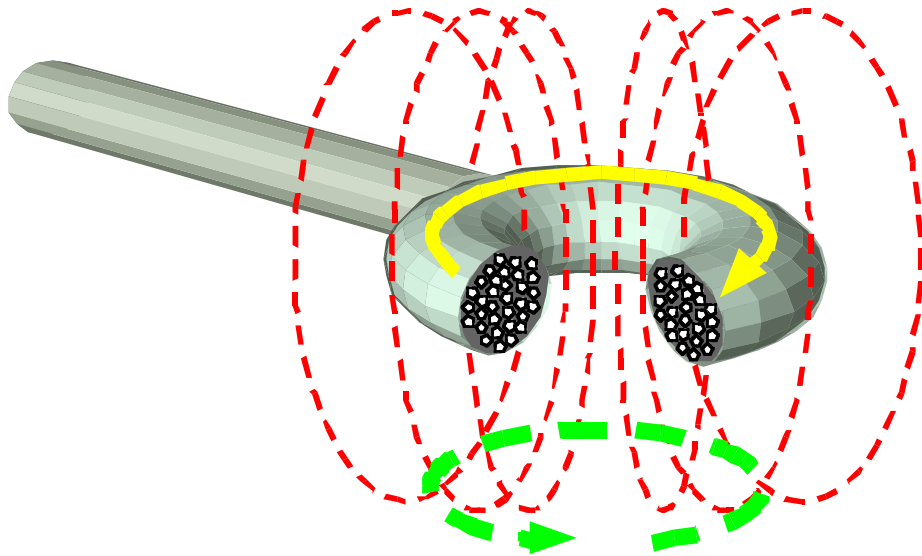


Combining devices with behavioral performance to produce cognitive enhancement

Bruce Luber, PhD
Noninvasive Neuromodulation Unit
Experimental Therapeutics and Pathophysiology
Branch
National Institute of Mental Health

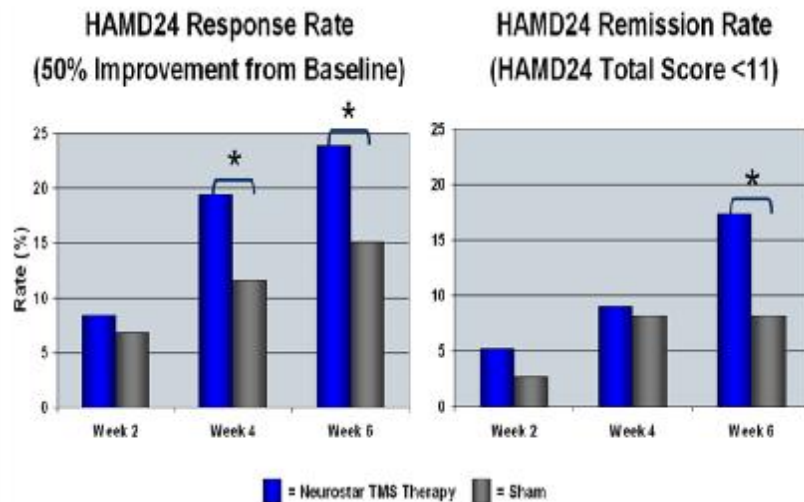
Non-invasive Brain Stimulation (NIBS)

- NIBS: applying energy to the brain in a noninvasive way to modulate its activity
 - here focused on electromagnetic energy
 - Transcranial magnetic stimulation (TMS) in particular



Modulatory effects of TMS

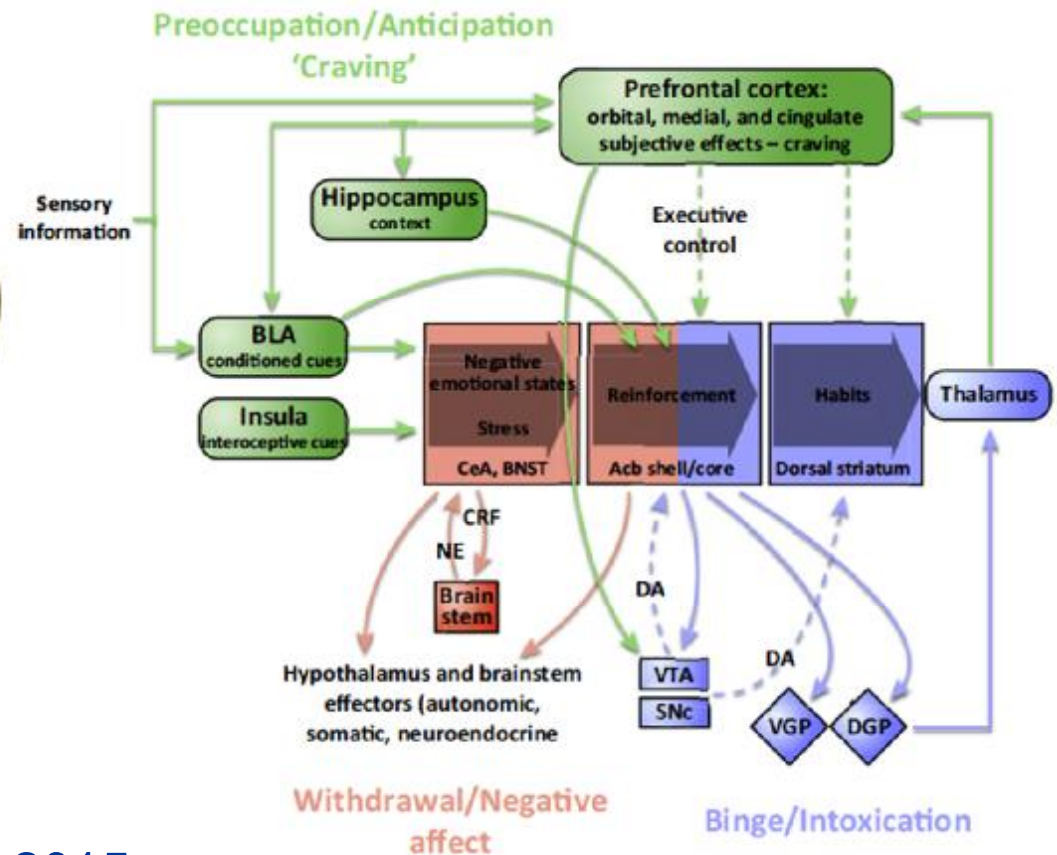
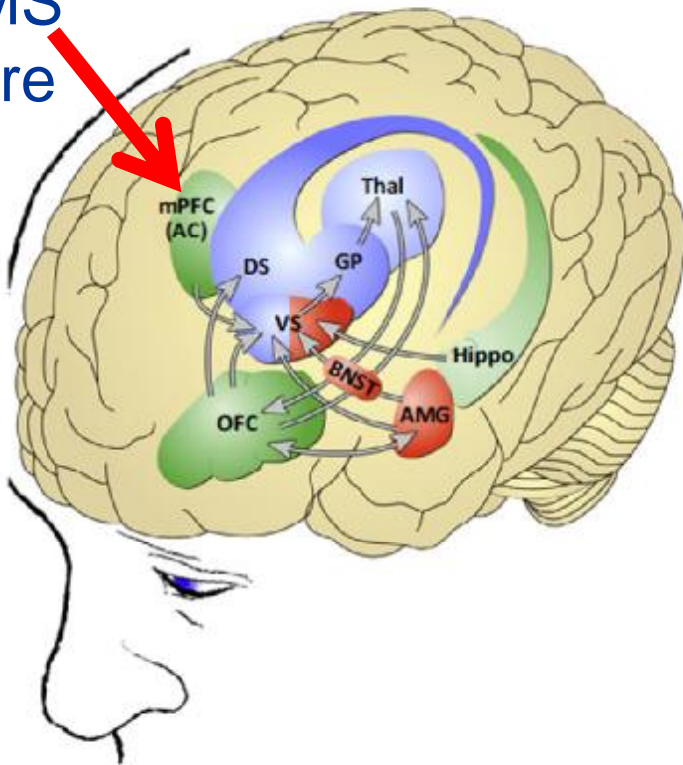
- Acute effects - Mapping
 - Direct activation of circuits
 - Elicits observable responses (motor twitch)
 - Disrupts (e.g. speech arrest) or facilitates (e.g. speeds RT) ongoing processing
- Lasting effects - Modulation
 - Neuroplasticity
 - Synaptic efficacy, LTP/LTD
 - Modulation of cortical excitability
 - Modulation of functional connectivity



The Promise: NeuroModulation for Therapeutics

- Complementary to Neuropharm and Psychosocial Interventions
- Promise to turn knowledge of circuitry into therapeutic targets

TMS
here



Tang, Posner, Rothbart, Volkow. 2015

TMS enhancement of cognitive performance

- As originally conceived, TMS was disruptive
- However: 62 reports of significant improvements in speed and accuracy on a range of tasks in healthy individuals (Luber and Lisanby, Neuroimaging 2014; 85:961-970).
- Reports could be divided into 3 categories of enhancement mechanisms
 - Artifact: Intersensory facilitation
 - *Addition by subtraction* – disruption of processing which competes or distracts from task performance
 - *Direct modulation* of cortical region/network supporting efficient processing

Paired Associated Stimulation

The direct modulation of networks to cause cognitive enhancement suggests a more active approach

- Pairing of TMS with peripheral stimulation enhances motor excitability for >1hr
- Synaptic coincidence (Hebbian plasticity) might be achieved via behavioral activation coupled with TMS

Interventional paired stimulation



90 pairs
ISI 25 ms

Stefan et al. 2000; Ridding et al. 2001



NIH National Institute of Mental Health

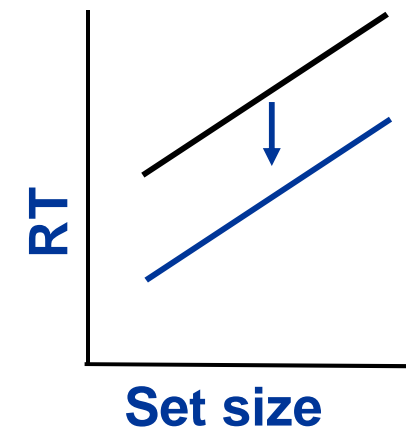
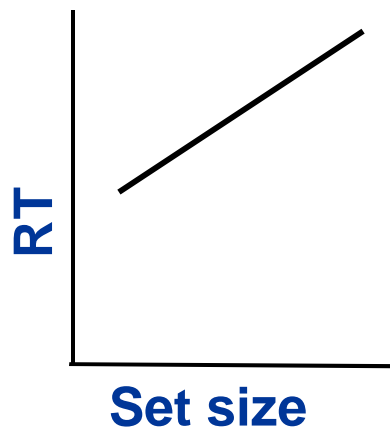
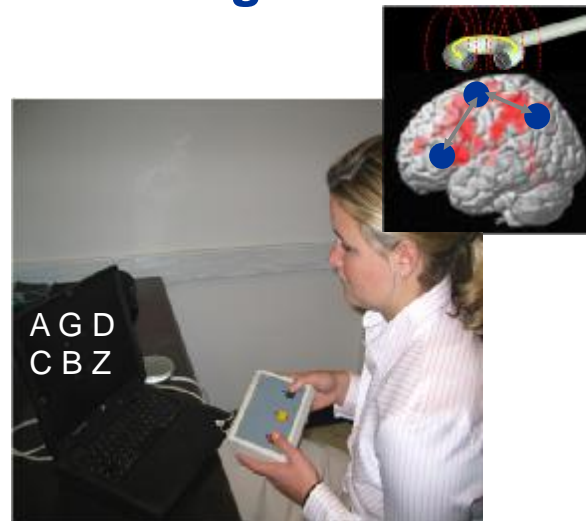
Cognitive Paired Associative Stimulation (C-PAS): TMS + Cognitive Task Performance

Pre

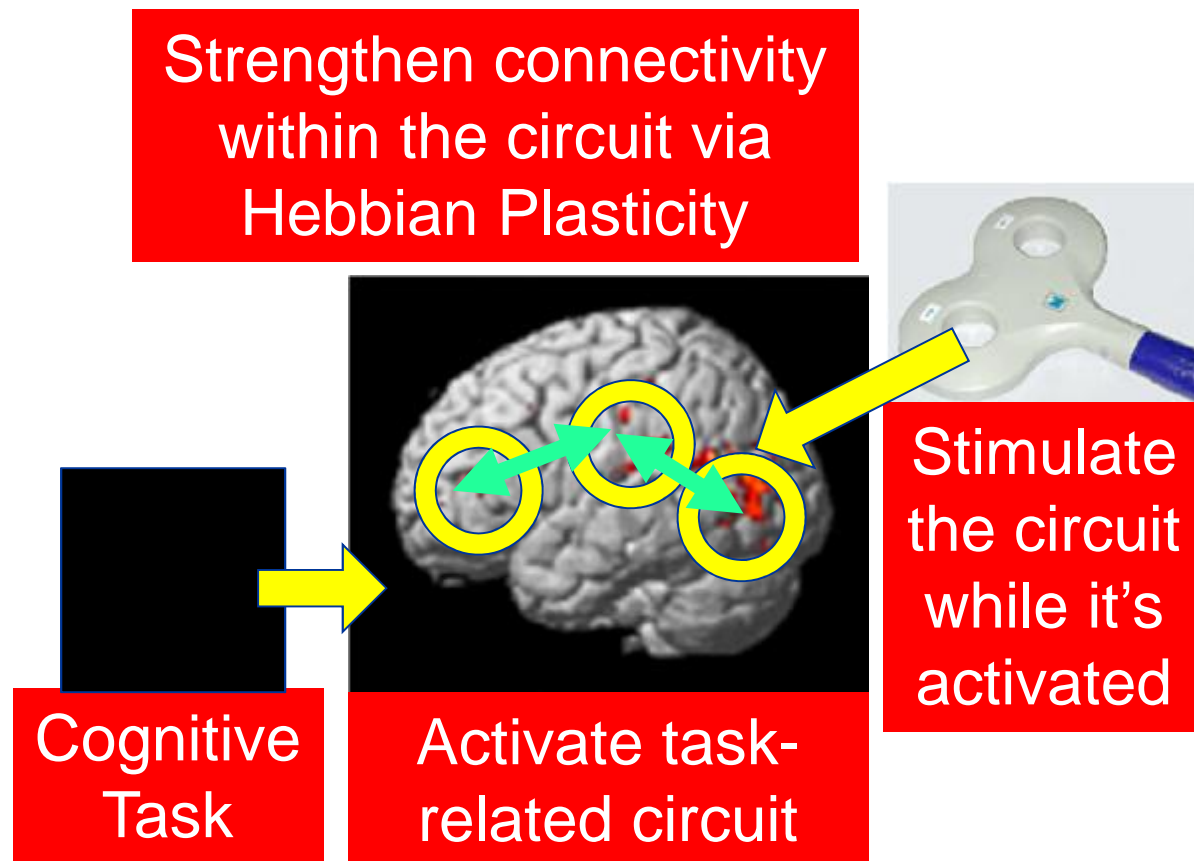
Intervention:

Post

TMS+Cognitive Activation



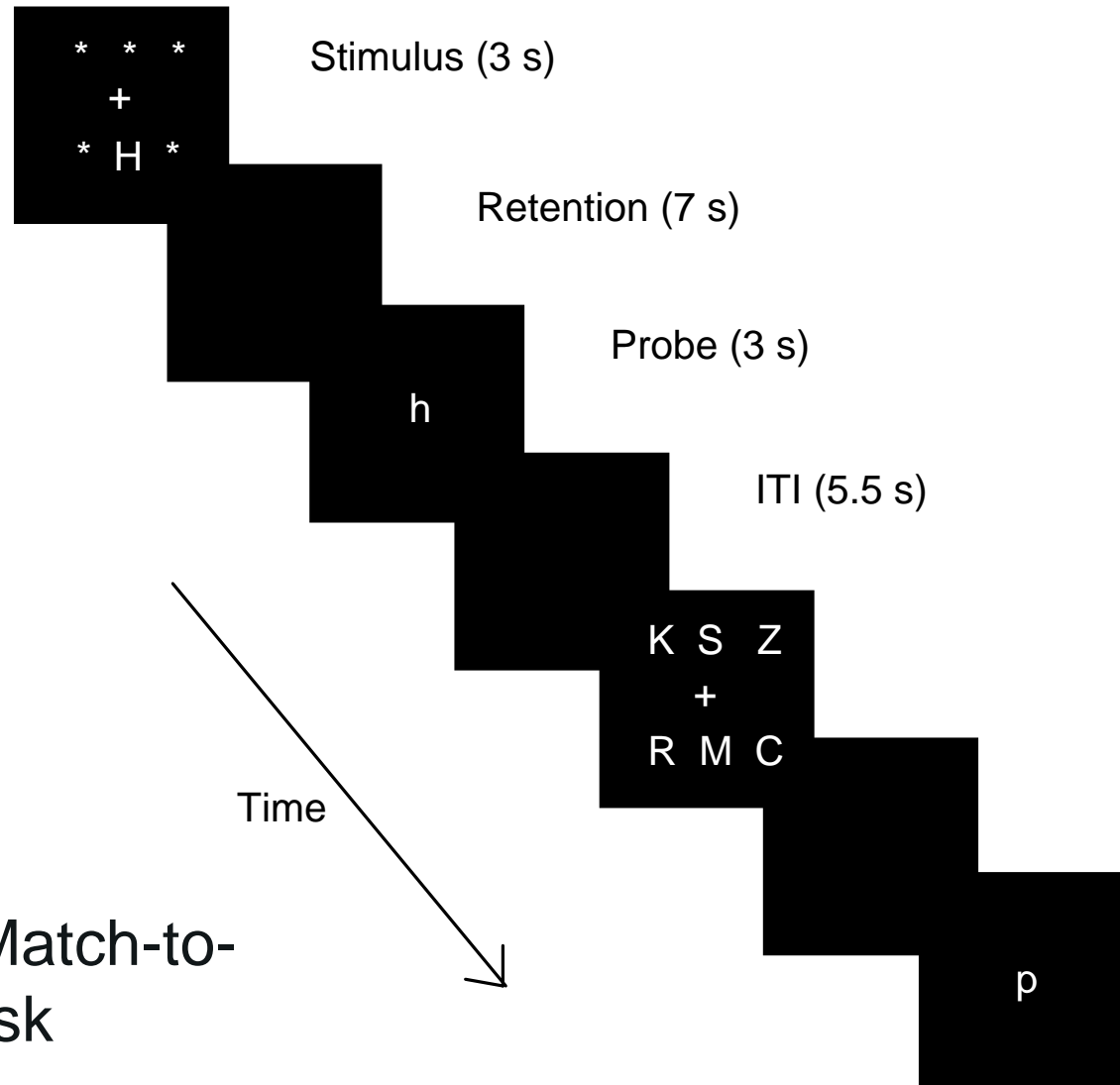
Cognitive Paired Associative Stimulation (C-PAS):



Enhancing Network Function with TMS+Cognitive Training



- Domain of Function – *Working Memory*



Sternberg
Delayed-Match-to-
sample task

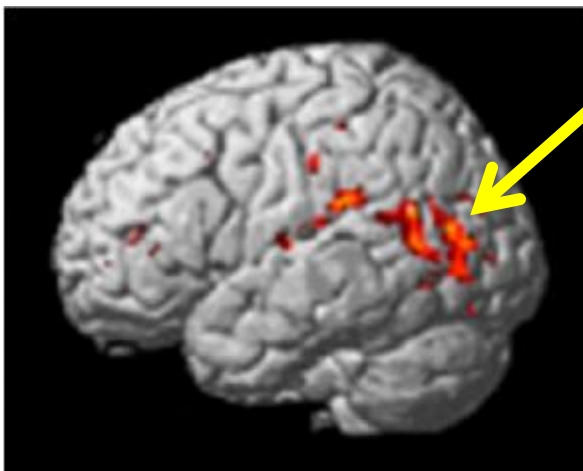


Enhancing Network Function with TMS+Cognitive Training



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

fMRI-Guided TMS



Simultaneous

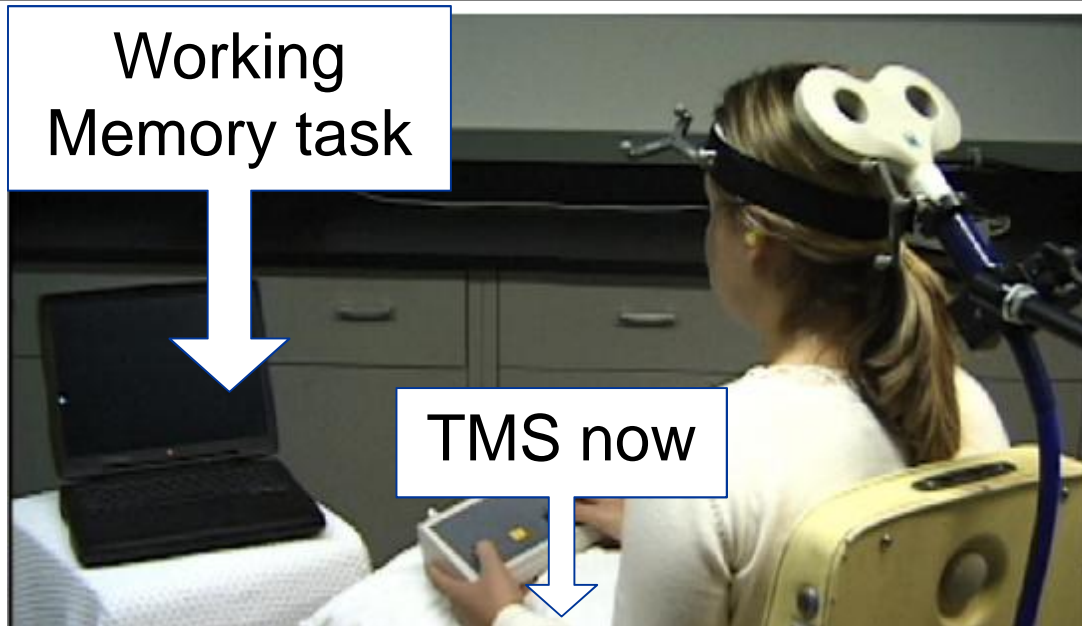
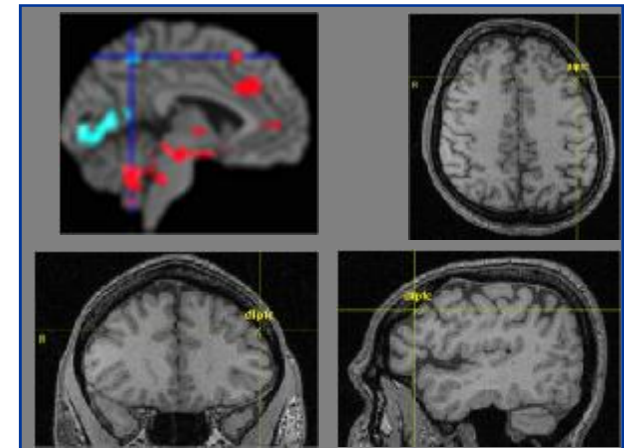
Working Memory Training



fMRI Targeted, Stereotaxic Neuronavigation, Time-locked

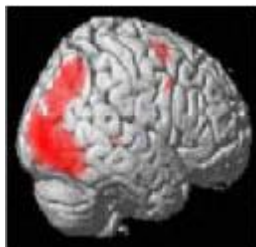


Frameless Stereotaxy
Neuro-navigation to
individualized target



Stimulus

Q A K
+
Y R P



Retention



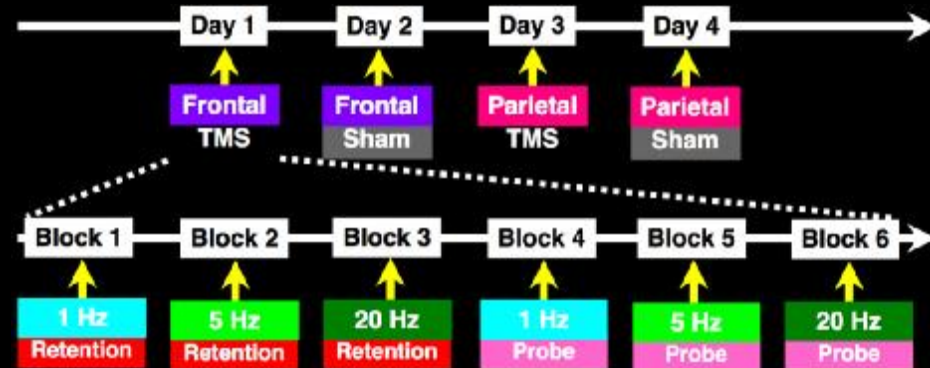
Probe

m

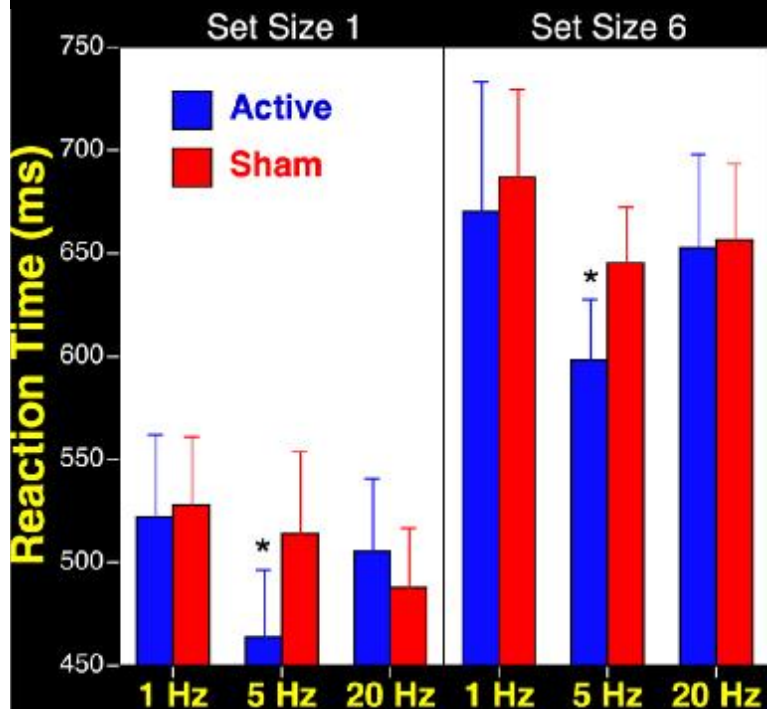


TMS + Simultaneous Working Memory Training Improves Cognitive Performance

Network associated with better task performance



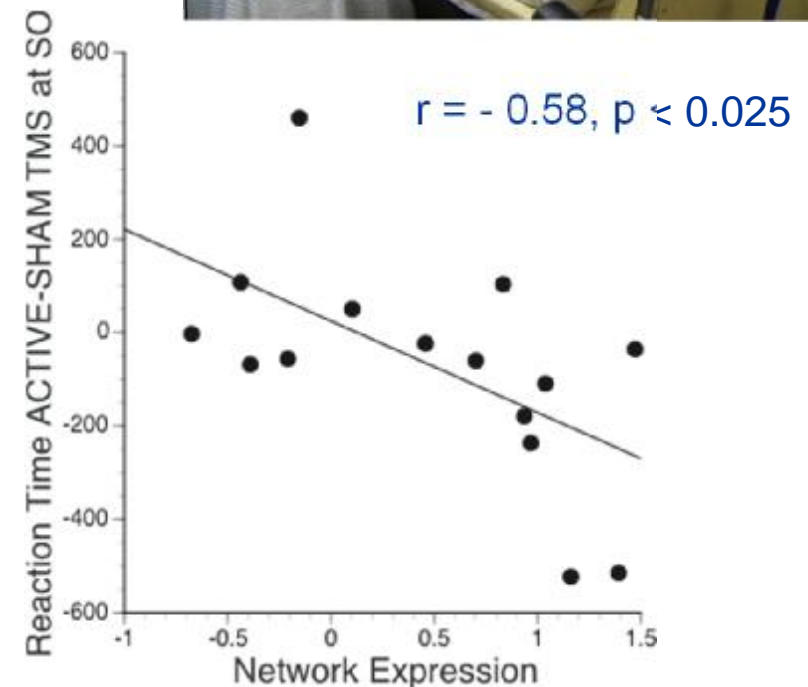
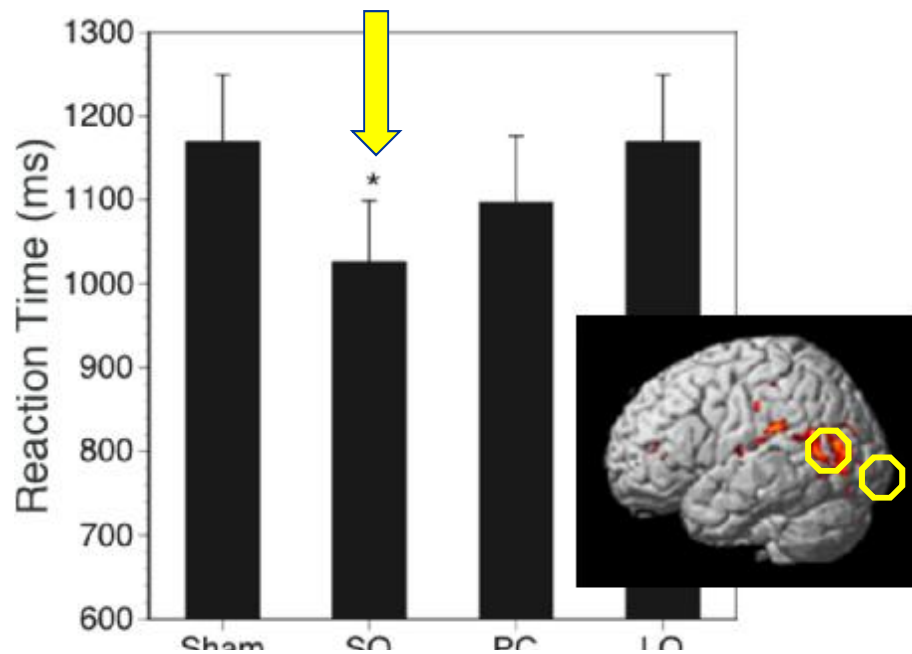
- Dose-finding, within-subject cross-over, n=44
- Improved cognition (reduced RT by 75 ms, $p < 0.002$)
- Frequency-dependent (5Hz)
- Site-specific (precuneus)
- Context-specific (retention phase of the task)



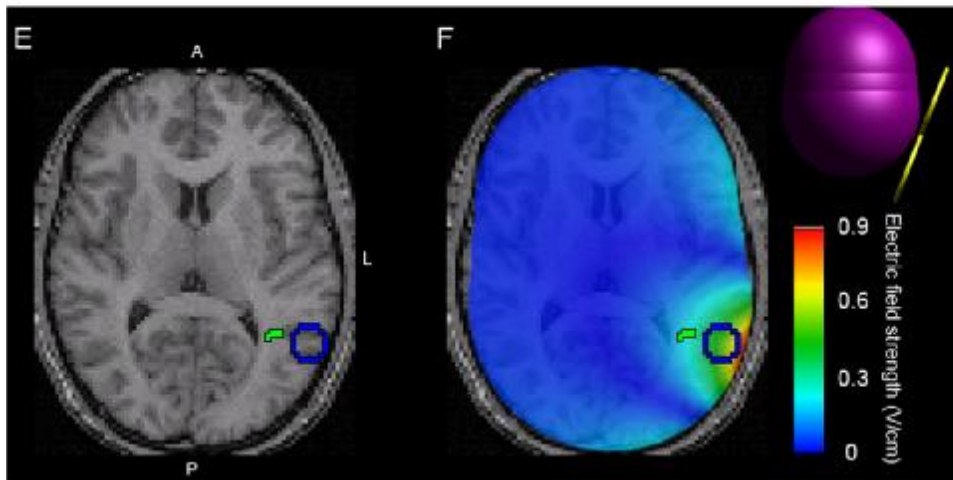
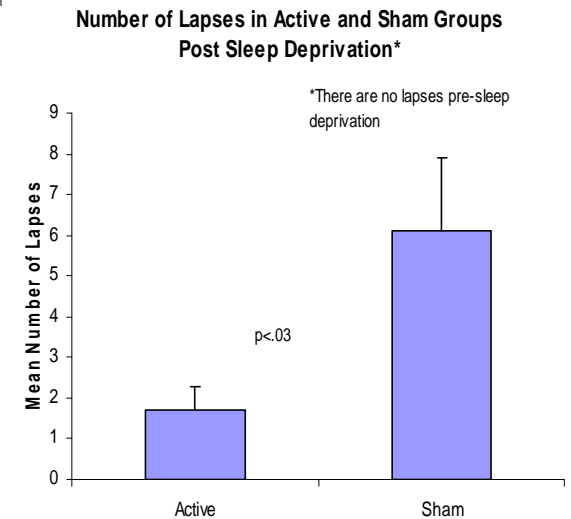
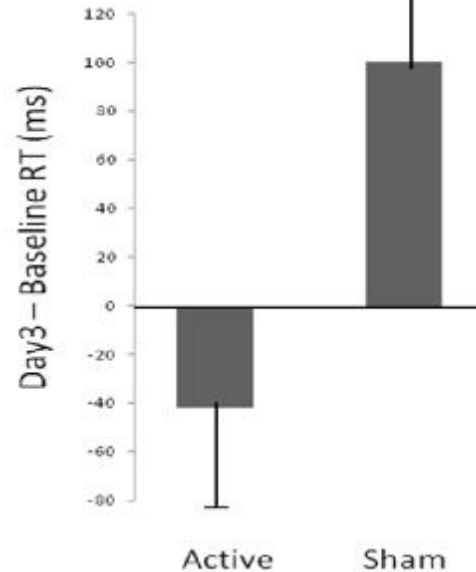
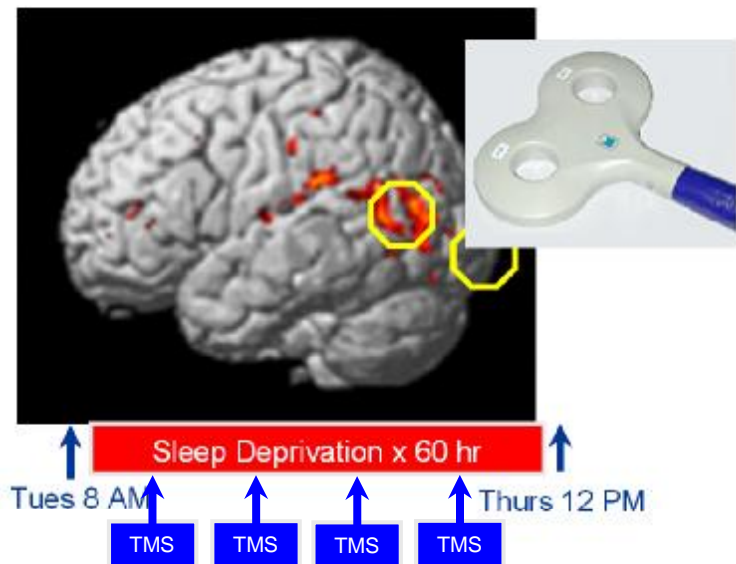
Luber et al Brain Research 2007;1128:120-129

TMS + Simultaneous Working Memory Training Remediate Cognitive Performance

- Site-specific cognitive enhancement with 5 Hz TMS to sleep deprivation resilience network
- Degree of improvement correlated with degree of network expression



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

CPAS: problems and challenges

- **Temporal parameters:**
- Relative timing of TMS and cognitive tasks:
 - There is evidence for the validity of CPAS
 - Random timing of TMS and tasks doesn't work (Anderson et al., 2006 J ECT)
 - Relative timing is essential in acute TMS effects
 - Motor training in stroke recovery
 - But there is no direct evidence at a mechanistic level: NHP work is needed
- In general, the mechanisms behind cognitive enhancement are not known: why does 5Hz work?
 - Again, NHP work is needed

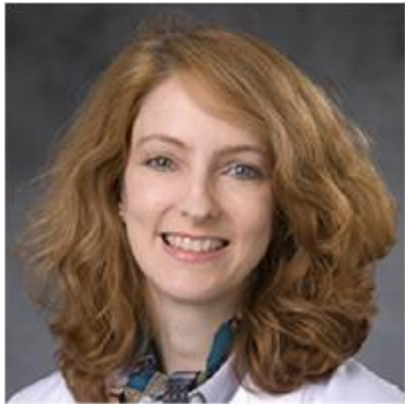
CPAS: problems and challenges

- **Spatial targeting:**
- Brain imaging and neuronavigation provide powerful means to engage brain networks
- But dosing of TMS is still an issue: based on motor thresholds, but problematic when leave motor cortex
- Some of the technology is in place: Realistic head modeling and coil design
- A measure of cortical excitability outside motor cortex is needed, such as TMS evoked potentials measured by EEG

CPAS: problems and challenges

- **Temporal targeting** (knowing when to stimulate):
- State dependence is now probably the greatest source of variability
- In addition, we are not taking endogenous neural oscillations into account
- One possible solution is development of closed loop systems using EEG

NIMH Experimental Therapeutics & Pathophysiology Branch: Noninvasive Neuromodulation Unit (NNU)



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Experimental
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Pathophysiology
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Deng, PhD



Goetz, PhD



Strauman,
PhD



McClintock,
PhD



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