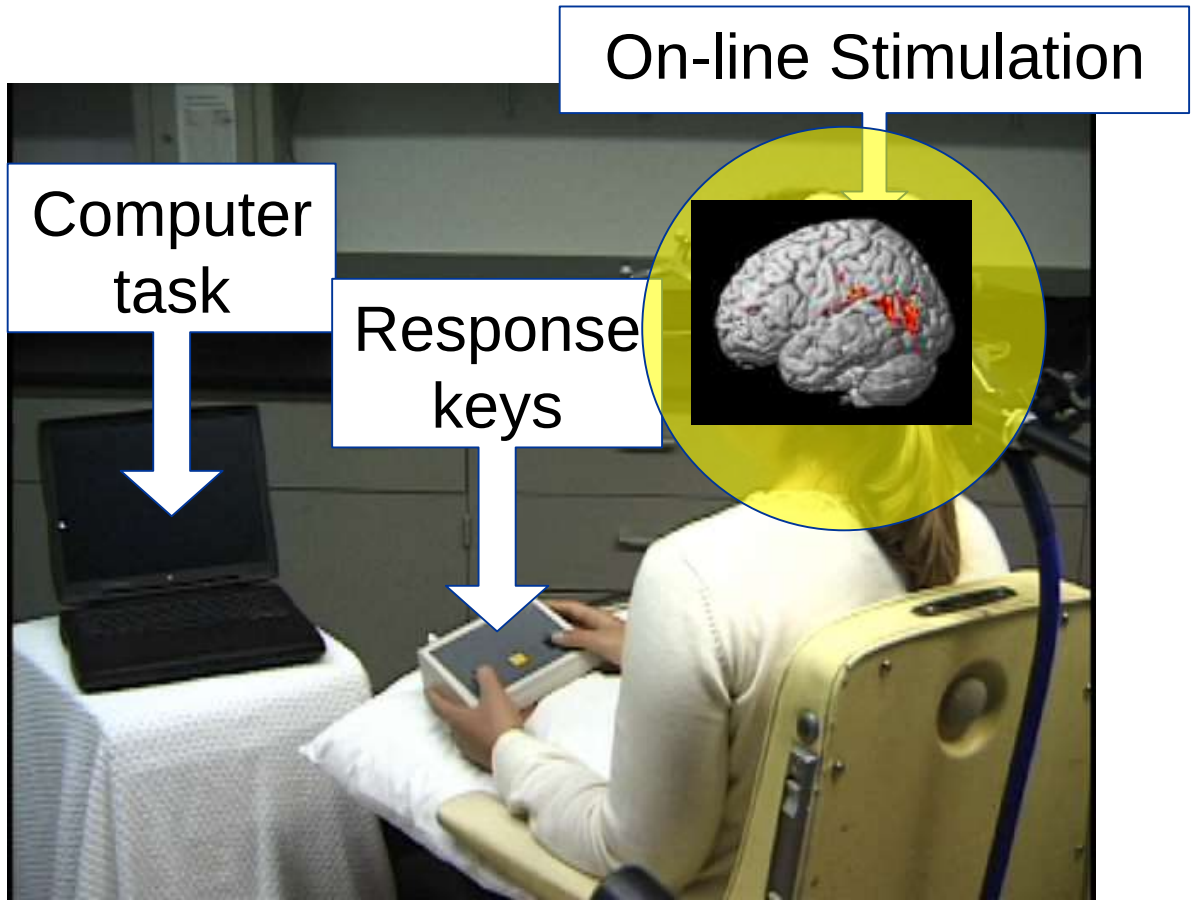
# TMS Dose: Context

- TMS effects are state dependent
- Brain state can be controlled by
  - Instruction
  - Stimulation
  - Cognitive tasks

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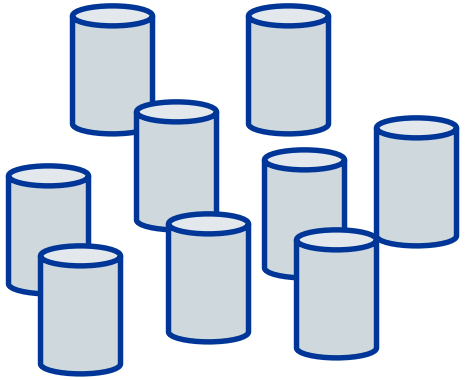
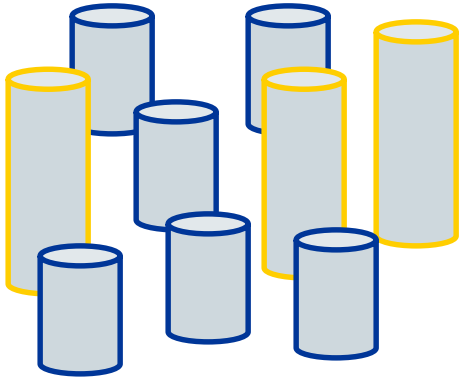
# Functional Targeting: Behavioral Activation of Circuits During TMS

neural ensemble at “rest”

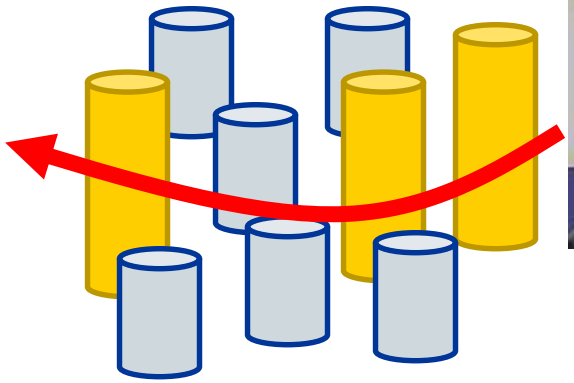


neural ensemble activation via behavior



Represents means of providing a “functional focality” to nonfocal interventions

Neurostim effects maximized at activated neurons



Stimulate the circuit while it’s activated

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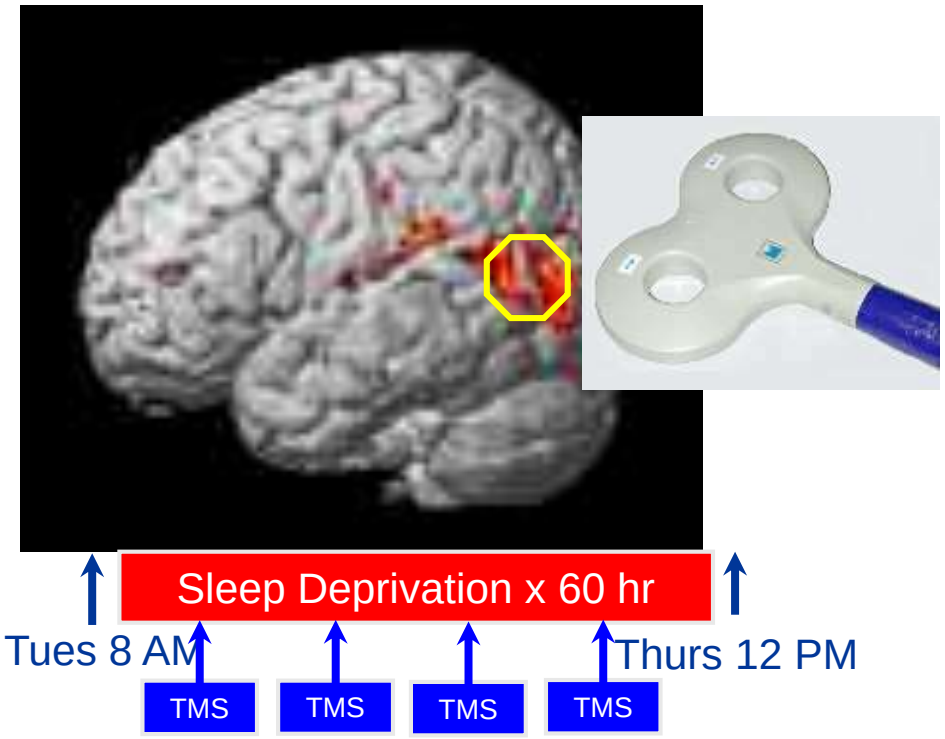
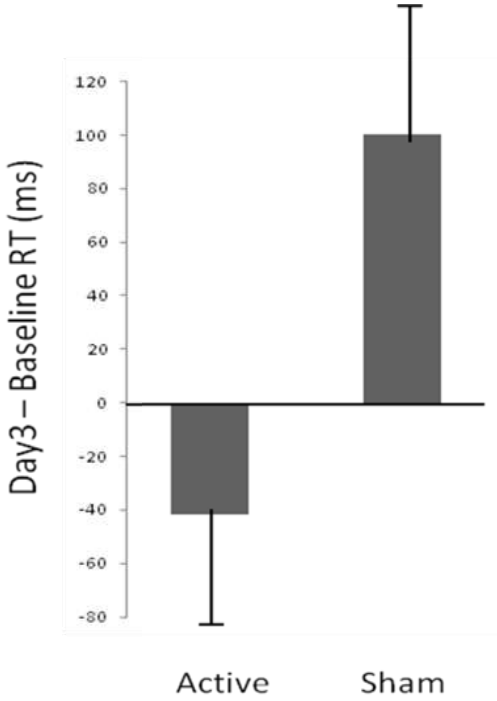
# Pairing TMS with Task Performance to Control State

- Cognitive Paired Associative Stimulation (C-PAS)
  - Cognitive task used to activate targeted circuit during TMS
  - Leverages spike-time dependent plasticity to enhance potency




- TMS+Working Memory Task during 48hrs sleep dep prevented memory decrement a full 18 hrs after the last TMS
- Clinical trial underway in healthy aging

Luber et al 2013; 2008; 2007

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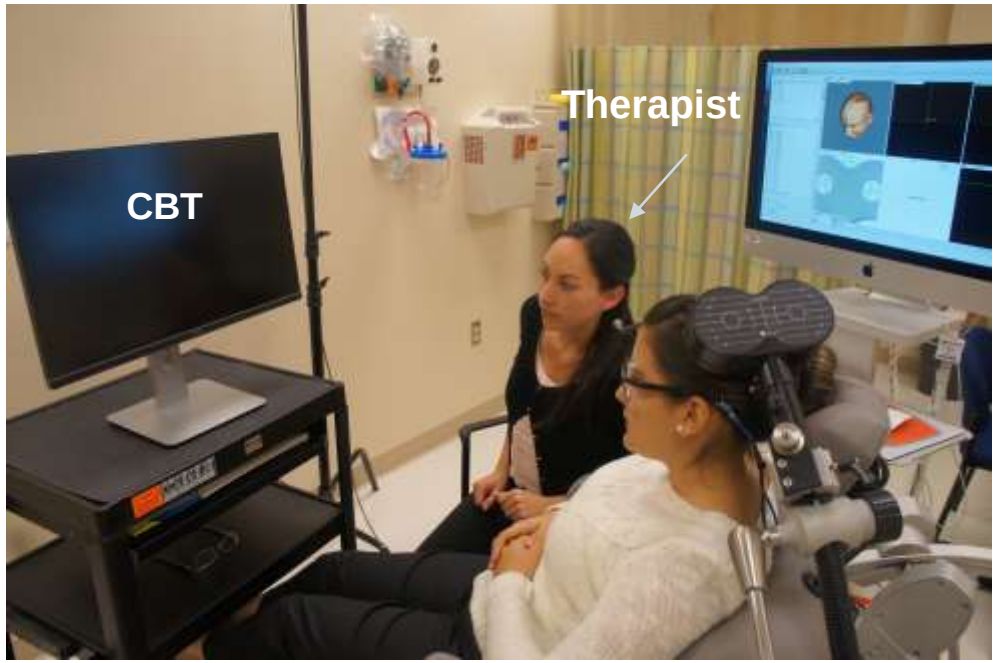
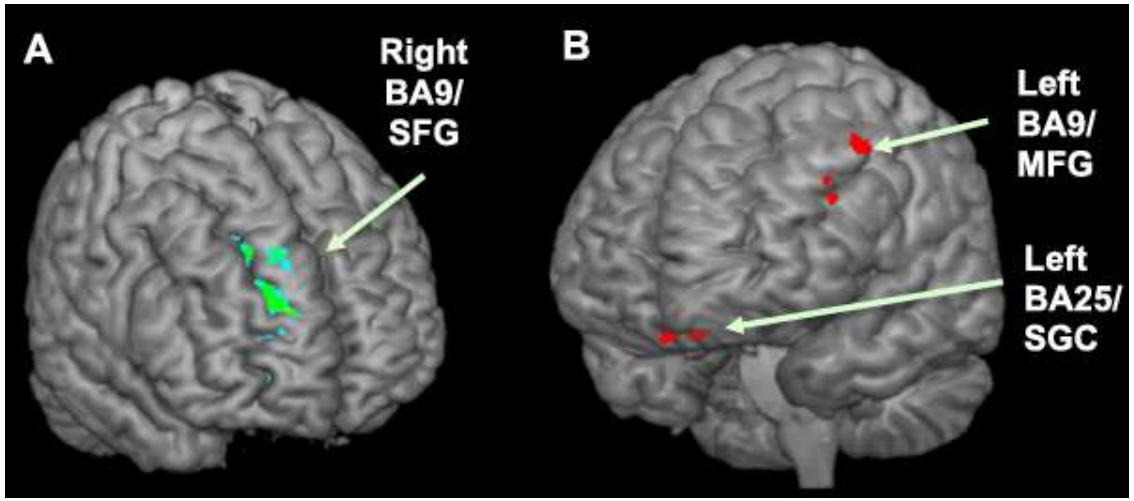
# Leveraging State-Dependency to Enhance Efficacy

- Translational Development of C-PAS for Depression Treatment
  - CBT elements to functionally localize, activate mood-related circuit during TMS therapy for depression, and test target engagement




Individualized task-activated targeting




Luber et al 2017; Neacsiu et al. 2018

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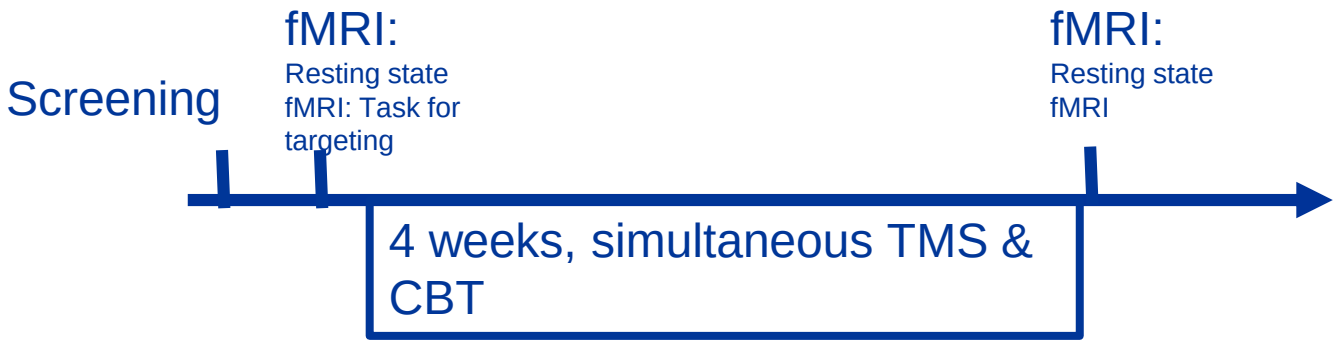
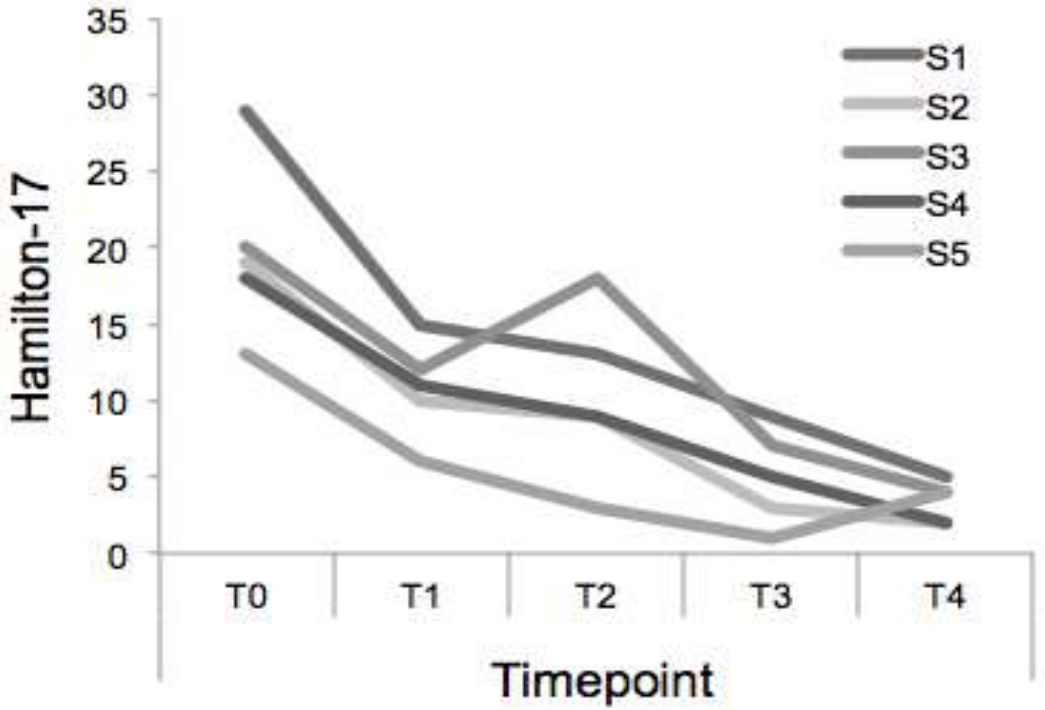
# C-PAS for Depression Treatment – Pilot Study

- 5 patients with treatment resistant depression
  - All patients responded




Neacsiu et al. 2018

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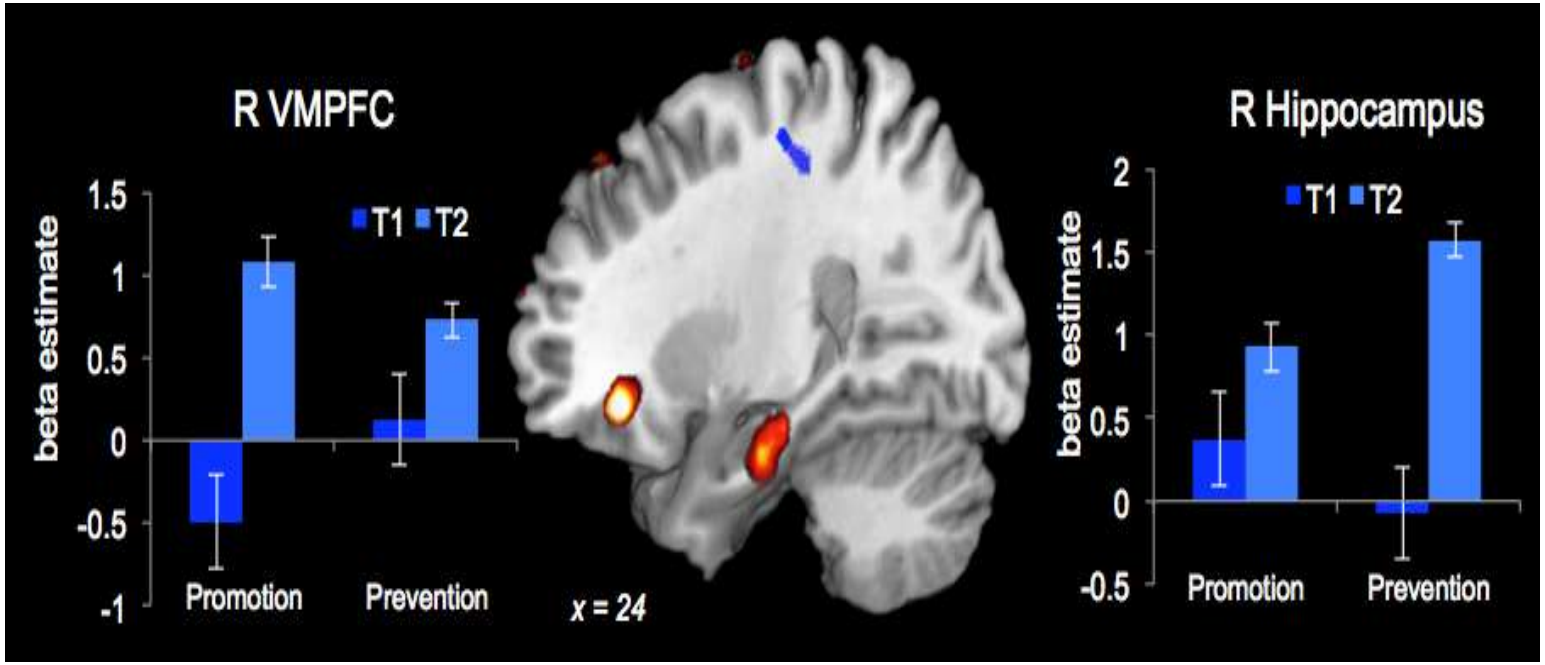
# C-PAS for Depression Treatment – Pilot Study

- 5 patients with treatment resistant depression
  - All patients responded
  - Activity in targeted network was enhanced

Functional activation pre- post. Contrasts between Promotion vs. Prevention goals, presented on a canonical brain in MNI space (t-test across 5 subjects). Strongest effects are present in VMPFC, a site of focus for depression. Warm colors: T2 > T1; cool colors: T1 > T2; results displayed at p < 0.005, uncorrected.




Neacsiu et al. 2018

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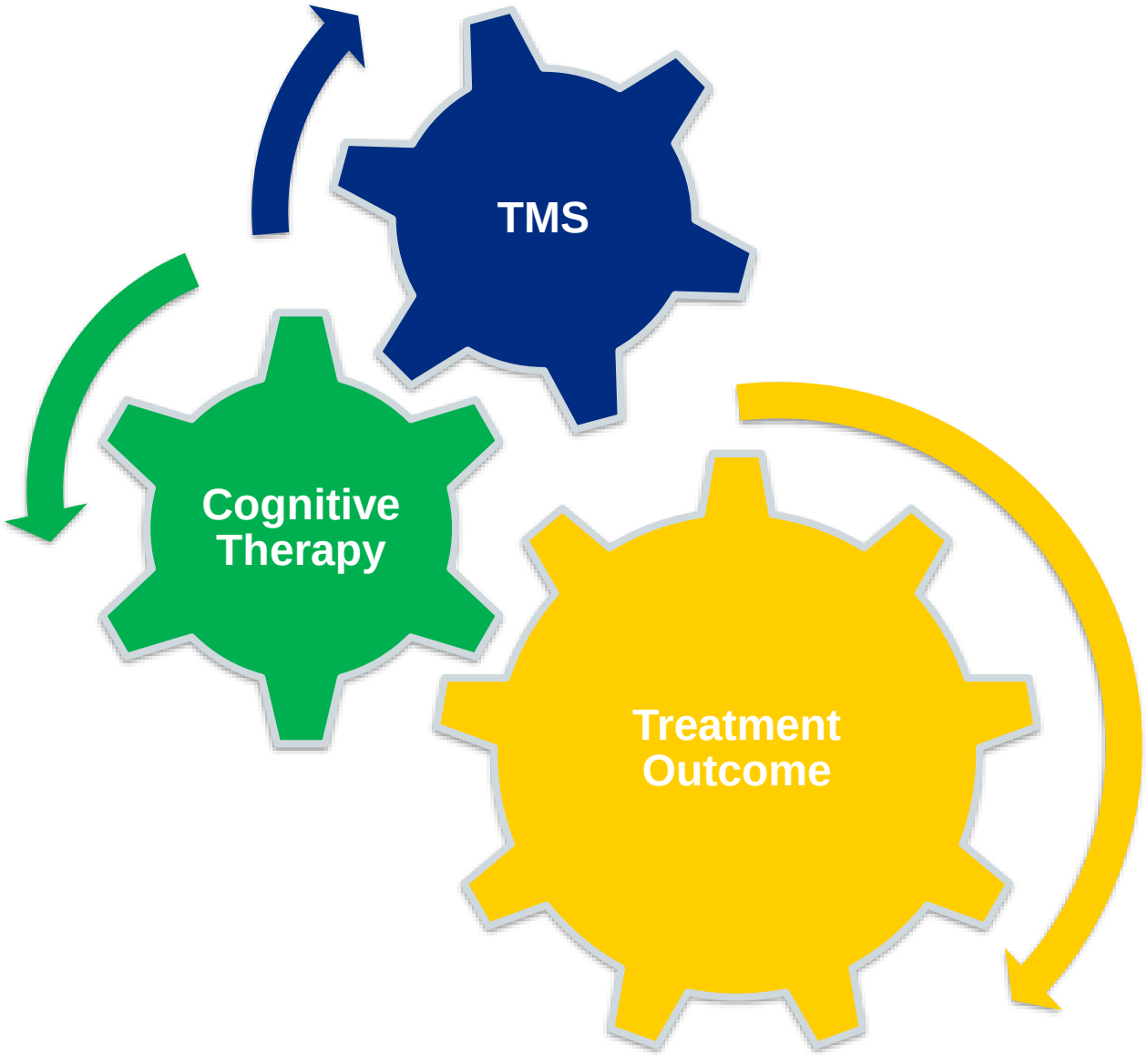
# Concurrent TMS + Cognitive Therapy for Depression




- **Goal:** Leverage state-dependency of TMS effects to enhance antidepressant efficacy
- **Approach:** Administer cognitive therapy to activate the network at the same time as TMS is applied to enhance network function

# Concurrent TMS + Cognitive Therapy for Depression



**Activate + Identify individual DLPFC location using fMRI**

**Neuronavigate TMS to individualized Target**

**Therapist CBT concurrent with TMS**

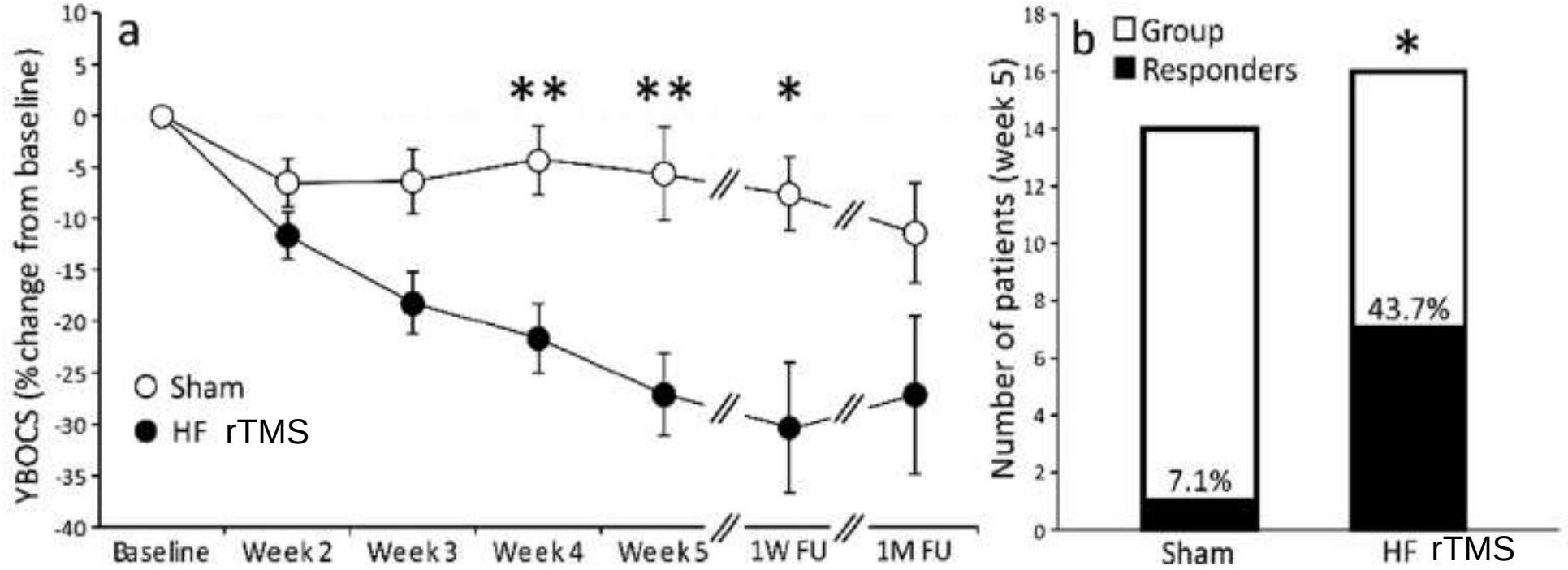
# Possible Outcomes


Sathappan, Luber, Lisanby. 2019

# Summary

- Novel investigational multimodal treatment for depression
  - Theory-based protocol for *individualized optimization* of TMS site of stimulation
- Concurrent behavioral interventions targets same dysfunctional neural circuitry being targeted by TMS
- Goal of enhancing plasticity in targeted circuit to improve depression outcomes

# C-PAS for OCD Receives FDA Clearance




- dTMS to mPFC-ACC after symptom provocation more effective than sham
- FDA-approved in 2018

Carmi et al. Brain Stimulation. 2018

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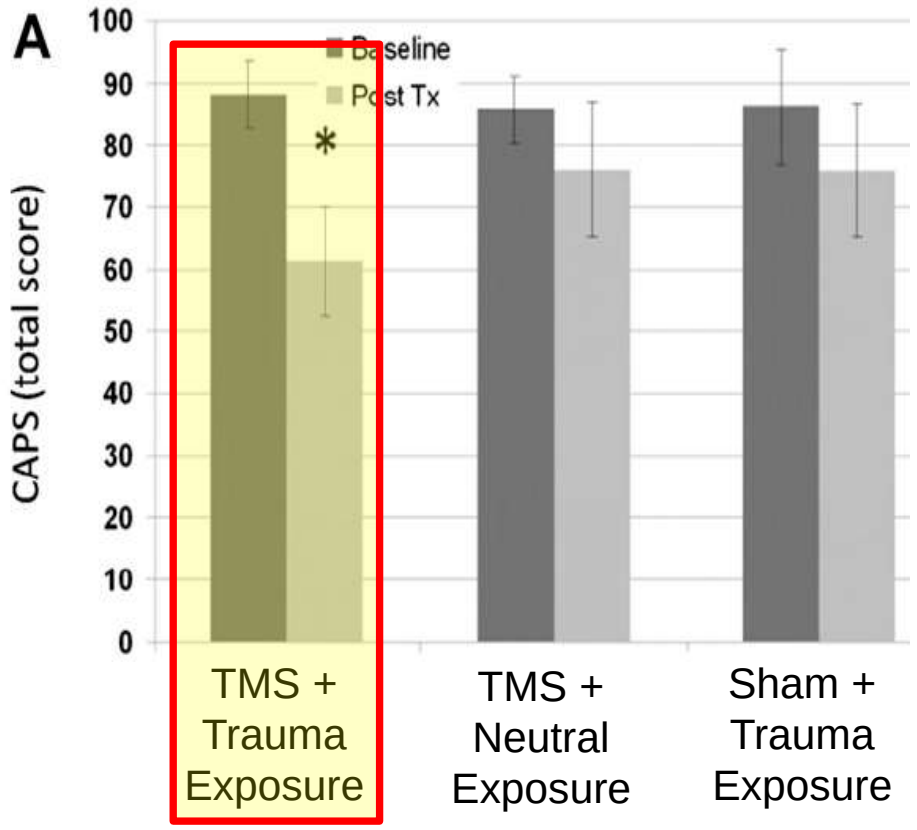
# Paired TMS + Exposure Therapy in PTSD




- dTMS to mPFC after exposure to trauma narrative cues to block reconsolidation of trauma memory
- Active dTMS+exposure showed efficacy

- Both studies used non-focal dTMS coil
- Exposure may “functionally” localize the site of action

Isserles et al. Brain Stimulation 2013

# Multi-Modal Intervention Development

Neuromodulation Therapy

Psycho-social therapy

Pharmaco-therapy

Multi-Modal Treatment Paradigms

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# Take Home Points

- Depression and OCD can be disabling and current treatments are not effective for everyone
- Transcranial Magnetic Stimulation (TMS) is a new tool for treating depression and OCD
- TMS effects are state-dependent
- Combining elements of psychotherapy with TMS may improve outcomes by leveraging the state-dependency of TMS effects

# NIMH Noninvasive Neuromodulation Unit


Special Thanks to ETPB Medical and Nursing staff, George Dold, Bruce Pritchard, and the Section on Instrumentation

ETPB Shared Staff: Shora, Yi
NIAAA Collaborator: Ted George
Not pictured: Awasthi

* Special Volunteer

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# For More Information on our Study

Visit clinicaltrials.gov/ct2/show/NCT03289923
for more information on:

***Concurrent fMRI-guided rTMS and Cognitive Therapy for the Treatment of Major Depressive Episodes***

ClinicalTrials.gov Identifier: NCT03289923

Shannon.Exley@nih.gov -- 301-827-0176

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