



# Noninvasive Neuromodulation Applications

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*NIMH*

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7/13/2016



National Institute  
of Mental Health

# The Promise: NeuroMod for Therapeutics

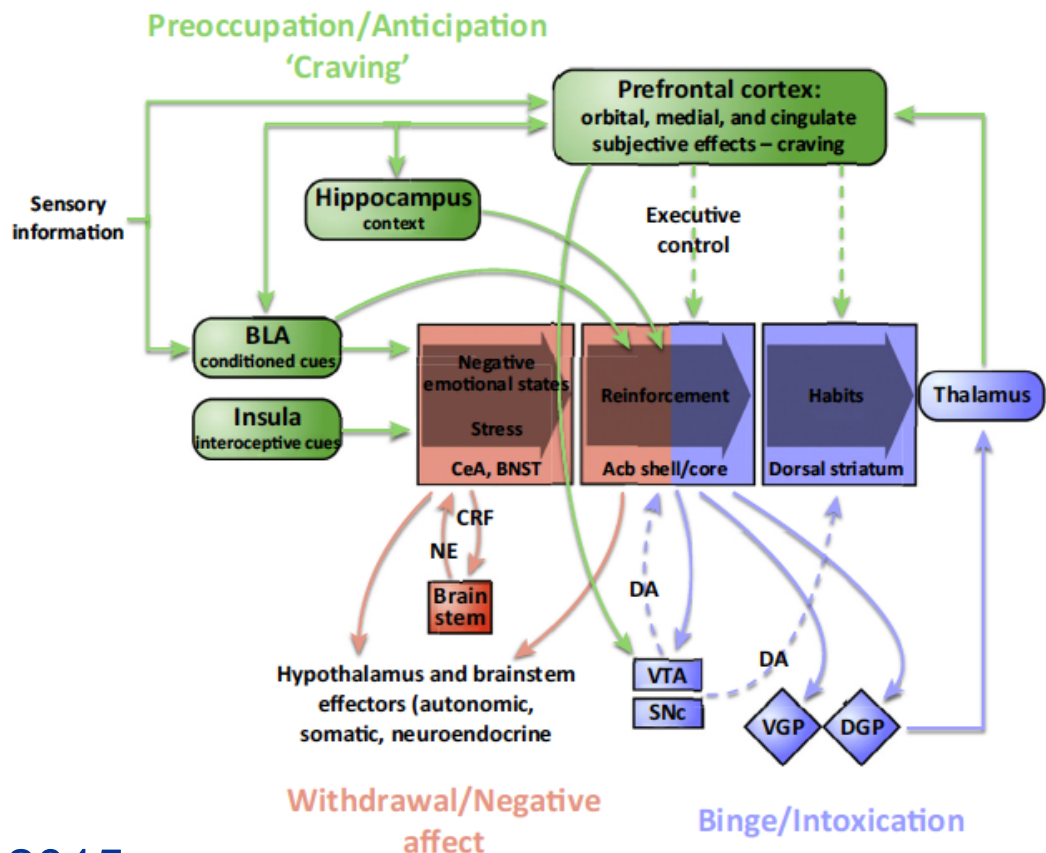
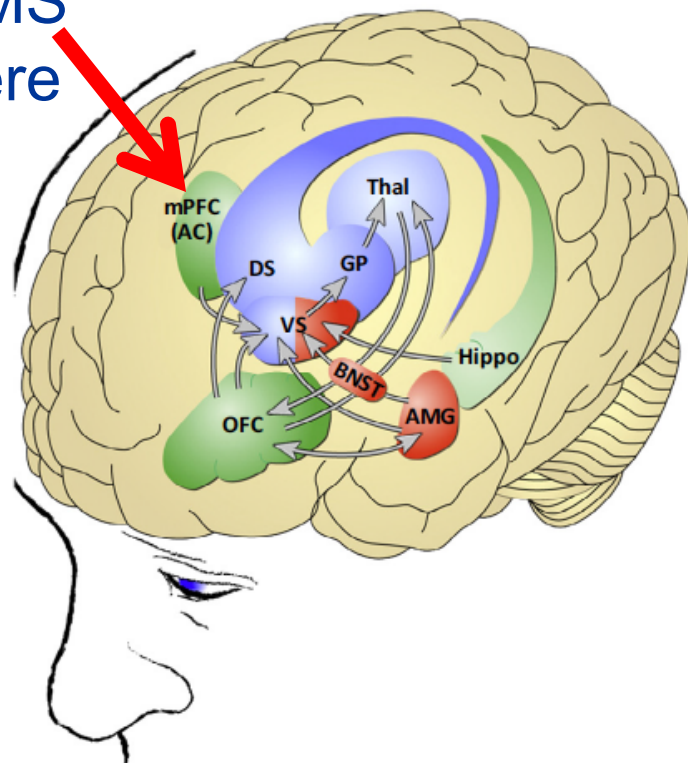
- Complementary to Neuropharm and Psychosocial Interventions
- 3<sup>rd</sup> pillar of modern clinical practice
- Promise to turn knowledge of circuitry into therapeutic targets



# The Promise: NeuroMod for Therapeutics

- Complementary to Neuropharm and Psychosocial Interventions
- 3<sup>rd</sup> pillar of modern clinical practice
- Promise to turn knowledge of circuitry into therapeutic targets

TMS  
here



Tang, Posner, Rothbart, Volkow. 2015

# Clinical NeuroMod: *Current State of the Art*

- Clinically effective, FDA-approved treatments

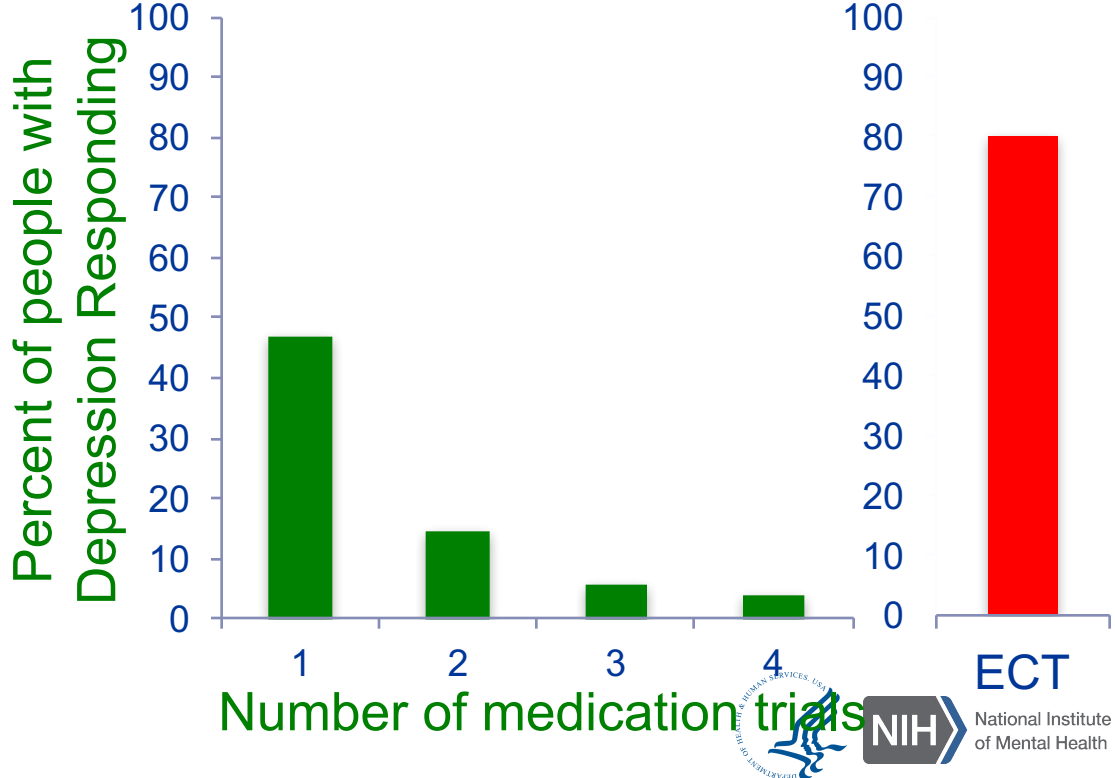


# Clinical NeuroMod: Current State of the Art

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- Unparalleled efficacy



Source: STAR-D Trial

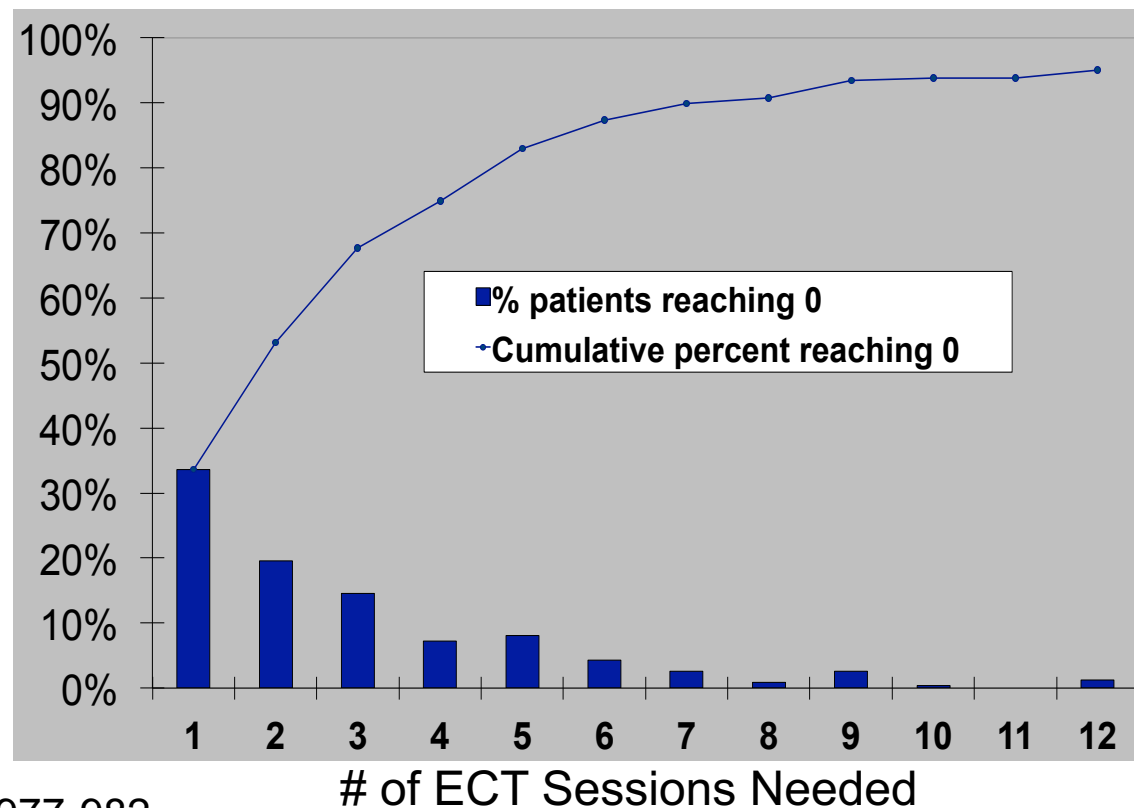


# Clinical NeuroMod: *Current State of the Art*

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- Unparalleled efficacy
- Rapidly resolves suicide risk



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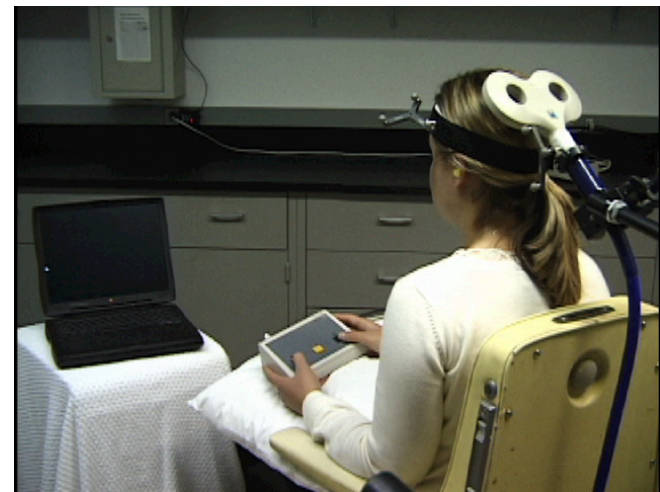
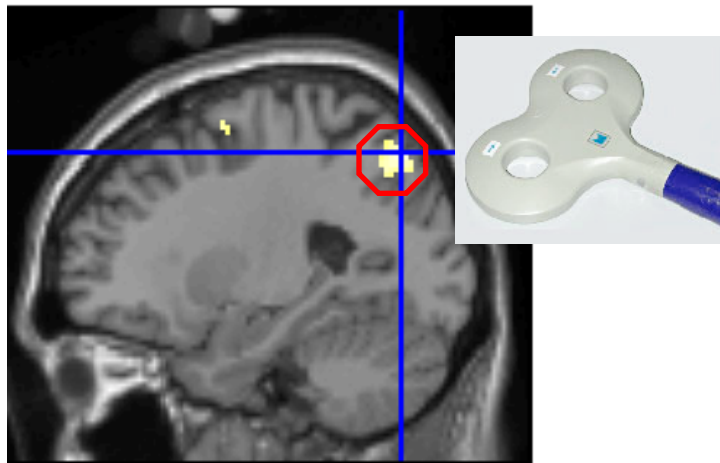


- Less invasive alternatives now on the market
- New devices in various stages of development



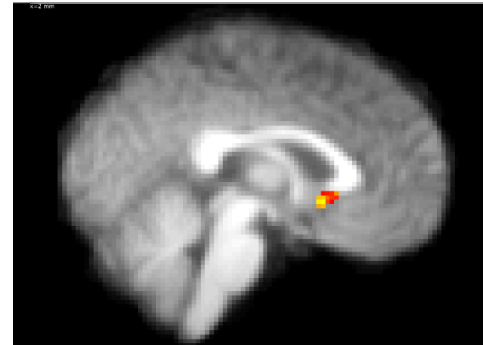
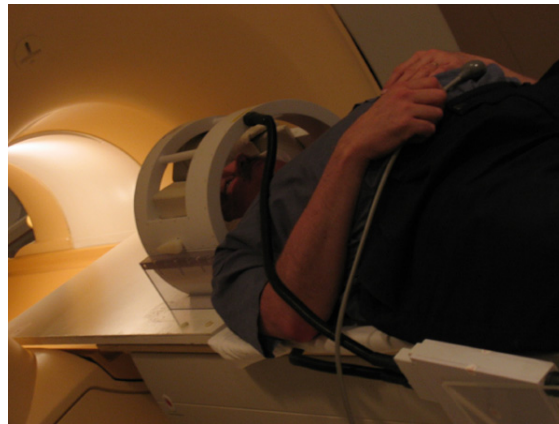
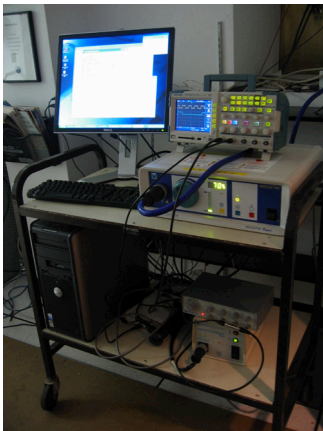
# Clinical NeuroMod: *Current State of the Art*

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- Safe, noninvasive brain-behavior mapping tools
  - Image-guided, stereotaxic stimulation
  - Precisely temporally coupled with cognitive/behavioral task performance



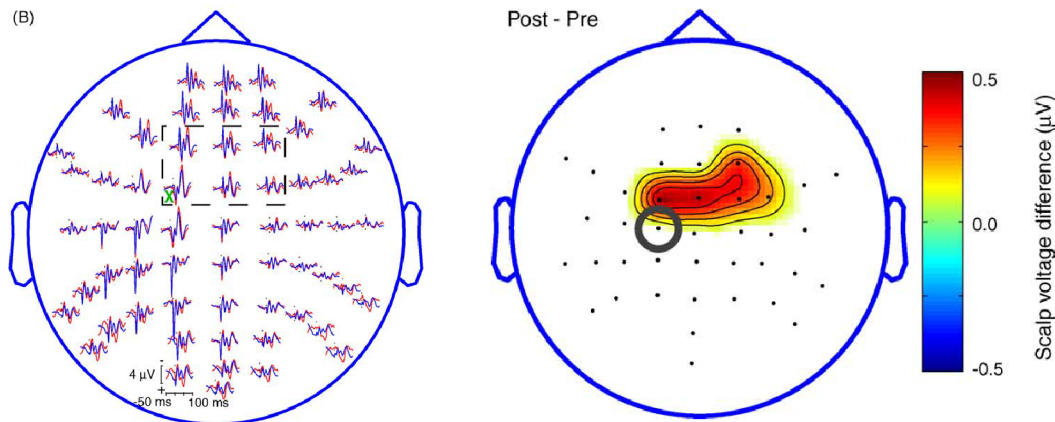
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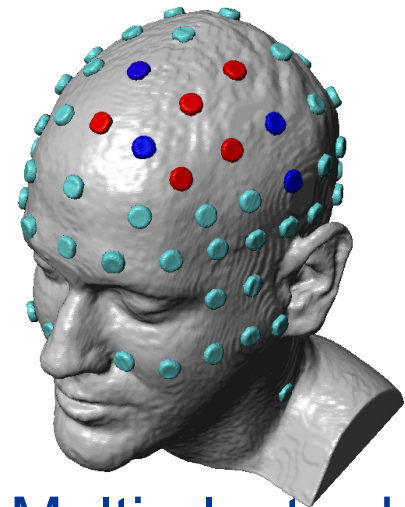
# Clinical NeuroMod: Current State of the Art

- Clinically effective, FDA-approved treatments
- Safe, noninvasive brain-behavior mapping tools
- Affordable, portable technologies on the horizon with excellent safety profiles

- tDCS
- tACS



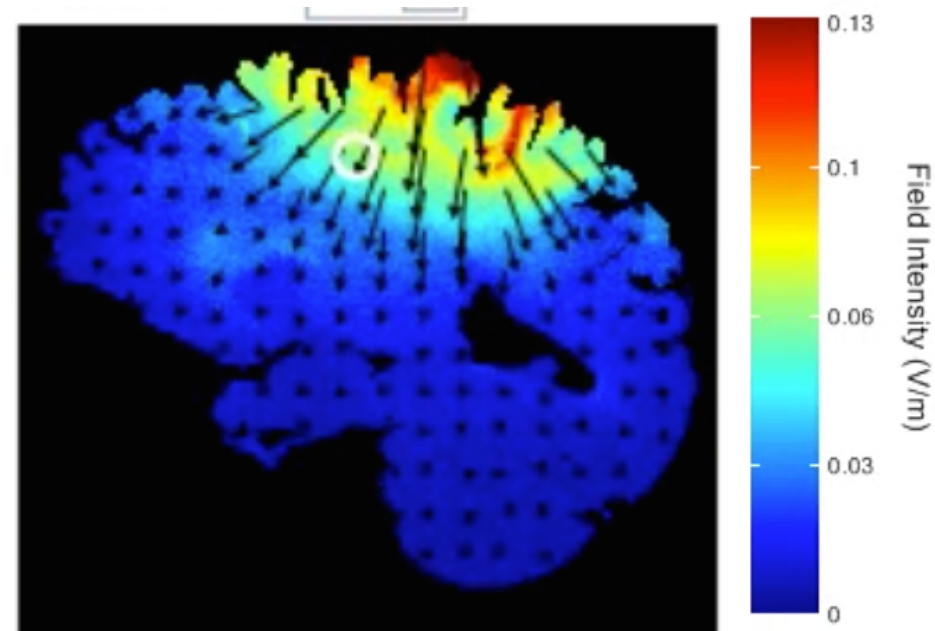
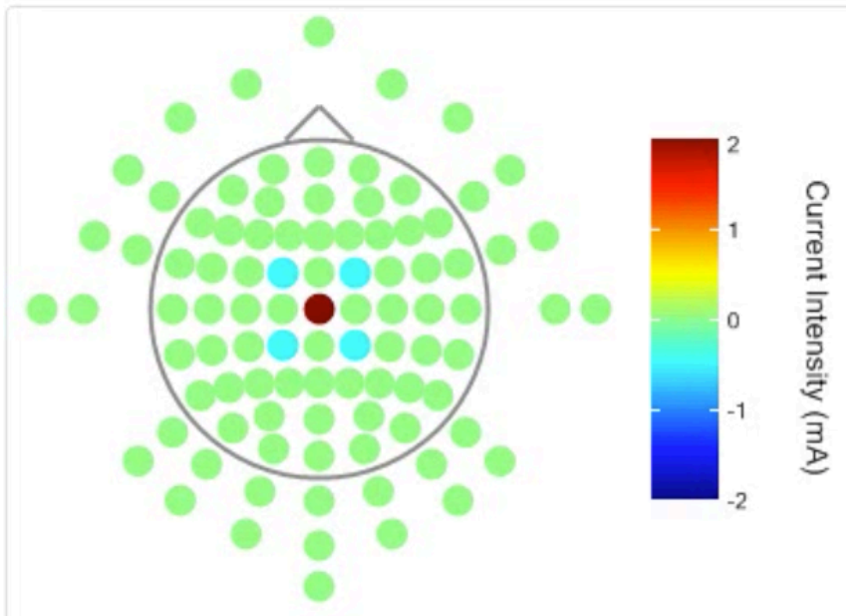
2-electrode config



Multi-electrode  
high def

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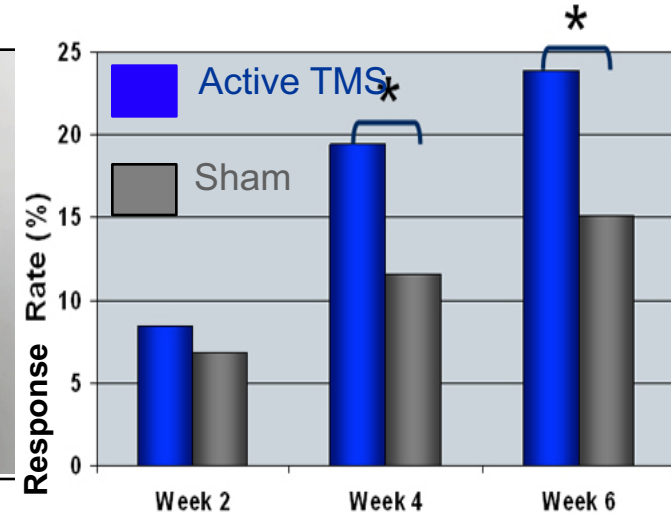
- Clinically effective, FDA-approved treatments
- Safe, non-invasive tools
- Affordable, accessible horizon with
- Excellent patient outcomes
- Growing market and insurance approvals
- Strong consumer uptake and growing demand
- Do-It-Yourself (DIY) community, and life-style companies entering the picture

So What's  
Wrong with this  
Picture?





# Noninvasive Neuromodulation: *Clinical State of the Art*



- ECT highly effective, but arguably under utilized
- TMS safer alternative, but efficacy presently falls short of ECT, and is comparable to available pharmacotherapy
- 2 major DBS-depression trials failed despite early promise
- Why?



# Limitations of Current NeuroMod Impacting Efficacy

- Variable practice, with variable results
- Lack of knowledge of optimal dosing
- Limited knowledge of mechanisms of action at a cellular and circuit level to inform dosing strategies

## Black Box Approach to Neuromod

Mechanism of action

Duration of action

Optimal dosing

Target engagement



# Key Research Opportunities

- Determine fundamental dose/response relationships employing expertise and equipment uniquely poised to address these questions, such as
  - NHP
  - Clinical populations intensively studied in the CC
  - MEG, Receptor PET
  - TMS/fMRI interleaving
- Collaborative studies across disciplines, esp. engineering
- Leverage depth of expertise in the physiological effects of noninvasive neuromod in neurological applications to address relatively less explored complex neurobehavioral conditions in psychiatry
- Innovate novel tools, informed by E-field modeling



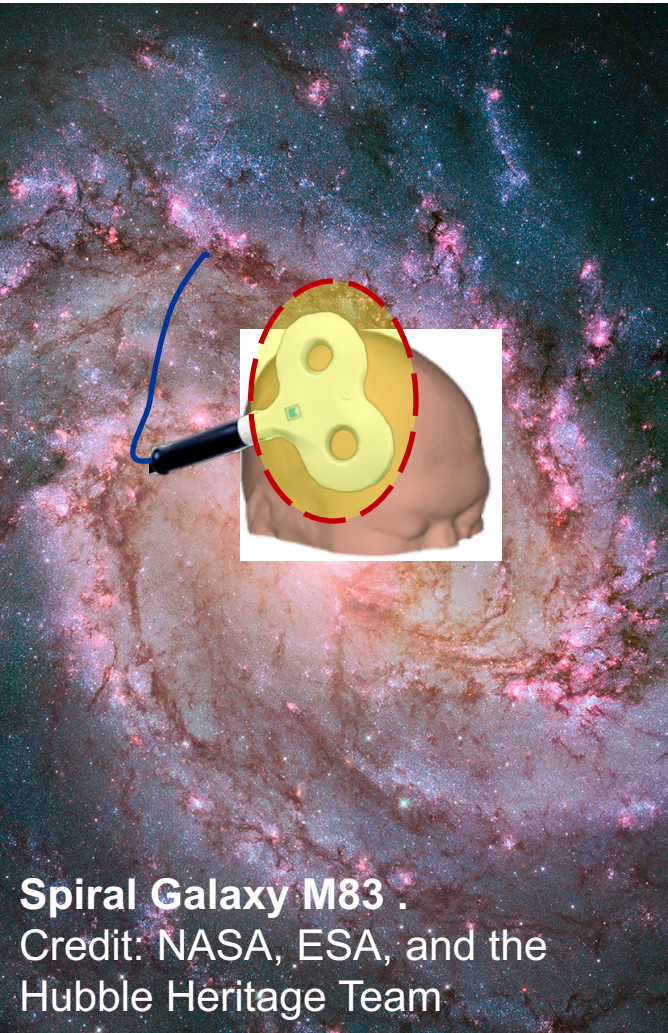
# Key Research Considerations

- Don't treat neuromod tools as off-the-shelf black boxes
- Innovate novel paradigms for
  - Stimulation
  - Analysis / signal processing
  - Perturbation/imaging
- Pay attention to precision in dosing – space/time/context



# 3 Dimensions of Dosing for NextGen NeuroMod

## Space

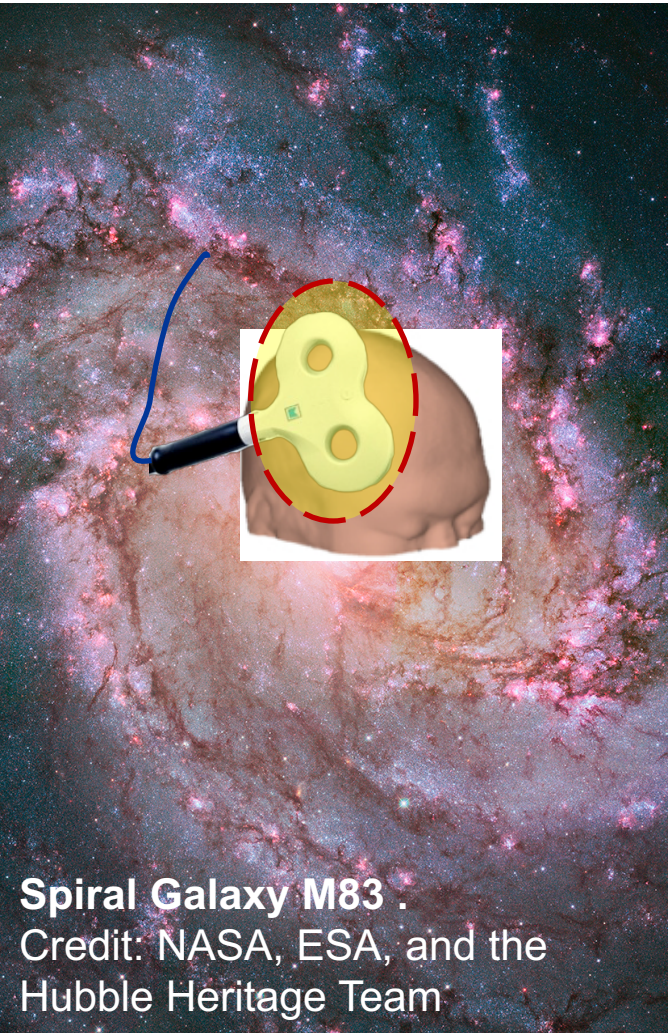


**Spiral Galaxy M83 .**  
Credit: NASA, ESA, and the  
Hubble Heritage Team



# 3 Dimensions of Dosing for NextGen NeuroMod

Space



Time



Context



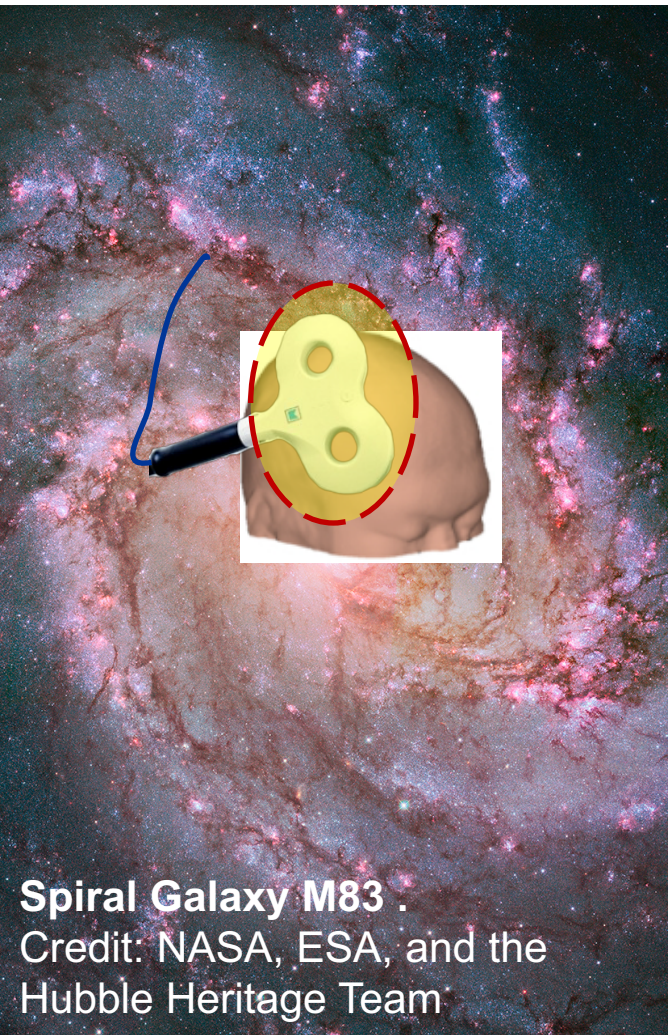
*"Never, ever, think outside the box."*

**Spiral Galaxy M83** .  
Credit: NASA, ESA, and the  
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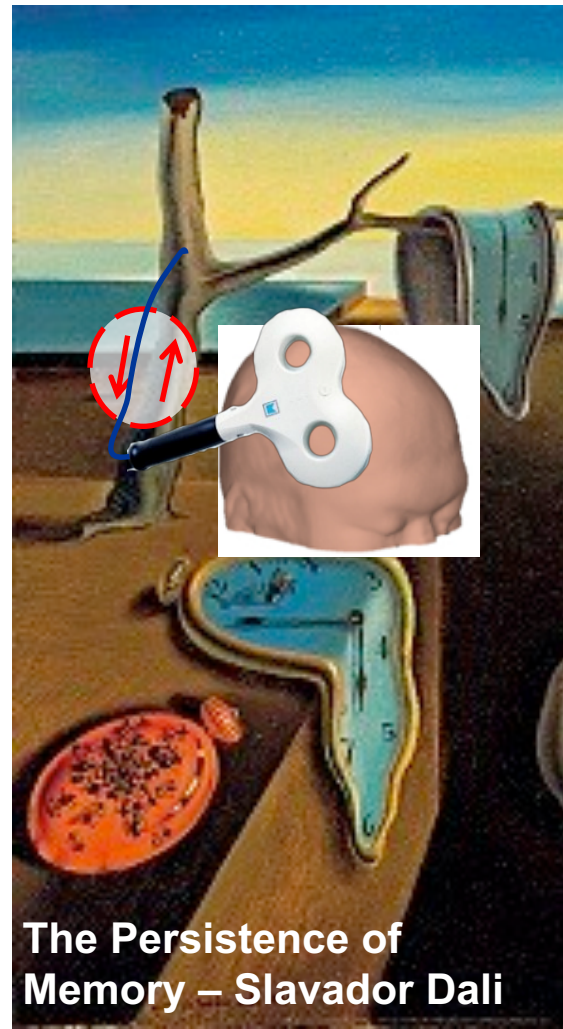
**The Persistence of  
Memory – Salvador Dali**

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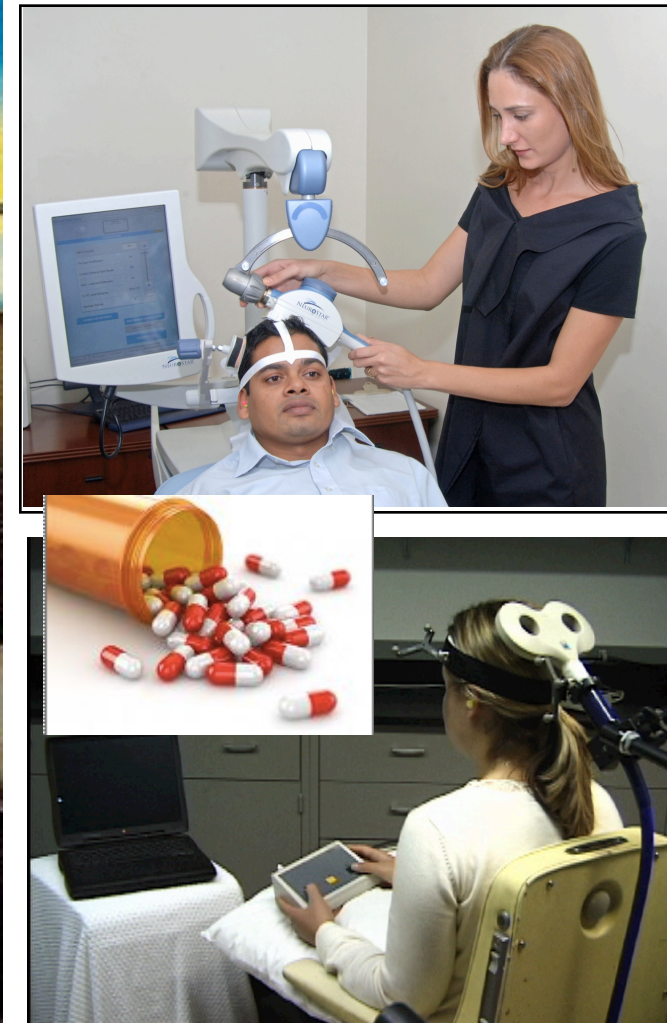
## Space



## Time

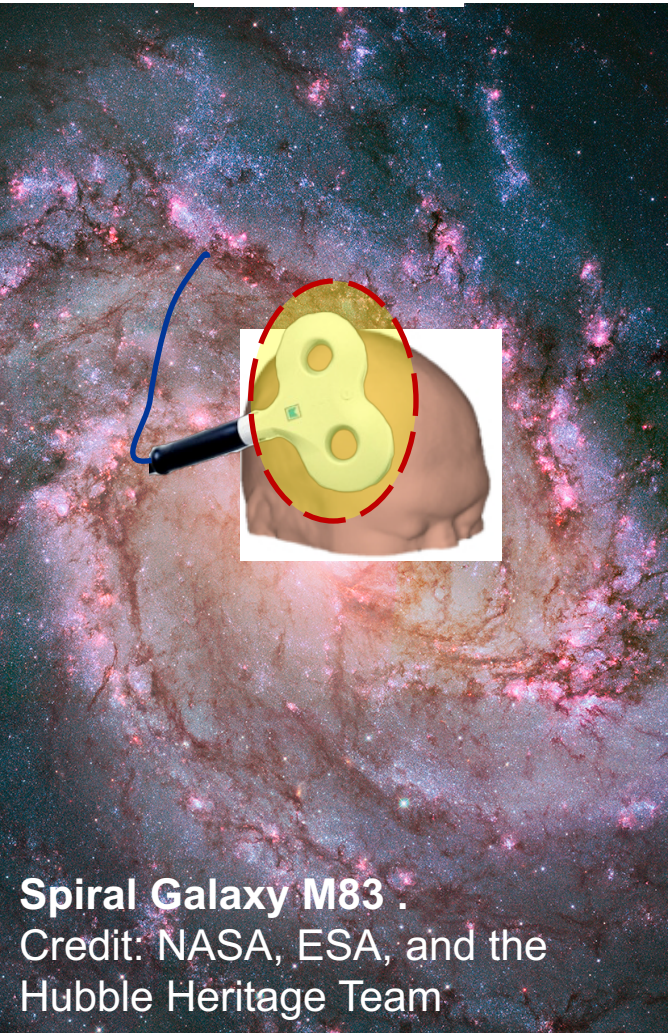


## Context



# 3 Dimensions of Dosing for NextGen NeuroMod

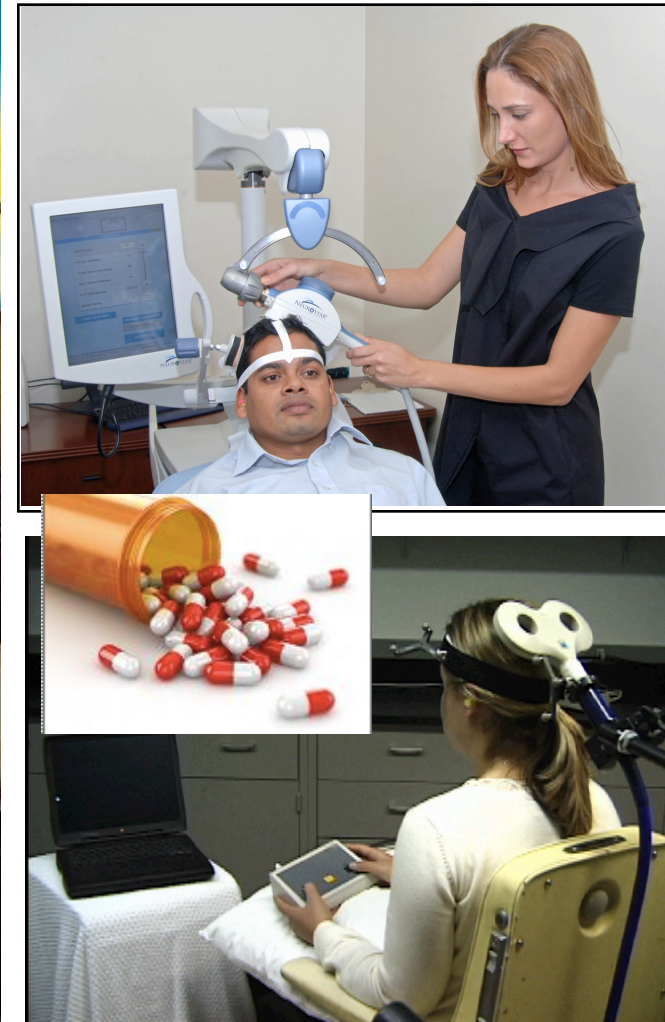
## Where



## When



## How





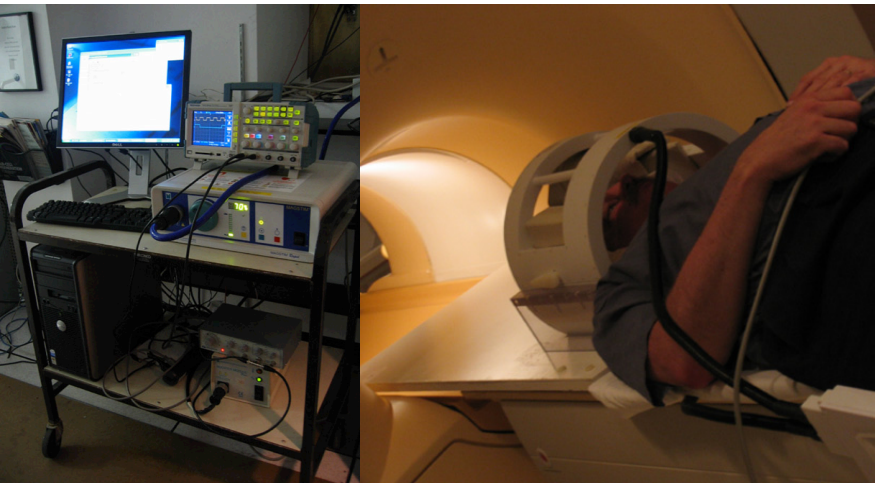
# Advice

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- Target distributed networks (circuits), not discrete locations under the coil (coordinates)



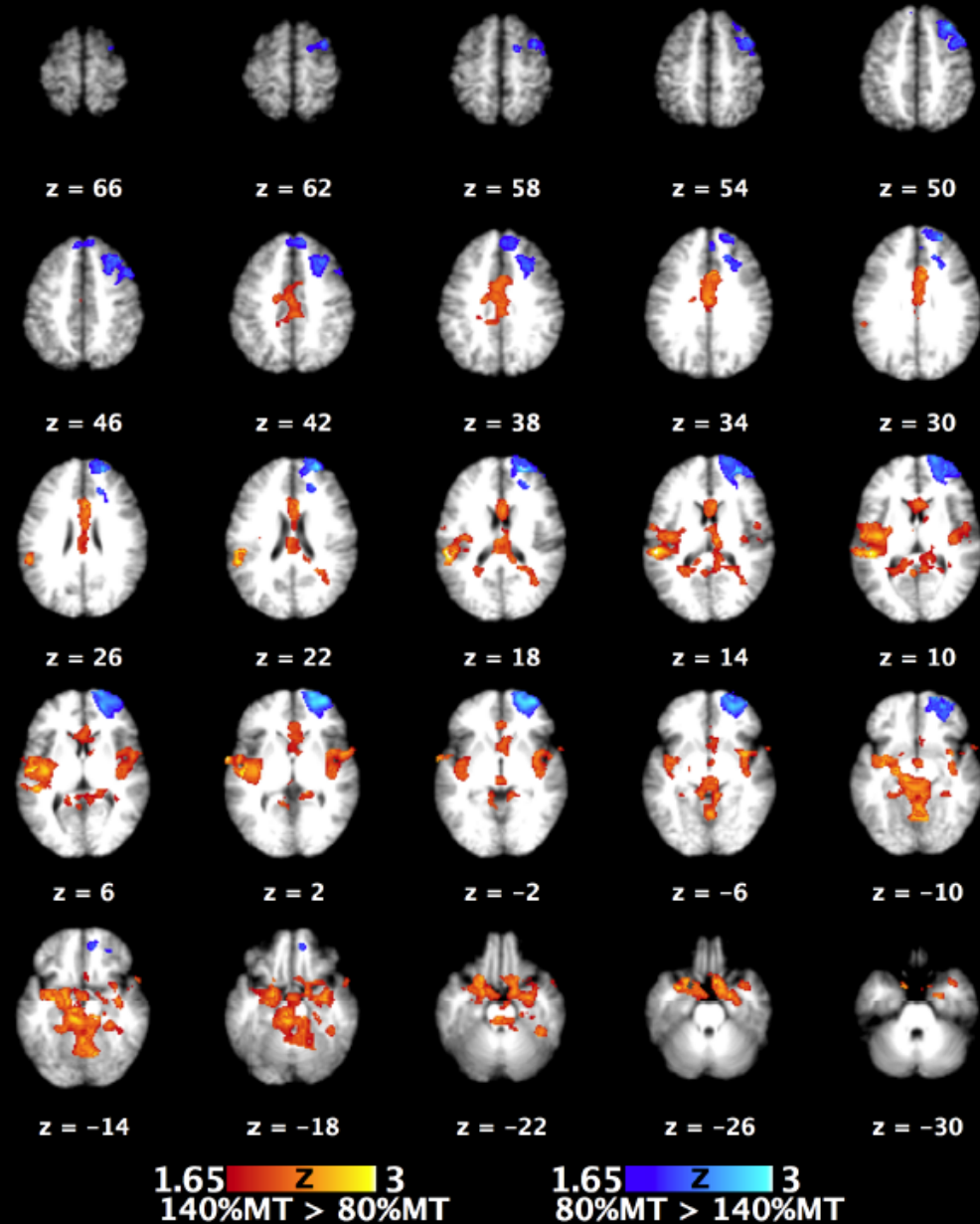
# Transsynaptic action of TMS

- TMS/fMRI interleaving paradigm
- Distal **activations** and **deactivations** induced by single pulse TMS to frontal cortex



Luber et al. In Submission

## 140%MT vs 80%MT



# Advice

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- Pay attention to precision in dosing – space/time/context
- Target distributed networks (circuits), not discrete locations under the coil (coordinates)
- Employ E-field modeling coupled with connectivity mapping to know where you stimulated

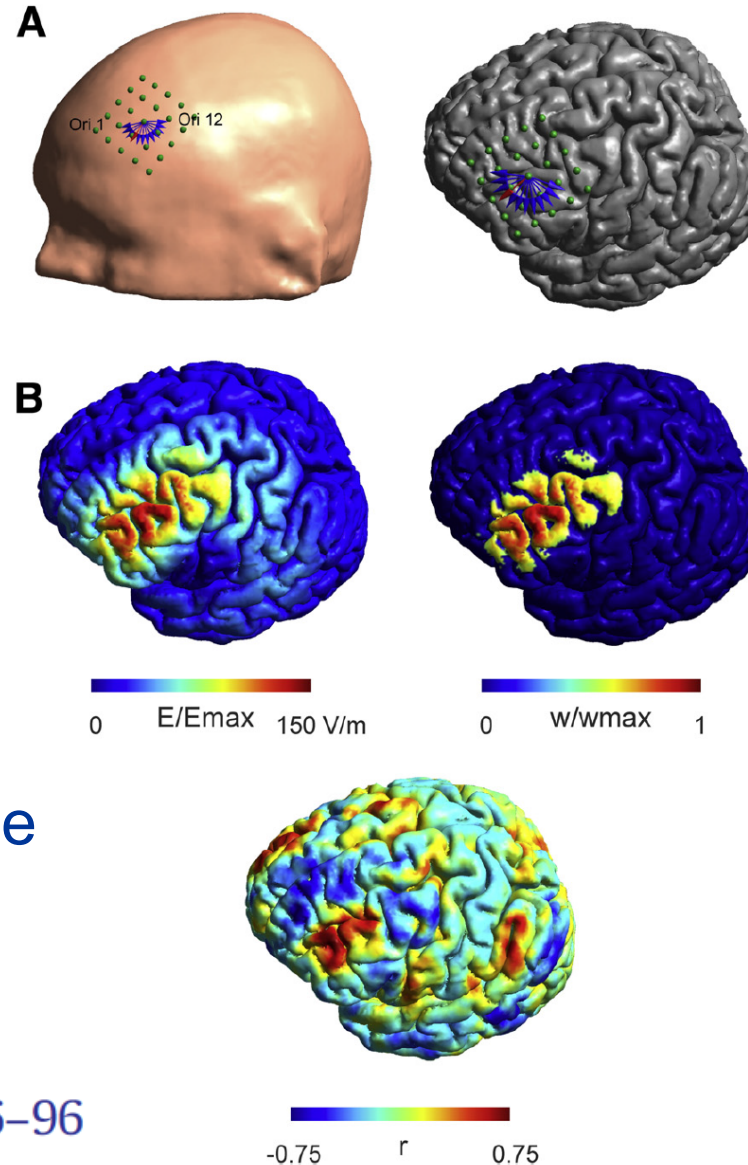


# An integrated framework for targeting functional networks via transcranial magnetic stimulation



Alexander Opitz <sup>a,b,\*</sup>, Michael D. Fox <sup>c,d,e</sup>, R. Cameron Craddock <sup>a,b</sup>, Stan Colcombe <sup>a</sup>, Michael P. Milham <sup>a,b,\*</sup>

## Realistic E-Field Modeling

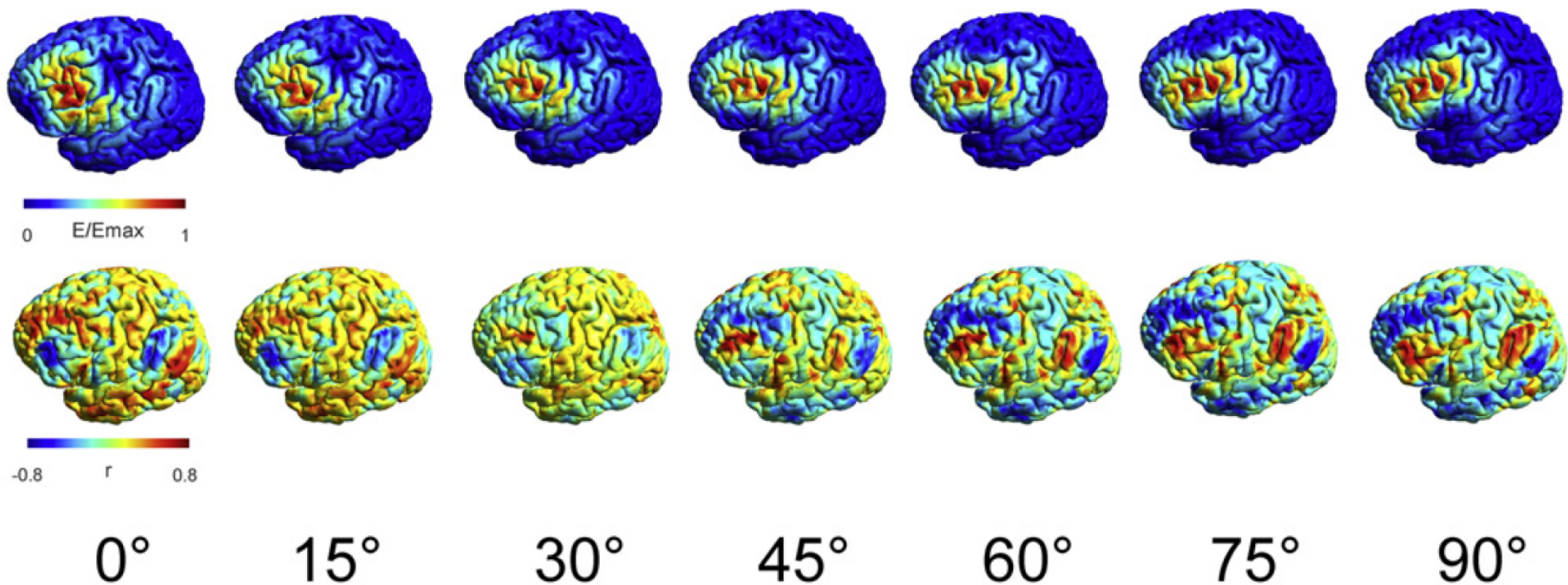


## Human Connectome Network Identification

NeuroImage 127 (2016) 86–96



# Impact of Coil Orientation

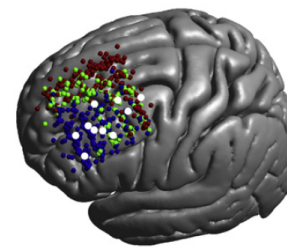
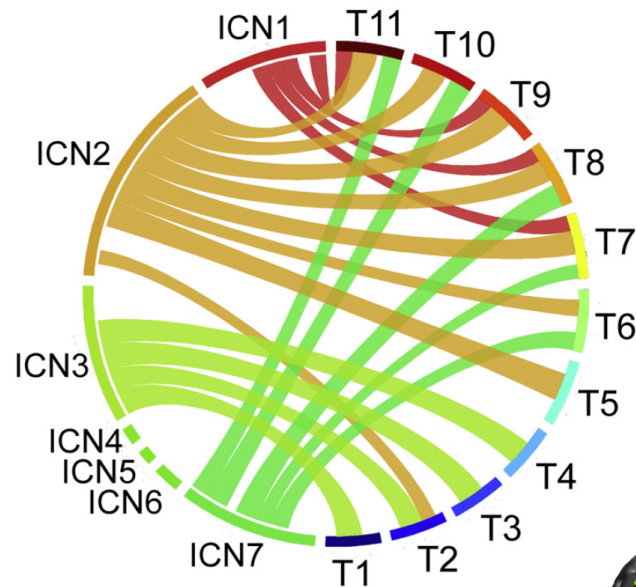
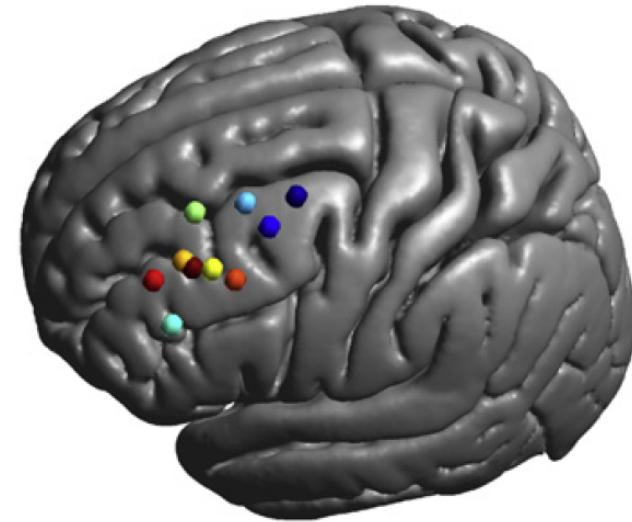


# Connectivity of TMS Depression Targets

## DLPFC Regions from Fox et al. 2012

Study/Site

● Average 5 cm Coordinates	-41	18	49	-41	16	54
● Herbsman <i>et al.</i> 2009 Responders	-46	25	44	-46	23	49
● Herbsman <i>et al.</i> 2009 Nonresponders	-41	19	50	-41	17	55
● Herwig <i>et al.</i> 2003 EEG (F3) Site	-37	27	44	-37	26	49
● Rajkowska and Goldman-Rakic 1995 BA46 Definition	-44	40	25	-44	40	29
● Rajkowska and Goldman-Rakic 1995 BA9 Definition	-36	40	38	-36	39	43
● Paus <i>et al.</i> 2001 TMS Target	-40	32	30	-40	31	34
● Fitzgerald <i>et al.</i> 2009 TMS Target	-46	45	35	-46	45	38
● Rusjan <i>et al.</i> 2010 TMS Target	-50	31	32	-50	30	36
● Fox <i>et al.</i> 2012 optimal TMS Target				-38	44	26
● Fox <i>et al.</i> 2012 peak TMS Target				-44	38	34



# Advice

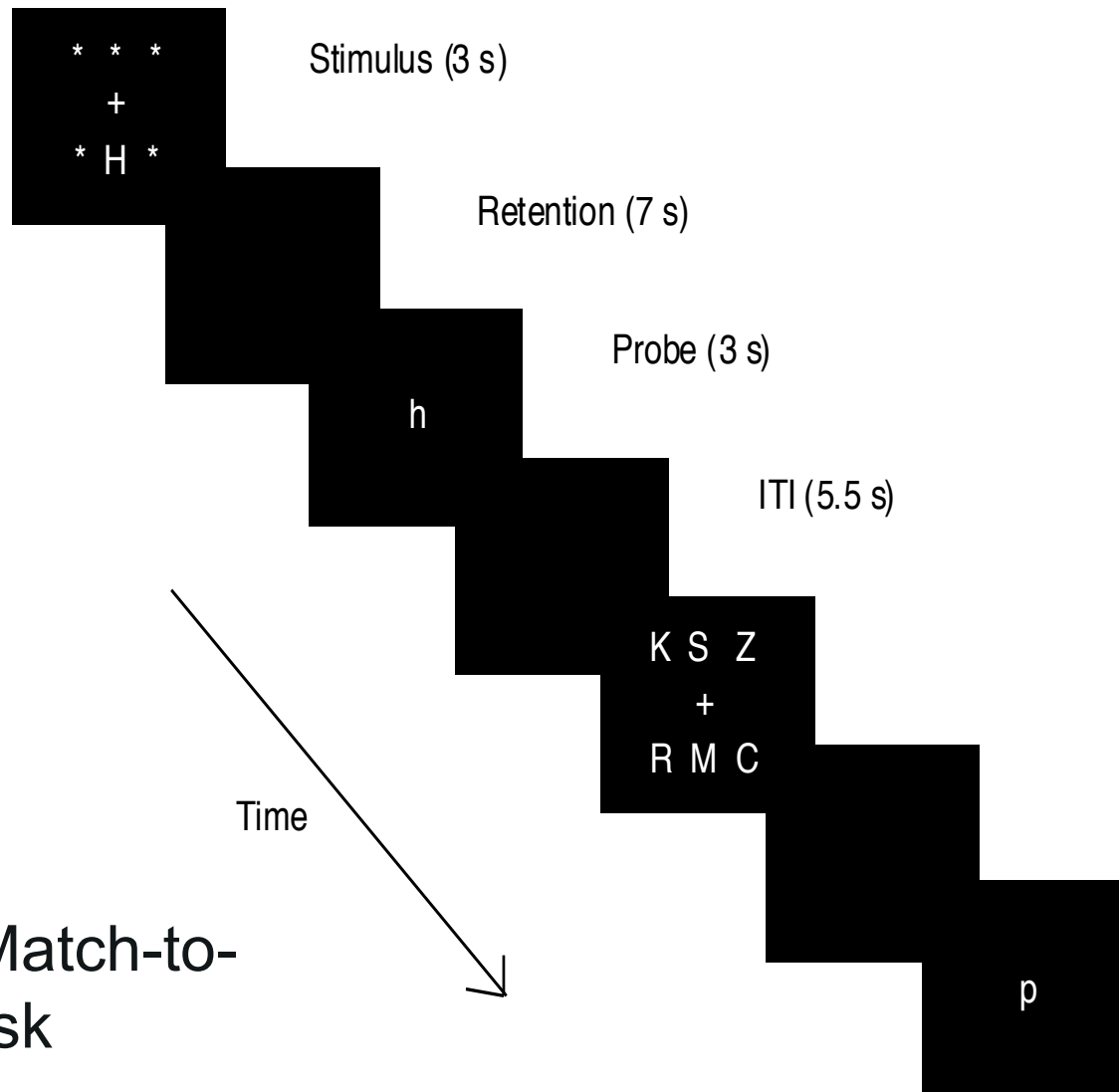
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- Target distributed networks (circuits), not discrete locations under the coil (coordinates)
- Employ E-field modeling coupled with connectivity mapping to know where you stimulated
- Employ measures of target engagement (TMS/fMRI, TMS/EEG) to demonstrate target engagement and be able to interpret results (both successes and failures)



# Target Engagement – Working Memory



- Domain of Function – *Working Memory*

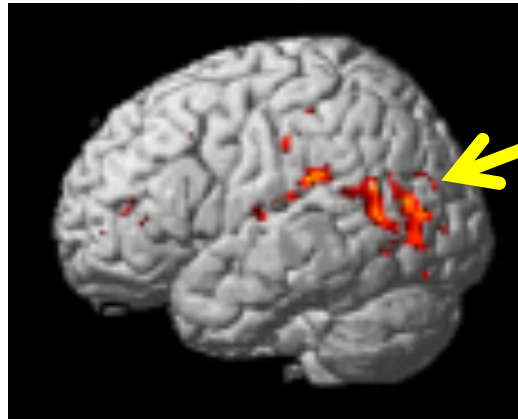




# Target Engagement – Working Memory



- Domain of Function – *Working Memory*
- Target – *Neural Reserve & Compensation Circuit*

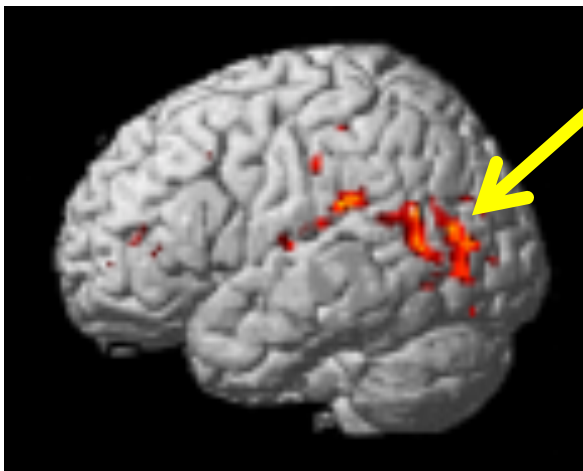


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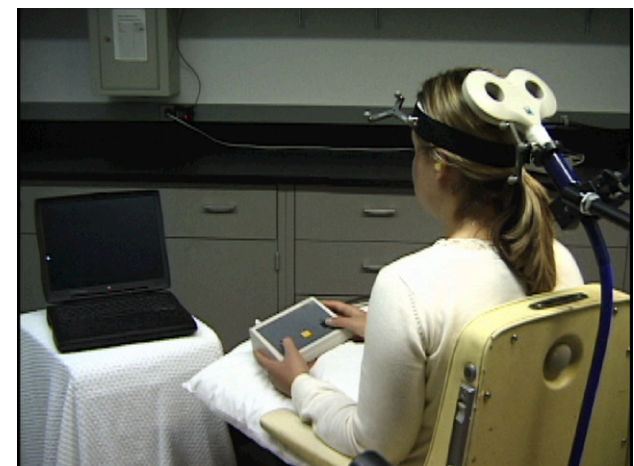


- Domain of Function – *Working Memory*
- Target – *Neural Reserve & Compensation Circuit*
- Intervention – *TMS + WM-training*
  - TMS Neuronavigated to WM-resilience network
  - Simultaneous WM-Training + TMS paired delivery paradigm

fMRI-Guided TMS



Working Memory Training



# Target Engagement – *Working Memory*



- Domain of Function – *Working Memory*
- Target – *Neural Reserve & Compensation Circuit*
- Intervention – *TMS + WM-training*
- Demonstration of target engagement – *Compensation Circuit expression*
  - Predicted shift in fMRI network expression during WM task performance



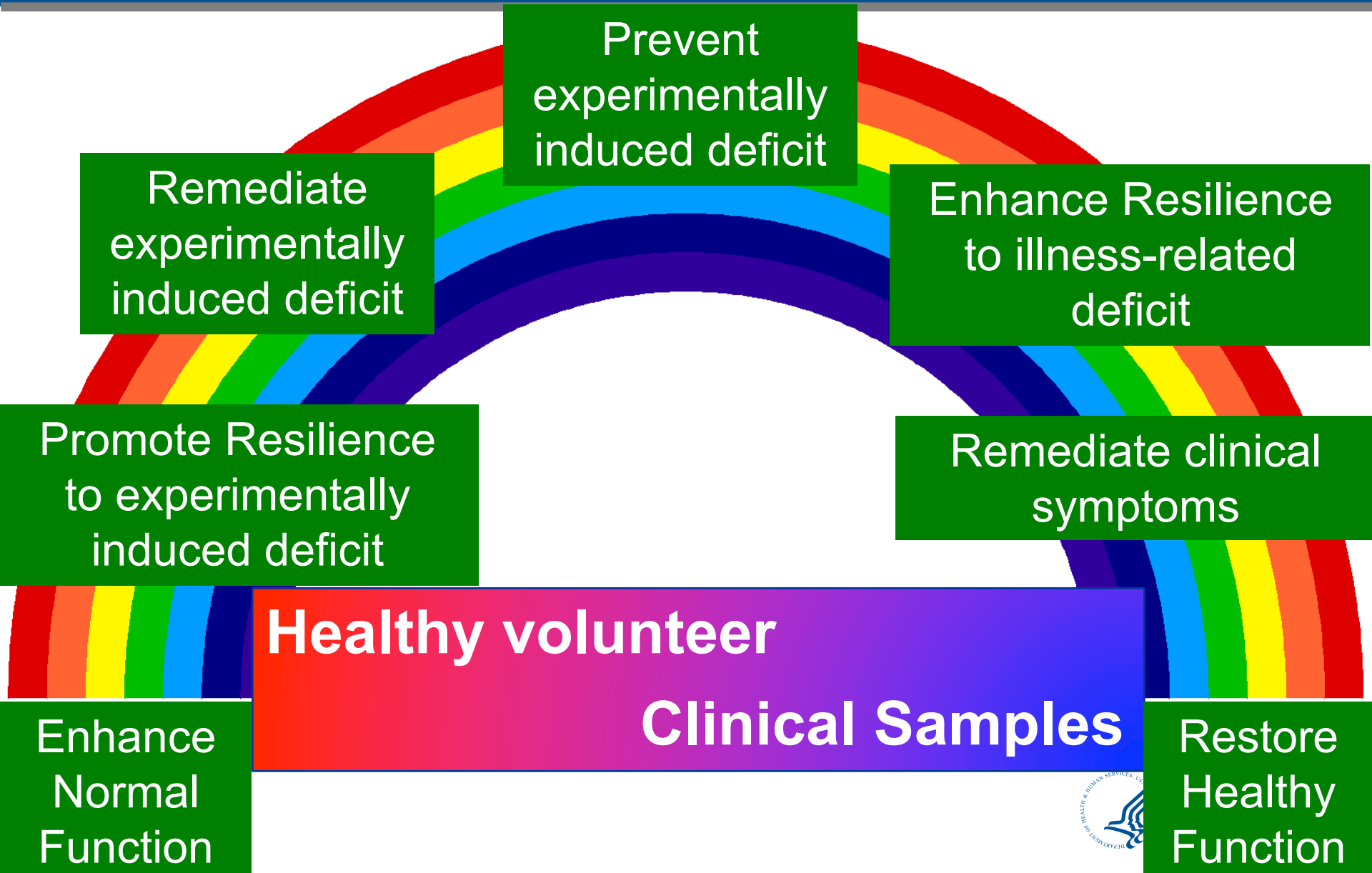
# Target Engagement – *Working Memory*



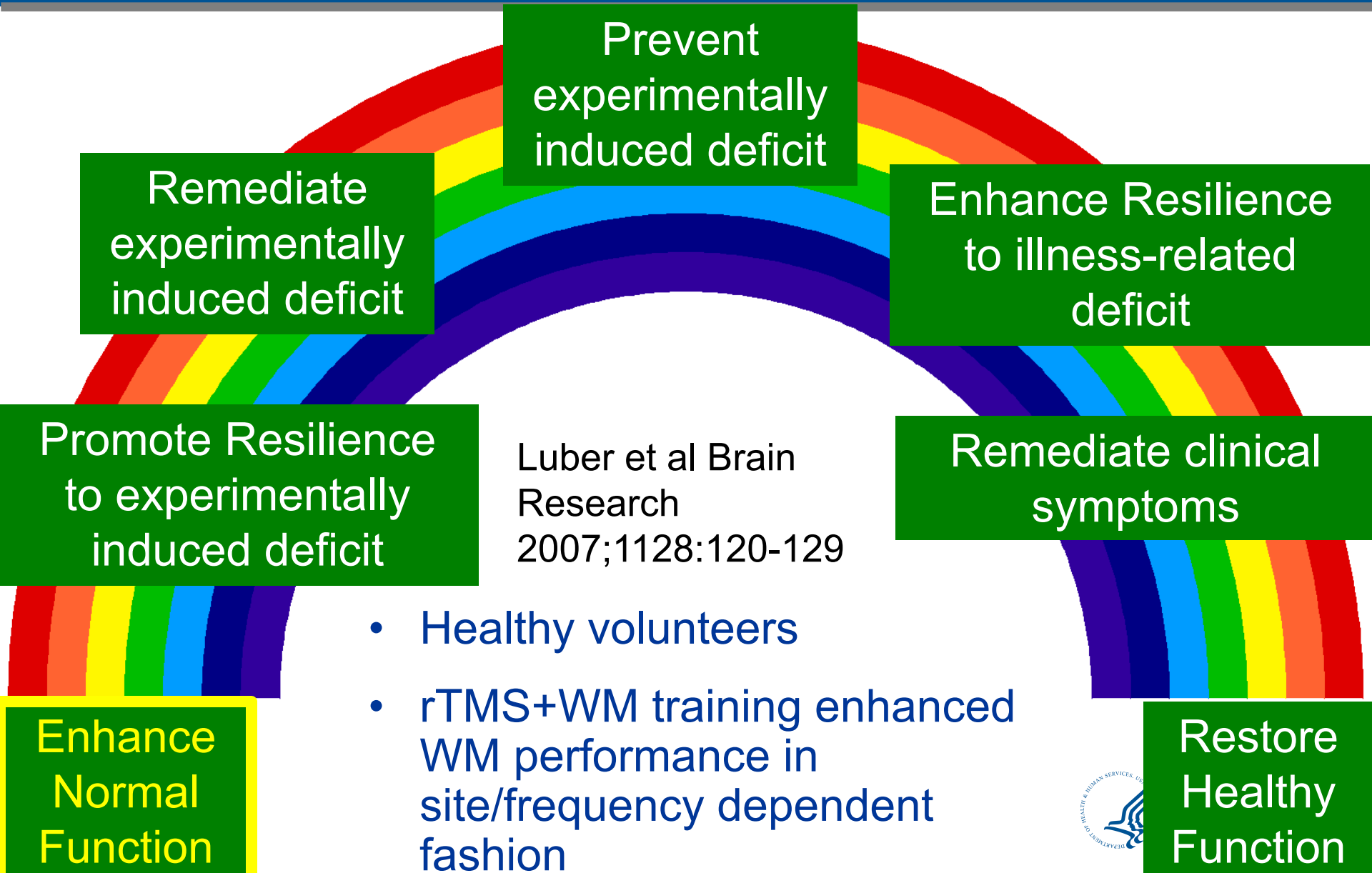
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- Translational trajectory strategy



# A Translational Trajectory for Targeted Intervention Development



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Prevent  
experimentally  
induced deficit

Remediate  
experimentally  
induced deficit

Enhance Resilience  
to illness-related  
deficit

Luber et al. Cereb. Cortex  
2008;18:2077-85

Promote Resilience  
to experimentally  
induced deficit

Remediate clinical  
symptoms

- Targeted circuit associated with resilience to sleep deprivation

- rTMS+WM training remediated WM deficit after 2 full days of sleep deprivation

Enhance  
Normal  
Function

Restore  
Healthy  
Function



# A Translational Trajectory for Targeted Intervention Development



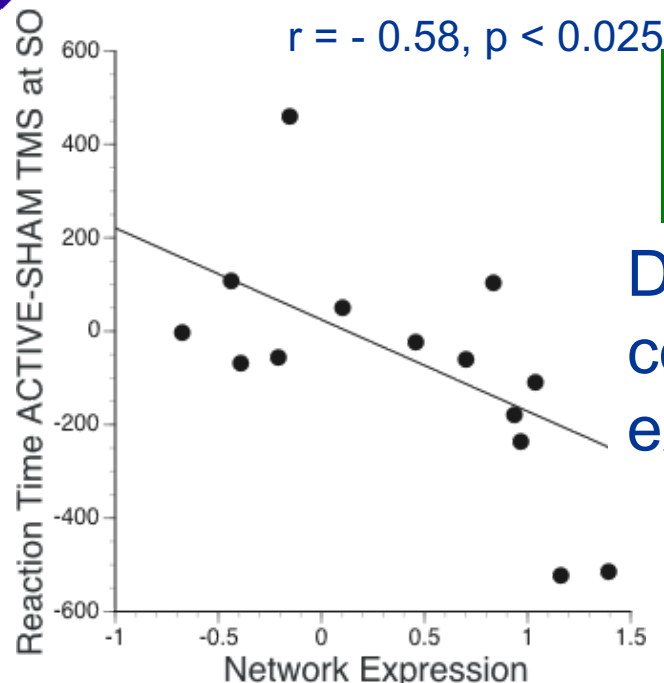
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Degree of improvement  
correlated with network  
expression

Remediate clinical  
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# A Translational Trajectory for Targeted Intervention Development



Prevent  
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Remediate  
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Enhance Resilience  
to illness-related  
deficit

Promote Resilience  
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induced deficit

Luber et al Sleep 2013;  
36:857-71

Remediate clinical  
symptoms

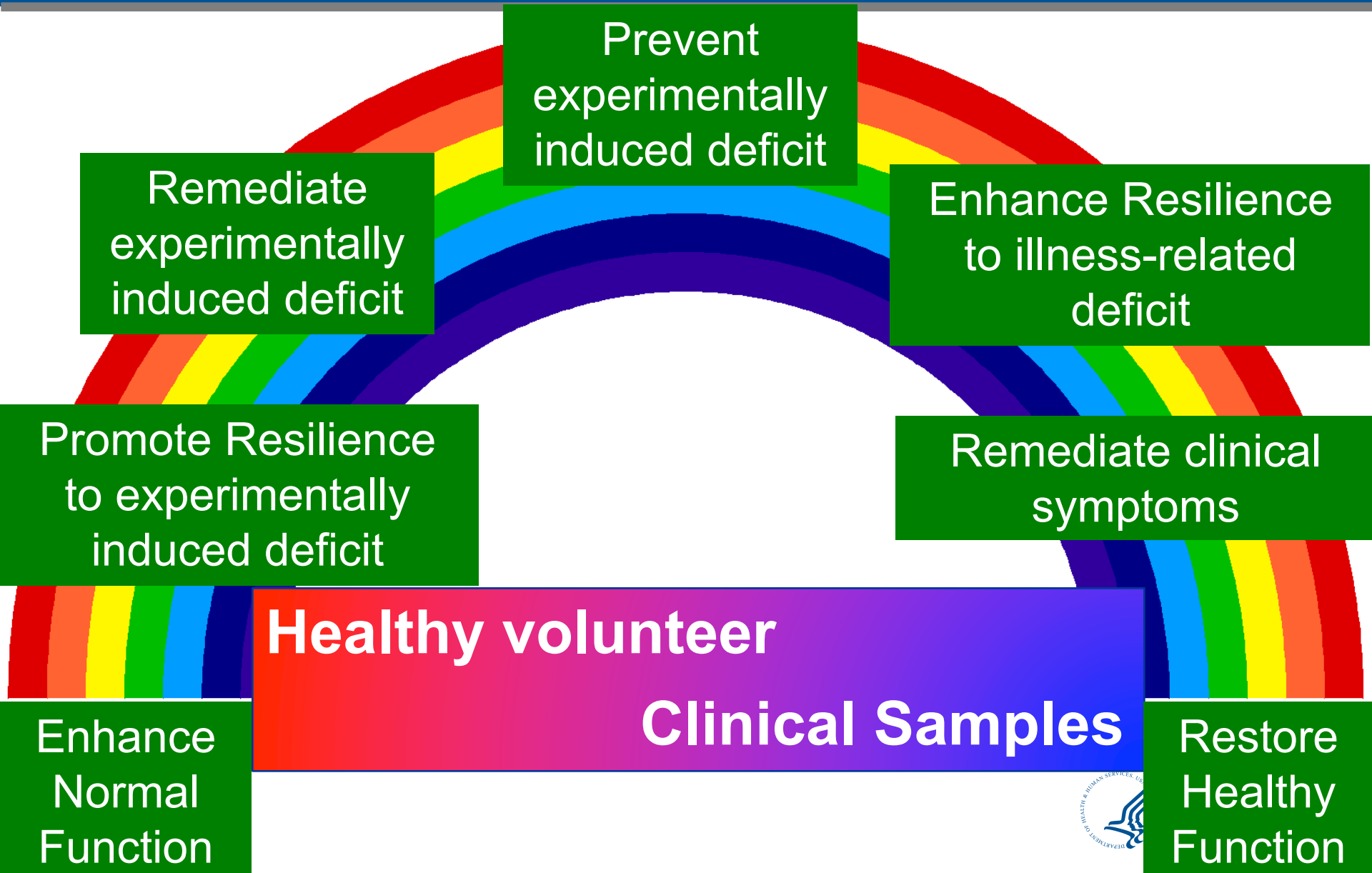
- RCT of TMS+Task to resilience target (2/day x 2 days)
- Prevented memory decrement and memory lapses a full 18 hrs after the last TMS

Enhance  
Normal  
Function

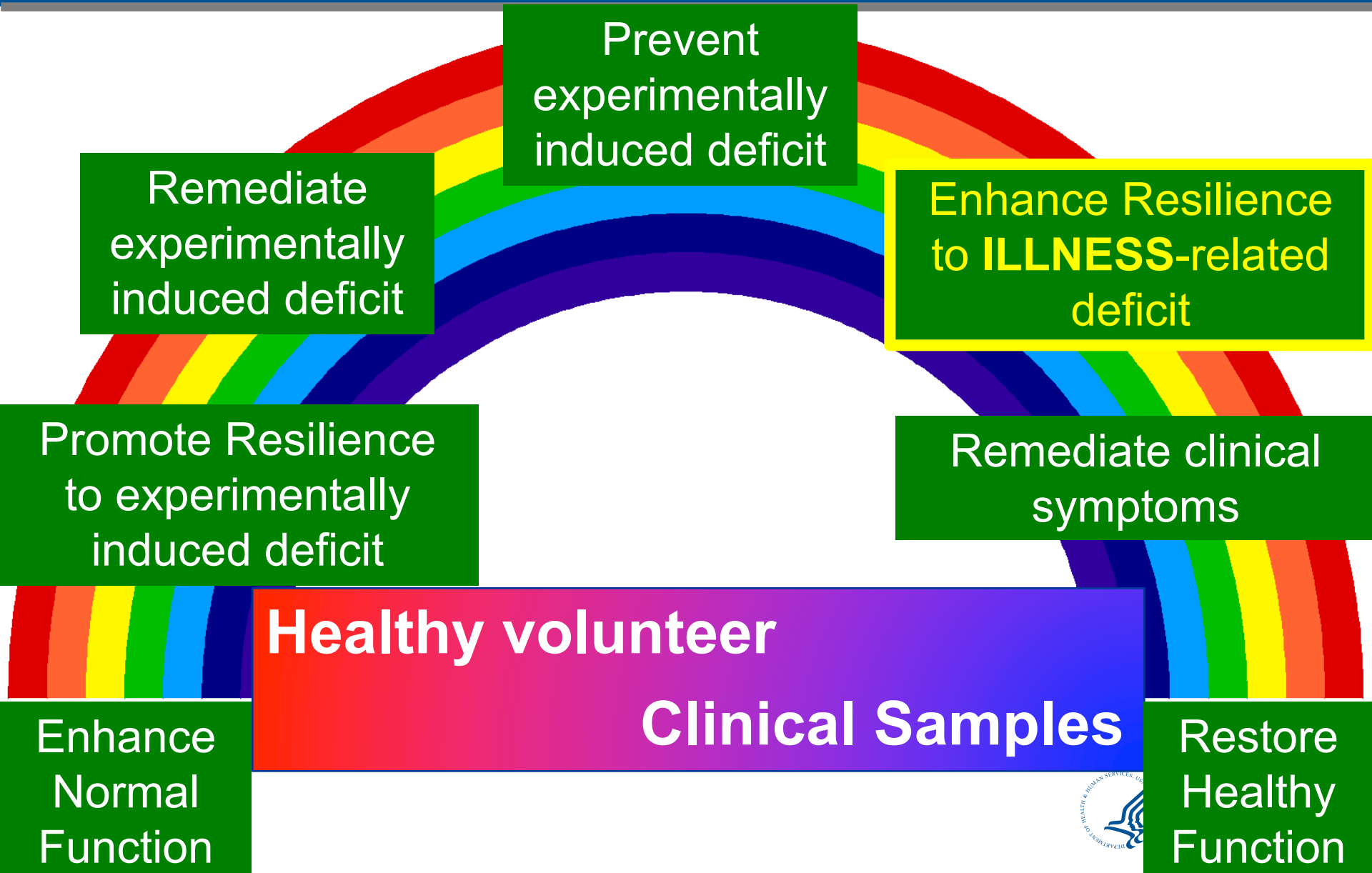
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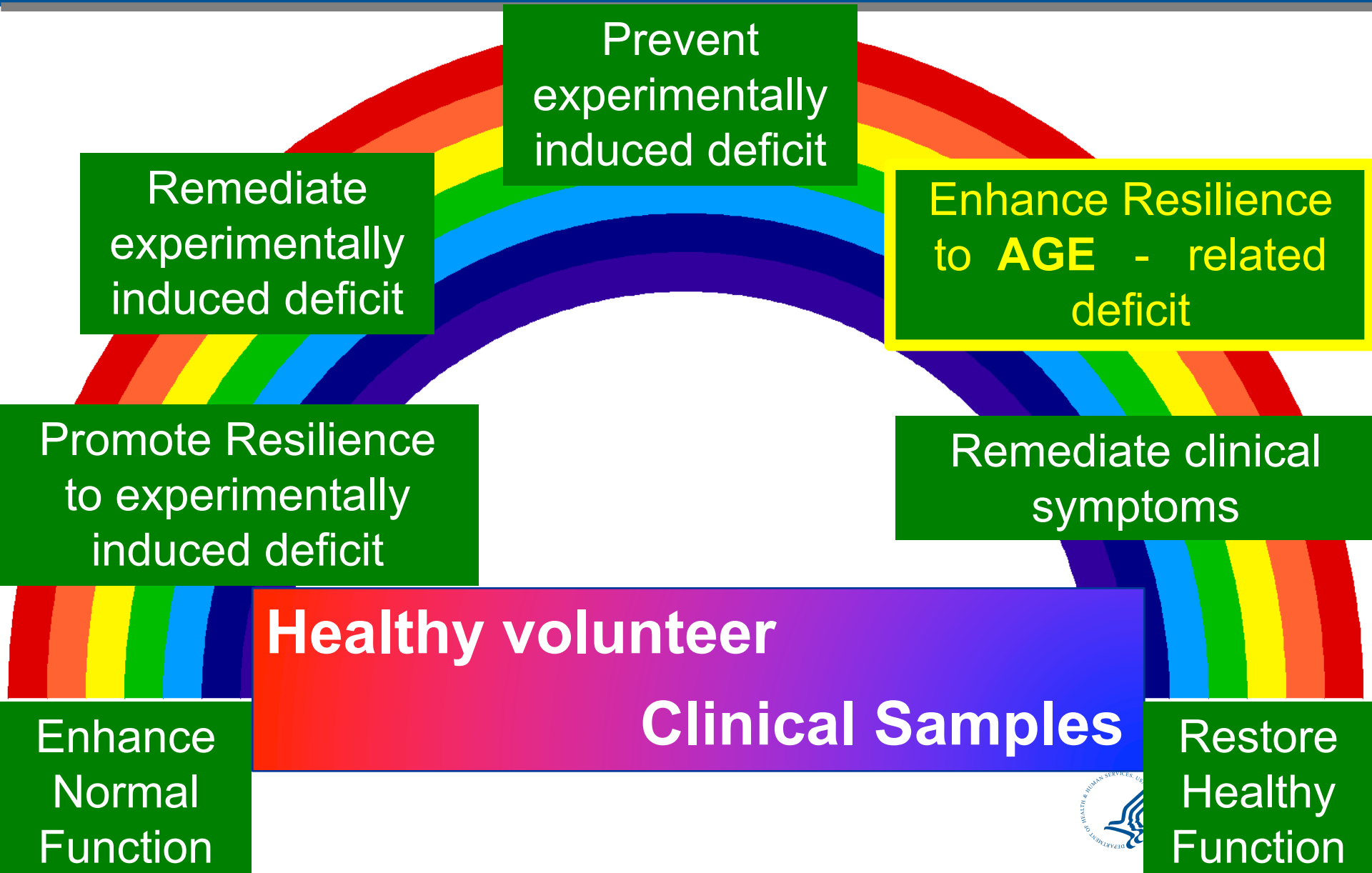
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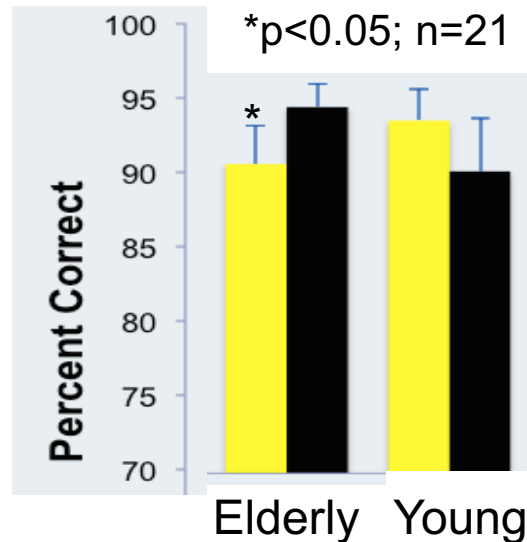
Prevent  
experimentally  
induced deficit

Remediate  
experimentally  
induced deficit

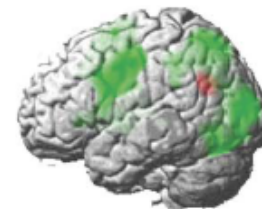
Enhance Resilience  
to **AGE** - related  
deficit

Promote Resilience  
to experimentally  
induced deficit

Luber et al in prep



Remediate clinical  
symptoms



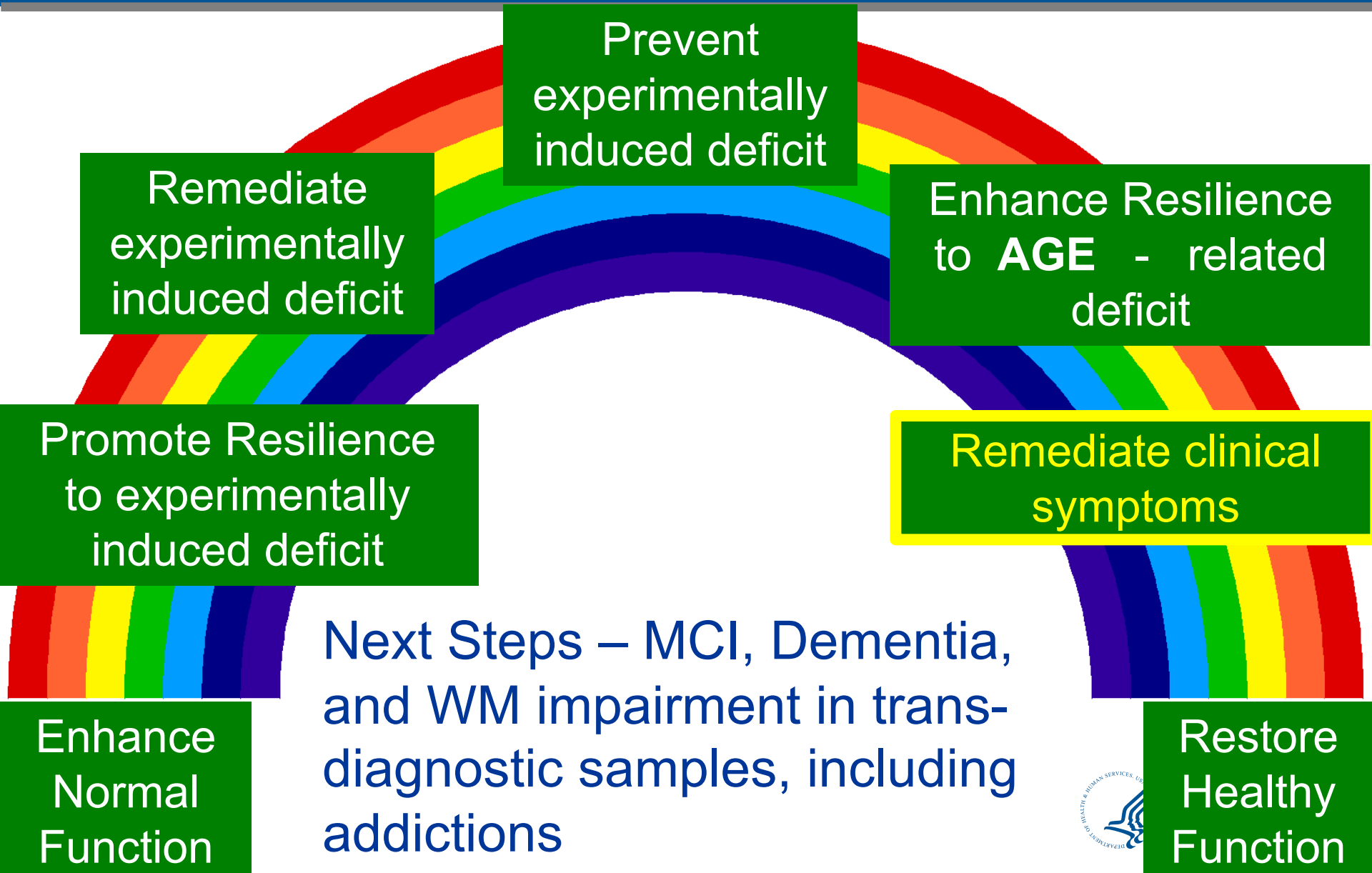
Enhance  
Normal  
Function

Targeting neural compensation network  
enhanced WM selectively in elderly

Restore  
Healthy  
Function



# A Translational Trajectory for Targeted Intervention Development



# The Delayed Match-to-Sample Task (Sternberg Variant)

Blank (3 sec)

Stimulus (3 sec)

Retention (7 sec)

Probe (3 sec)

TMS here



Either Set-Size 1



Or Set-Size 6



TMS here



Either a True Positive

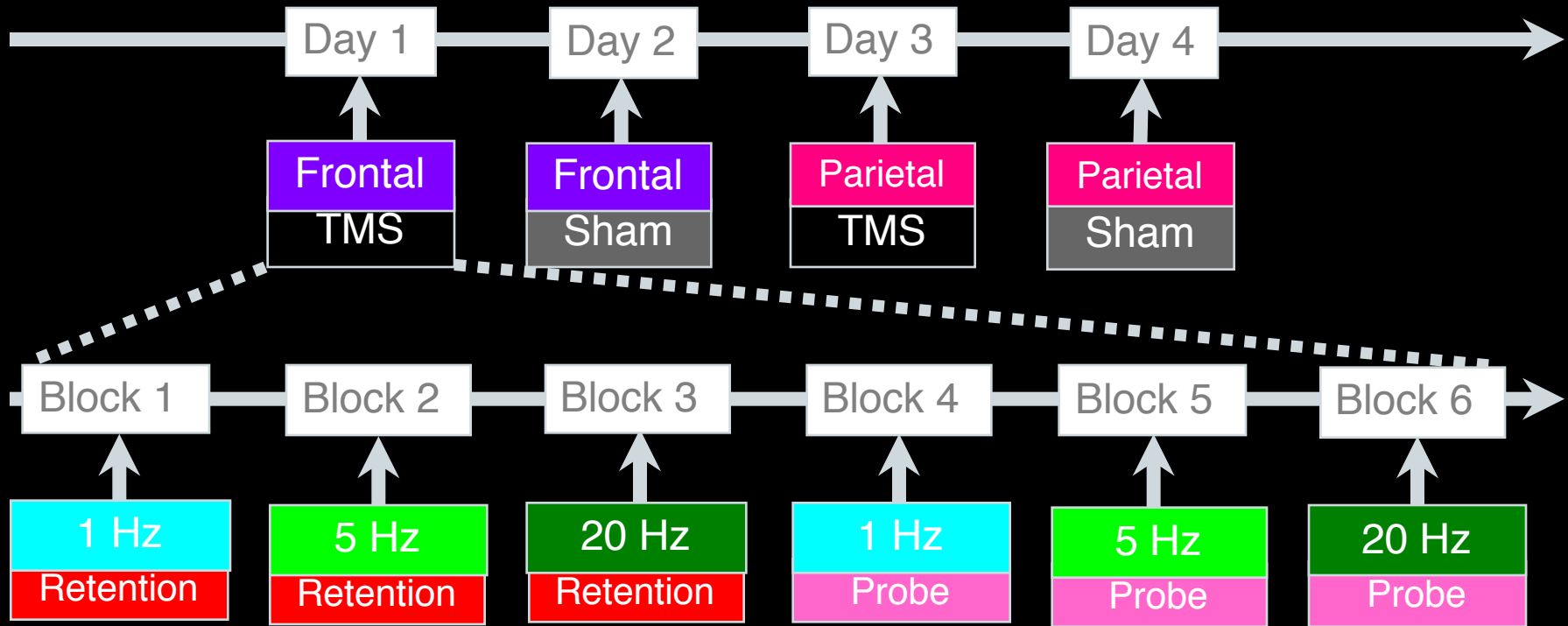


Or a True Negative



Time in Trial

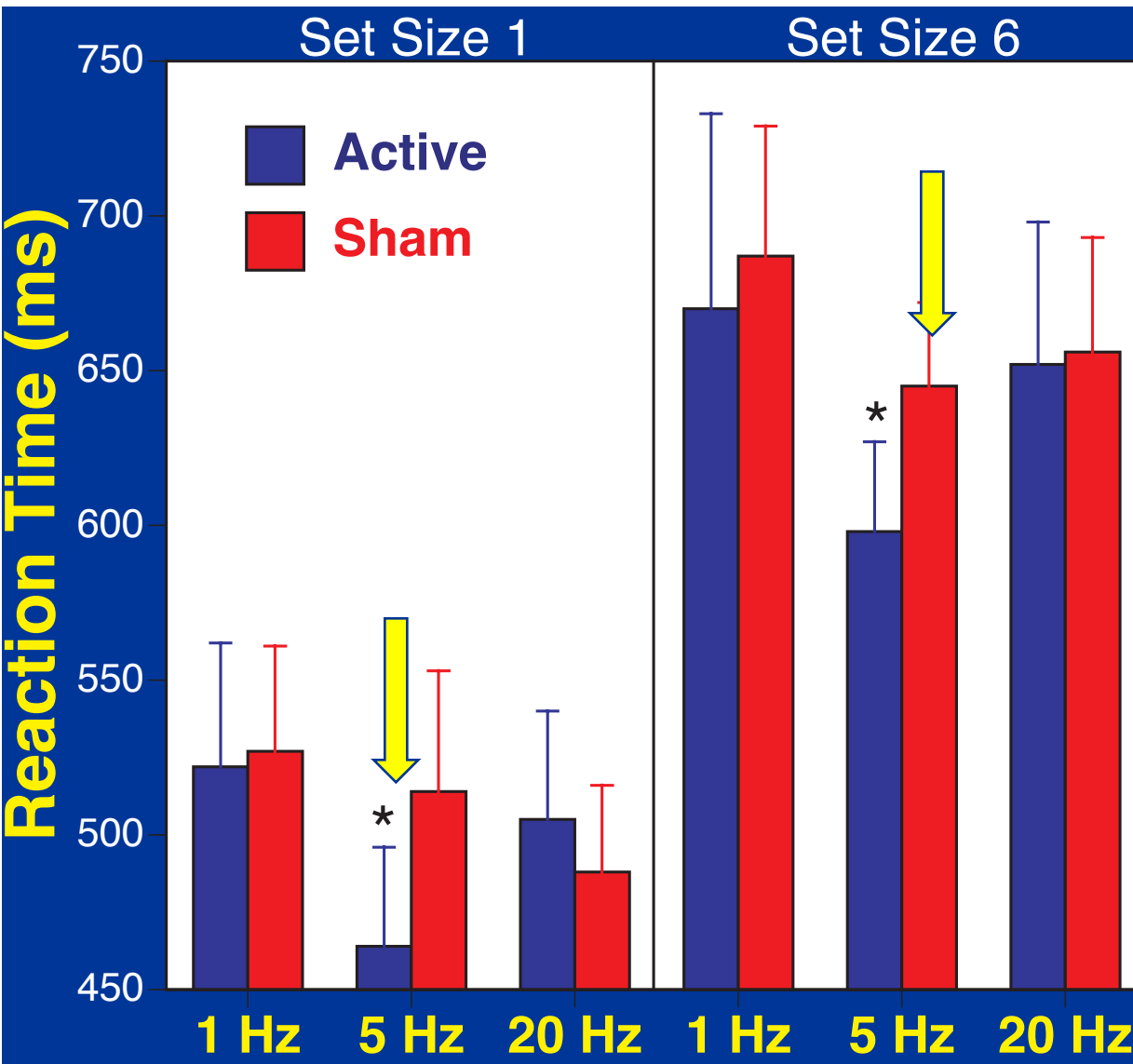
# Dose Finding to Select Optimal TMS Paradigm in Space / Time / Context



- TMS during during task performance to promote network utilization and enhance performance.
- Sham-controlled randomized trial, between subject



# Frequency-Dependent Effects of rTMS During WM Task Performance

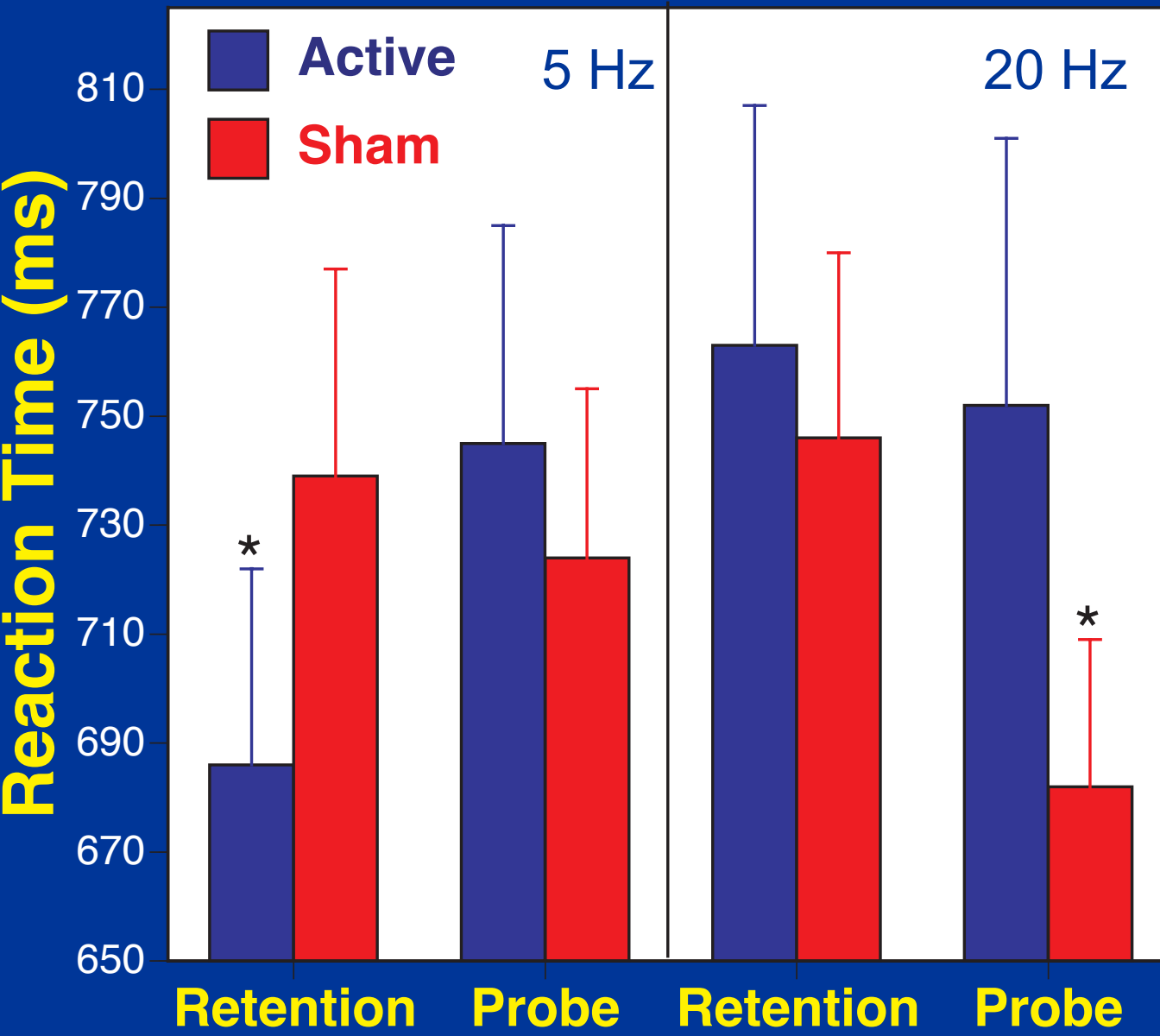


- 5 Hz TMS to precuneus during retention phase reduced RT by 50 ms ( $p < 0.002$ )
- Effect specific to precuneus - not seen with TMS at dorsolateral prefrontal cortex

Luber et al Brain Research  
2007;1128:120-129



# Phase-Frequency Interaction



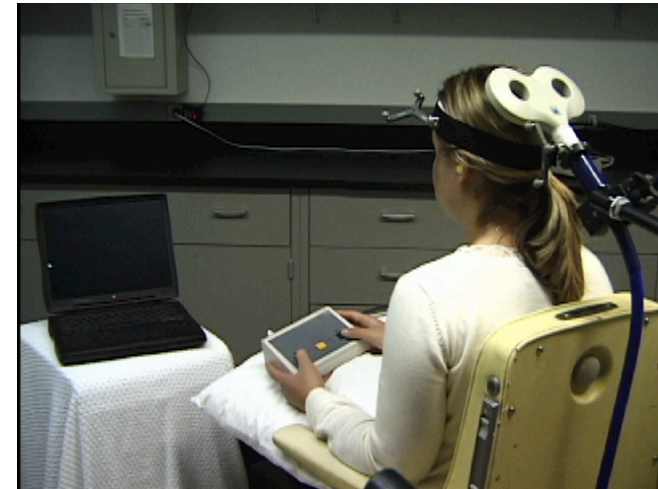
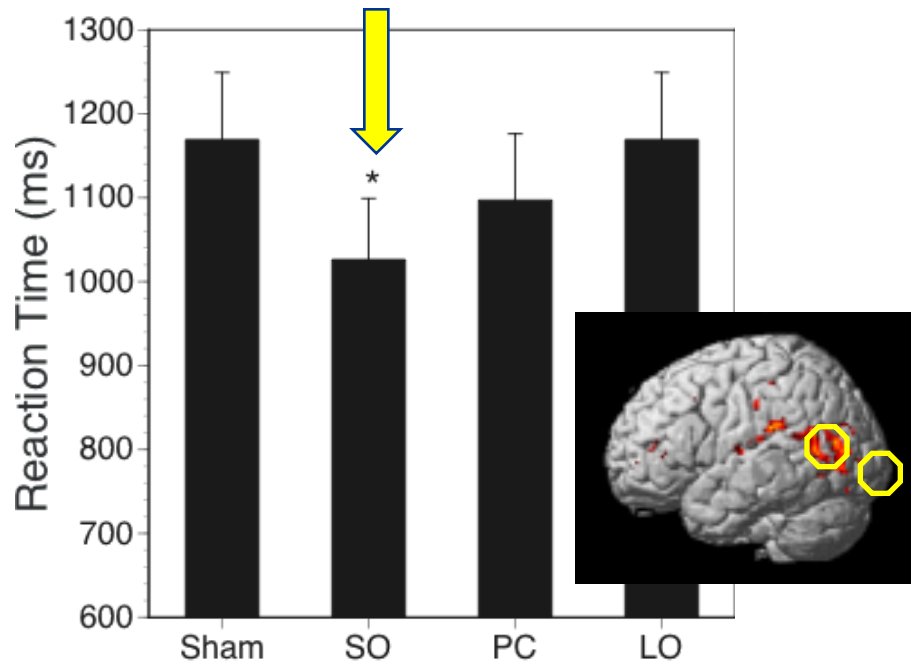
- Replication, in an independent sample, of 5 Hz retention phase improvement
- Probe phase 20 Hz worsened performance

Luber et al Brain Research  
2007;1128:120-129

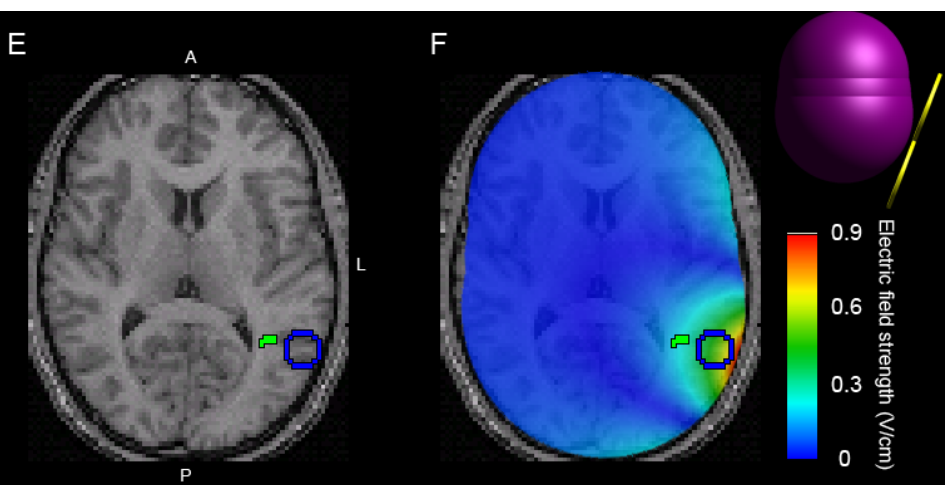
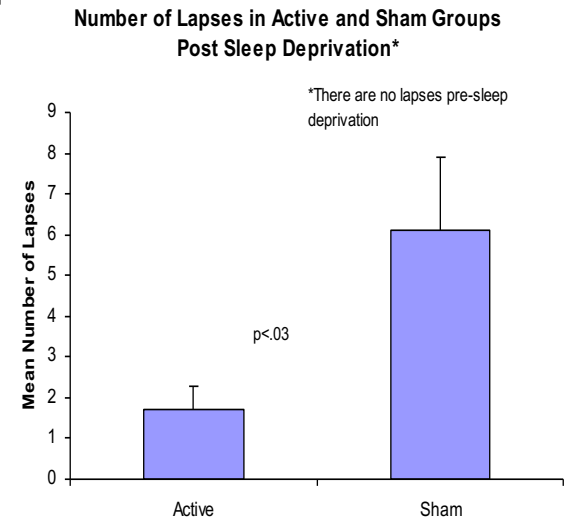
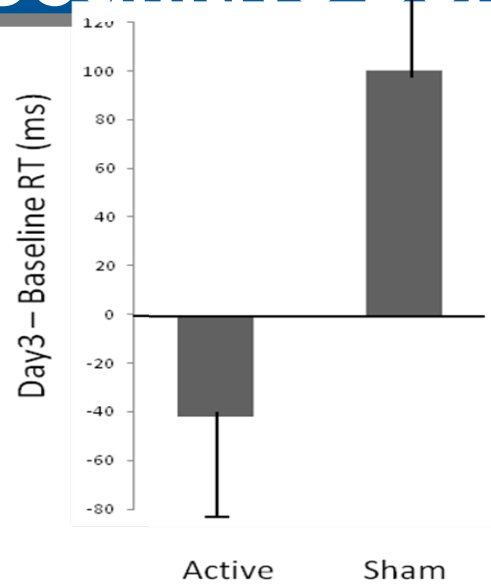
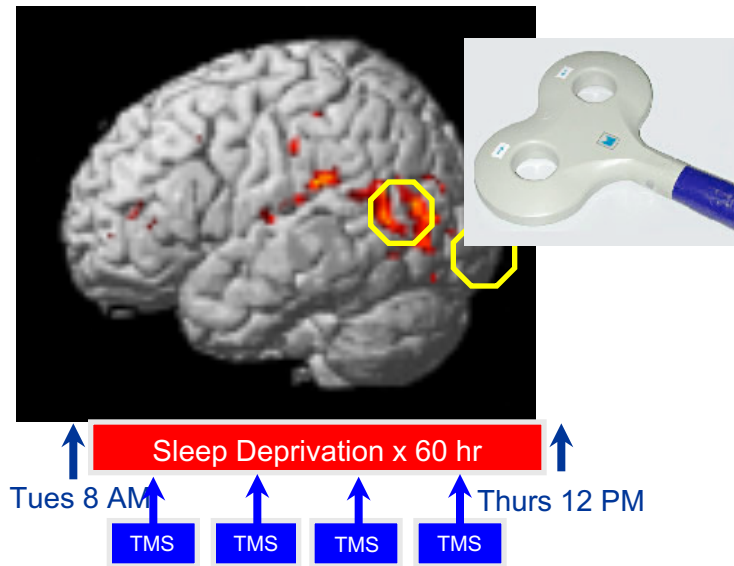


# TMS + Simultaneous Working Memory Training Remediates Cognitive Performance

- Frequency- and site-specific working memory enhancement with 5 Hz TMS to precuneus
- Site-specific cognitive enhancement with 5 Hz TMS to sleep deprivation resilience network



# TMS + Simultaneous Working Memory Training Prevents Cognitive Deficits



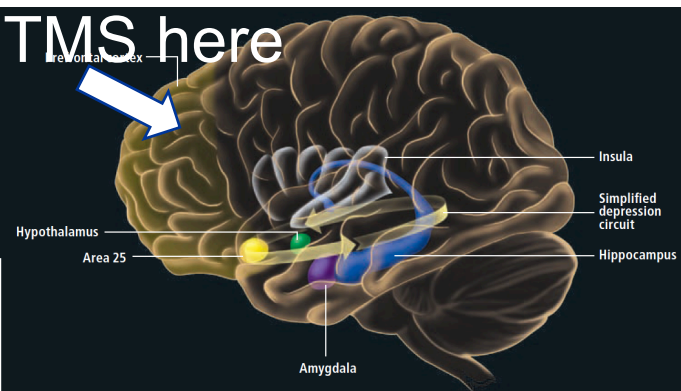
- RCT of TMS+Task to resilience target (2/day x 2 days)
- Prevented memory decrement and memory lapses a full 18 hrs after the last TMS
- Change in fMRI network localized under TMS coil

# Key Methodological Decisions

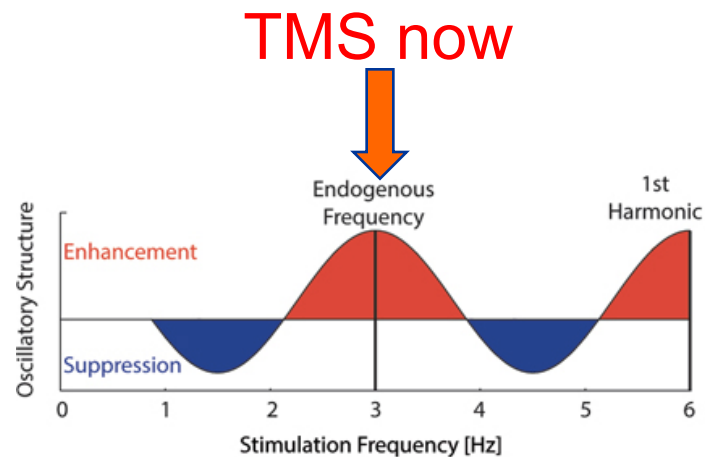
- Spatial aspects of dosing
  - Coil design, position, orientation
- Temporal aspects of dosing
  - Pulse shape, train parameters
- Contextual aspects of dosing
  - Concurrent task performance to engage network
- Sham / Comparison condition



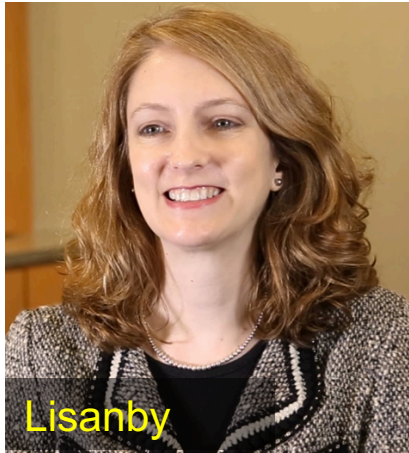
# Conclusions



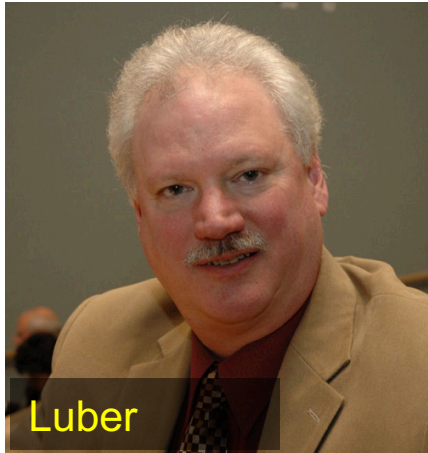
- **Spatial** maps of neurocircuitry underlying disorders have guided spatial targeting for depression, but
- **Temporal** targeting is presently lacking, but of great potential impact
- Understanding the interaction between **endogenous** neural dynamics underlying psychiatric disorders and **exogenously** applied electrical currents represents a key knowledge gap in the development noninvasive neuromodulation for psychiatric disorders.



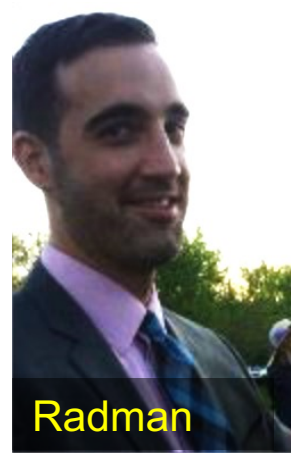
# Meet the NNU Team



Lisanby



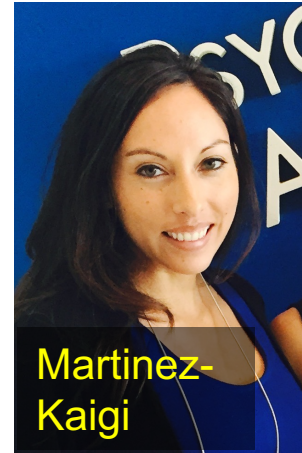
Lubber



Radman



Deng



Martinez-Kaigi

## Experimental Therapeutics & Pathophysiology Branch



Zarate

Park,  
Staff  
of 7SE



Noh, van Gelderen, Asturias



# Any Questions?



*Any Questions?*

