TMS as a Tool for Neuroscience

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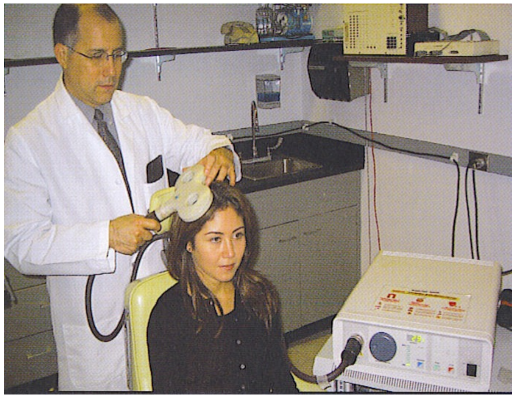
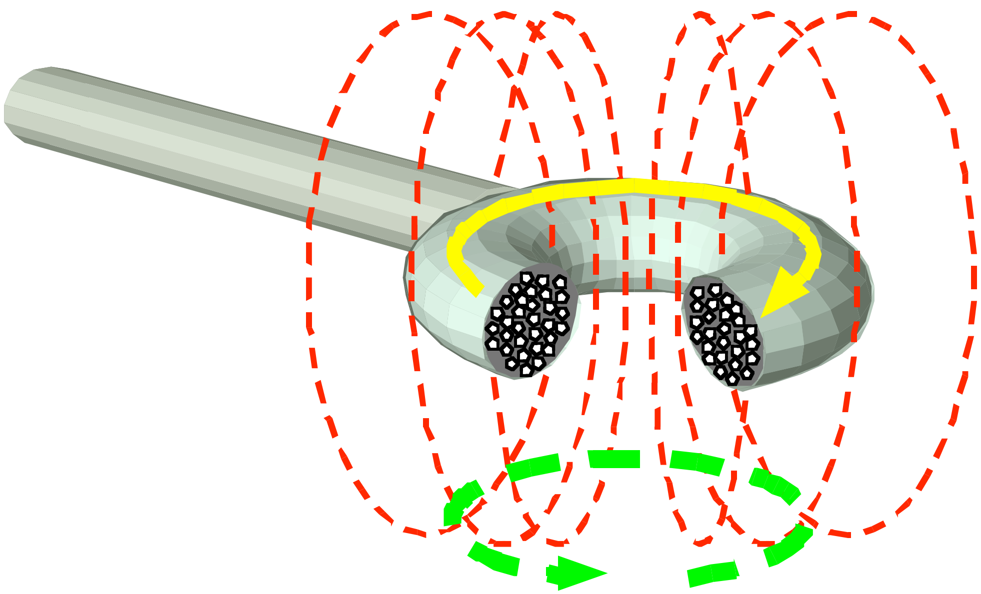
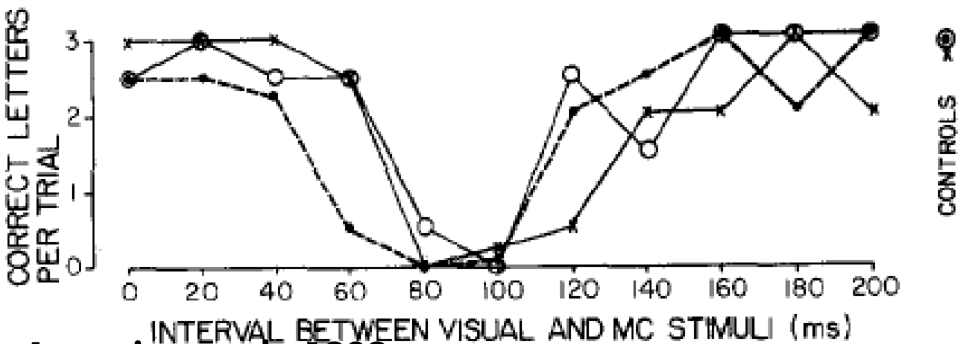


Non-invasive Brain Stimulation (NIBS)

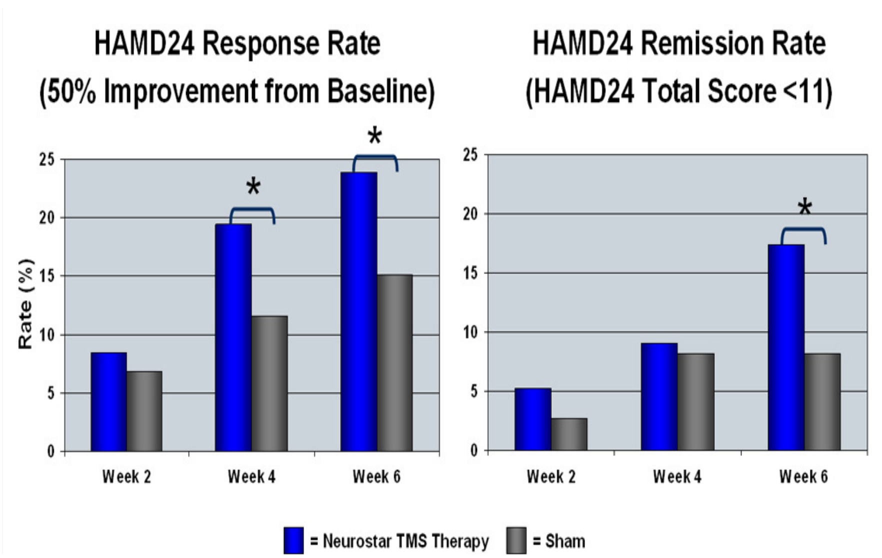
- NIBS: applying energy to the brain in a noninvasive way to modulate its activity
  - here focused on electromagnetic energy



Modulatory effects of TMS

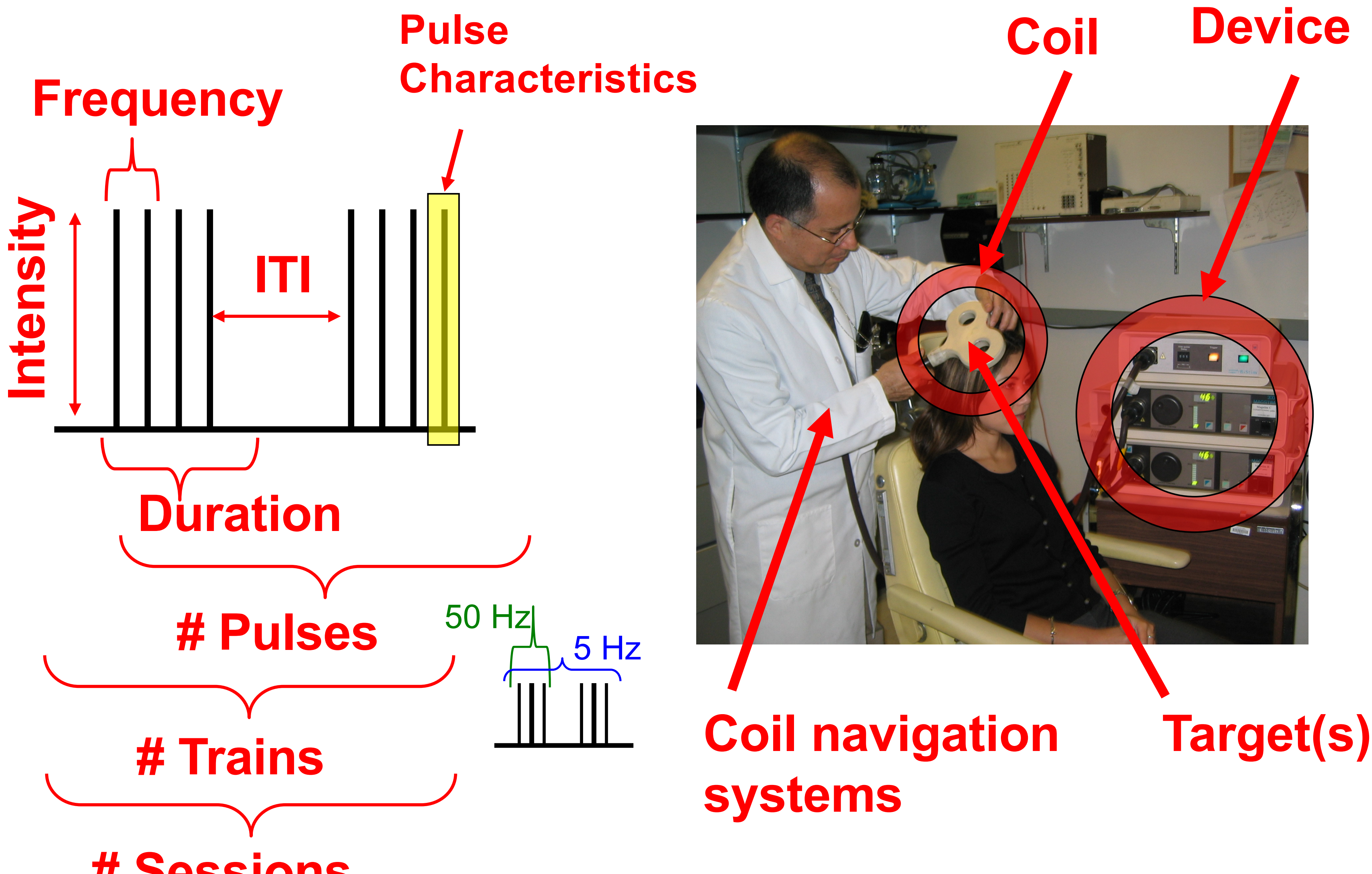


Amassian et al., 1989

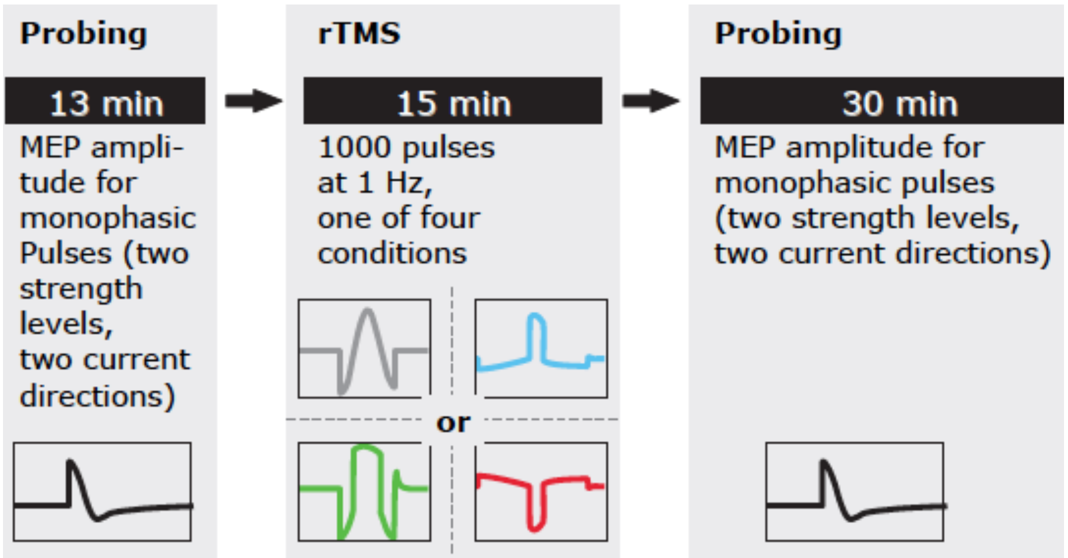


- Acute effects - Mapping
  - Direct activation of circuits
    - Elicits observable responses (motor twitch)
    - Disrupts (e.g. speech arrest) or facilitates (e.g. speeds RT) ongoing processing
- Lasting effects - Modulation
  - Neuroplasticity
    - Synaptic efficacy, LTP/LTD
    - Modulation of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

The space of all possible parameters for dosing in therapeutic Rx is extremely large



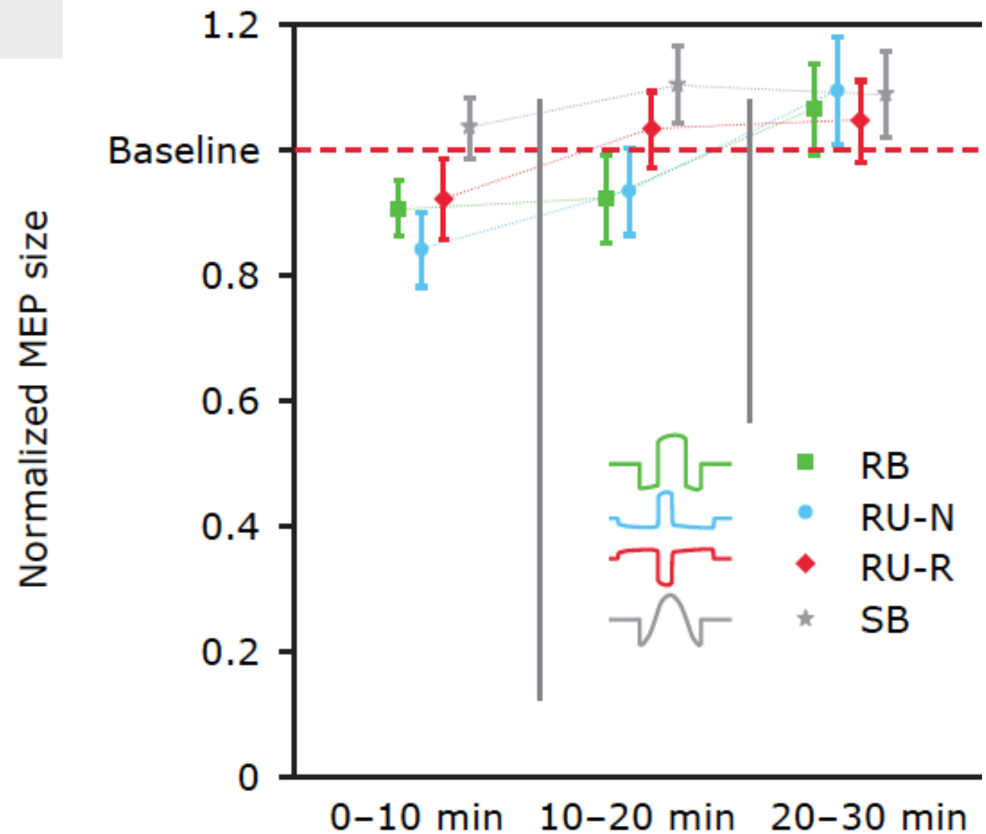
Waveform matters:



A comparison of the standard biphasic (cosine shape) with rectangular bidirectional and unidirectional waveforms

N = 13
Standard 1 Hz "inhibitory" paradigm

In this case, 1 Hz trains with the standard waveform did not result in lower MEP amplitude, while they did using rectangular waveforms



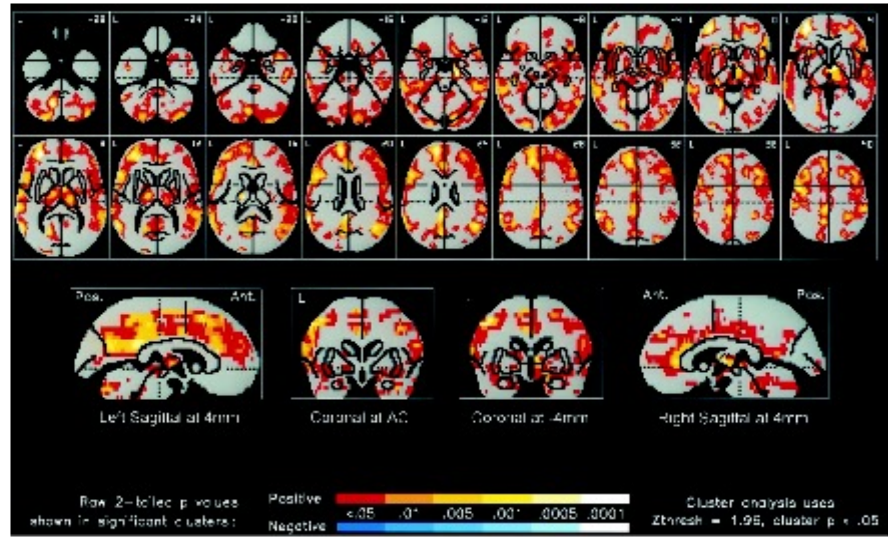
Goetz et al., 2016

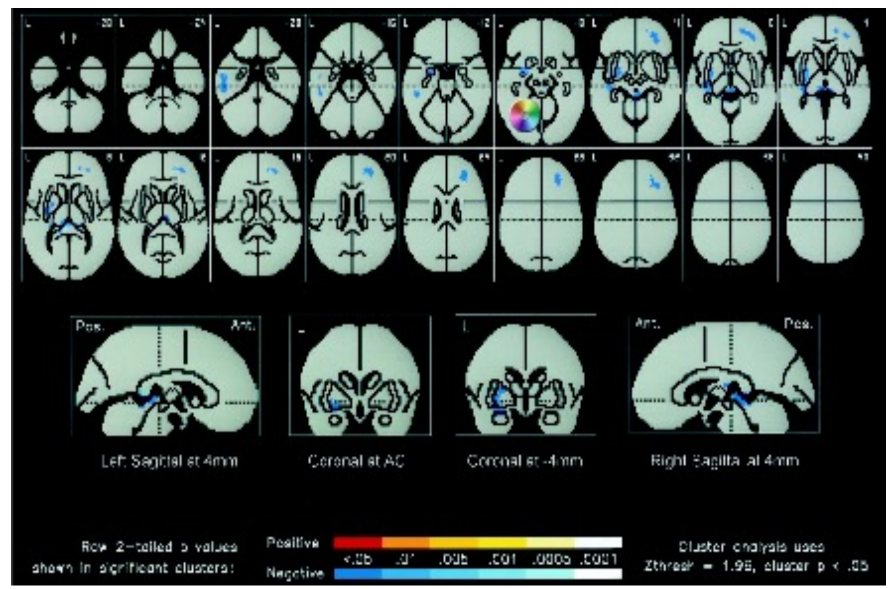
TMS frequency

Rule of thumb:

High frequency (>3Hz) **<u>up</u>**-regulates cortical excitability

Low frequency (1 Hz) **<u>down</u>**-regulates cortical excitability



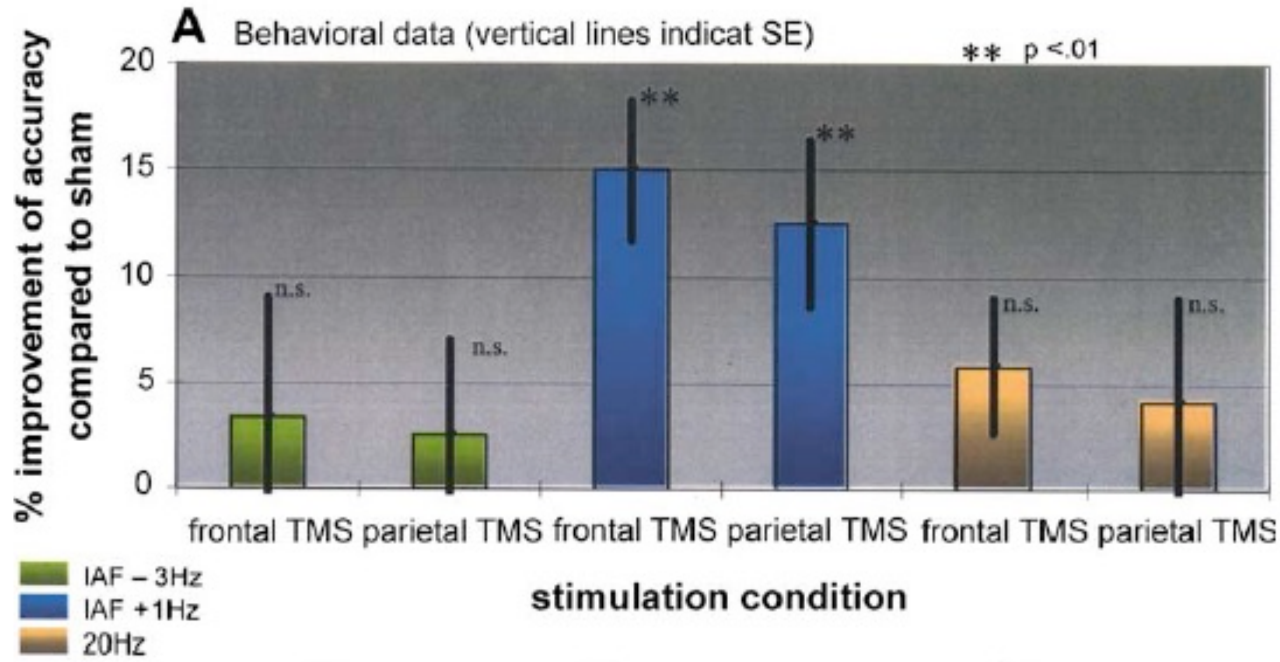


Speer et al Biol Psych 2000

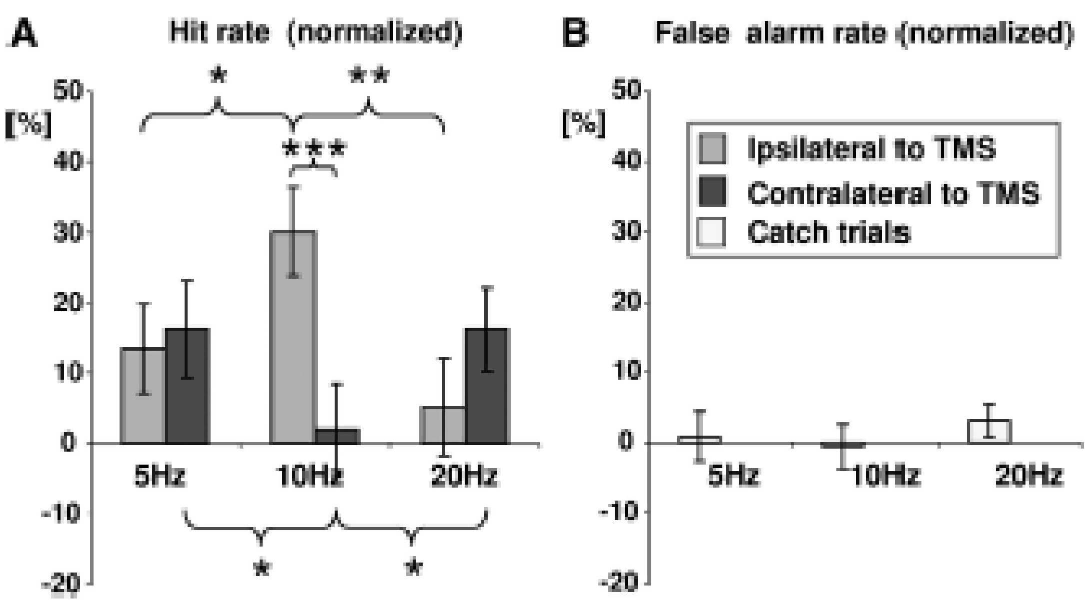
TMS enhancement: Tapping into brain's oscillatory dynamics?

2 s burst at peak alpha frequency (but not peak-3Hz or 20 Hz) immediately prior to trial increased accuracy of mental rotation

Klimesch et al., 2003 Eur J Neuosci 17: 1129-1133



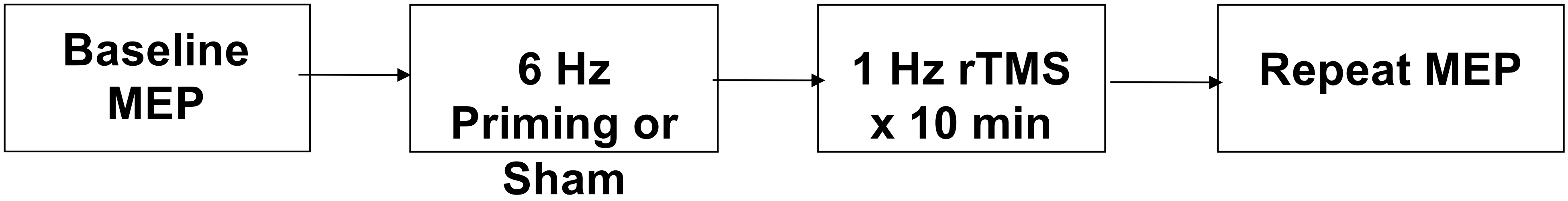
J. Neurosci., June 23, 2010 • 30(25):8692–8697 • 8695

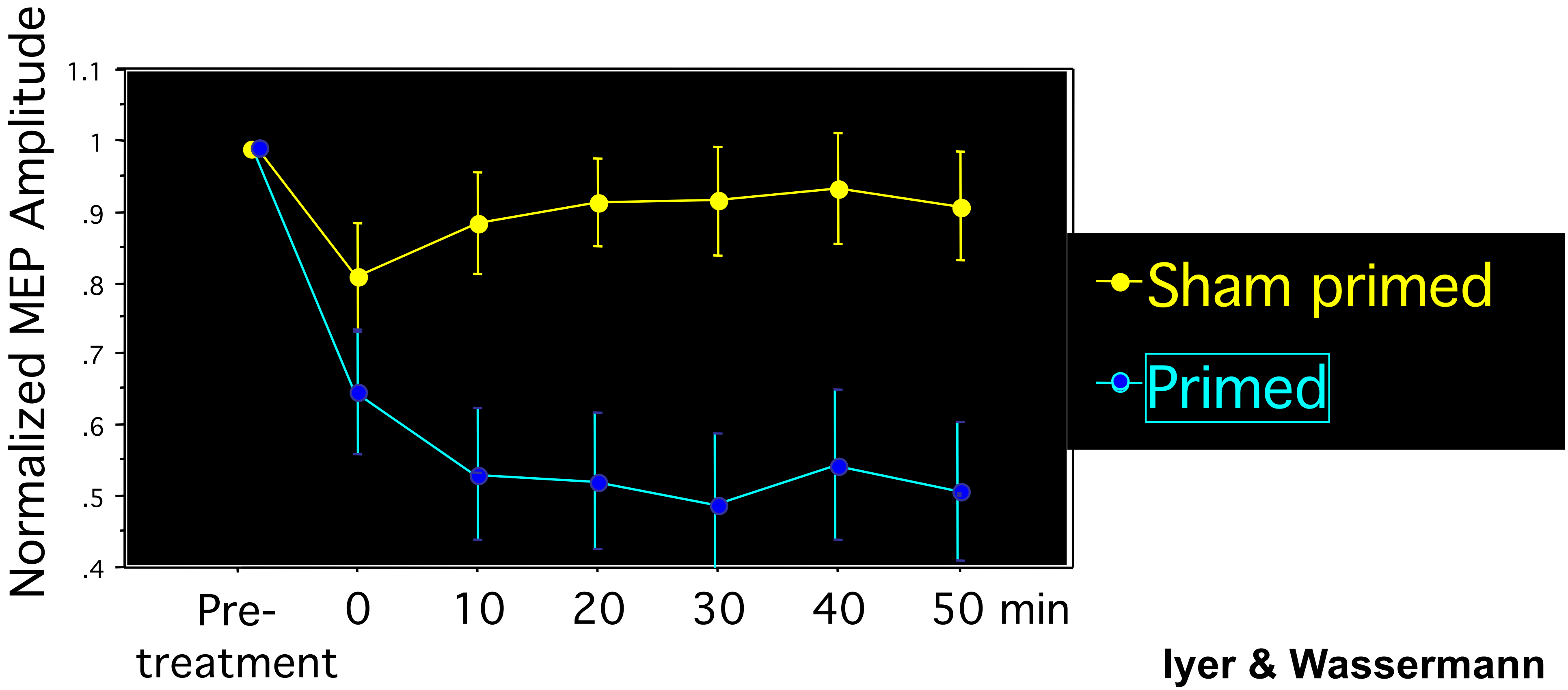


5 pulses at 10 Hz (but not 5 or 20 Hz) immediately prior to trials enhanced target detection

Romei et al., 2010, J Neurosci 30: 8692-8697

Another frequency effect: Priming of “LTD-like” Inhibition

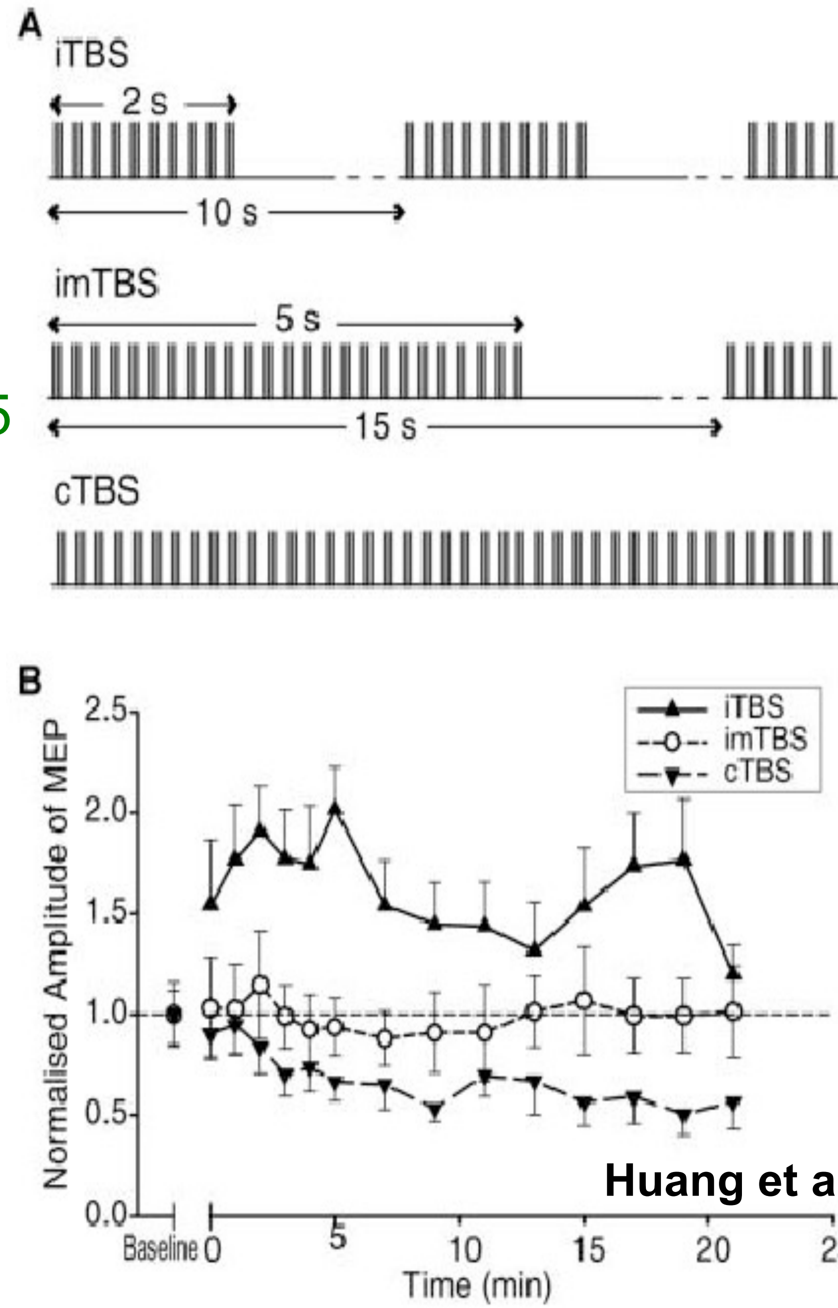




Iyer & Wassermann

Interaction of Frequency, Duration and ITI

- Theta Burst Stimulation (TBS)
- 2 nested "natural" frequencies:
  - Burst of 50 Hz (gamma) given at 5 Hz (theta)
- Produces sustained inhibition or facilitation
  - LTP/LTD-like
- Effects require:
  - a much shorter duration (40 s/192 s)
  - a lower intensity (90% active MT)
- Potential clinical applications unexplored

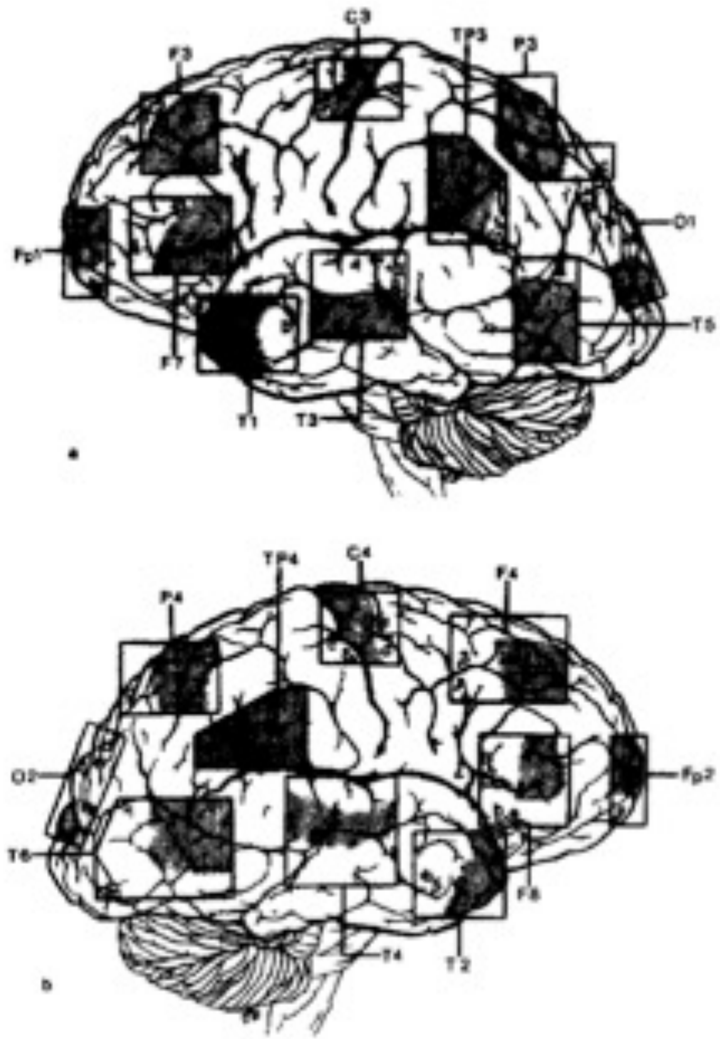


Huang et al. 2005

Target Localization Methods

- Scalp coordinate system: 10-20 EEG system
- Strict Anatomic – pick a spot based on a structural MRI
  - Problem: not functional location
- Functional imaging using group analysis
  - Take structural scan, transform to Talairach, find probabilistic location of behavior (from Group study), reverse transform, find the likely spot
  - Problem - only in the neighborhood in most subjects
- Functional Imaging on an individual basis
  - Do activation imaging, find region, direct TMS there

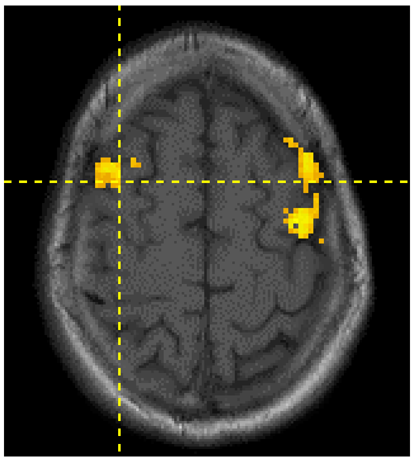
Using scalp/external anatomy to target

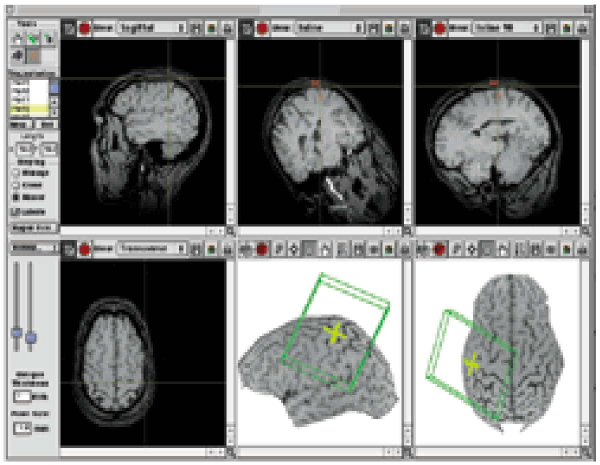


Squares show extent of possible cortical locations an electrode might end up over on any individual

Homan et al., 1987

Function-guided TMS Frameless Stereotaxy: Neuronavigation





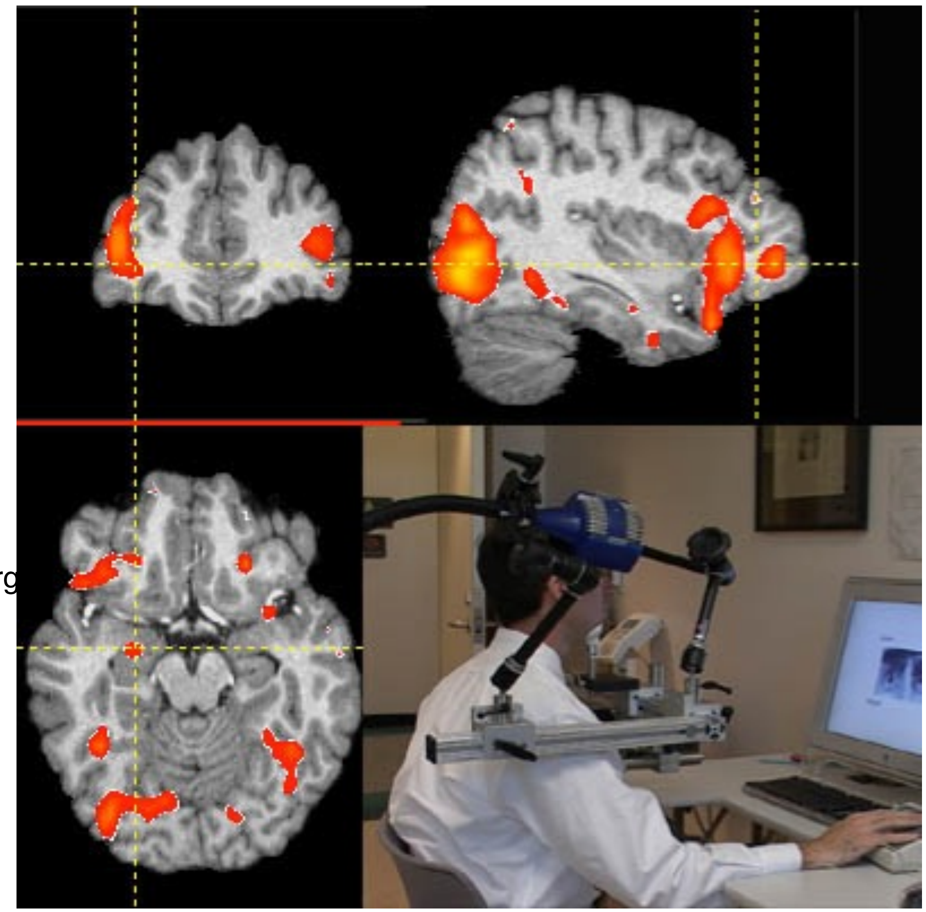
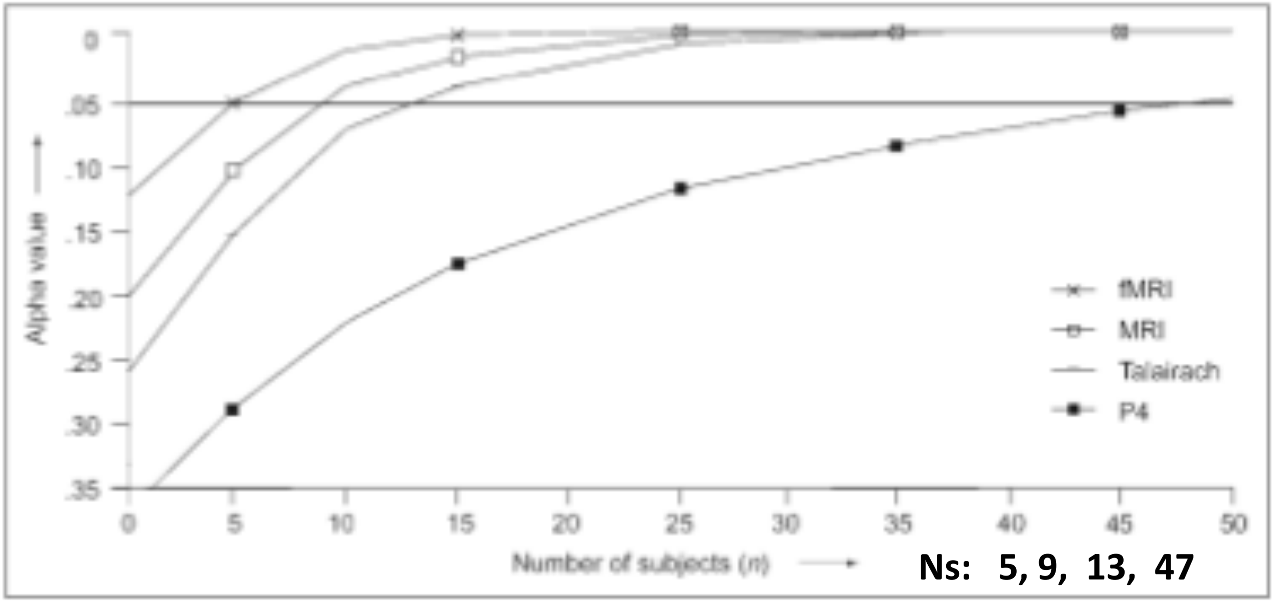
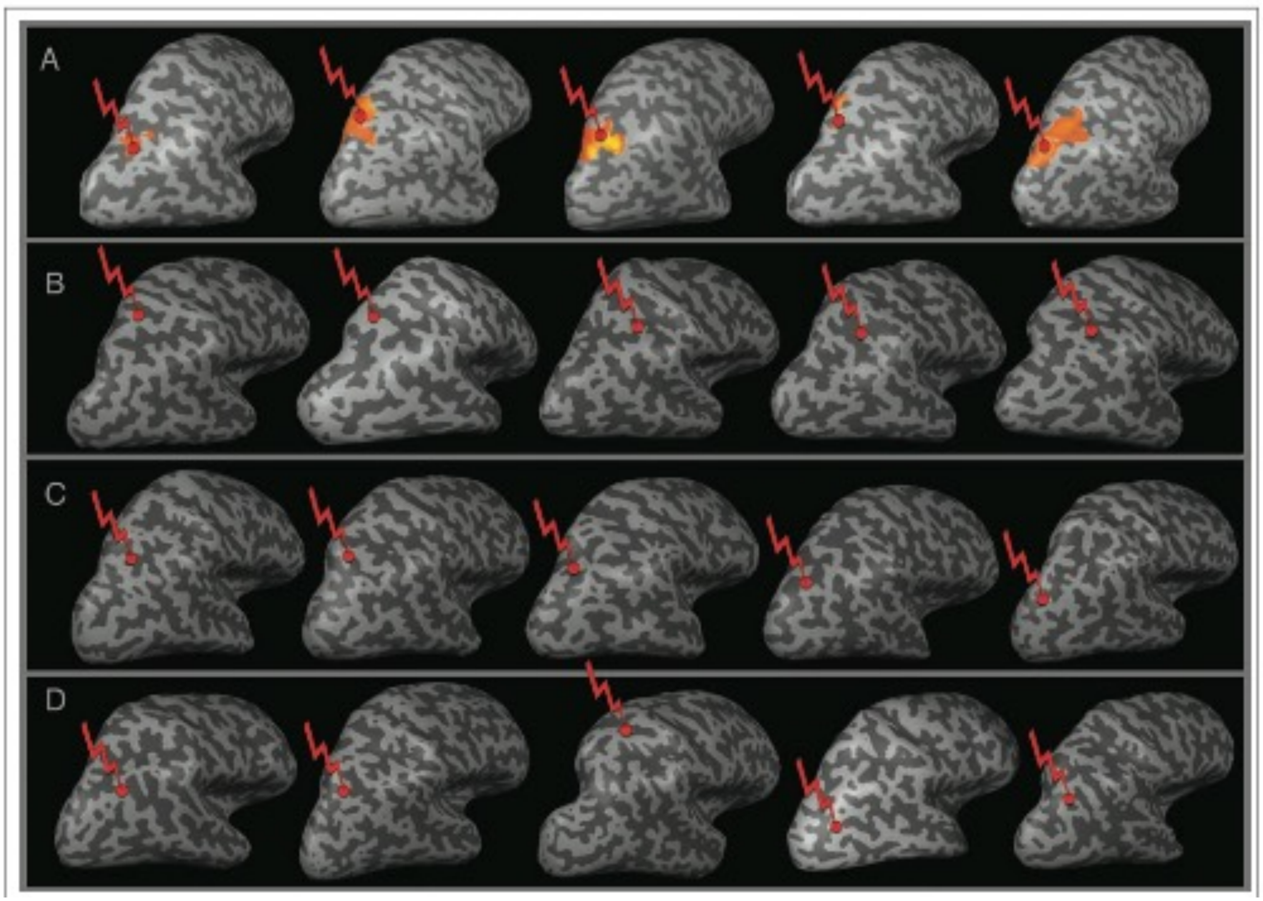


Figure 1: Increases in rCBF in prefrontal cortex while performing a Sternerg



Comparison of targeting techniques:

Individual fMRI targeting results in greatest statistical power for the TMS effect



fMRI-guided

MRI guided

Group-fMRI (Talairach)

10/20 (P4)

Targeting precision: Robot Arm

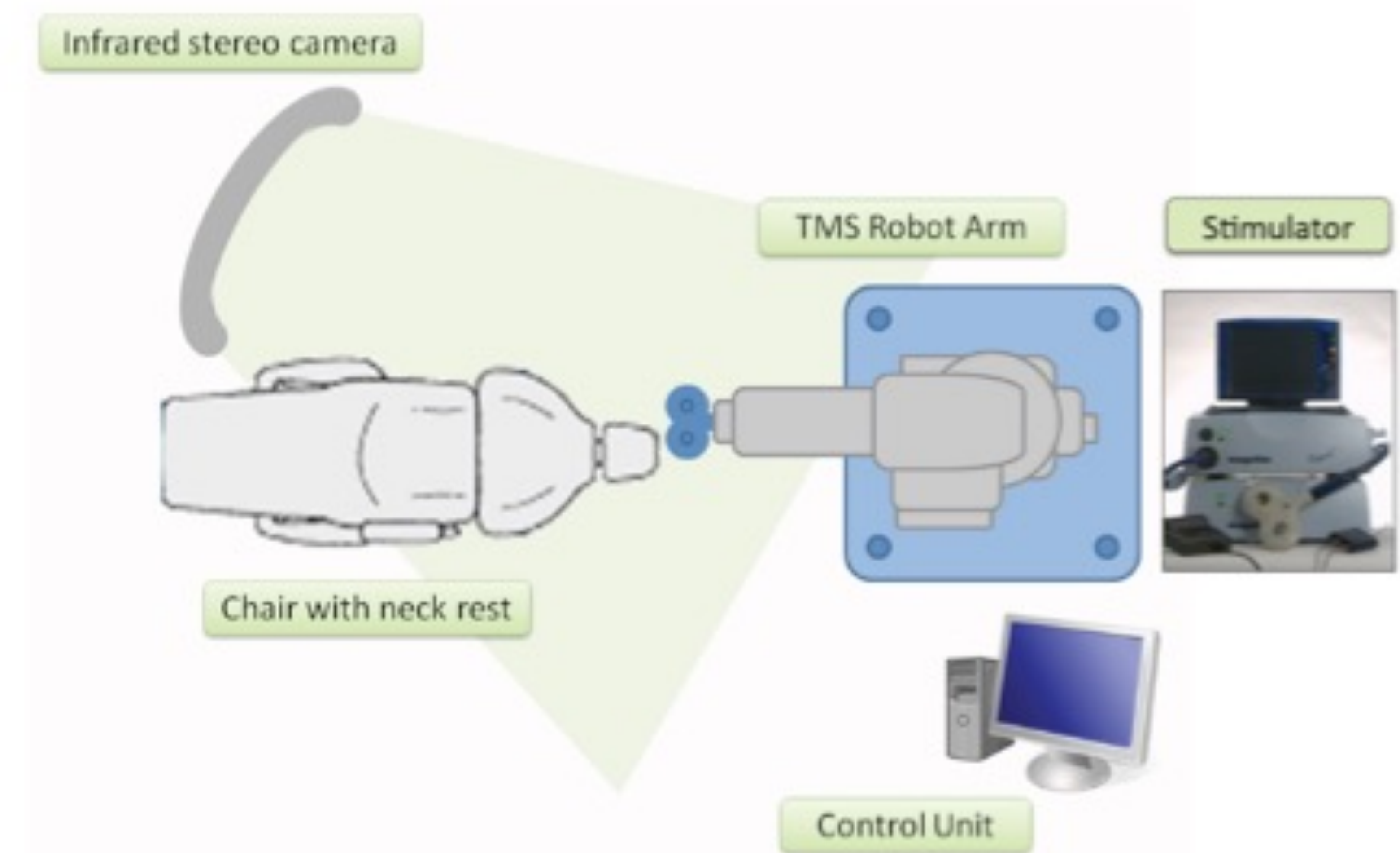
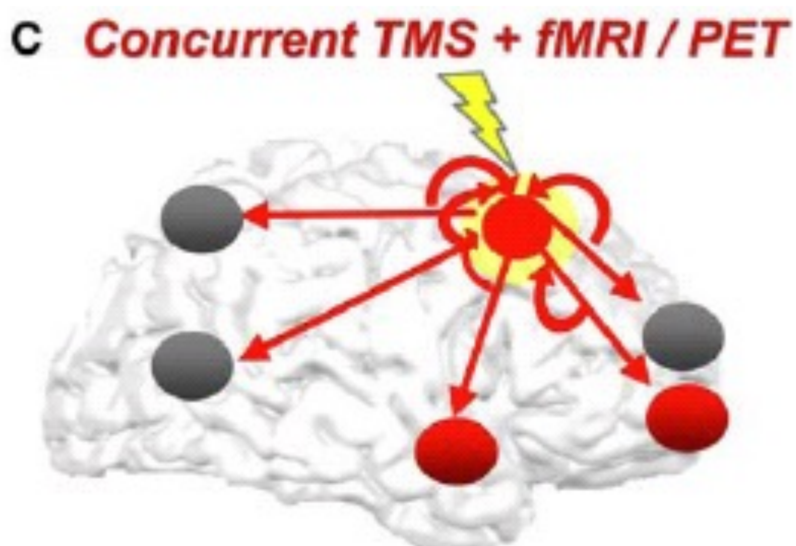


Figure 1. Schematic of the Robot Arm System. System components include: (a) Robot arm (Adept Viper s850) with power supply unit and remote control, (b) control unit for robot arm, (c) NDI Spectra infrared camera, (d) stimulator, (e) chair with neck rest.

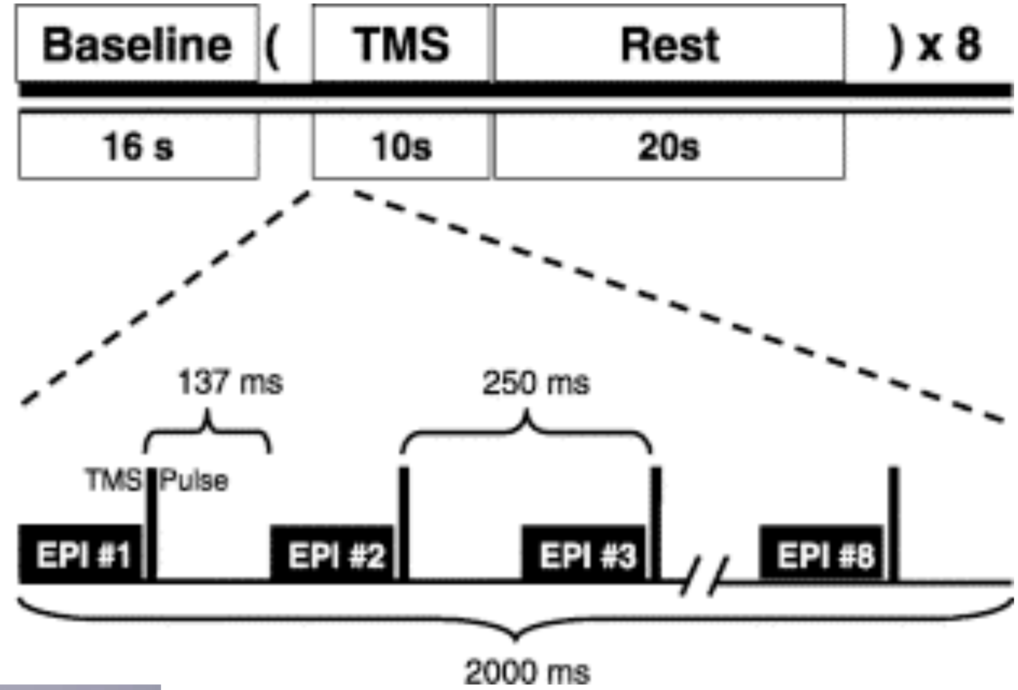
Stimulating one cortical site engages a network

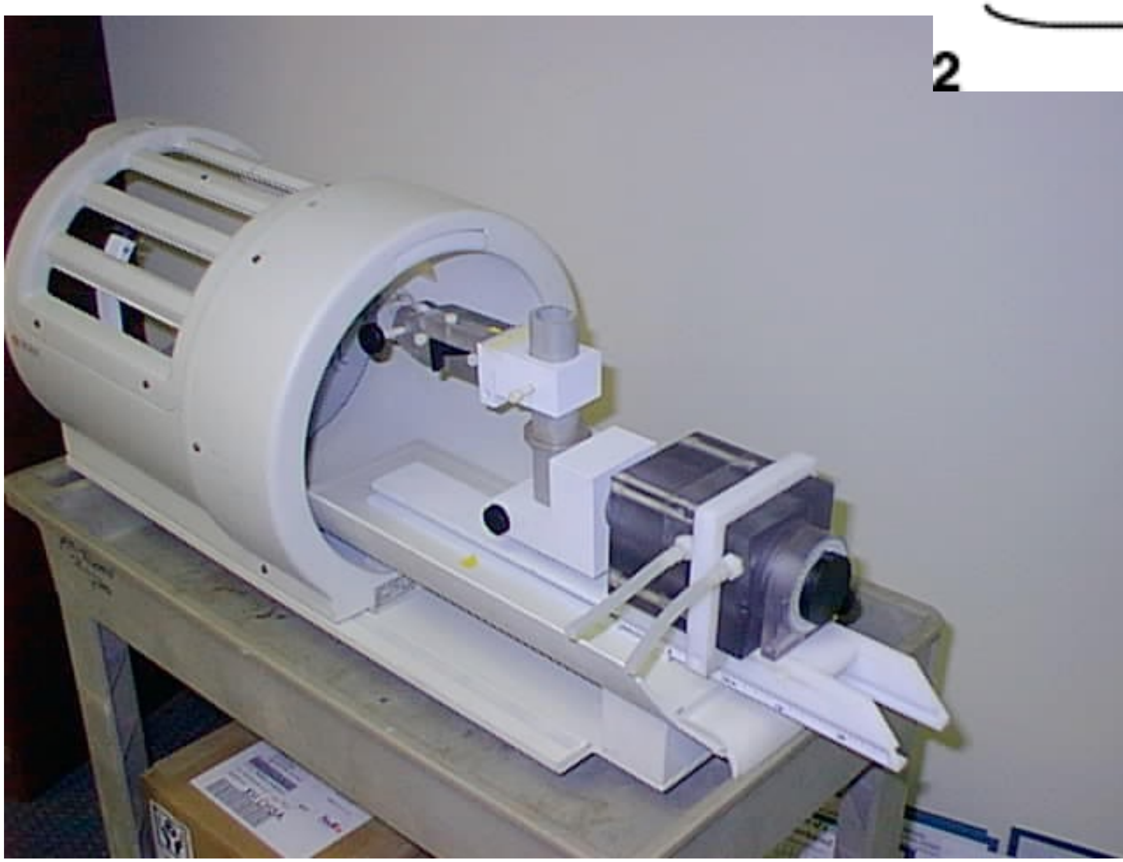
Pre-Post imaging with offline TMS

Concurrent imaging/TMS:



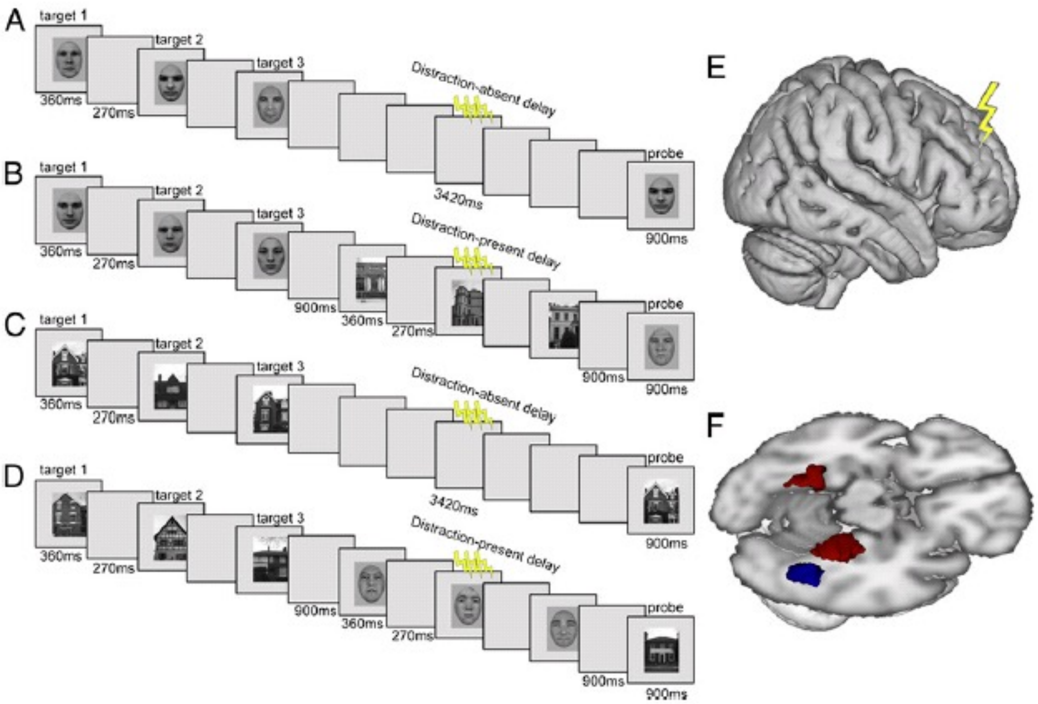
TMS/fMRI Interleaving

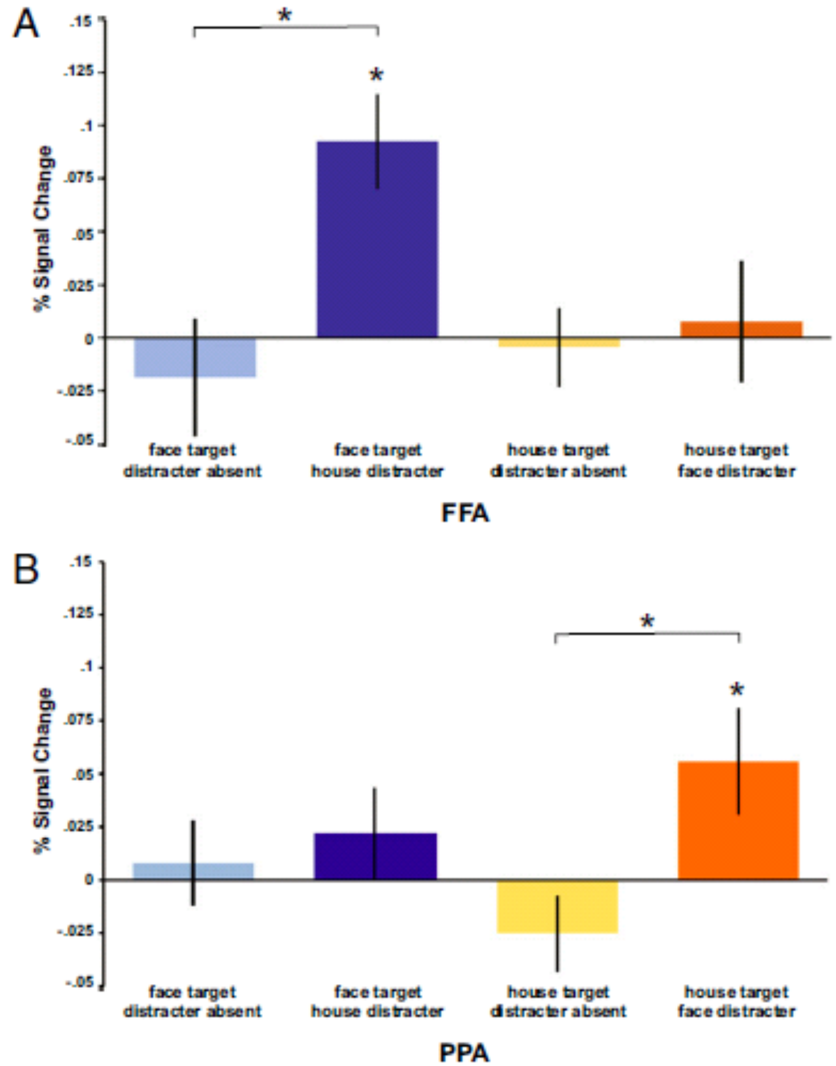




• **Firm, Fixed, Pin-point repositioning in scanner**

Exploring long-distance network effects with simultaneous TMS-fMRI



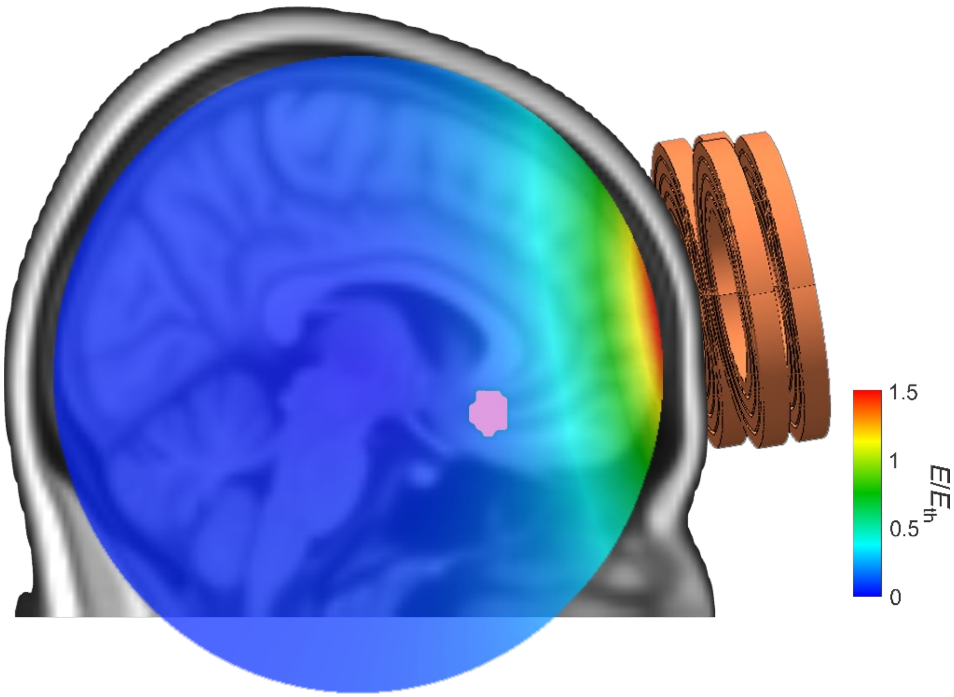


Picture working memory task
Faces (FFA activity)
Places (PPA activity)

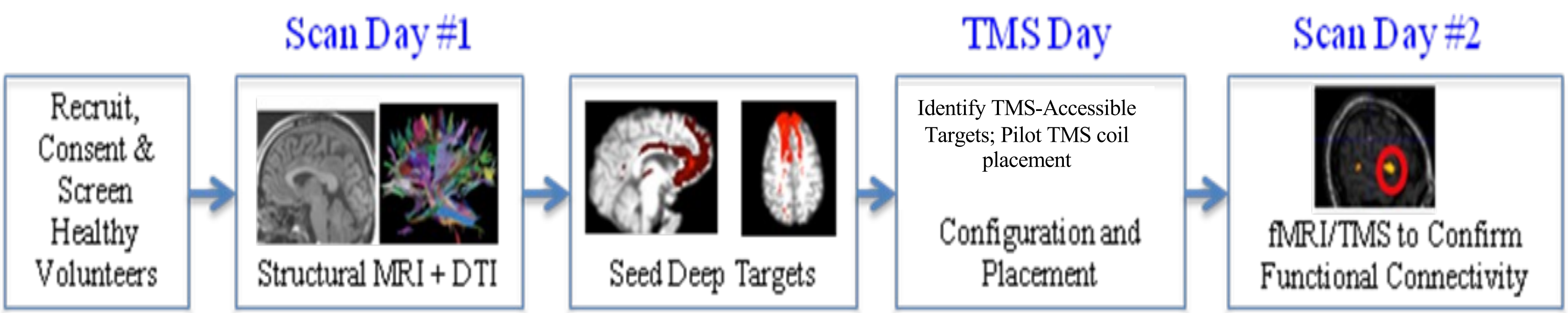
TMS to DLPFC during difficult conditions affects posterior activity

Feredoes et al., PNAS 2011 108: 17510-17515

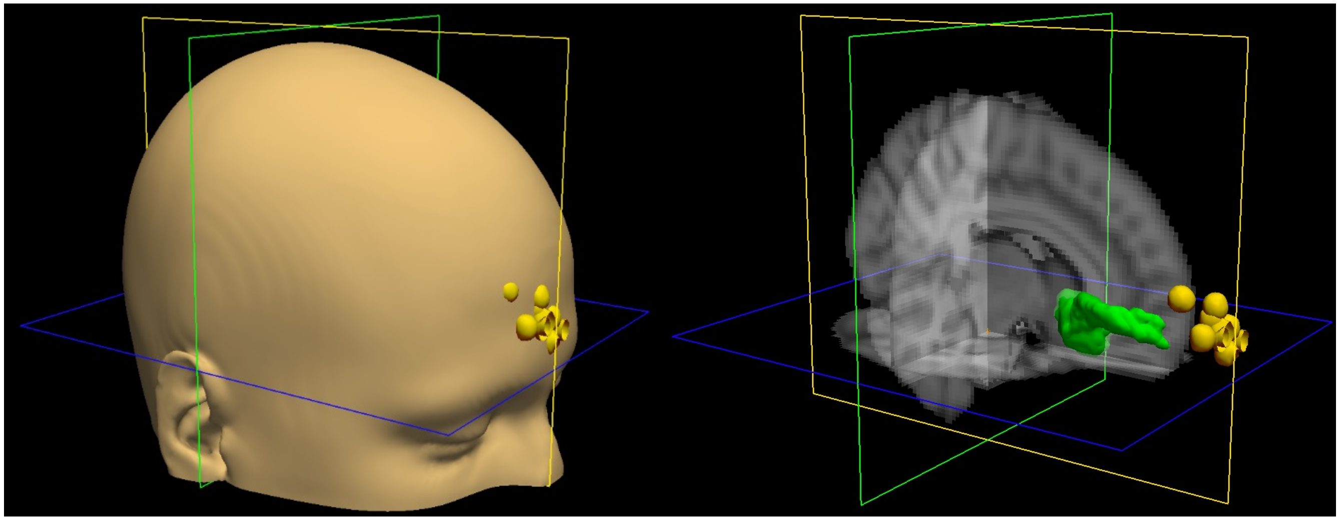
Overcoming depth limitation of TMS: Noninvasive Focal Deep Brain Stimulation

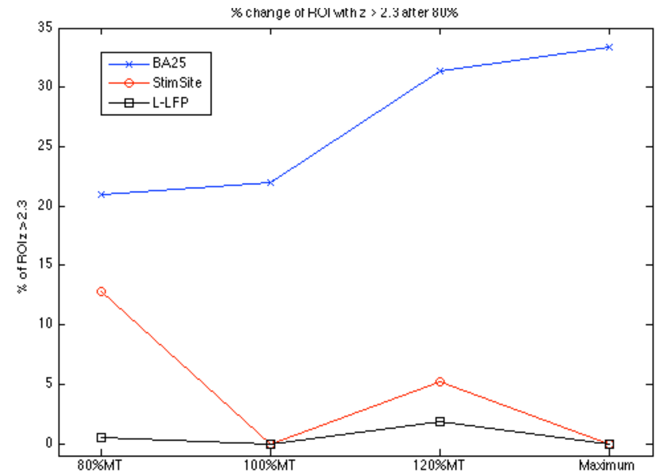


BA25 of interest as a target of stimulation in depression- but too deep to effectively reach with TMS



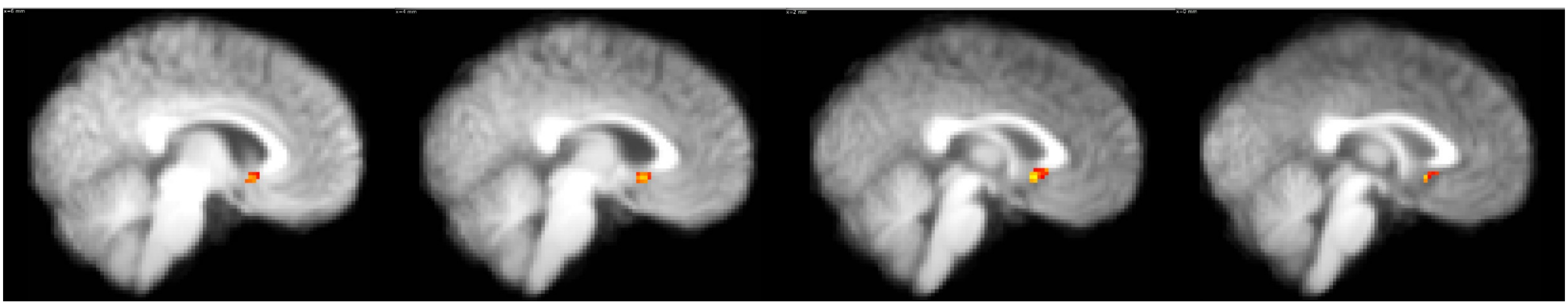
Noninvasive deep brain stimulation paradigm: Results





Individualized targeting **N=10**

Activation (% ROI w z>2.3) increased with TMS dosage

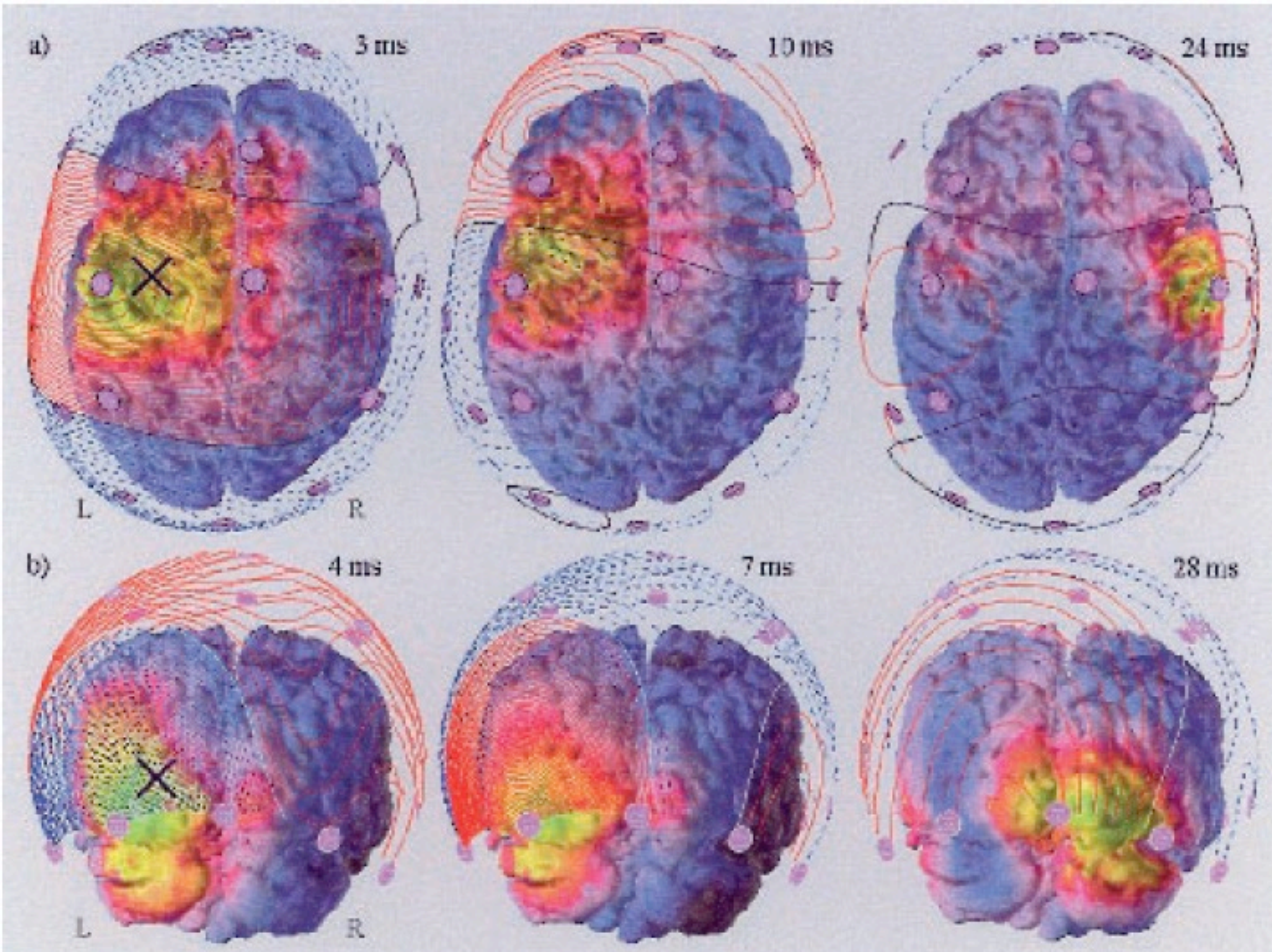


120% MT – 80% MT contrast; significant cluster (z>2.3, p<.05) in BA25 seed region

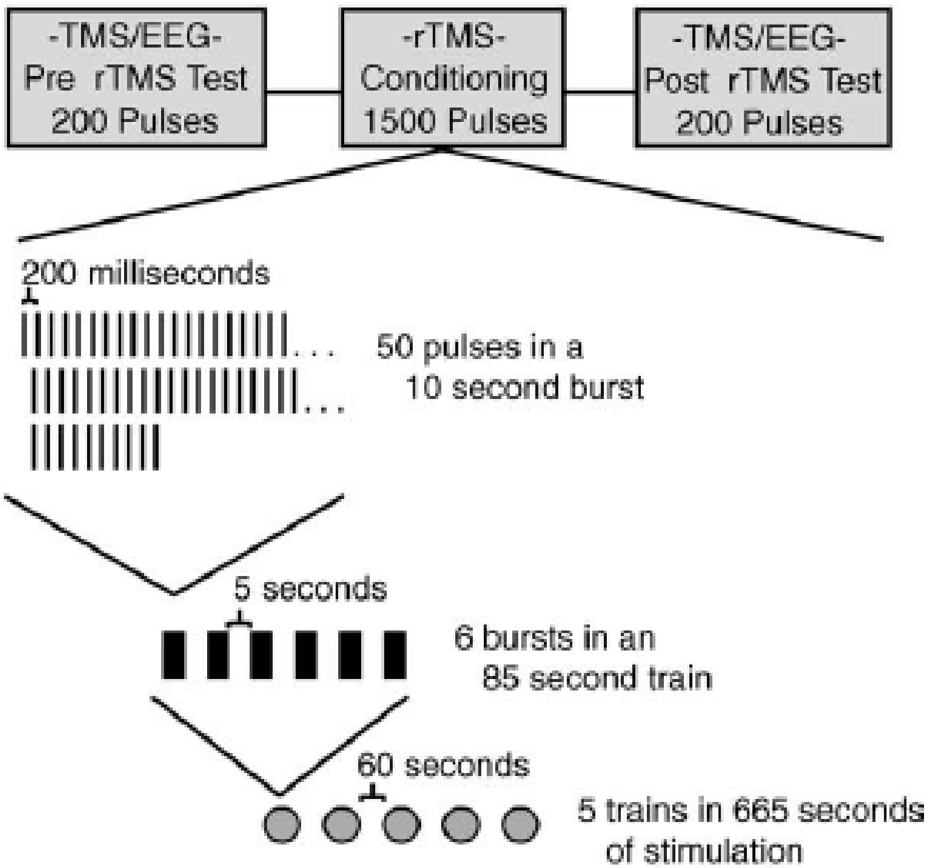
Exploring the spatio-temporal dynamics of brain networks with simultaneous TMS-EEG

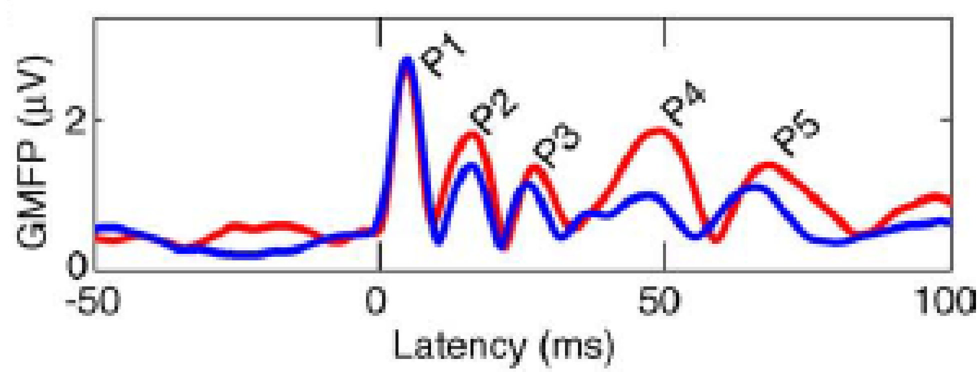
-Changes in topographic EEG activity due to TMS pulses

Illmoniemi et al., 1997



Observing LTP-like effects using simultaneous TMS/EEG





5 Hz conditioning rTMS results in enhanced amplitudes of TMS evoked potentials (TEPs)

Global averaged EEG power across 64 electrodes

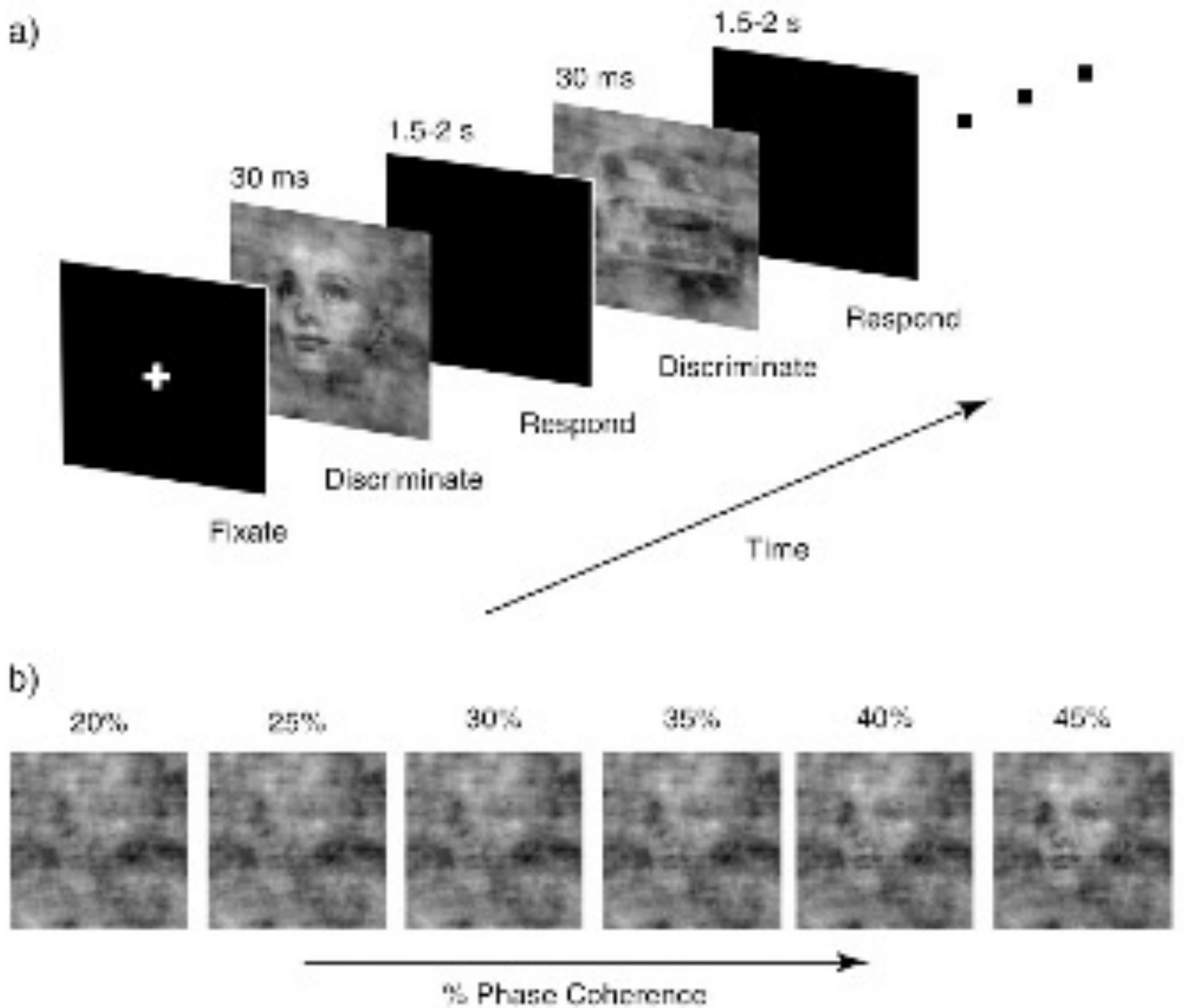
Esser et al., 2006 Brain Res Bull 69: 86-94

Summary: State of the art and the future

- The science and technology of TMS spatial parameters have become well-developed, in the sense that we can deliver a specific dose with precision
  - Neuronavigation, TMS/fMRI, TMS/EEG, robotic coil positioning, realistic head modeling
- But what happens next- the interaction of the TMS with the brain (the temporal parameters)- is less well-understood
  - TMS waveform <-> membrane time constants
  - TMS frequency <-> endogenous oscillations
  - Train duration and ITI <-> LTP and plasticity
  - Repeated TMS sessions <-> long term network changes
- We can aim, and we know we cause changes- but we are just learning how to direct the changes

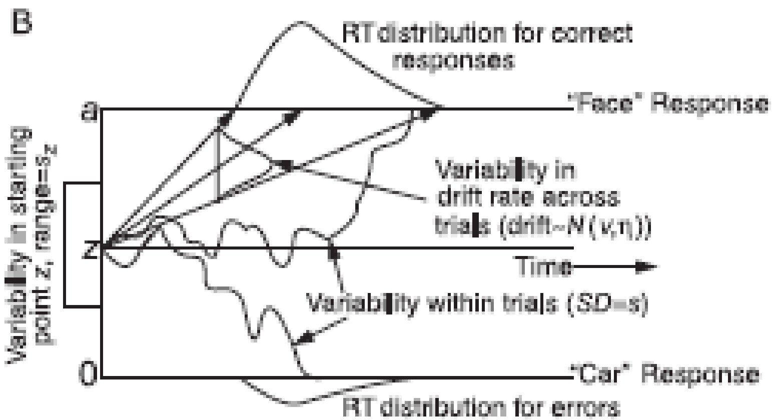
Visual discrimination 2AFC task used:

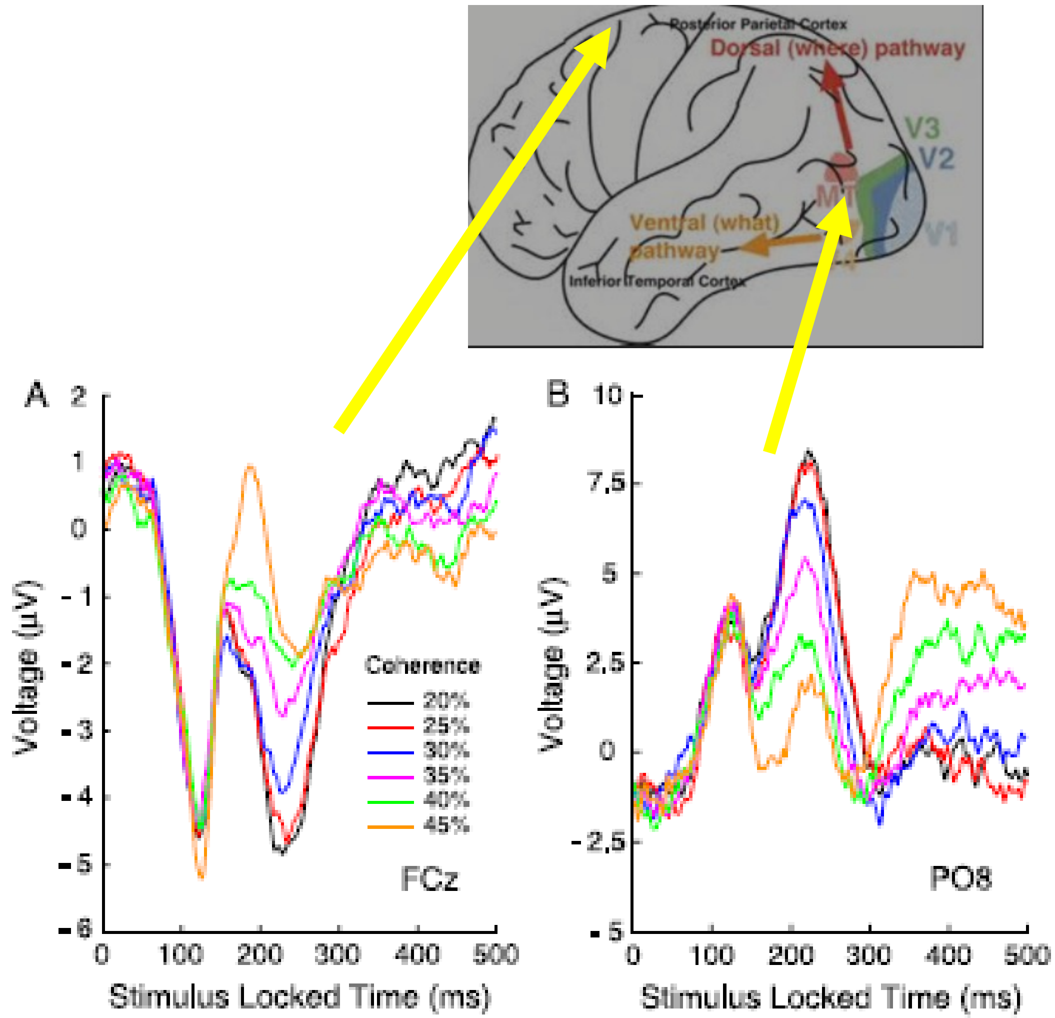
Adaptive staircasing (adding and subtracting visual noise) for accuracy in determining cars vs. faces



Psychophysics and electrophysiology determined a critical decision period

The duration of this period depended on coherence level





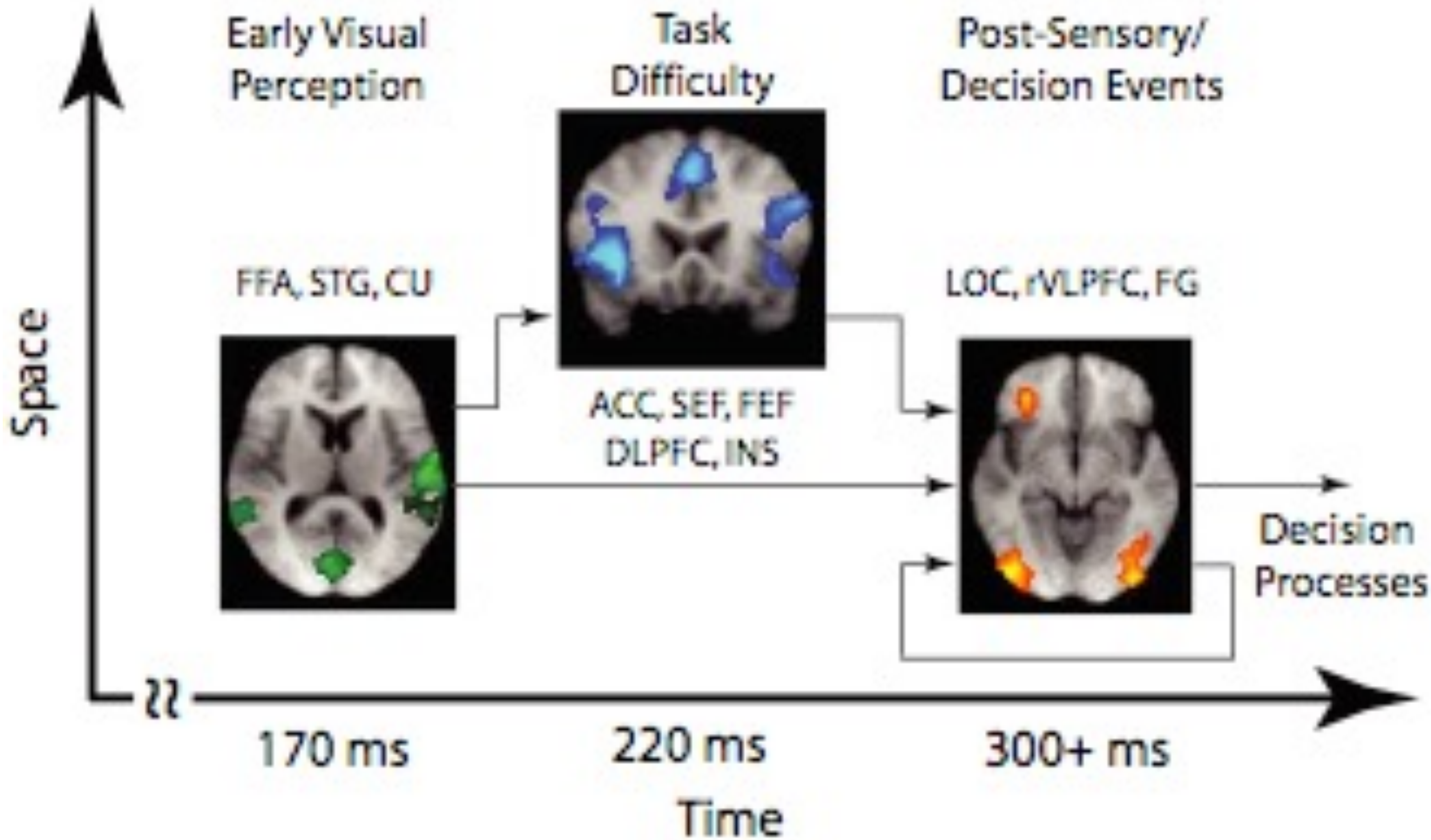
Three components were found:
-The 1st (~100 ms) did not depend on difficulty; the 2nd & 3rd did
-The 3rd (after 300 ms) was analyzed with diffusion/random walk modeling (above)
-the peak of the 3rd increased with difficulty

FCz **PO 8**

Philiastides, Ratcliff & Sajda, J. Neuroscience, 2006; Philiastides et al., Cerebral Cortex, 2006

Brain substrate involved in visual discrimination:

Spatiotemporal diagram of the processes involved in perceptual decision making.



Philiastides and Sajda, J. Neuroscience, 2007

Visual discrimination TMS experiment:

Apply to LOC to test whether can disrupt/slow down decision process

Session 1:	Session 2:	Session 3:	Session 4:
Task training and accuracy staircase	Structural MRI	TMS to left or right LOC	TMS to left or right LOC

Session 1 → Session 2 → Session 3 → Session 4

-13 Ss (5 female); -TMS intensity = 100% motor threshold

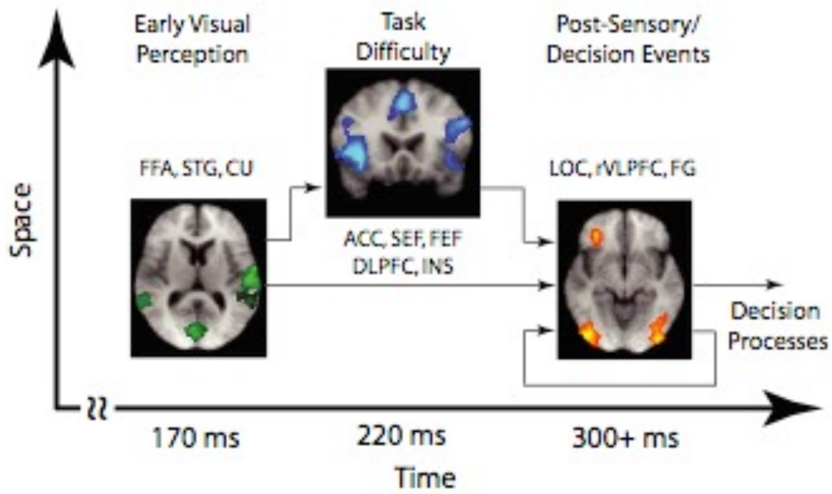
-Task run at coherence levels for cars and faces that produced 78% accuracy levels during simultaneous staircasing

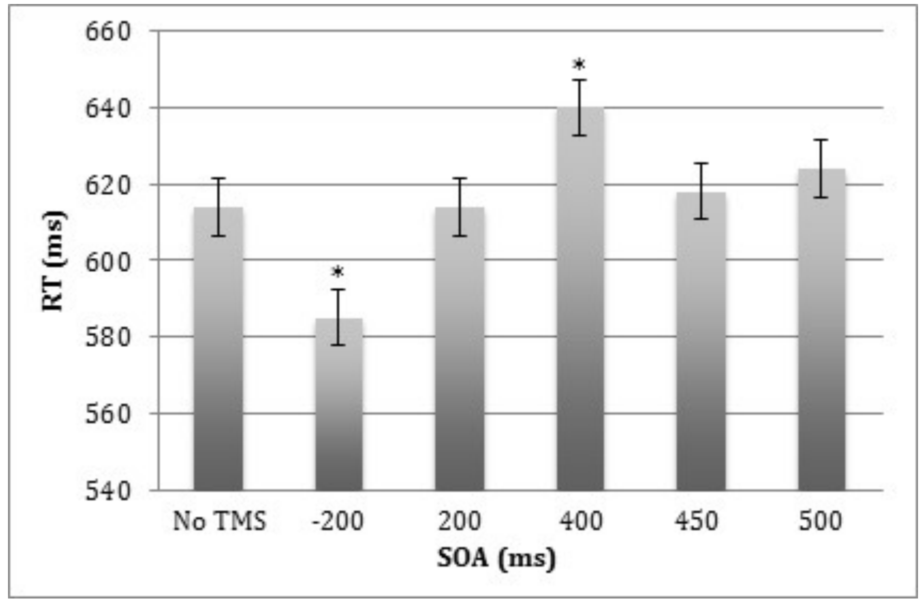
-TMS: paired pulses, 50 ms apart, beginning at -200, 200, 400, 450 or 500 ms SOAs from stimulus onset, pseudo-randomly chosen for each trial: 163 trials for each SOA condition (+ another 163 trials with no TMS)

-Paired pulse TMS applied to LOC has been shown to disrupt visual processing Ellison & Cowey, 2007; Mullin & Steeves, 2011; Pitcher et al., 2007; 2008; 2012

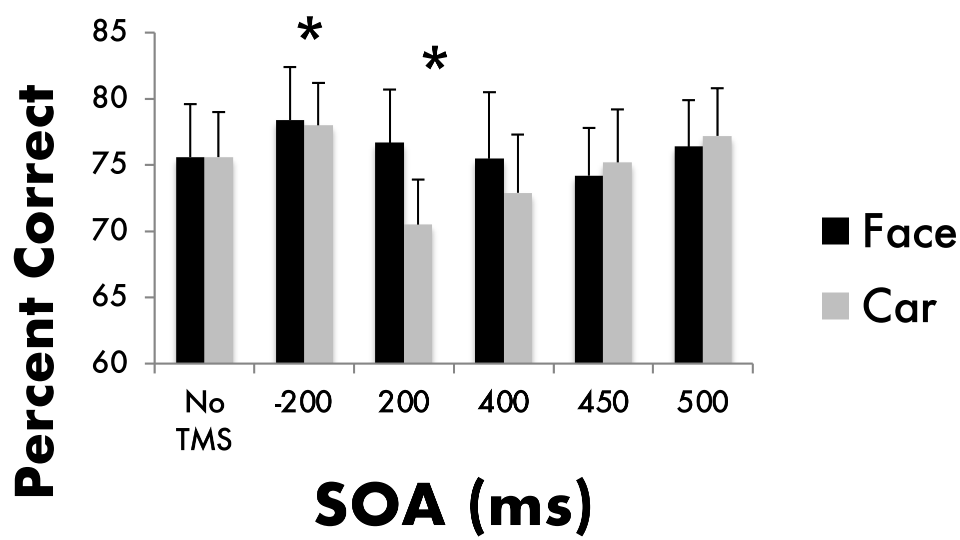
-Notably, these were done with easily discriminable stimuli and TMS effects were seen quite early

Visual Discrimination Experiment: Results



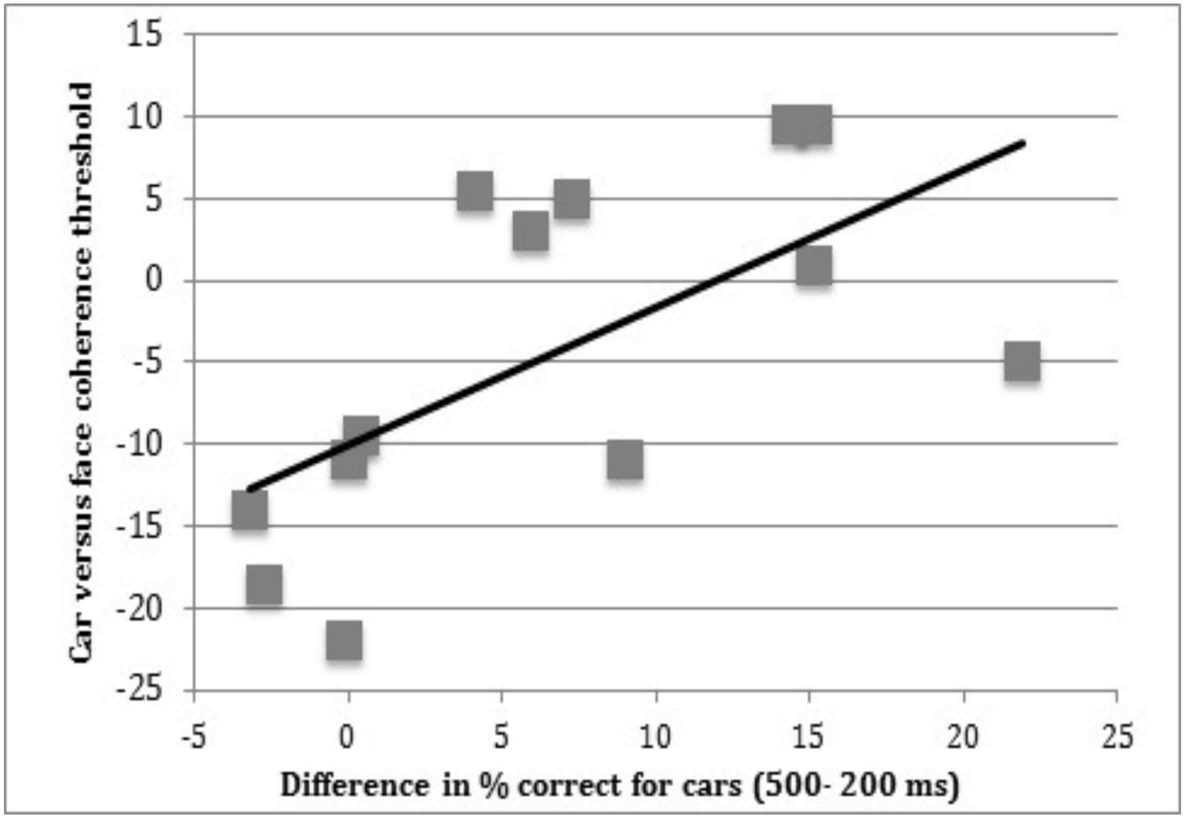


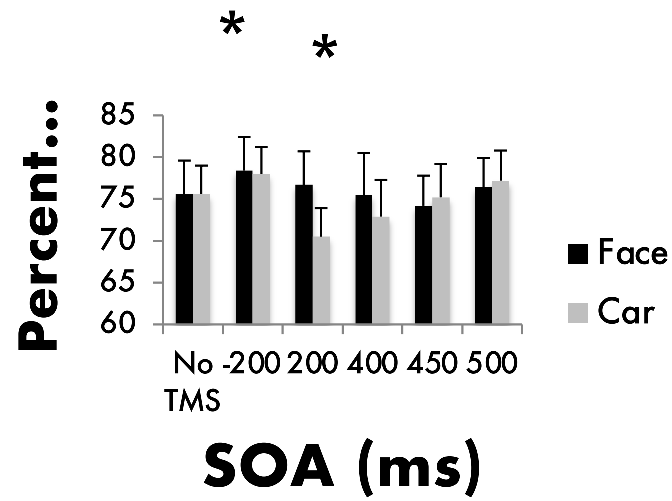
TMS to LOC (right and left) interfered with task processing: slower RT at 400 ms (slowed decision making); decreased accuracy for car discrimination at 200 ms

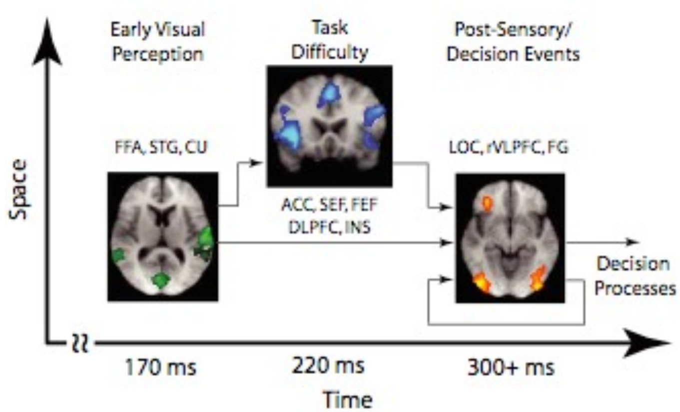


Unexpected: increased accuracy and speed at -200

Individuals who discriminated cars best (relative to faces) were most affected by TMS at 200 ms.



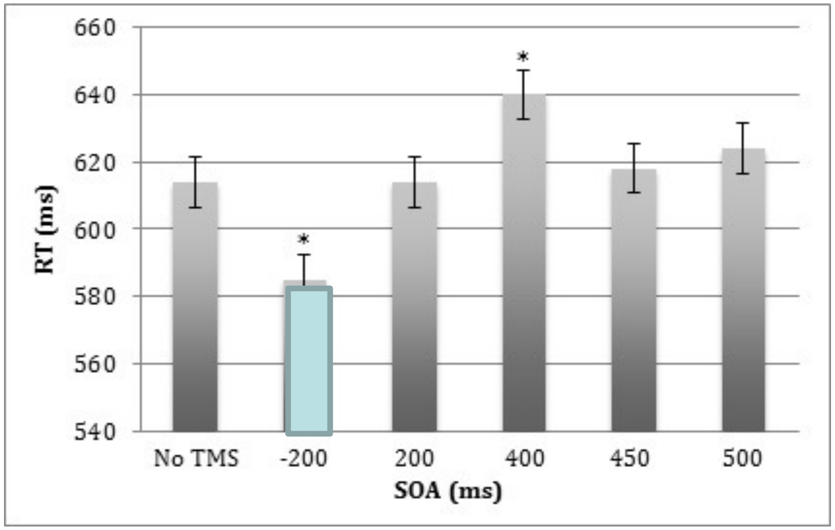


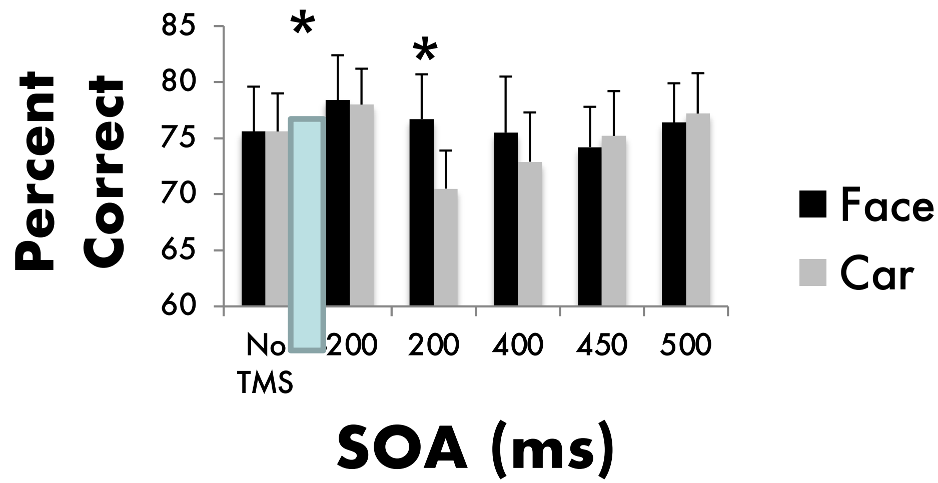


Qualitatively different than 400 ms effect

The second network is thought to provide top-down control to aid processing when the discrimination becomes difficult.

Performance enhancement with -200 ms stimulation

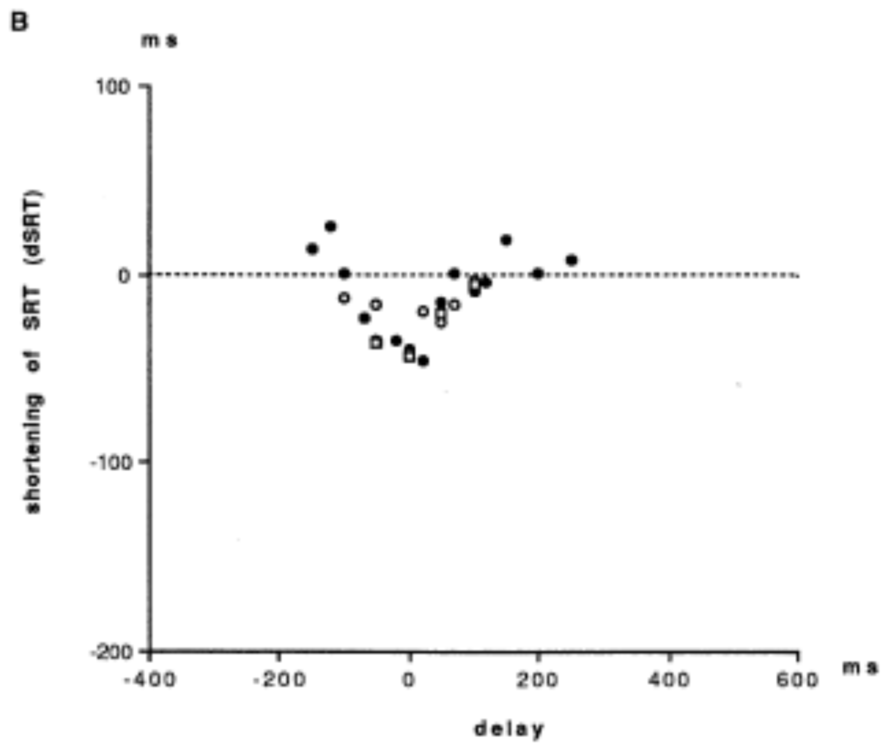




<u>Intersensory facilitation</u> caused by subthreshold TMS

In 8 subjects, simple RT to light flashes with TMS pulses applied at various times relative to the flash

TMS near (-100-100 ms) the flash enhanced performance



Terao et al., 1997

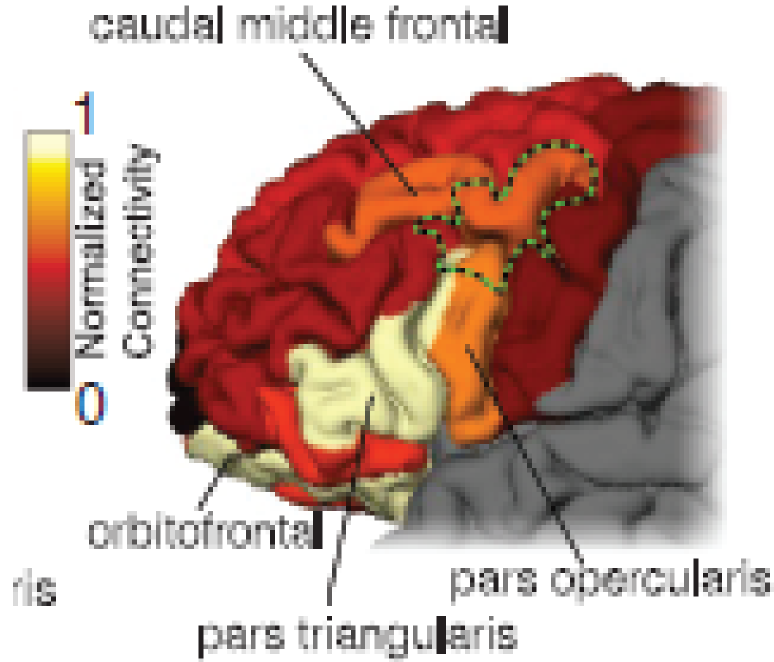
Performance enhancement can be planned

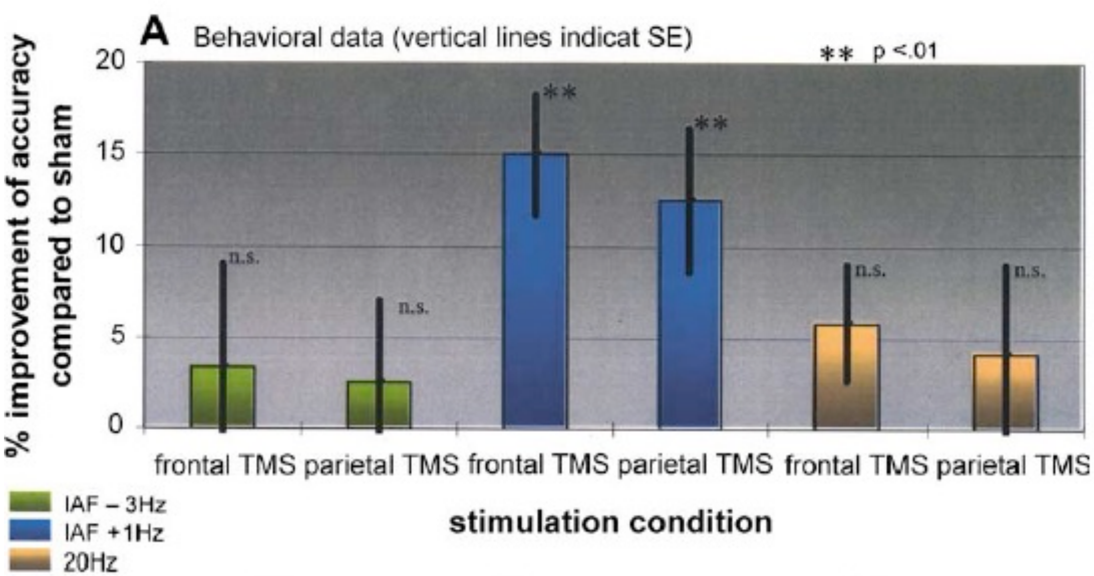
- The visual discrimination experiment resulted in an unplanned and “paradoxical” performance enhancement effect
- In recent years, 3 categories of TMS performance enhancement have been identified (Luber & Lisanby, Neuroimage, 2014):
  - Artifactual
  - Addition by subtraction
  - Direct engagement of functional networks
    - Stochastic resonance
    - Post-tetanic facilitation (an increase in excitatory post-synaptic potentials due to trains of electrical stimulation found in animal studies (Iriki et al., 1989)
    - Interactions with endogenous oscillatory activity of networks

Planned engagement of network processing involved in visual search

- The inferior frontal junction (IFJ) has been implicated in top-down processing during visual search (Baldauf and Desimone, 2014)
  - In analogy to FEF control over spatial attention, Desimone has suggested that IFJ exerts top-down control in cases of non-spatial attention

- Take advantage of endogenous oscillatory activity



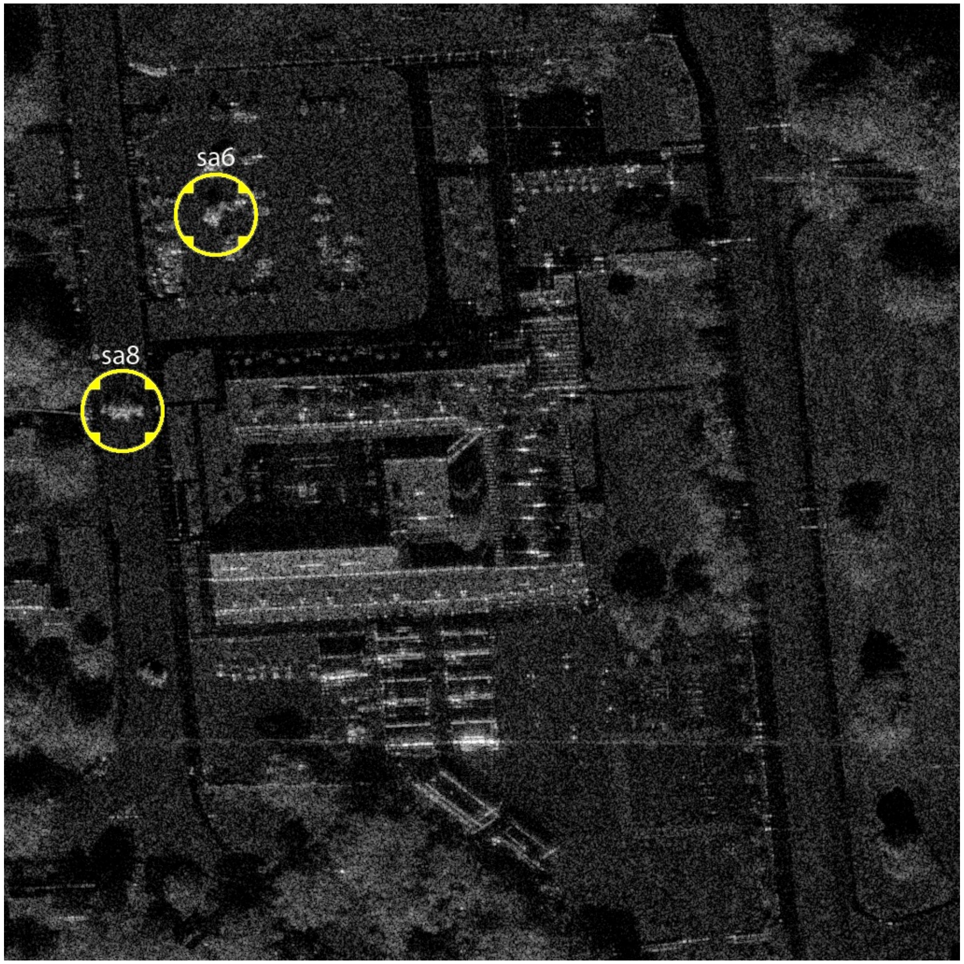


A 2 s burst at peak alpha frequency (but not peak-3Hz or 20 Hz) immediately prior to trial increased accuracy of mental rotation

Klimesch et al., 2003

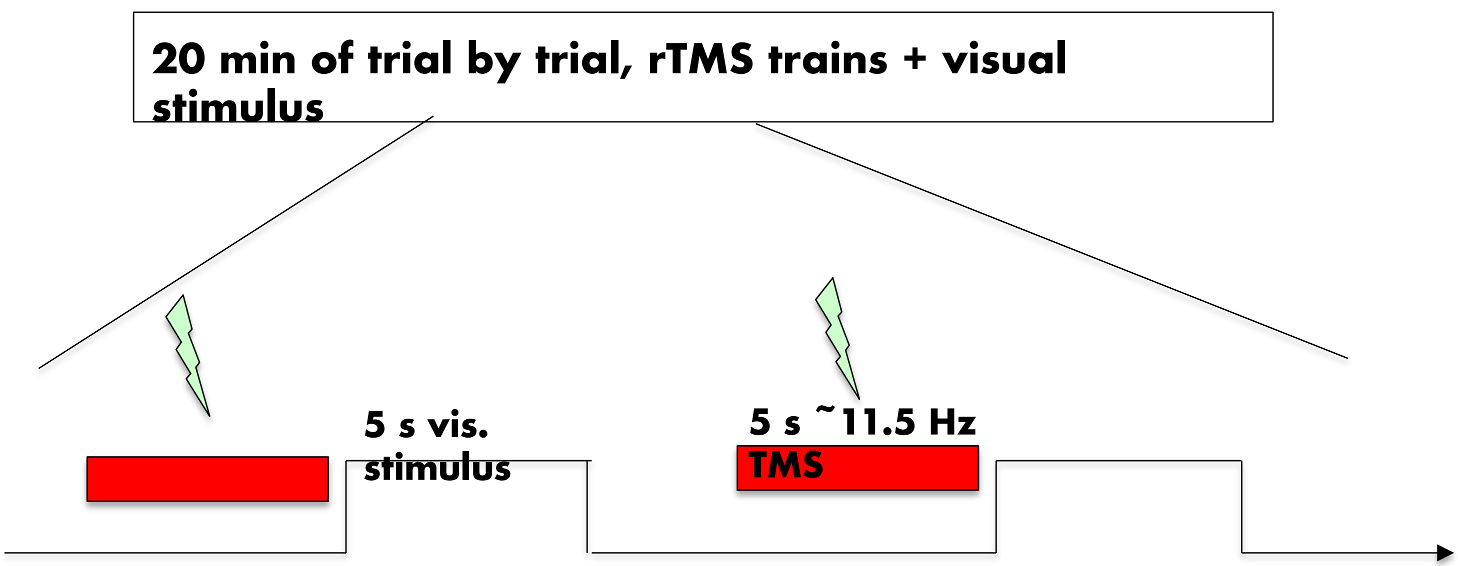
To involve IFJ, we thought to use a very difficult target object recognition in our visual search task

- Most visual search tasks studies use simple, highly over-learned items (such as letters and numbers).
- We tried a more ecologically-valid set of targets within Simulated Aerial Reconnaissance images



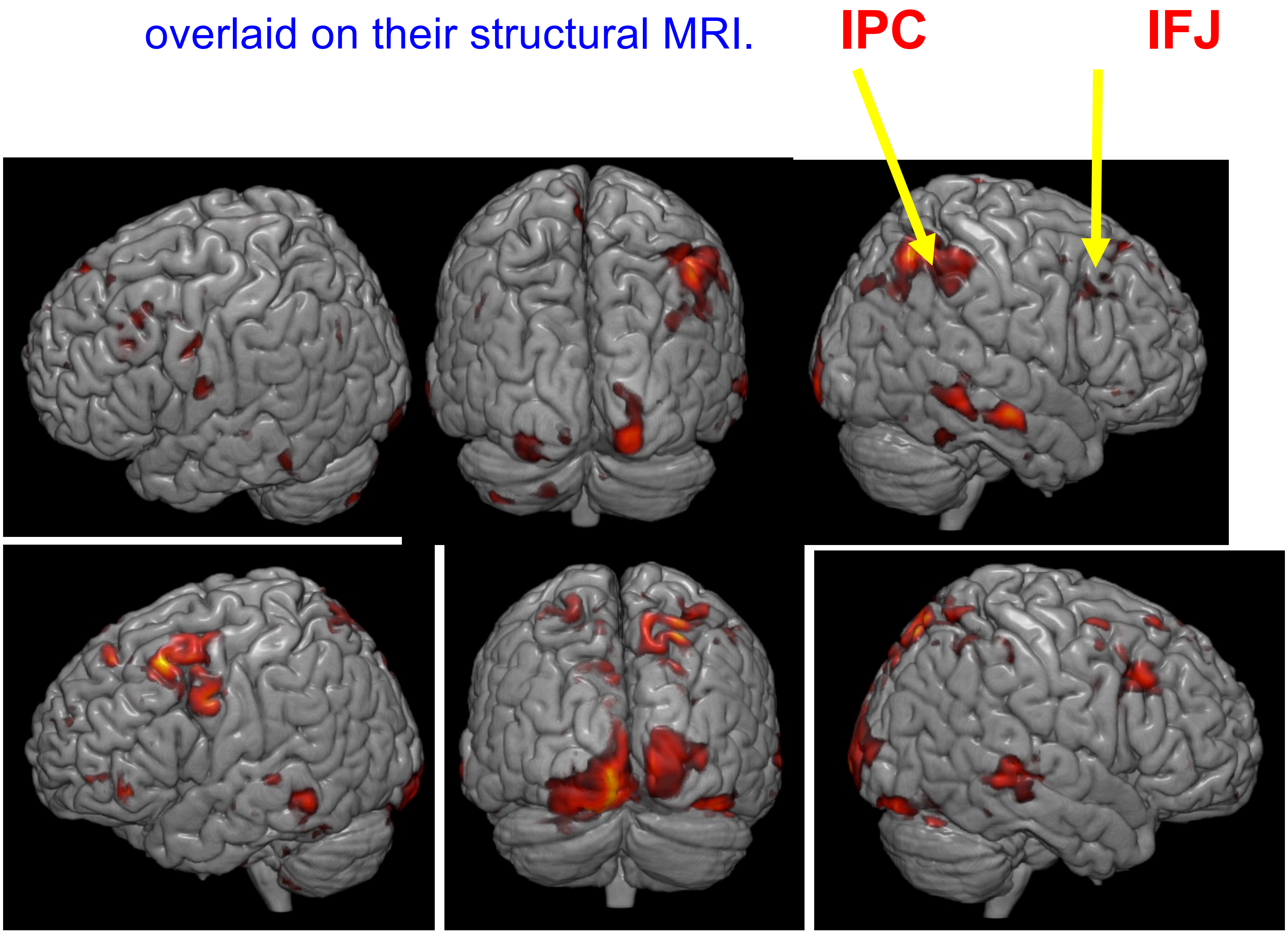
Visual Search Experiment: Design

- In a within subjects design, after an MRI session to obtain structural and fMRI scans, 2 TMS sessions were run
- In a session, subjects were given **active and sham** rTMS at their individual peak alpha frequency (IAF, mean 11.5 Hz)
  - applied either to **right IFJ** or right inferior parietal cortex (**IPC**).



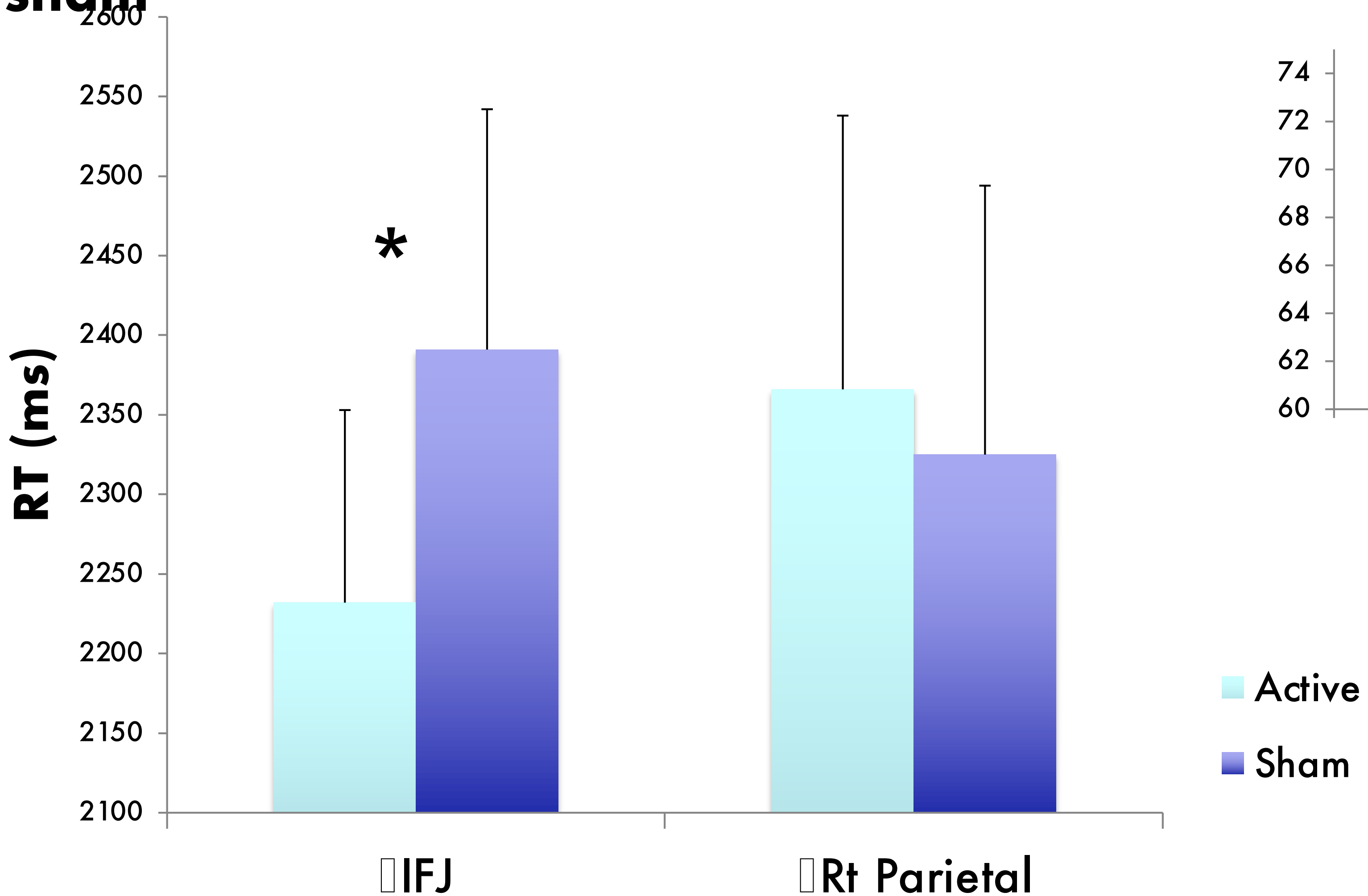
TMS Targeting:

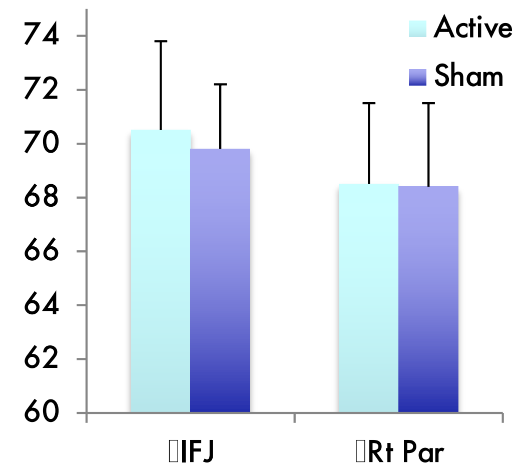
IFJ or IPC were defined individually by selecting the voxel showing the maximal fMRI activation during the visual search task. The TMS coil placement was guided with neuronavigation using the subject's fMRI image overlaid on their structural MRI.



Results: **Active IAF stimulation to IFJ resulted in significant speeding of reaction time (RT) compared to sham**

N=13





Accuracy

-At IFJ, a significant 160 ms decrease in mean RT for active compared to sham IAF rTMS

*** p < .015**

-The site-specific enhancement of performance provides direct evidence for the involvement of IFJ in guiding visual search

Functional targeting: An additional tool to engage and modulate networks

- The most common approach has been: apply TMS to the brain, and see what happens
- But this leaves a huge source of variability: the TMS pulse interacts with whatever activity is ongoing at the target
- But active contraction and imagery experiments in motor cortex show that controlling **the state of the brain** may be more effective
- Further, activating the neurons in the target that are of interest gives them an edge for firing
- Repeated pairings of local functional activity and TMS pulses may create a cumulative synaptic change along Hebbian lines
- This suggests the more active approach of **functional targeting**: simultaneous activation of a network with NIBS and behavioral performance

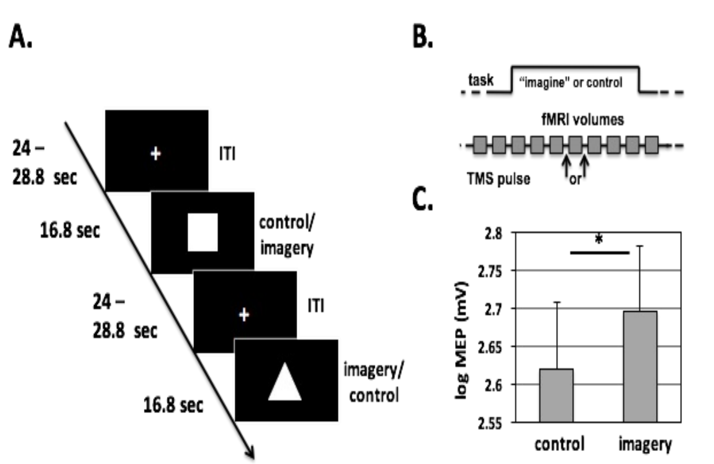
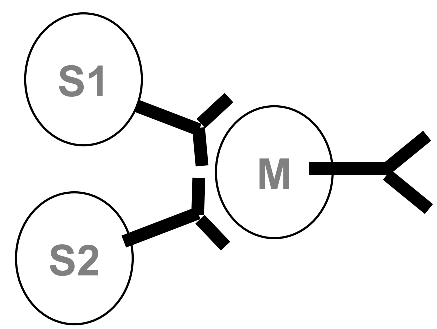


Figure 1. *A.* Experimental design: blocks of 16.8 seconds of motor imagery or control alternate (pseudo-random order) with inter-trial intervals (ITIs) of 24 – 28.8 sec (jittered). *B.* During each block, participants receive a supra- or sub- threshold TMS pulse to the motor cortex. Pulses are delivered within 400 ms gaps inserted between 2000 ms volumes, 7400 ms or 9600 ms after the onset of the block. *C.* Mean log motor evoked potentials (MEPs) for control and imagery runs. *p = 0.037, one tailed

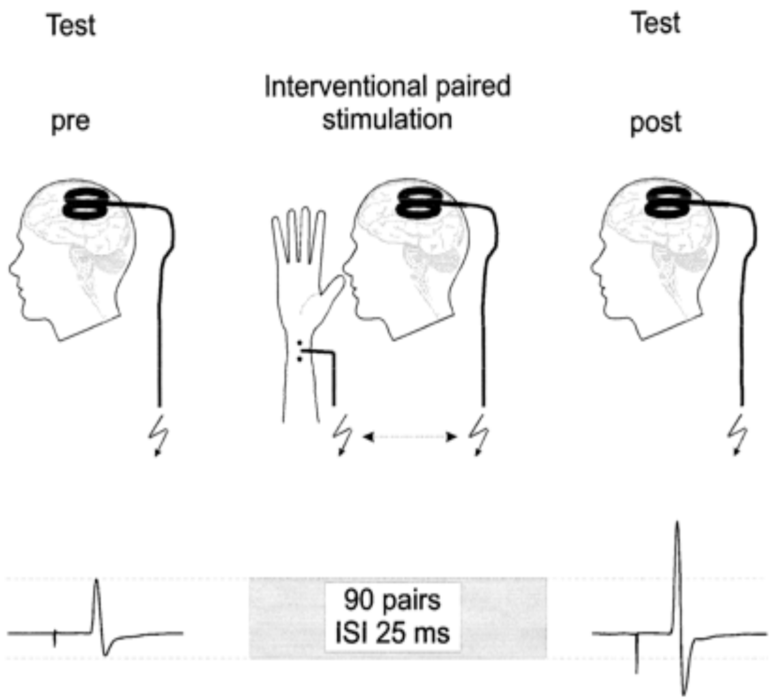


Synaptic coincidence: Hebbian plasticity

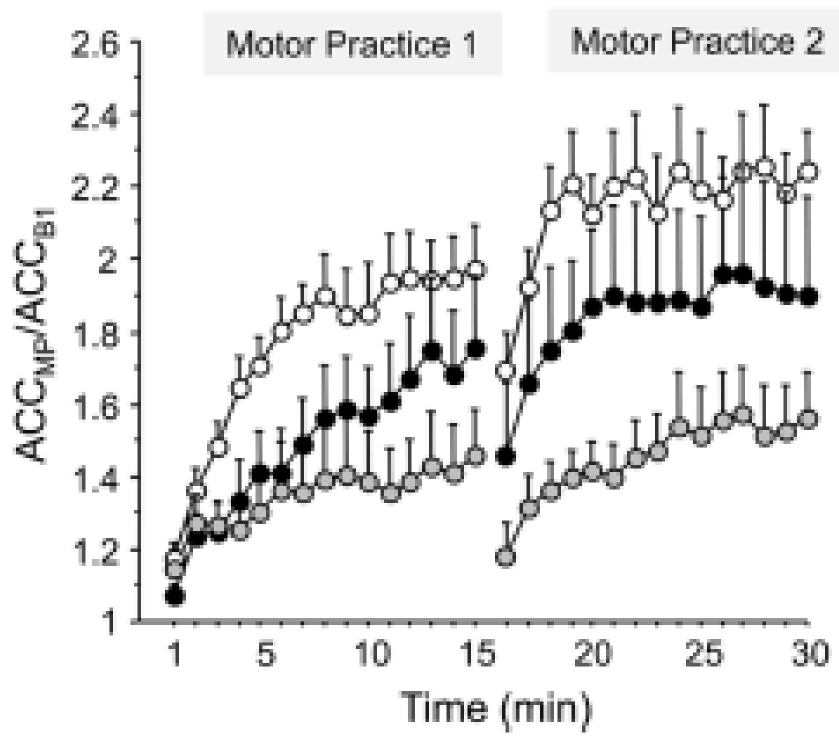
Most elementary form of functional targeting: Paired Associate Stimulation (PAS)

Long-lasting enhancements: creating LTP/LTD-like plasticity effects

Paired Associated Stimulation (PAS)



Stefan et al. 2000; Ridding et al. 2001



LTP PAS
(N20+2ms)

Control PAS
(N20+100 ms)

LDP PAS
(N20-5ms)

PAS stimulation increases effectiveness (accuracy in a motor task), in a cumulative way

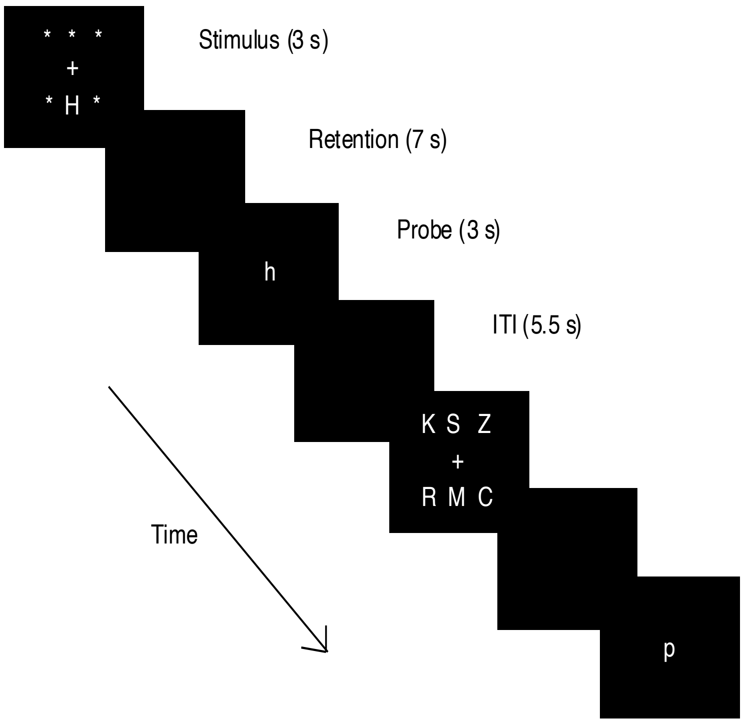
Ziemann 2009 J Neurosci 29: 5597-5604

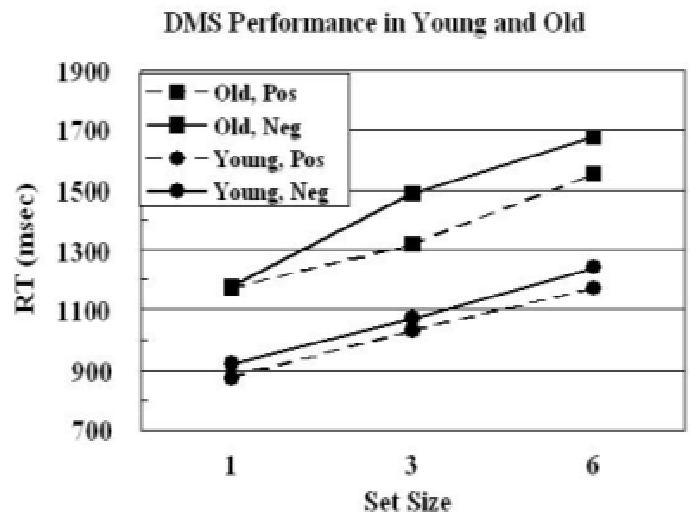
Generalizing PAS:
CPAS: Cognitive paired associate stimulation

Using CPAS in treating cognitive deficits:

- - a multi-modal approach to stimulation: concurrent TMS and task performance to enhance plasticity changes in targeted functions
- - repeated sessions to create a cumulative effect in those plasticity changes
- - requires an RDoC approach: link the treatment to a comprehensive model of the neurocircuitry underlying the cognitive deficit.

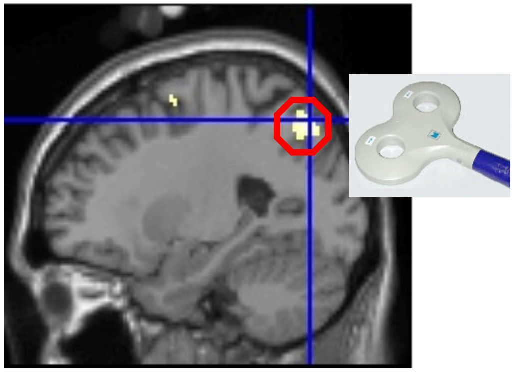
fMRI-guided rTMS paradigm: Working Memory (WM) Task





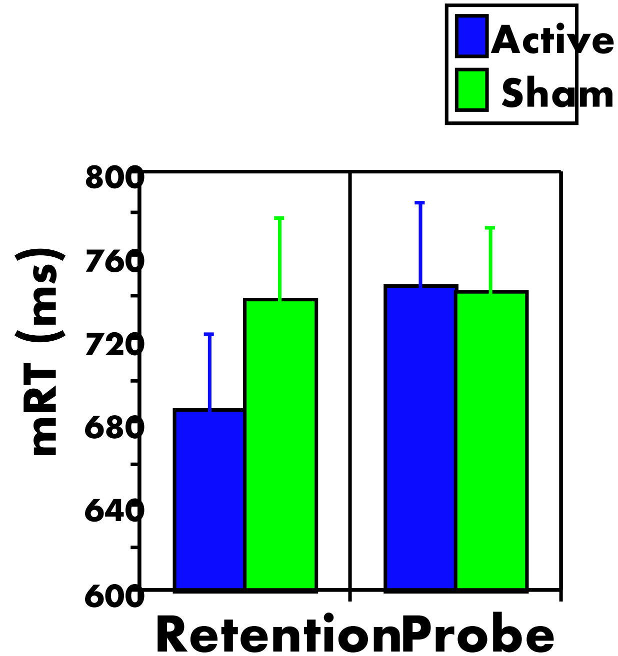
In collaboration with Yaakov Stern

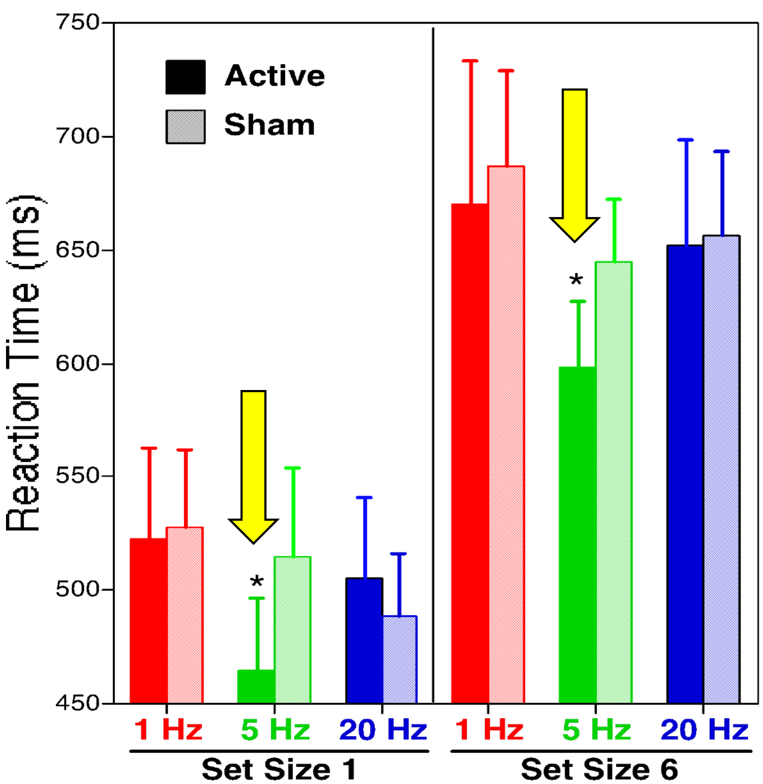
TMS enhancement of working memory



Site specific effect:
mParietal but not DLPFC

Frequency specific effect:
5 Hz rTMS during the retention phase reduced RT for set size 1 and 6 (p<0.01).

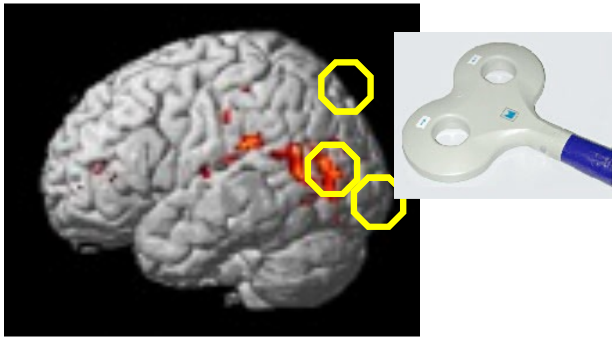


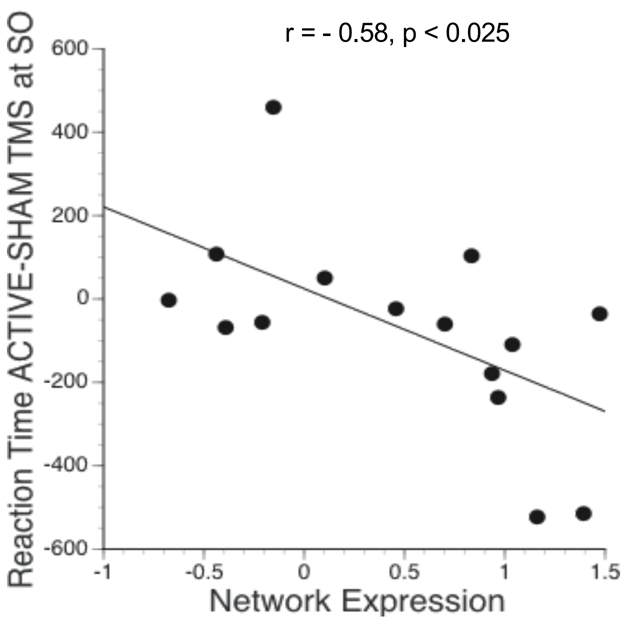


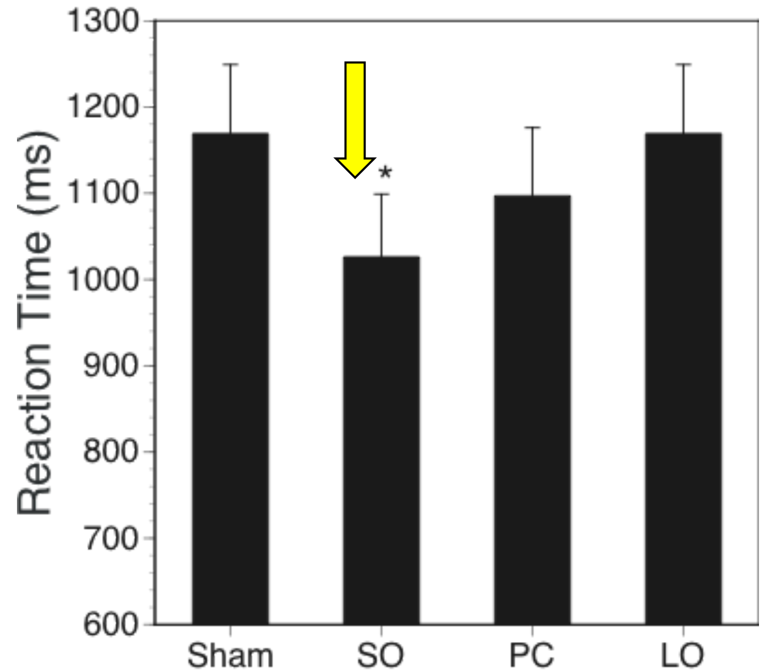
Task Phase specific effect:
With a new group (N=22), 5Hz to mPar reduced RT only during retention period

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

Acute fMRI-guided remediation of working memory deficits in sleep deprivation







Mapped network associated with resilience to sleep deprivation (N=15)

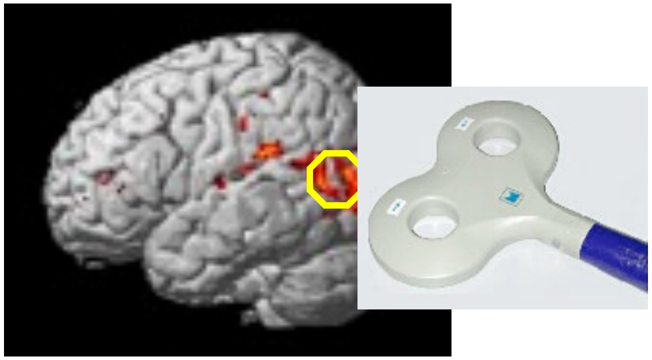
TMS to resilience targets during task

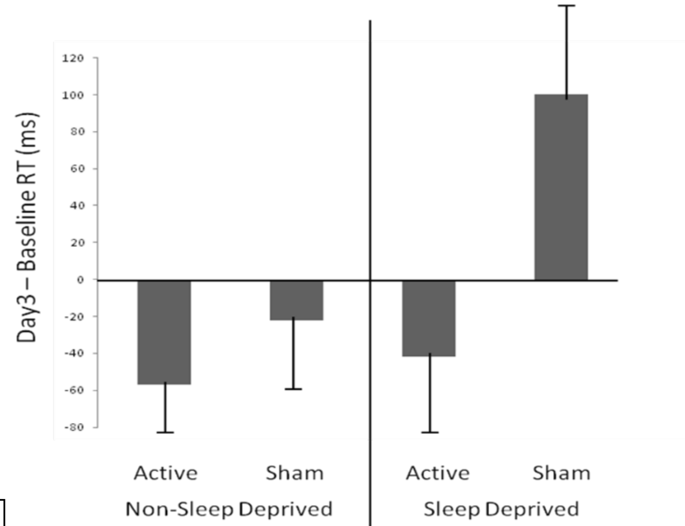
Site-specific enhancement found with TMS applied to lateral occipital cortex

Degree of improvement correlated with network expression

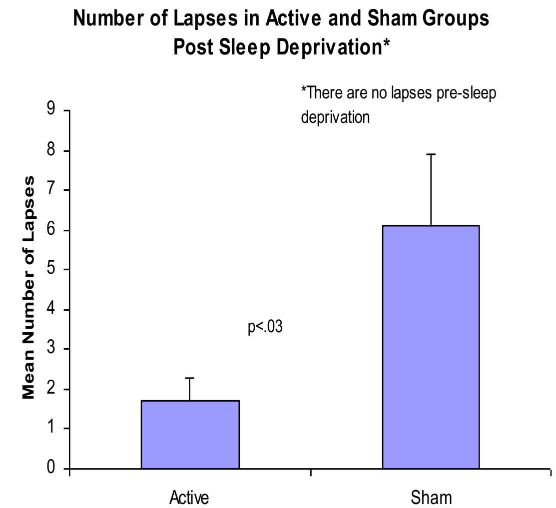
Luber et al. Cereb. Cortex 2008;18:2077-85

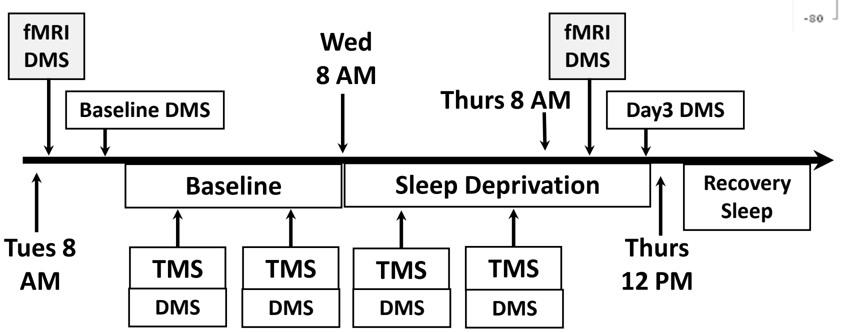
Prevention of memory deficit due to sleep deprivation





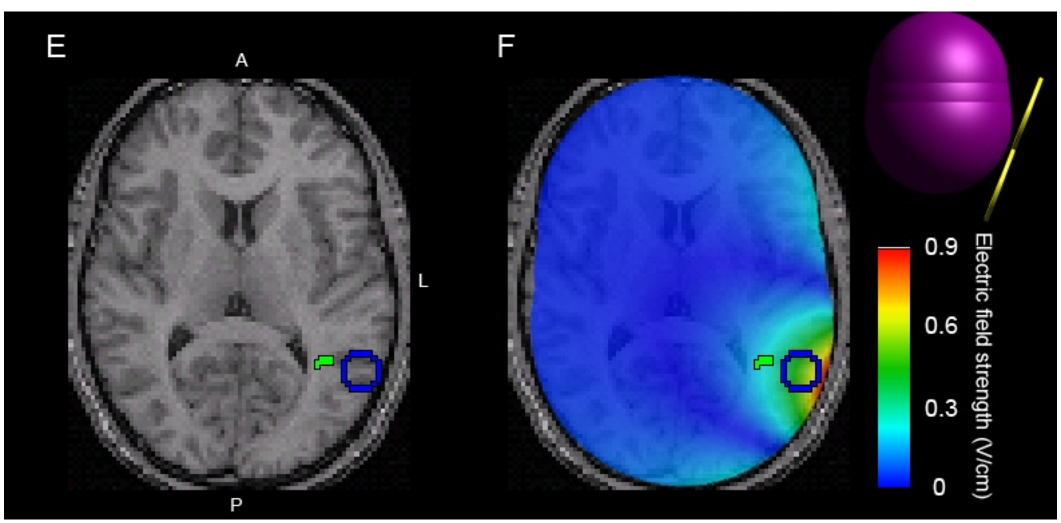
Post – Pre fMRI difference in RT between Active and Sham groups





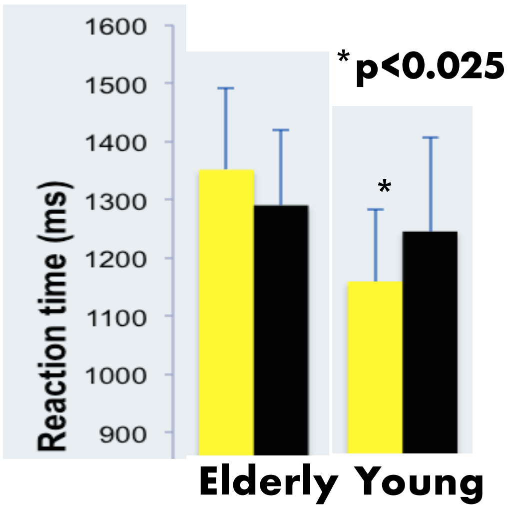
5 Hz <u>TMS+Task</u> to LOC (2/day x 2 days) Prevented slowing and memory lapses a full 18 hrs after the last TMS

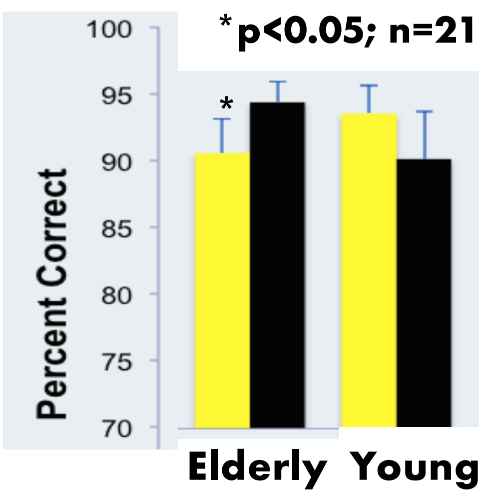
Change in fMRI network localized under TMS coil

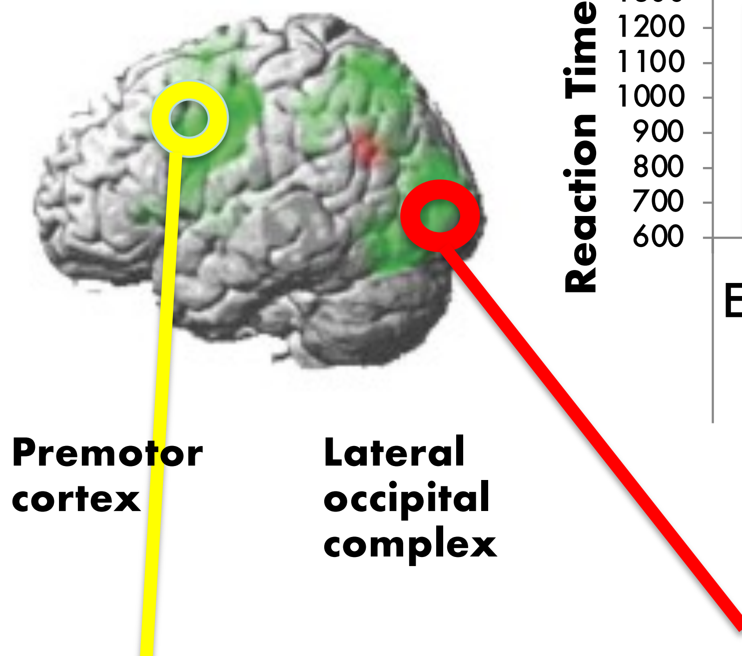


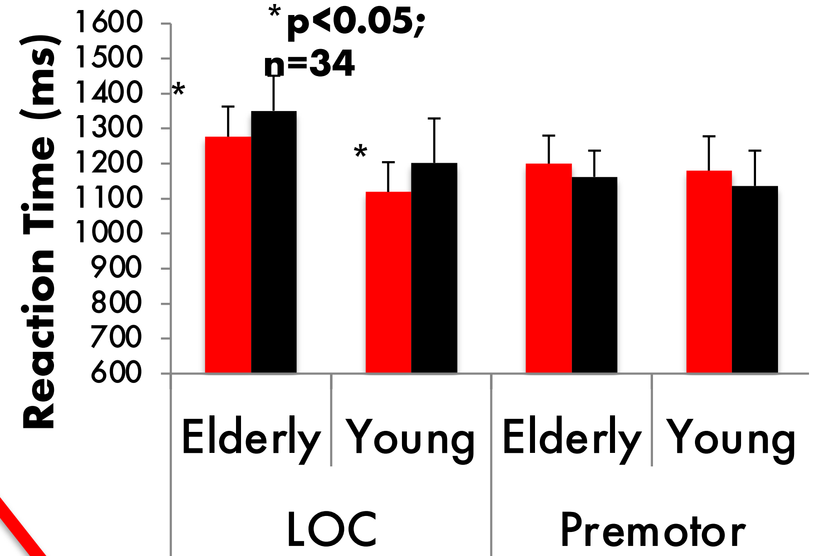
Luber et al Sleep 2013;36:857-71

TMS Remediation of Memory in Aging





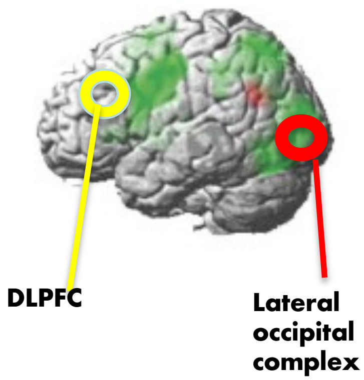




5Hz rTMS to PM before retention period improved RT and accuracy in

5Hz rTMS to LOC during retention period improved RT in both young group and

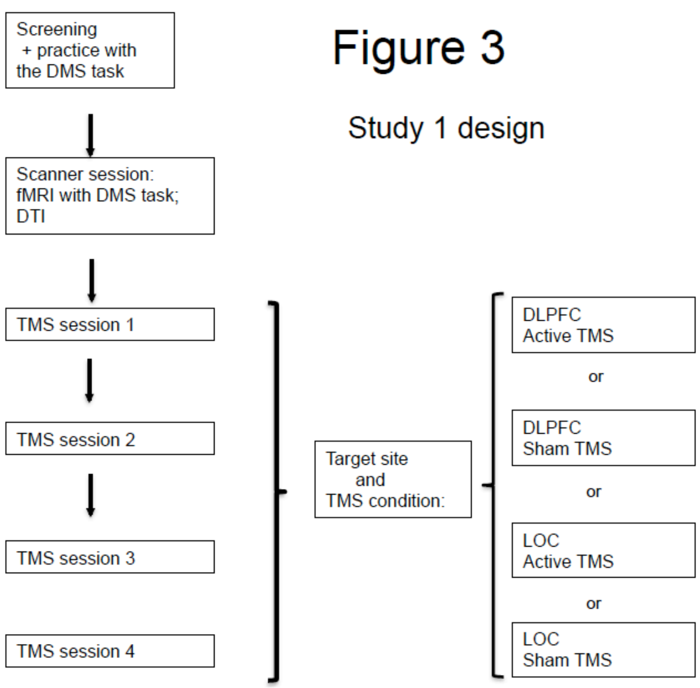
CPAS to generate long-lasting working memory improvements in older adults



Ongoing U01 from the NIA: In Older subjects:
-engage the working memory network from DLPFC using individualized fMRI guidance, functional targeting, and electric field modeling
-over 2 weeks of working memory training, attempt to prolong performance enhancement using our methods of cumulative enhancement: CPAS

Figure 3

Study 1 design



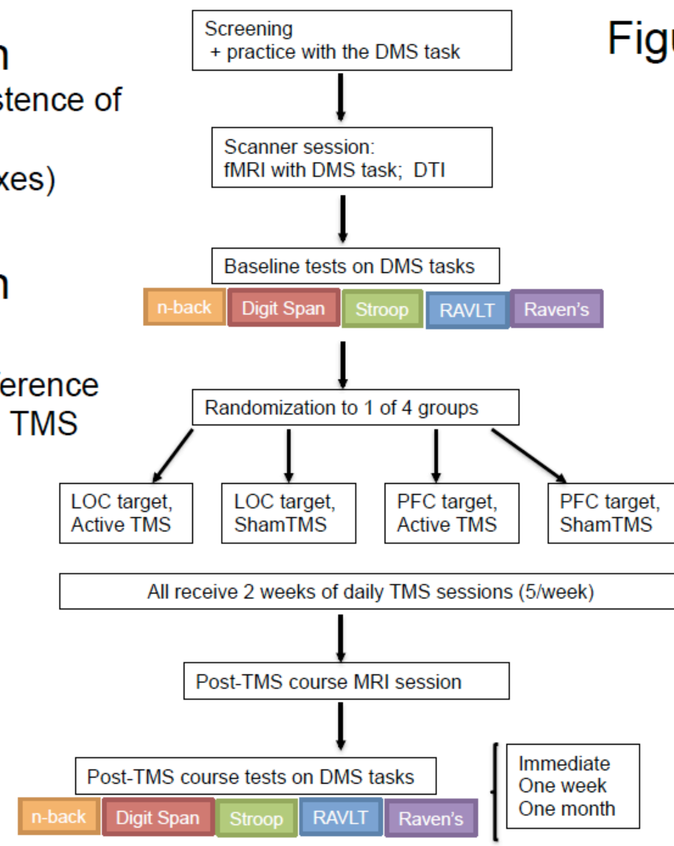
Study 2 design

To investigate persistence of enhancement (black-and-white boxes)

Study 3 design additions

To investigate transference of WM benefits from TMS (added near and far tasks in colored boxes)

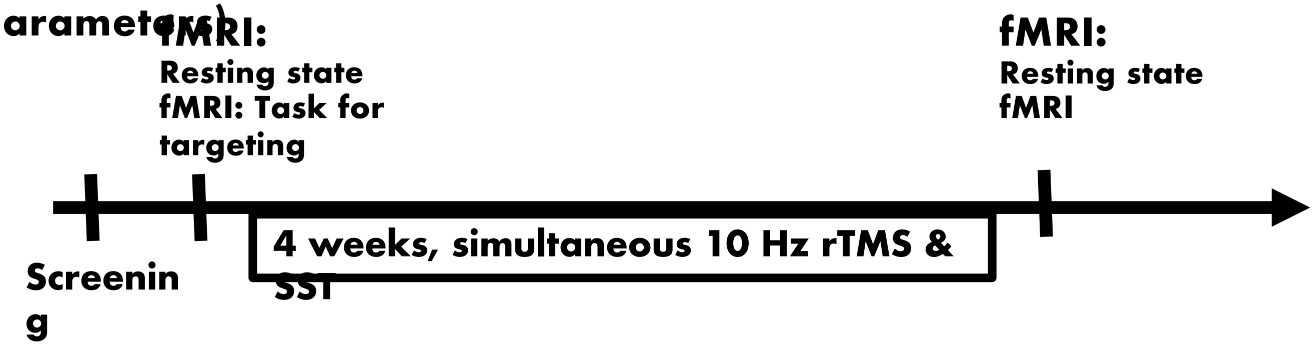
Figure 5



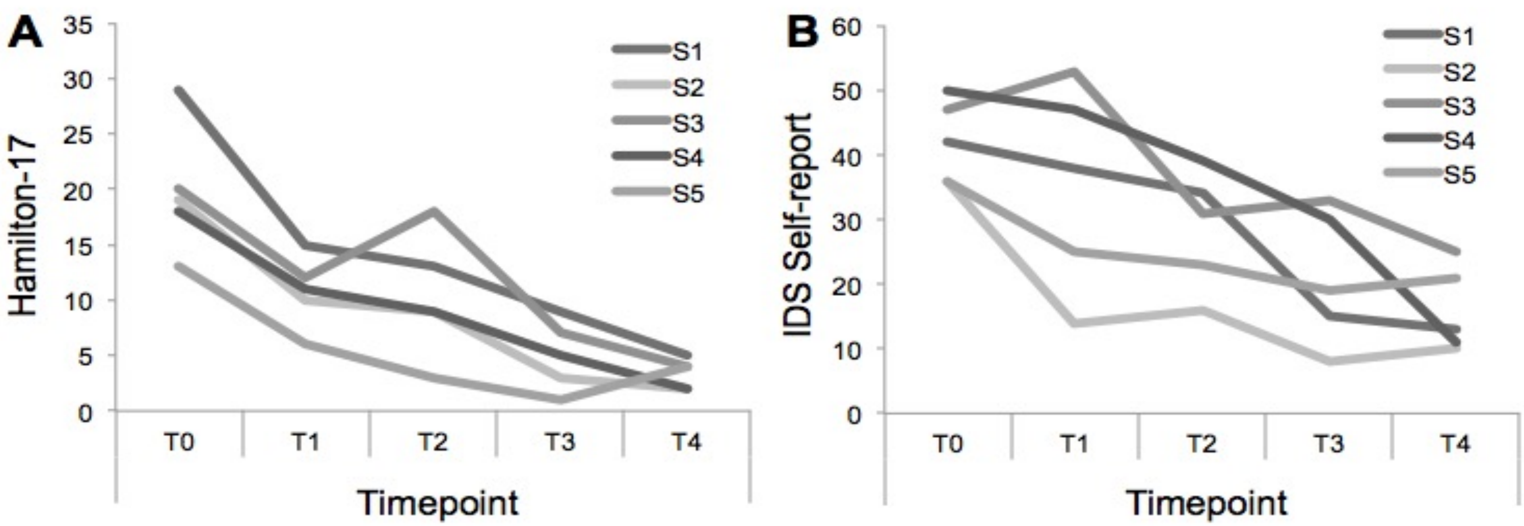
We tried the CPAS approach to depression out: Pilot experiment (open label, 5 TRD patients)

-individualized targeting: left PFC promotion region activated in fMRI by priming task

-plasticity component: simultaneous Self System Therapy (SST) with rTMS (standard parameters)



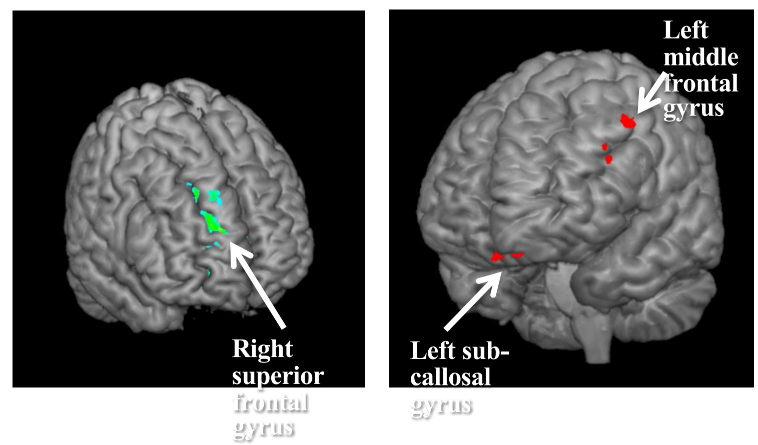
By 4 weeks, all 5 patients remitted:



Conclusions

- TMS as a field is maturing to the point where we can integrate stimulation with imaging, EEG, and computational modeling to efficiently engage and modulate target neural systems with the goal of producing long-lasting benefits
- We are already doing so in the areas of memory deficits in aging and more generally with cognitive deficits

- **CPAS approach to depression represents a neuroscience based use of the most recent developments in TMS, with the promise of individualized treatment for comorbid MDD and GAD**



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