TMS as a Tool for Neuroscience

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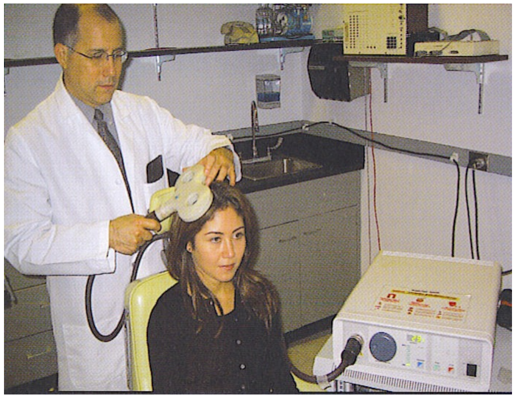
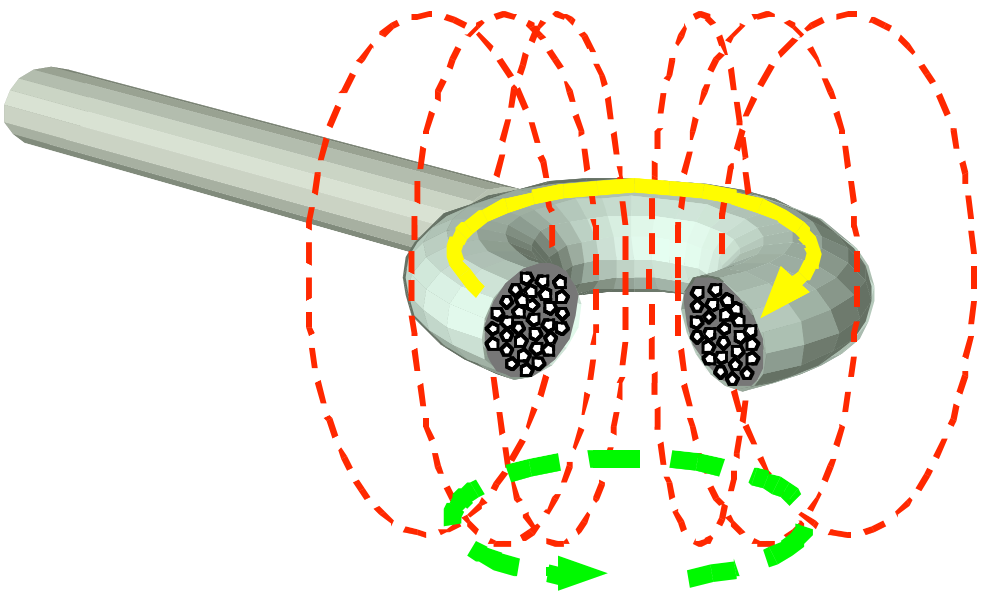
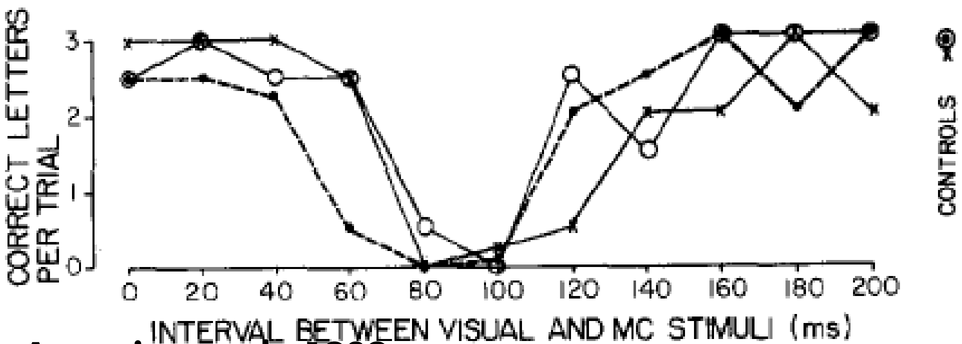


Non-invasive Brain Stimulation (NIBS)

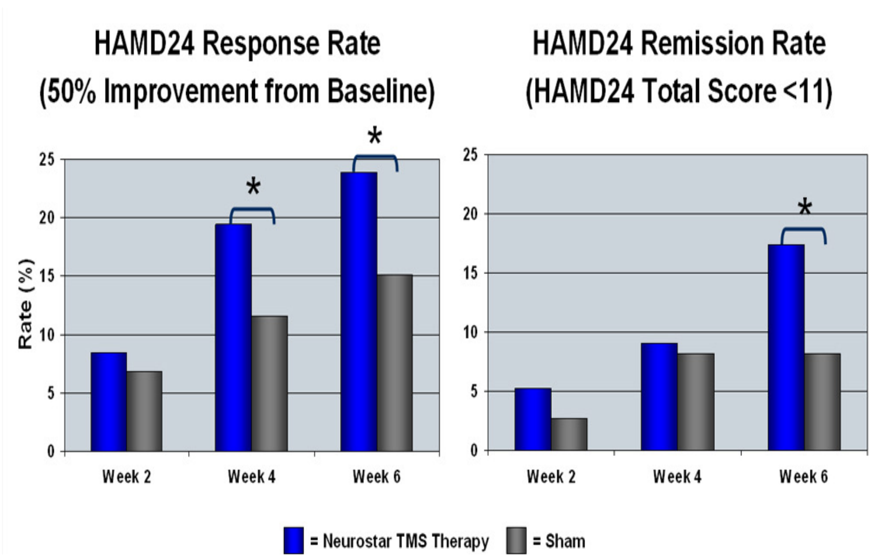
- NIBS: applying energy to the brain in a noninvasive way to modulate its activity
  - here focused on electromagnetic energy



Modulatory effects of TMS

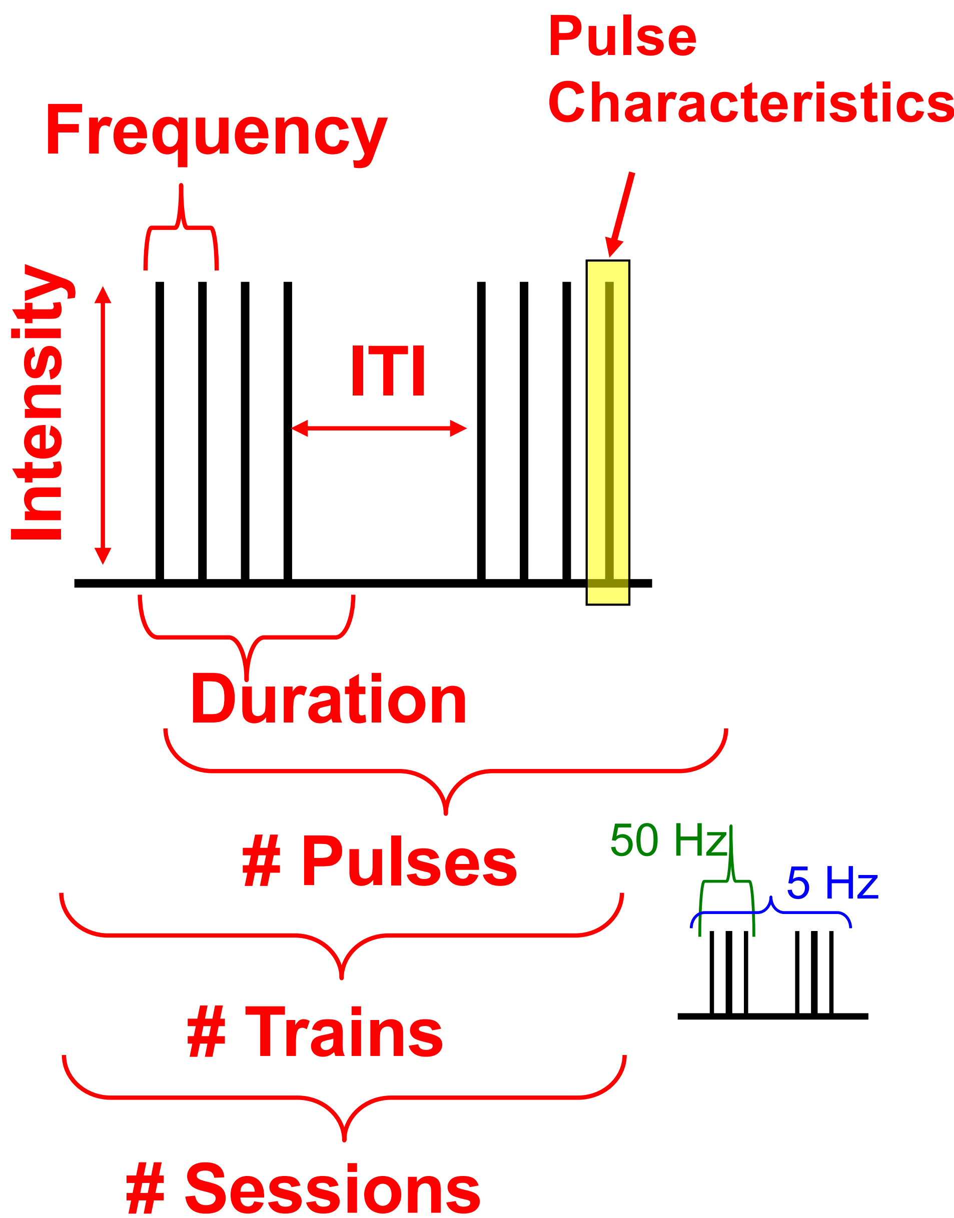


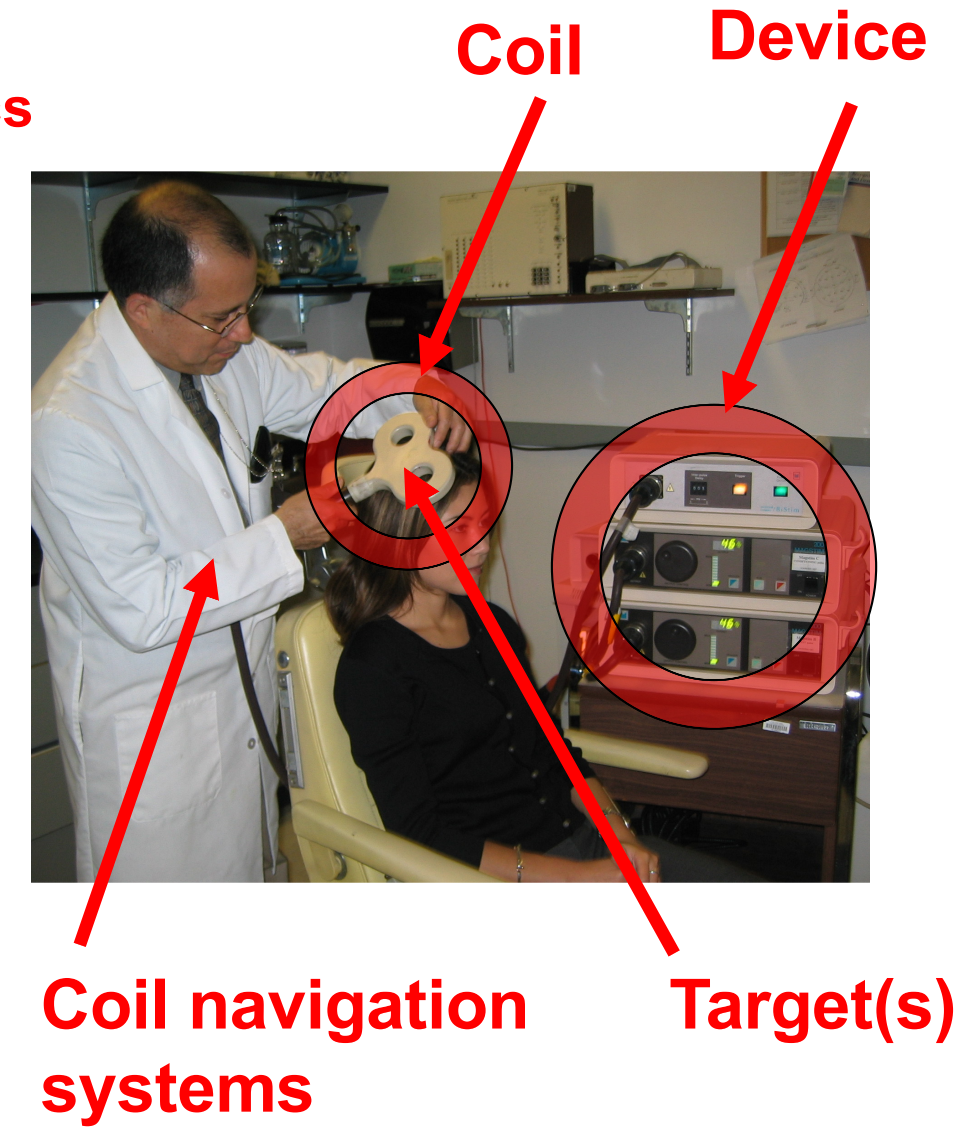
Amassian et al., 1989



- 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

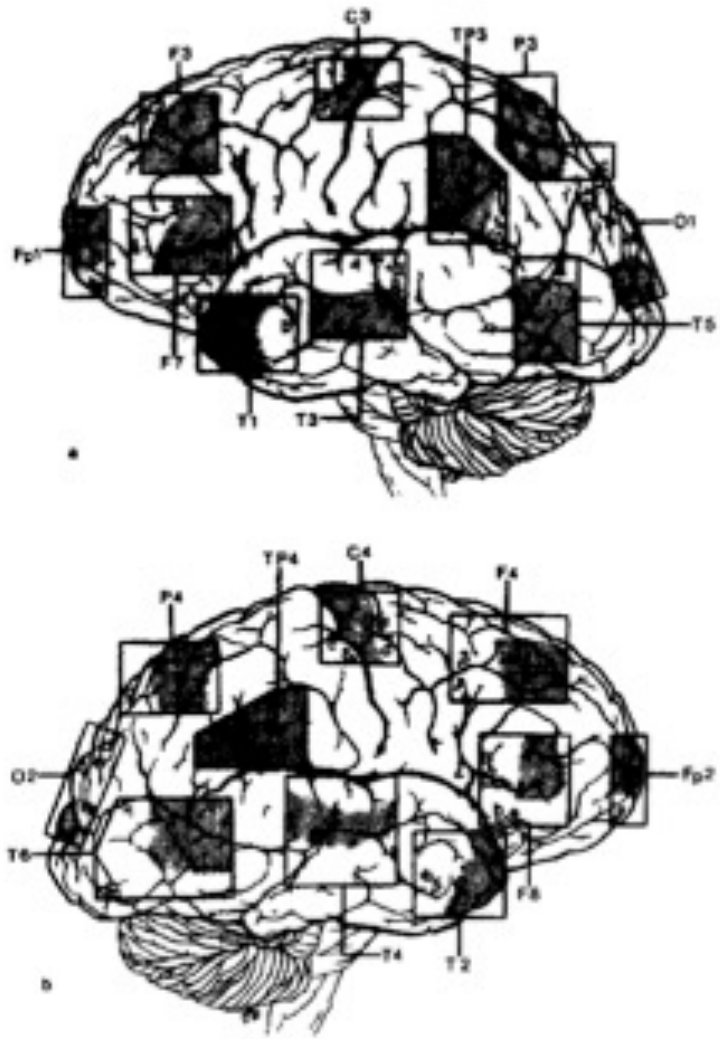
The space of all possible parameters for dosing in therapeutic Rx is extremely large





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

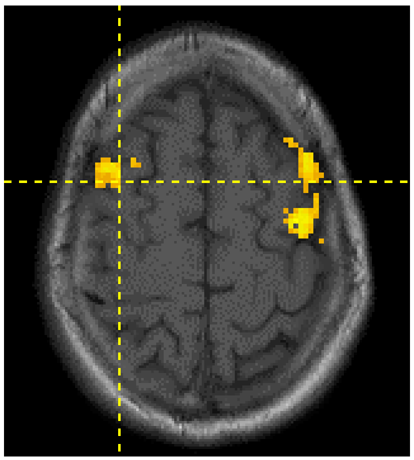


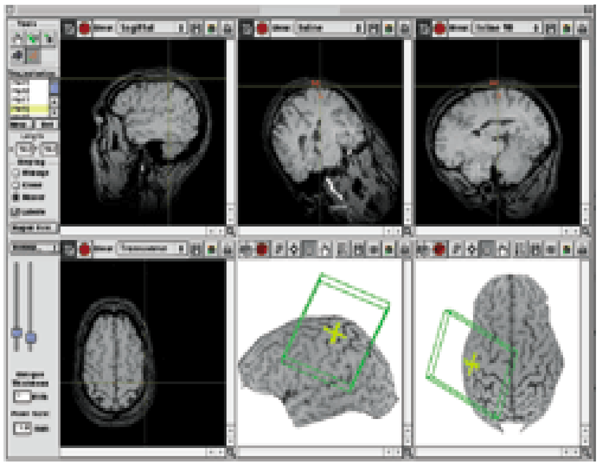
Using scalp/external anatomy to target

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





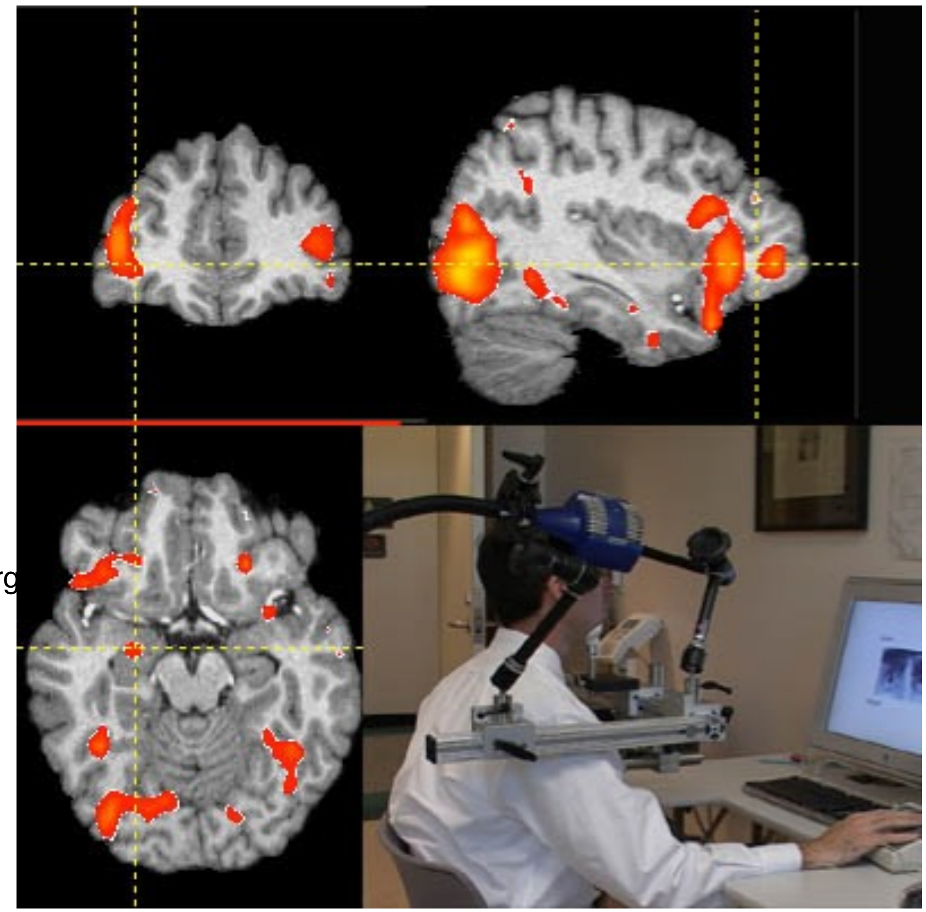
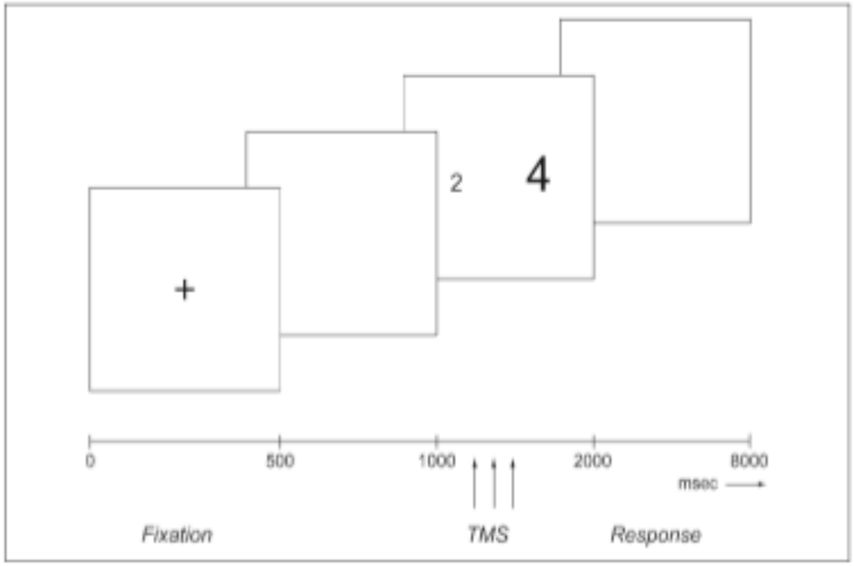


Figure 1: Increases in rCBF in prefrontal cortex while performing a Sternerg

Study comparing 10/20, structural MRI, group fMRI, and individualized fMRI methods



Congruent:

2 **4**

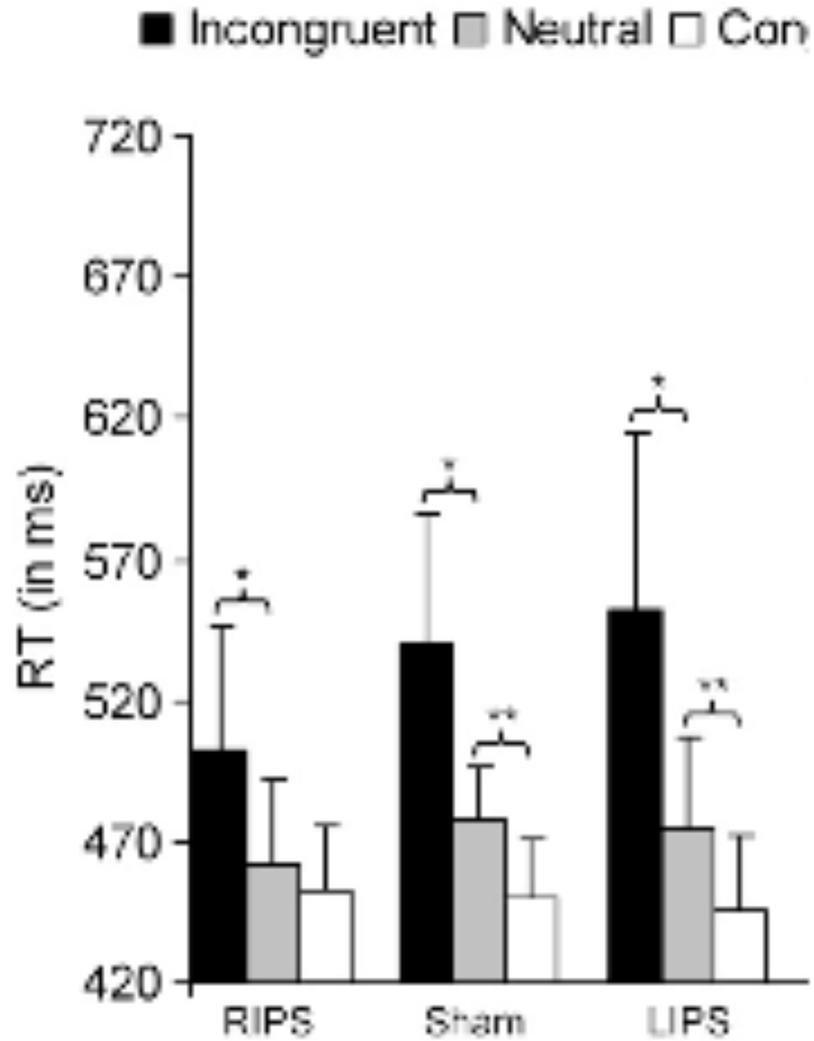
Incongruent:

2 **4**

Neutral:

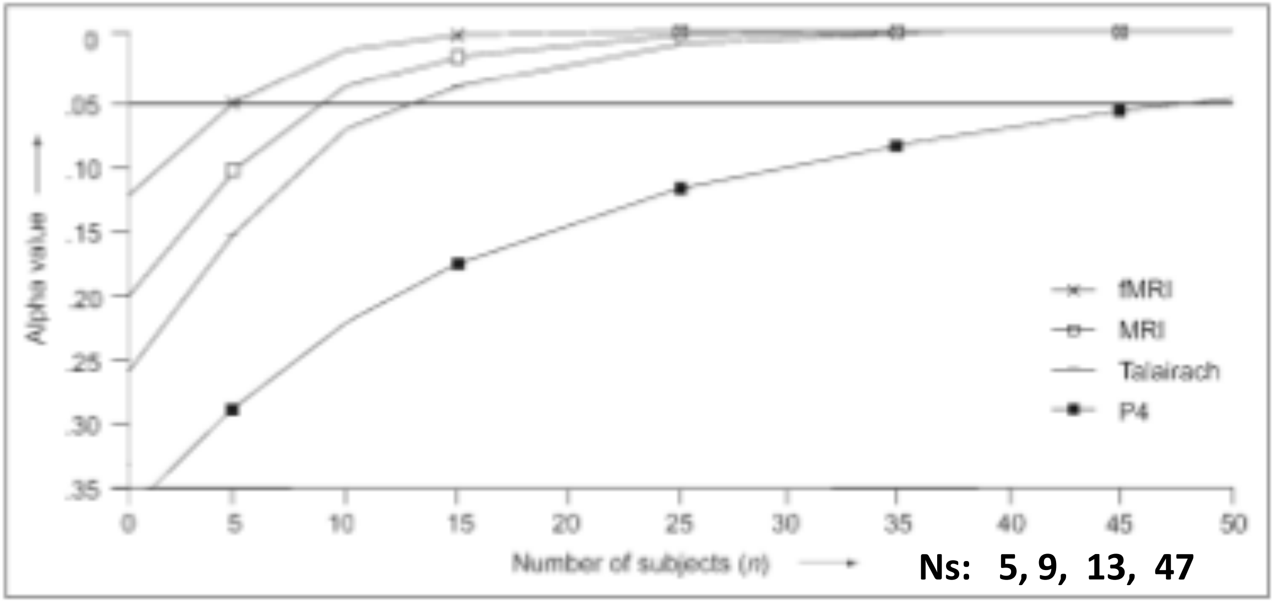
2 **4**

Stroop-like task



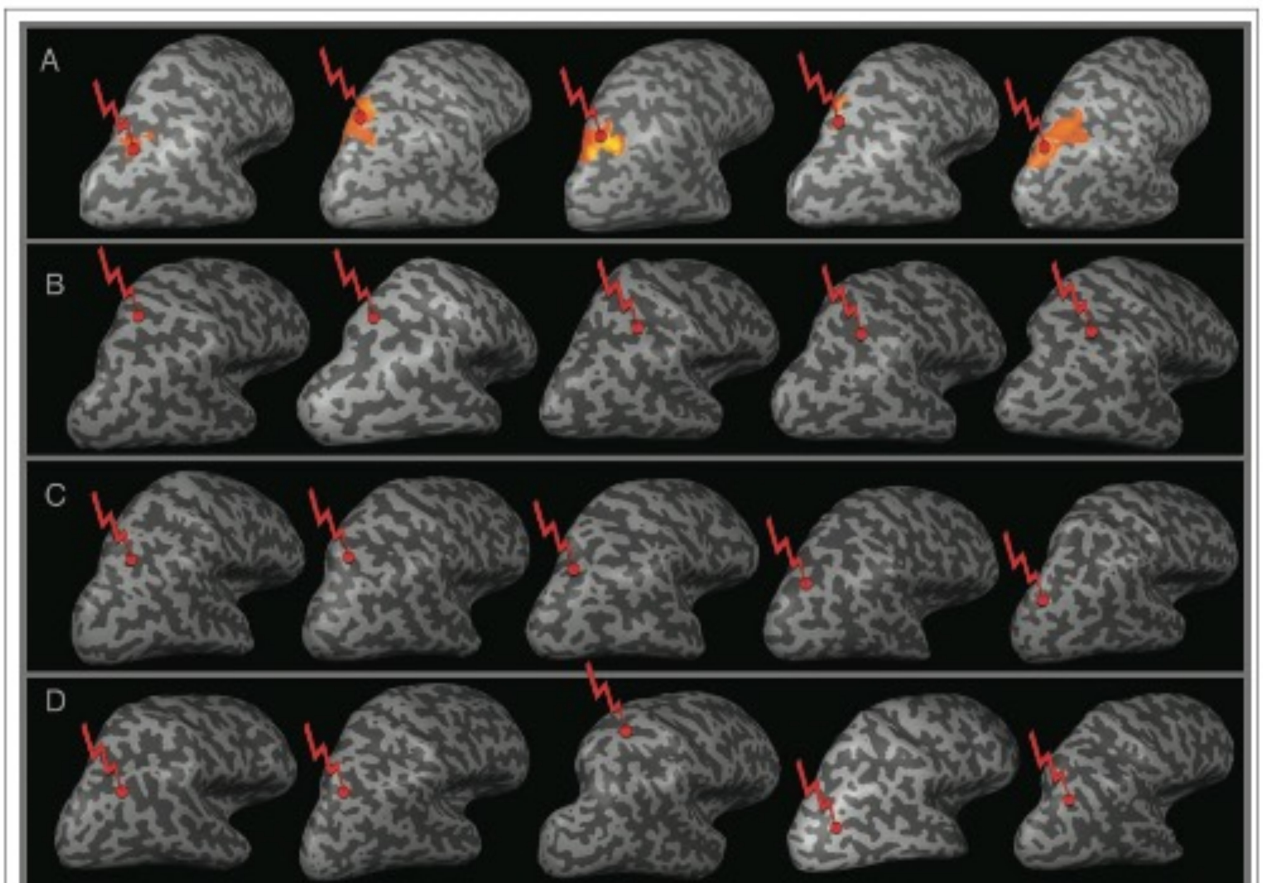
Sack et al., 2009, J Cog Neurosci 21: 207-221

TMS to parietal cortex modulates RT



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

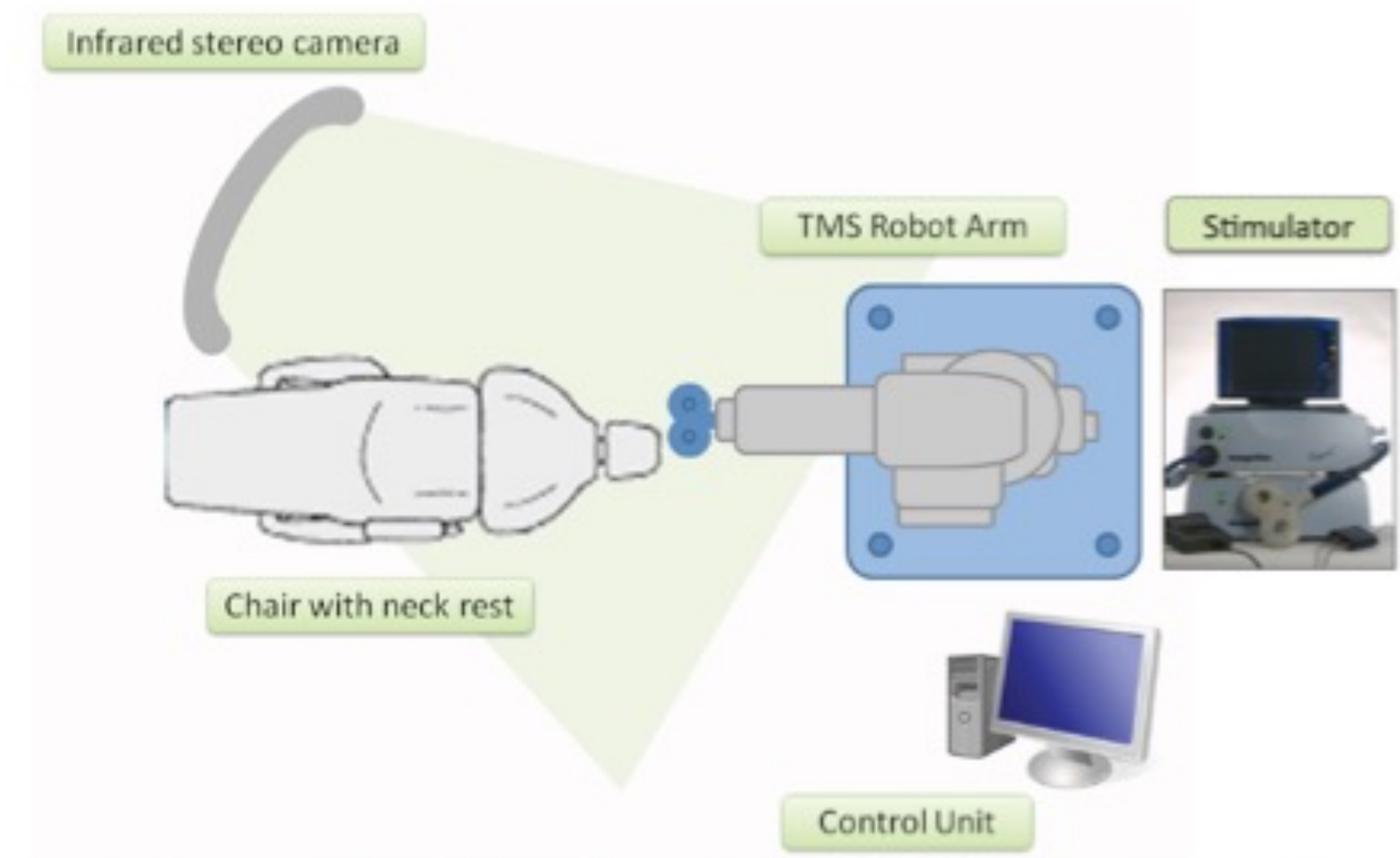
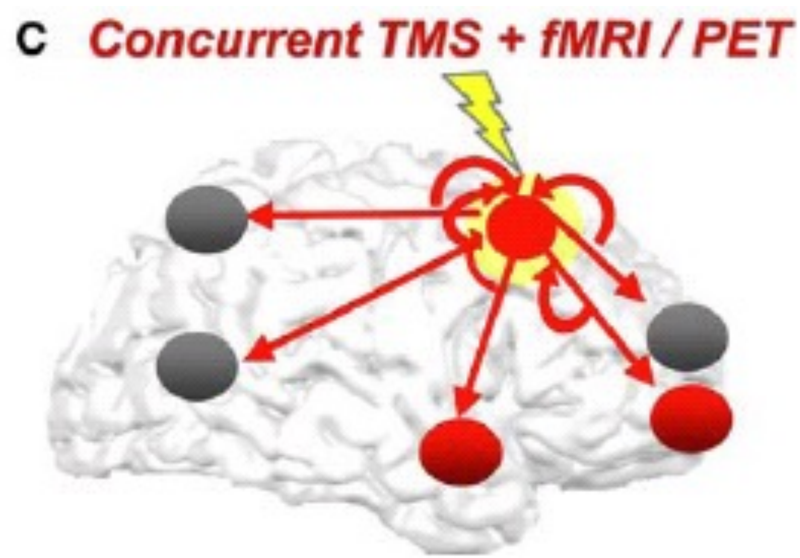


Figure 1. Schematic of the Robot Arm System. System components include: (a) Robot arm (Adept Viper s850) with power supply unit and remote control, (b) control unit for robot arm, (c) NDI Spectra infrared camera, (d) stimulator, (e) chair with neck rest.

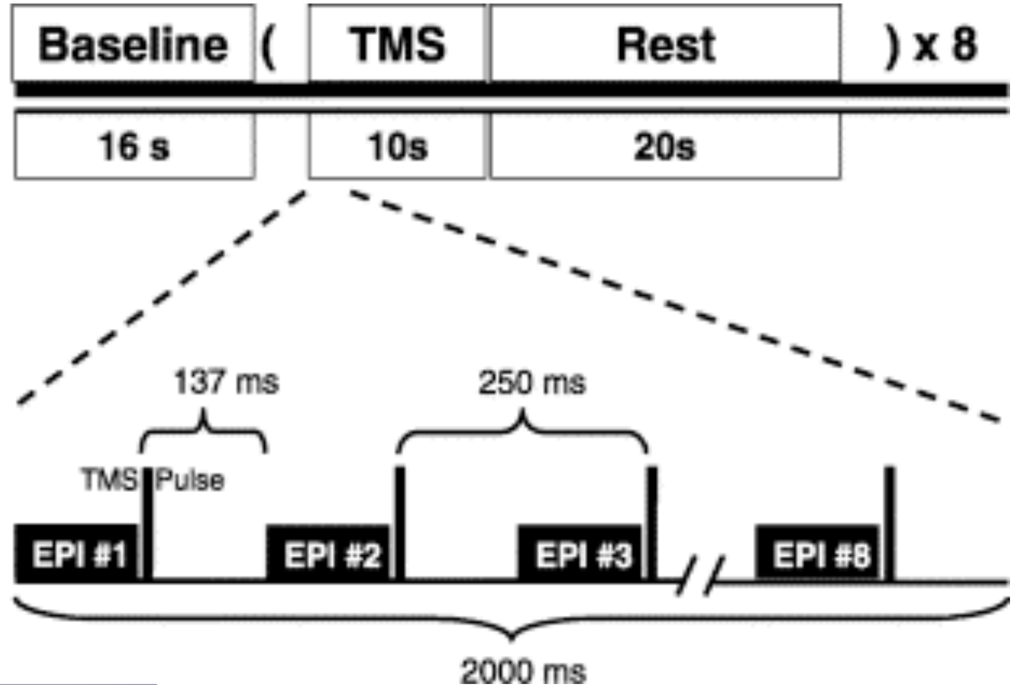
Stimulating one cortical site engages a network

Pre-Post imaging with offline TMS

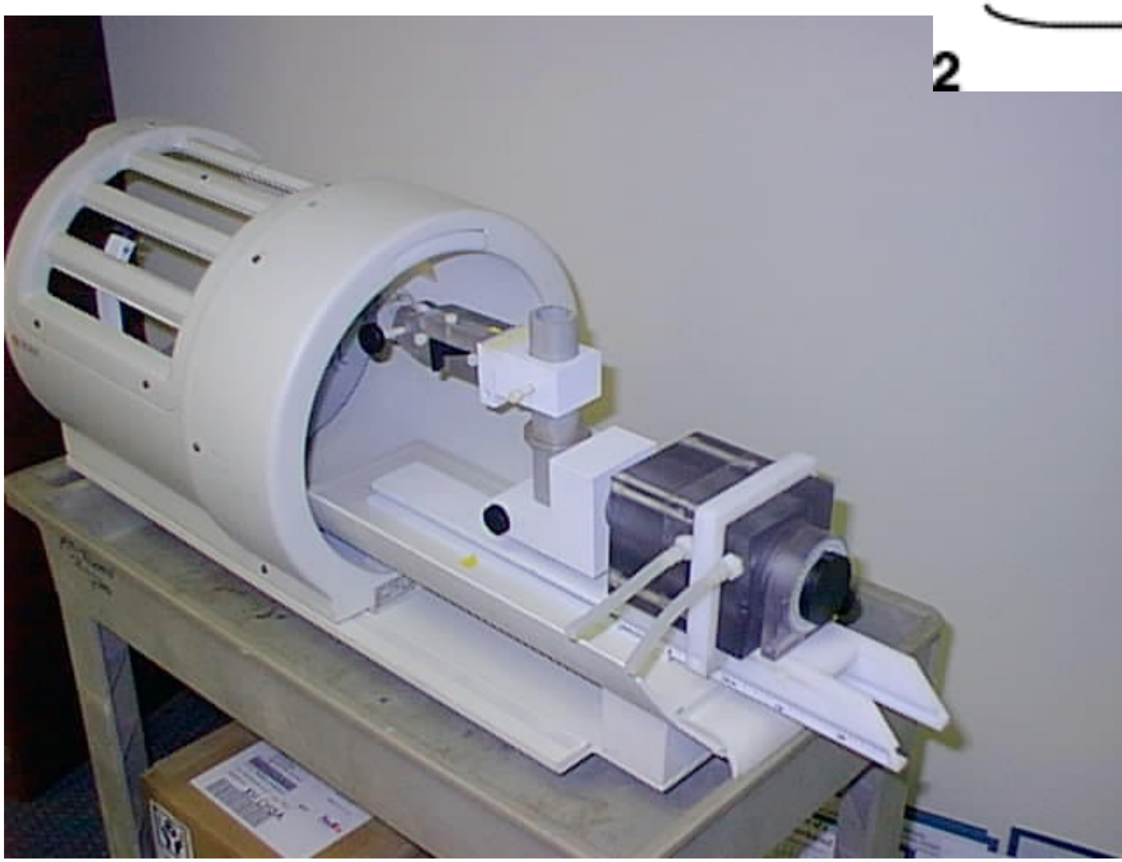
Concurrent imaging/TMS:



TMS/fMRI Interleaving

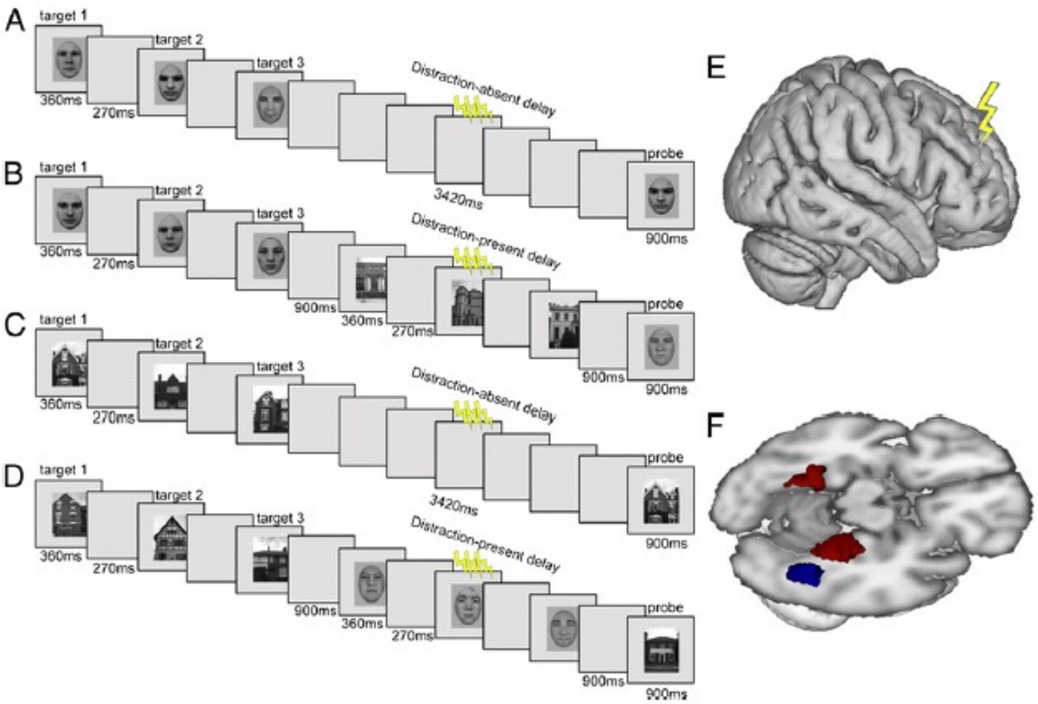


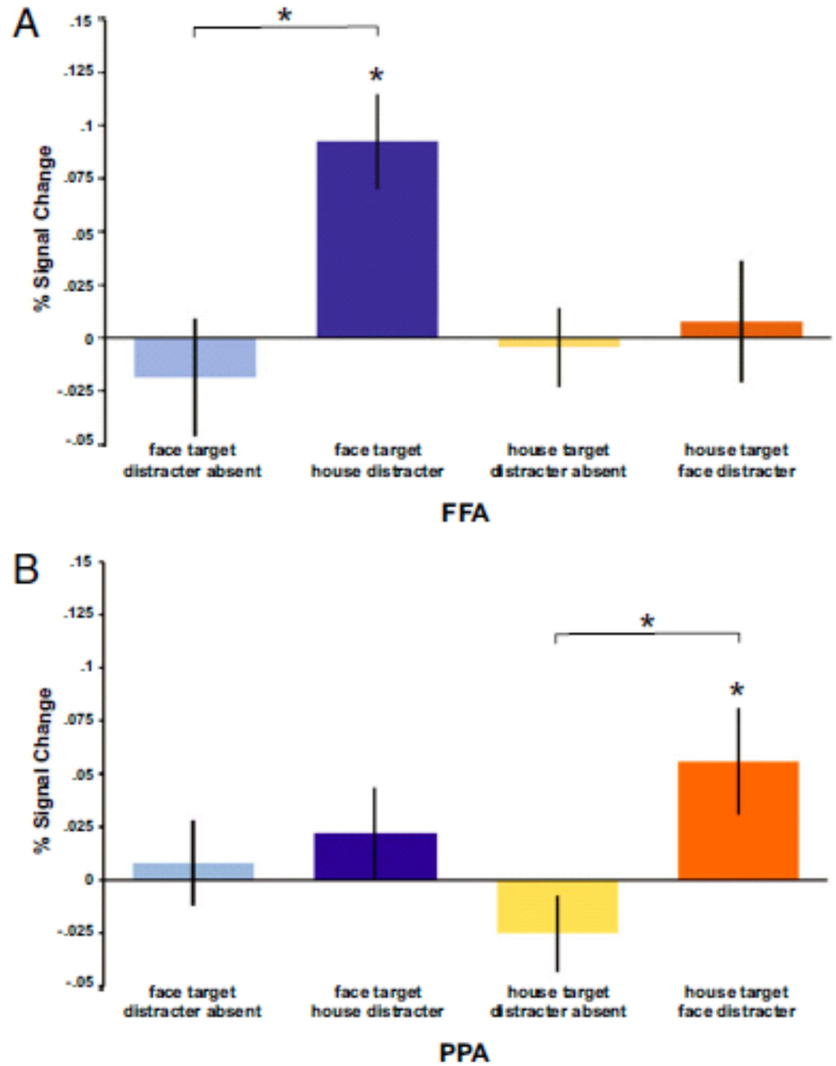
2



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

Exploring long-distance network effects with simultaneous TMS-fMRI



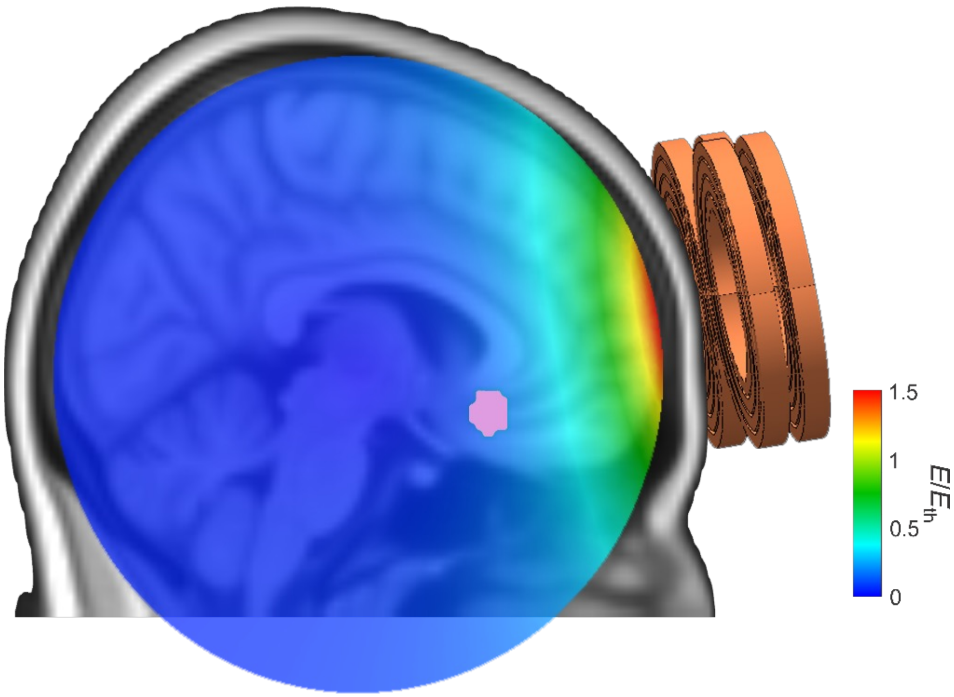


Picture working memory task
Faces (FFA activity)
Places (PPA activity)

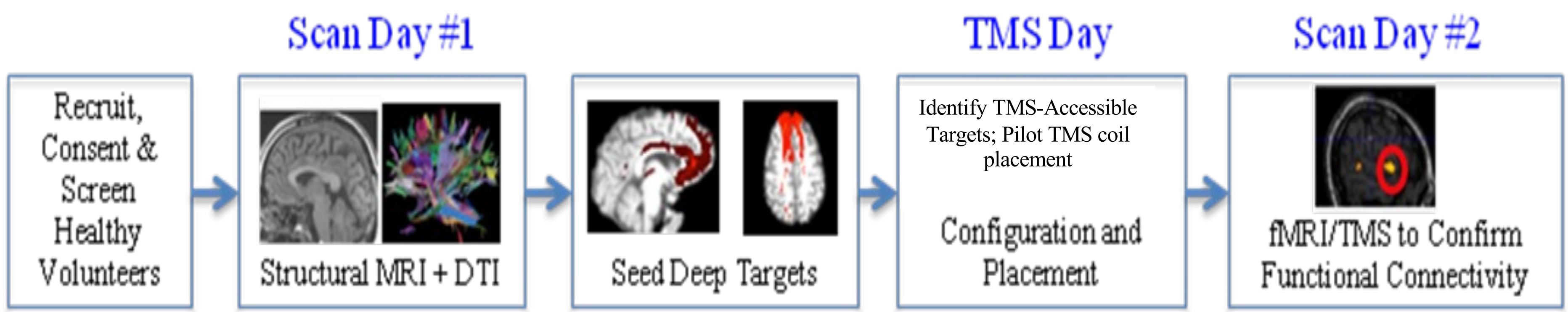
TMS to DLPFC during difficult conditions affects posterior activity

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

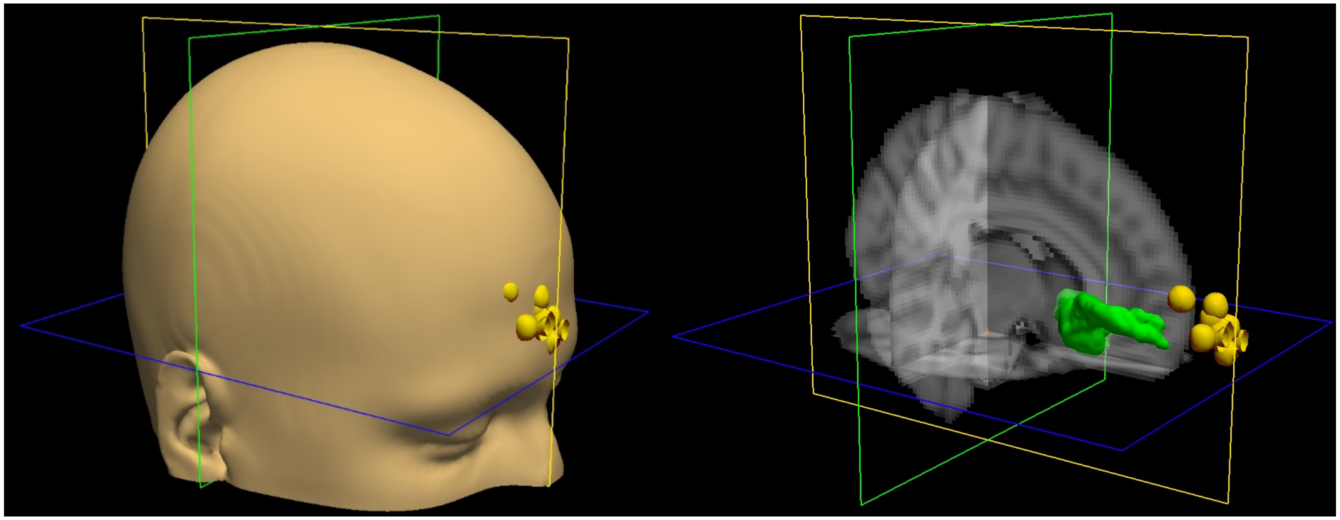
Overcoming depth limitation of TMS: Noninvasive Focal Deep Brain Stimulation

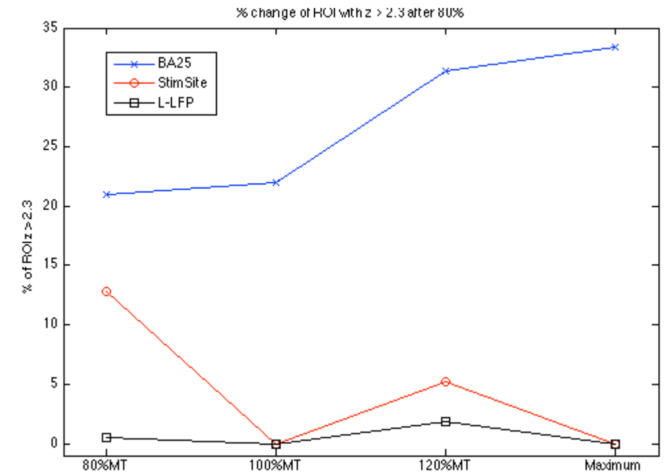


BA25 of interest as a target of stimulation in depression- but too deep to effectively reach with TMS



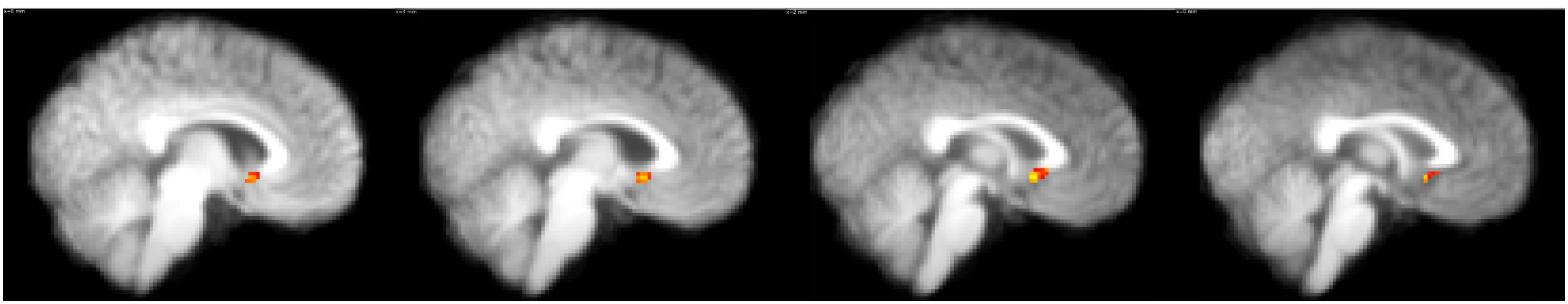
Noninvasive deep brain stimulation paradigm: Results





Individualized targeting **N=10**

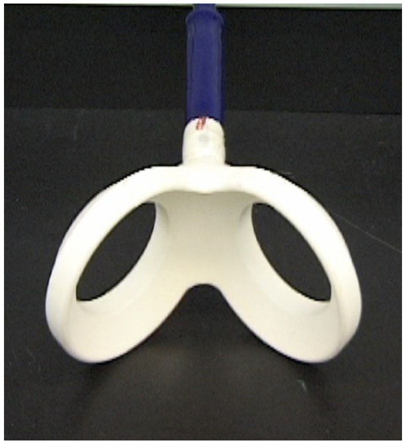
Activation (% ROI w z>2.3) increased with TMS dosage



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

Magnetic Field Characteristics: Coil Shape

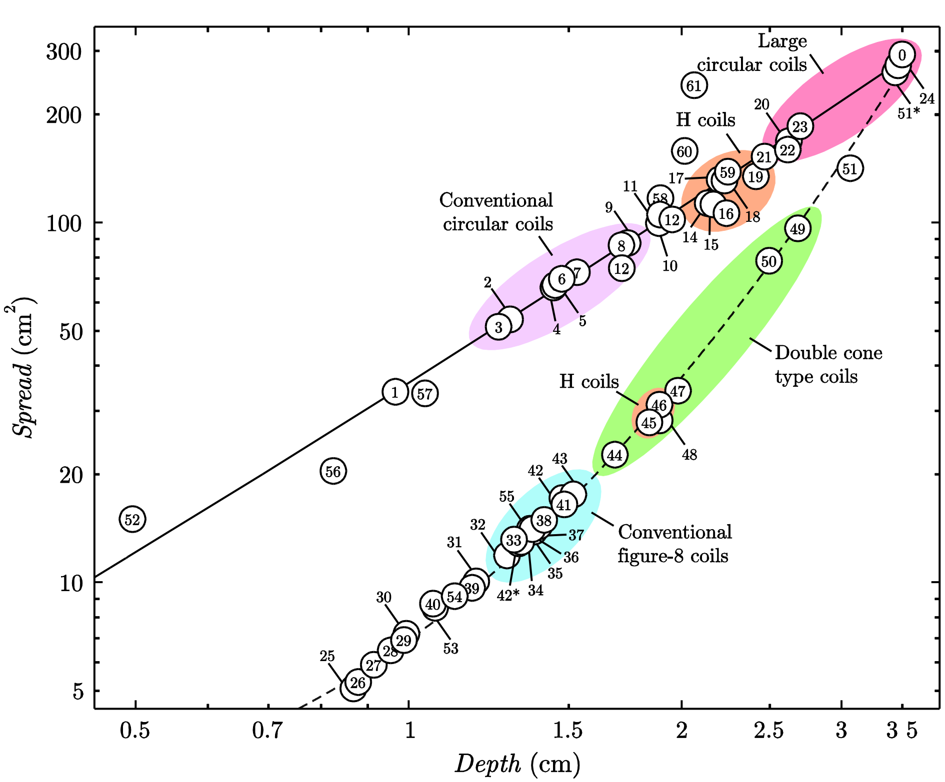
Figure 8

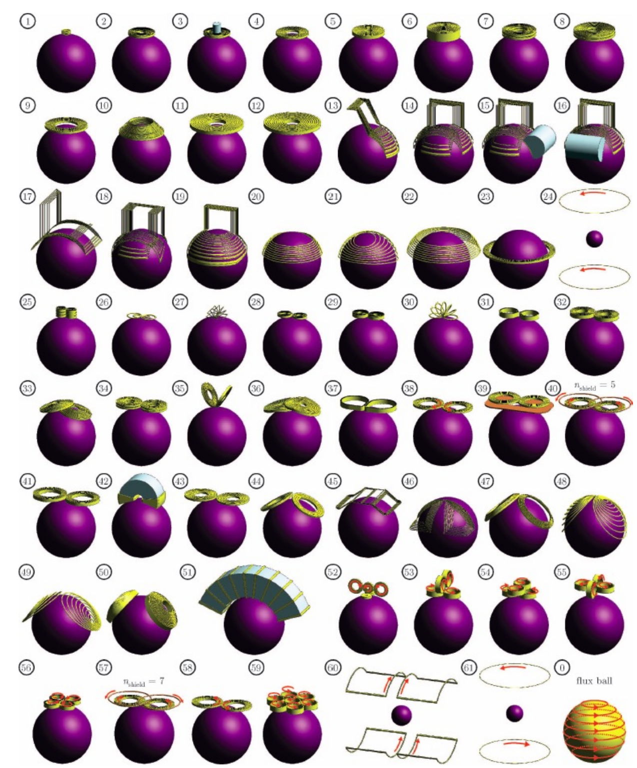


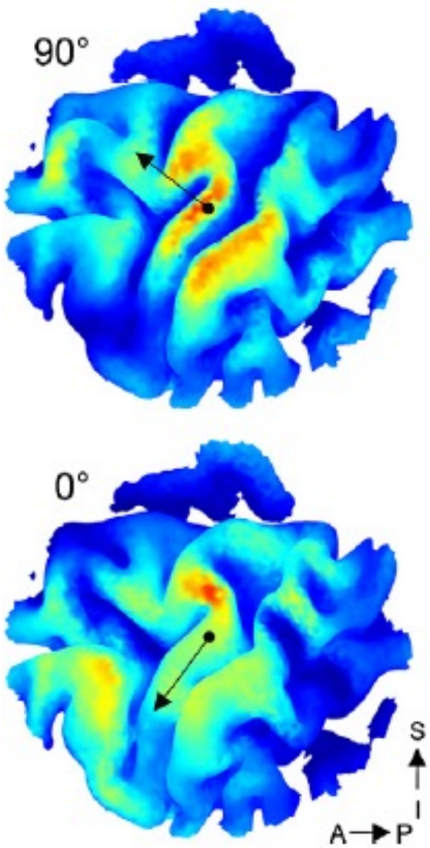
Double Cone

Round

Metal Core





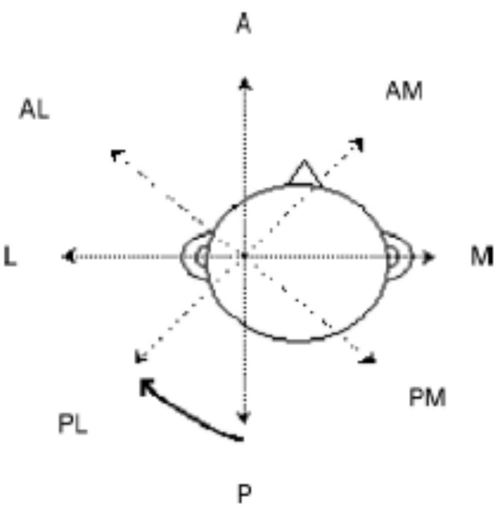


Effects of coil orientation:

Current direction relative to gyri

Inter-individual variability

A. Thielscher et al. / NeuroImage 54 (2011) 234–243



Balslev et al., Journal of Neuroscience Methods 162 (2007) 309–313

Subj	Sess	Corr	Motor thresholds at 8 coil orientations								PC
			A	*AL*	*L*	*PL*	*P*	*PM*	*M*	*AM*	angle°
5	1	0.98	70	70	69	**61**	67	70	70	70	38.50
	2		70	70	70	**60**	65	70	70	70	31.27
6	1	0.96	63	69	59	**48**	54	68	61	53	42.76
	2		60	70	59	**49**	55	70	66	55	37.33
4	1	0.95	60	67	54	**46**	53	65	66	58	37.78
	2		60	69	61	**45**	55	70	68	58	34.24
7	1	0.95	67	66	61	**59**	**59**	70	64	60	44.20
	2		69	69	62	**57**	61	78	71	59	47.90
9	1	0.89	66	64	48	**44**	51	63	58	50	36.62
	2		55	66	48	**37**	42	62	55	44	49.76
8	1	0.88	70	88	78	**64**	69	76	80	68	60.18
	2		72	86	74	**59**	68	86	81	62	52.28
2	1	0.86	60	70	57	**48**	56	70	70	56	36.30
	2		59	70	61	54	**47**	69	70	58	24.65
1	1	0.83	65	70	59	**46**	55	70	61	54	45.15
	2		70	64	55	**52**	58	67	66	55	53.56
10	1	0.78	55	66	54	50	**48**	60	58	51	35.63
	2		55	60	53	**48**	**48**	57	58	58	27.35
3	1	0.72	70	70	66	**63**	68	70	70	66	50.18
	2		65	70	65	**64**	70	70	70	65	45.03
12	1	0.70	59	66	50	52	**48**	55	60	60	39.17
	2		62	65	**52**	55	57	67	67	60	42.93
11	1	0.60	**40**	53	53	50	**40**	50	54	51	88.50
	2		50	54	51	**46**	**46**	52	58	50	68.50
13	1	0.41	**24**	29	31	34	**24**	29	30	37	24.95
	2		32	33	36	36	**31**	38	36	33	6.75

Intensity

- Direct effects are clear: with greater intensity, have greater effective depth and spread
  - Risk of seizure
- Also more subtle effects: e.g., paired-pulse
  - Subthreshold effects may be profound- As the clear effects of tiny voltage changes caused by tDCS point out
- Dosage: Set relative to individual motor threshold for convenience - no other benchmark readily available

% Motor Threshold

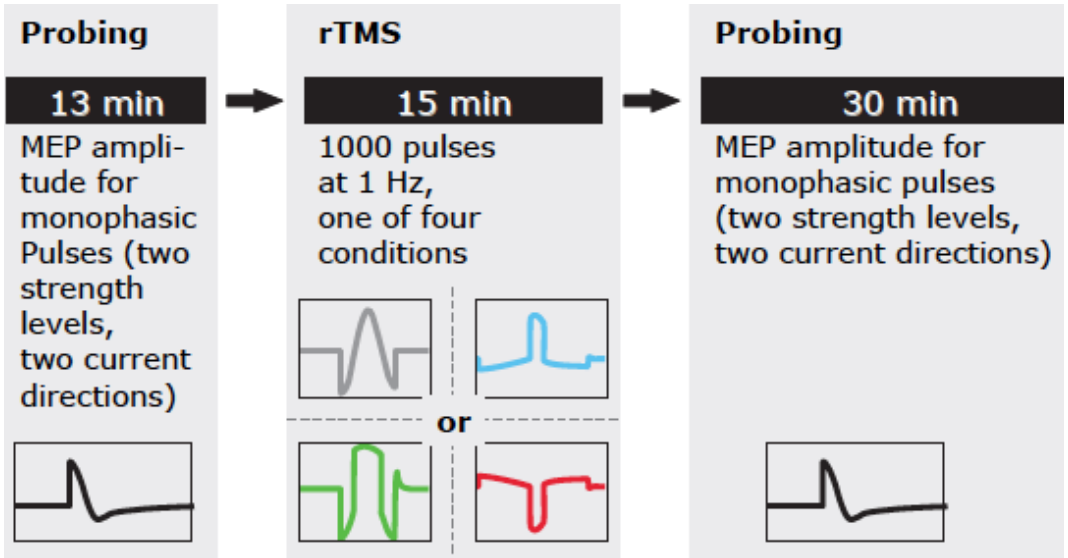
Hz	100%	110%	120%	130%	140%
1	>1800	>1800	360	>50	>50
5	>10	>10	>10	<10	7.6
10	>5	>5	4.2	2.9	1.3
20	2.05	1.6	1.0	0.55	0.35
25	1.28	0.84	0.4	0.24	0.2

Wassermann. Electroencephalogr Clin Neurophysiol. 1998 Jan;108(1):1-16.

TMS Dosage Parameters

- Spatial/Targeting
  - xyz position in space
  - Target localization method
  - Magnetic field characteristics: Determined by
    - Coil shape
    - Coil orientation
    - Intensity
- <u>Temporal</u>
  - Waveform
  - Frequency
  - Inter-train interval
  - Cumulative effects:
    - train duration
    - # trains/session
    - # sessions

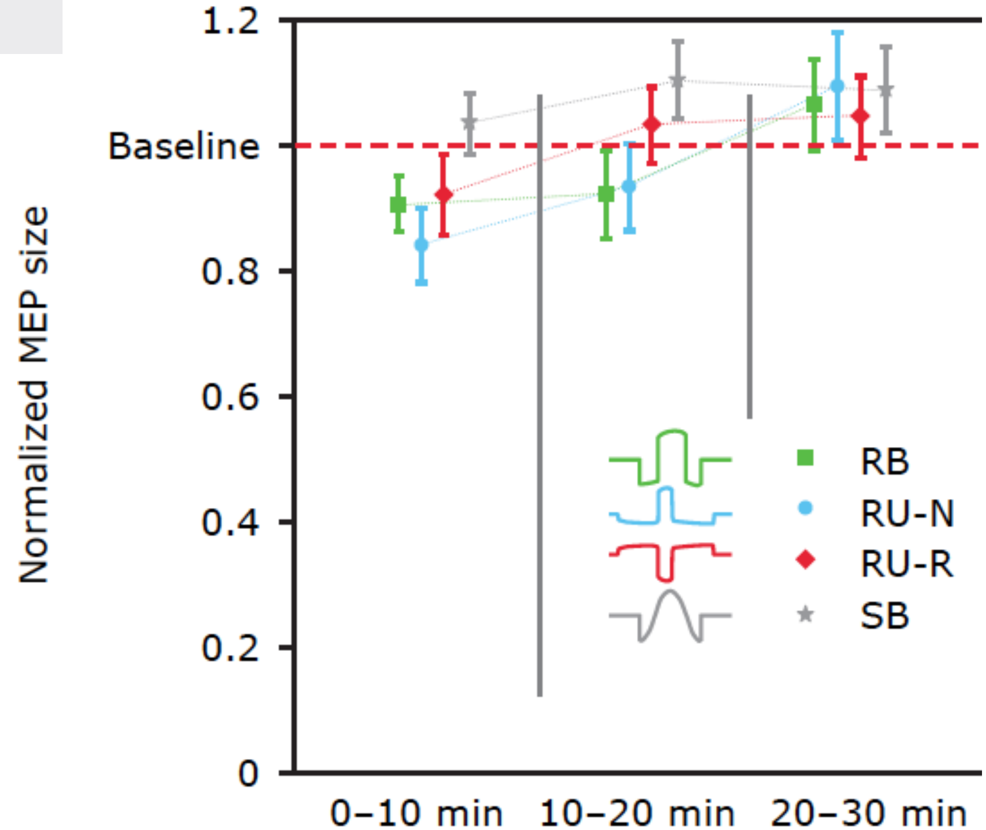
Waveform matters:



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



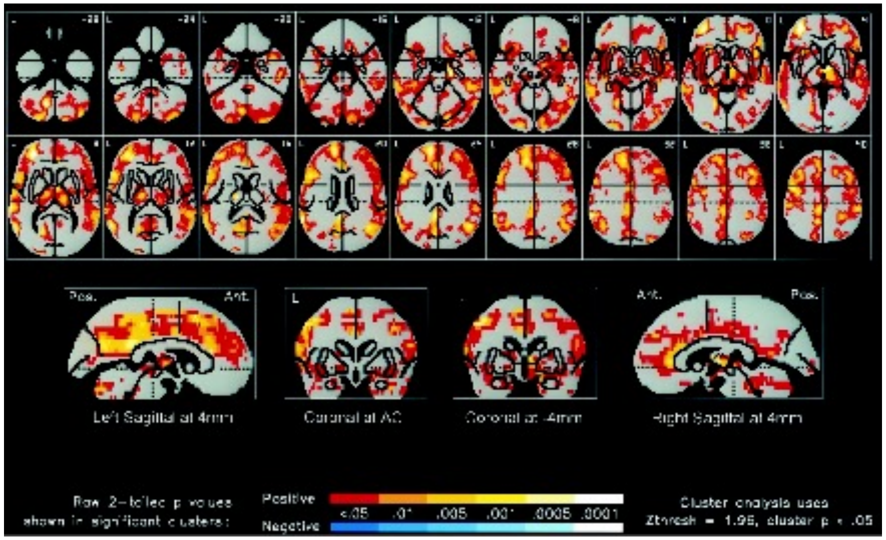
Goetz et al., 2016

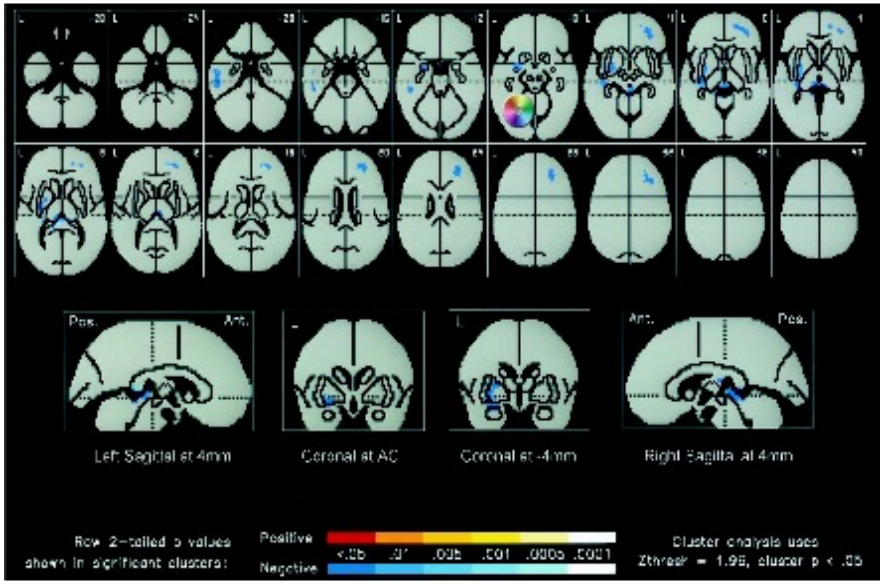
TMS frequency

Rule of thumb:

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

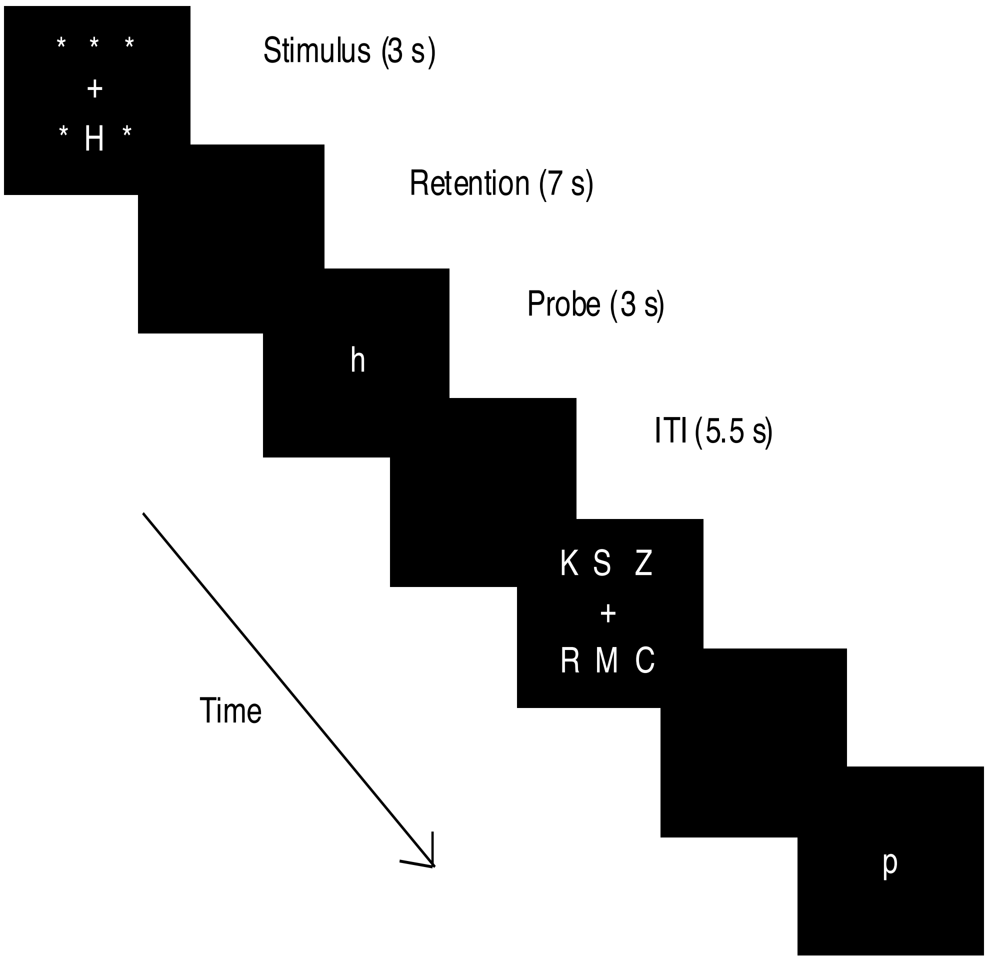
Low frequency (1 Hz) **down**-regulates cortical excitability

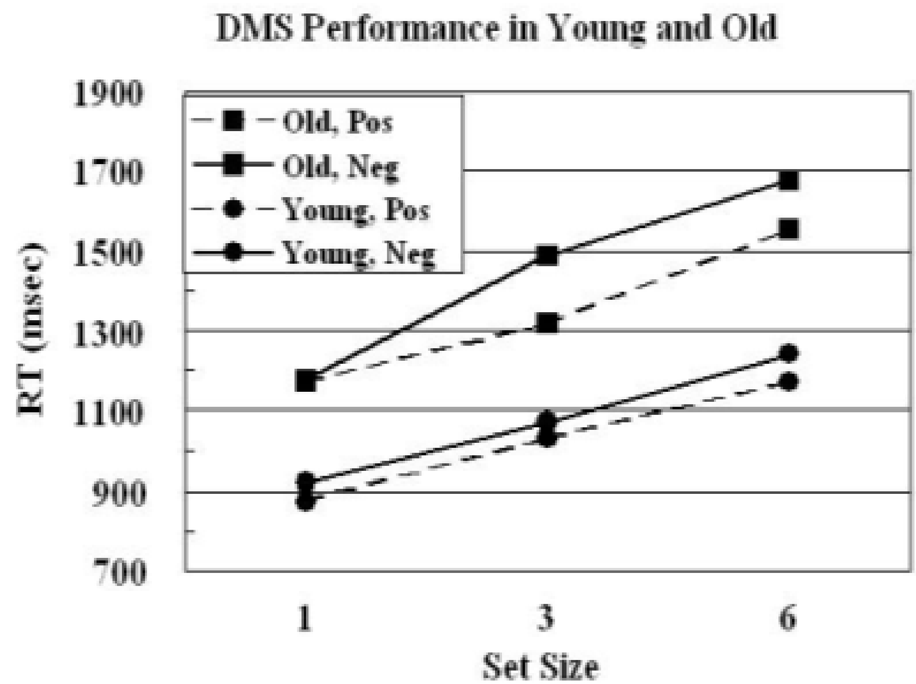




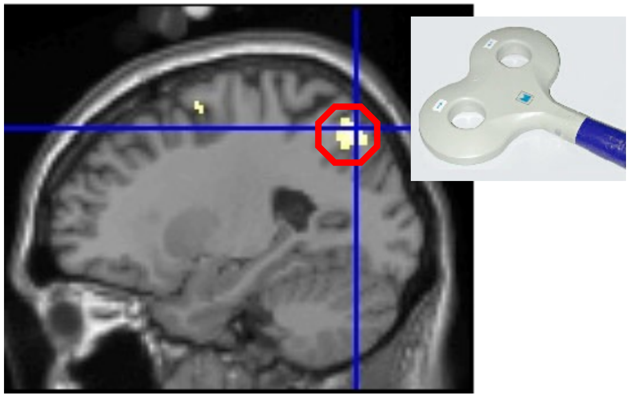
Speer et al Biol Psych 2000

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



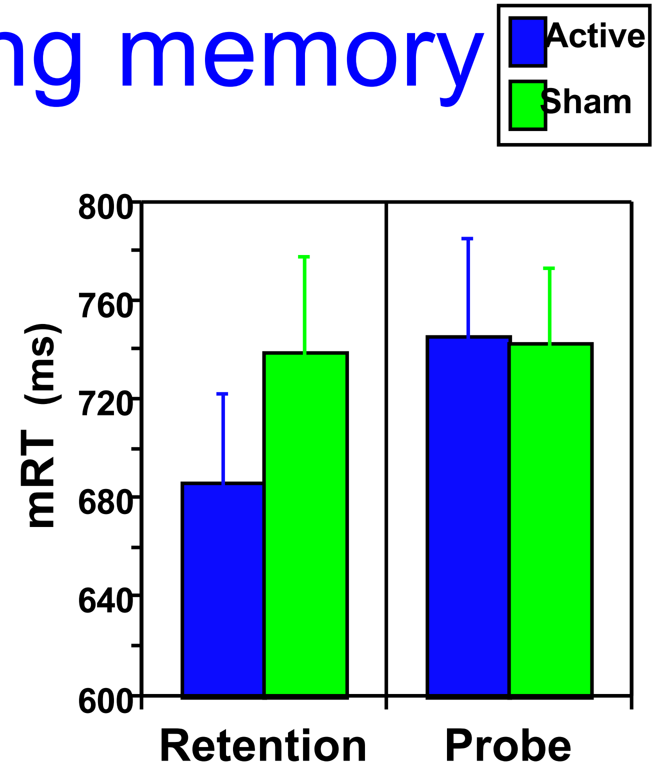


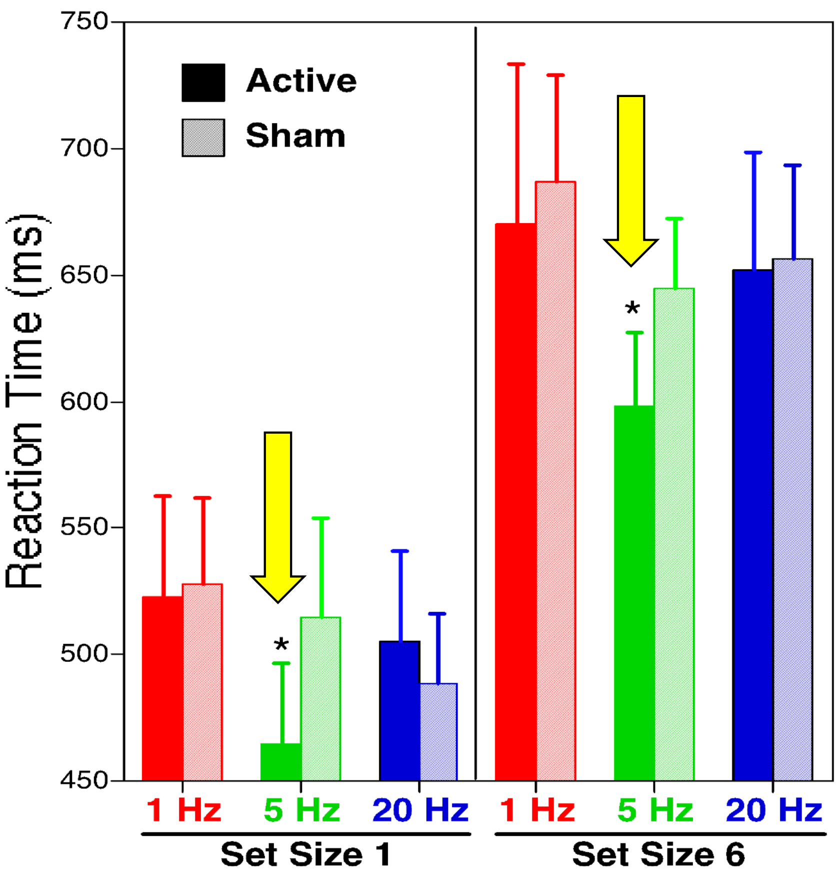
TMS enhancement of working memory



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 ($p<0.01$).



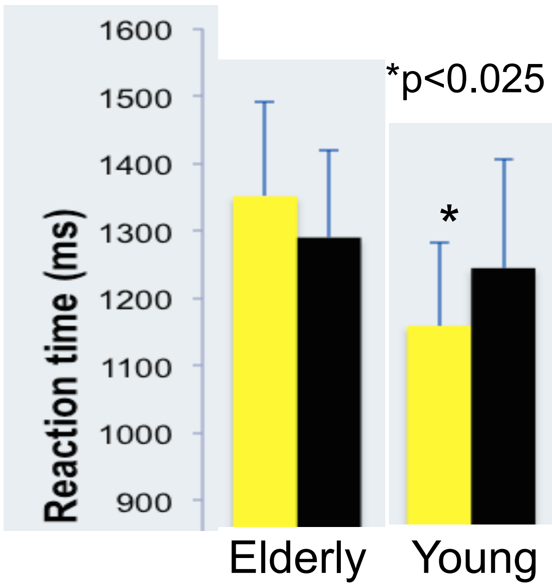


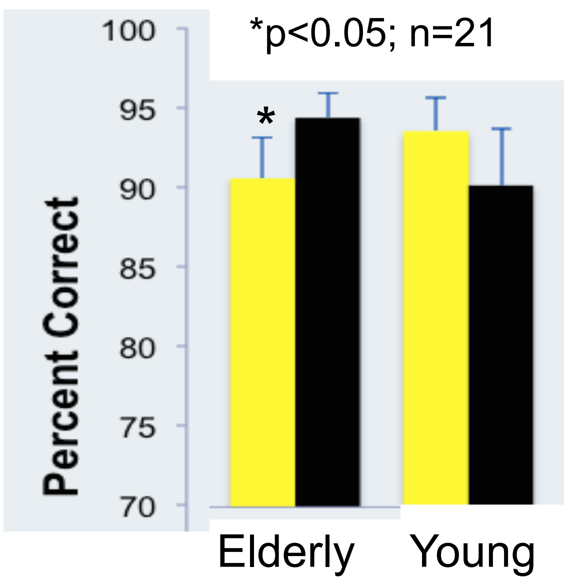
Task Phase specific effect: With a new group (N=22), 5Hz to mPar reduced RT only during retention period

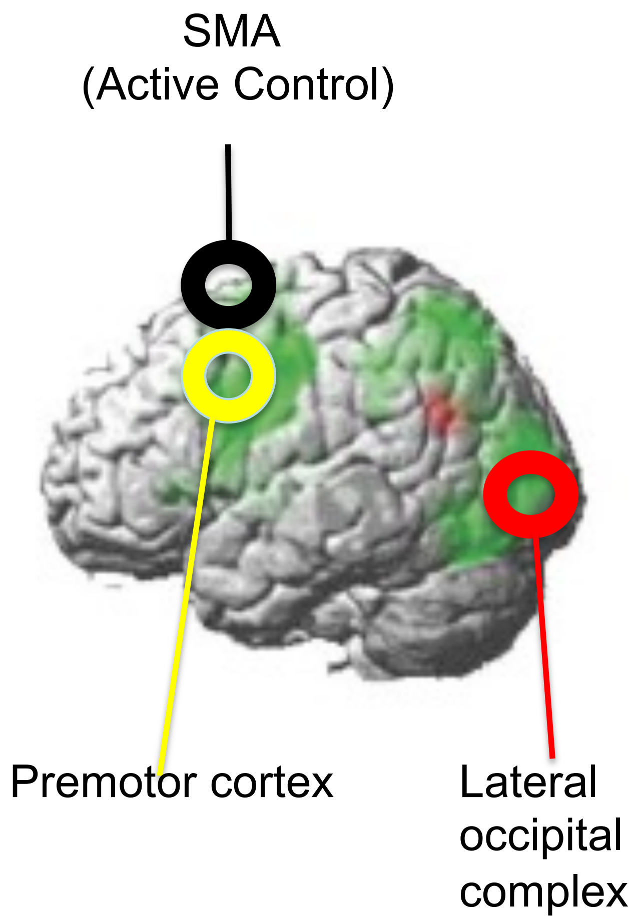
mPar active during probe?

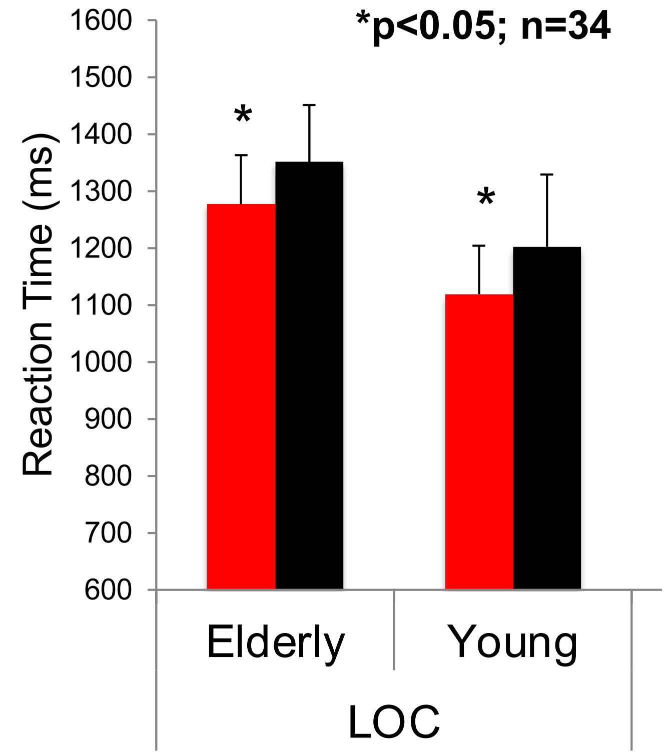
Luber et al Brain Research 2007;1128:120-129

TMS Remediation of Memory in Aging









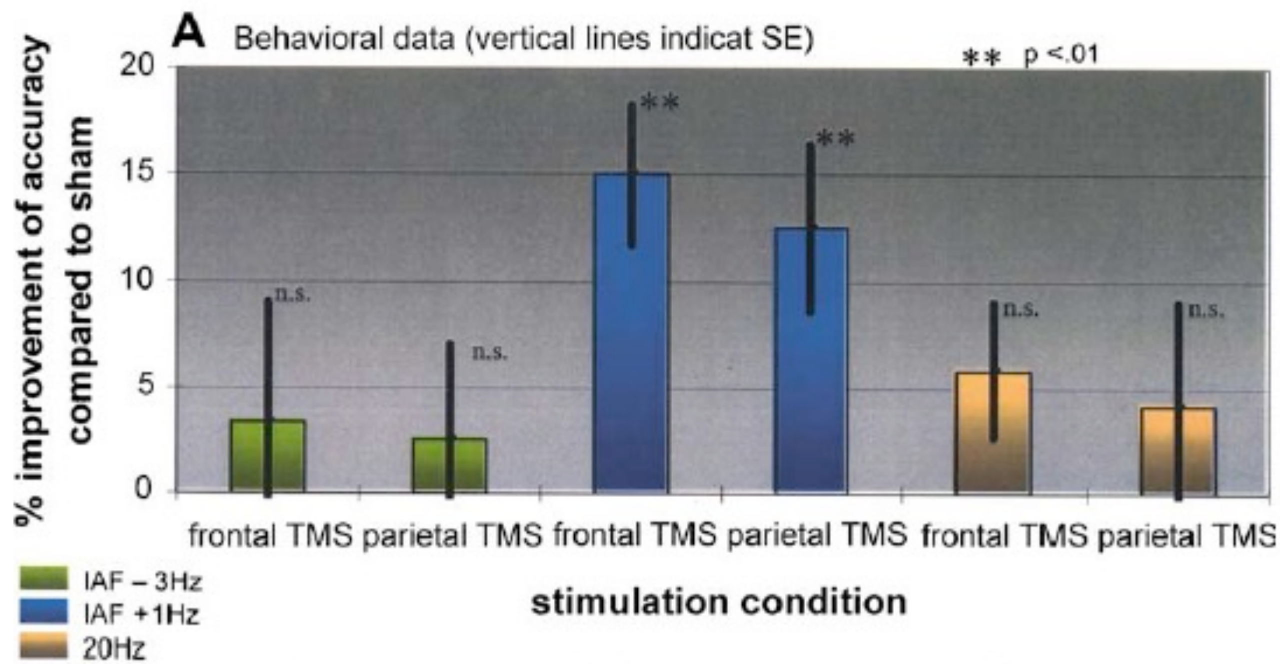
5Hz rTMS to PM before retention period improved RT and accuracy in young group but not elderly

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

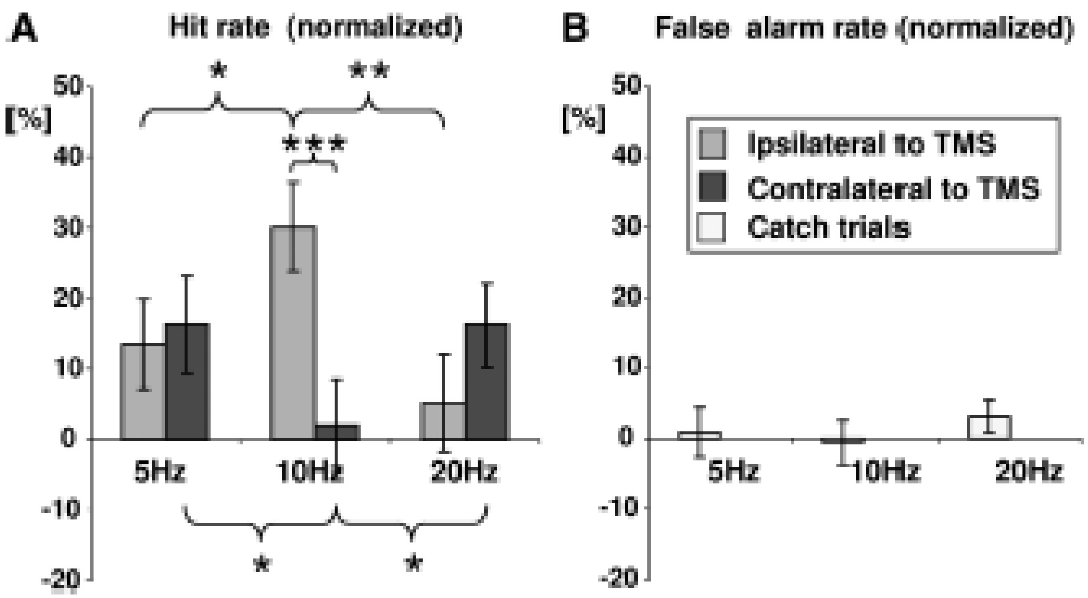
TMS enhancement: Tapping into brain's oscillatory dynamics?

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

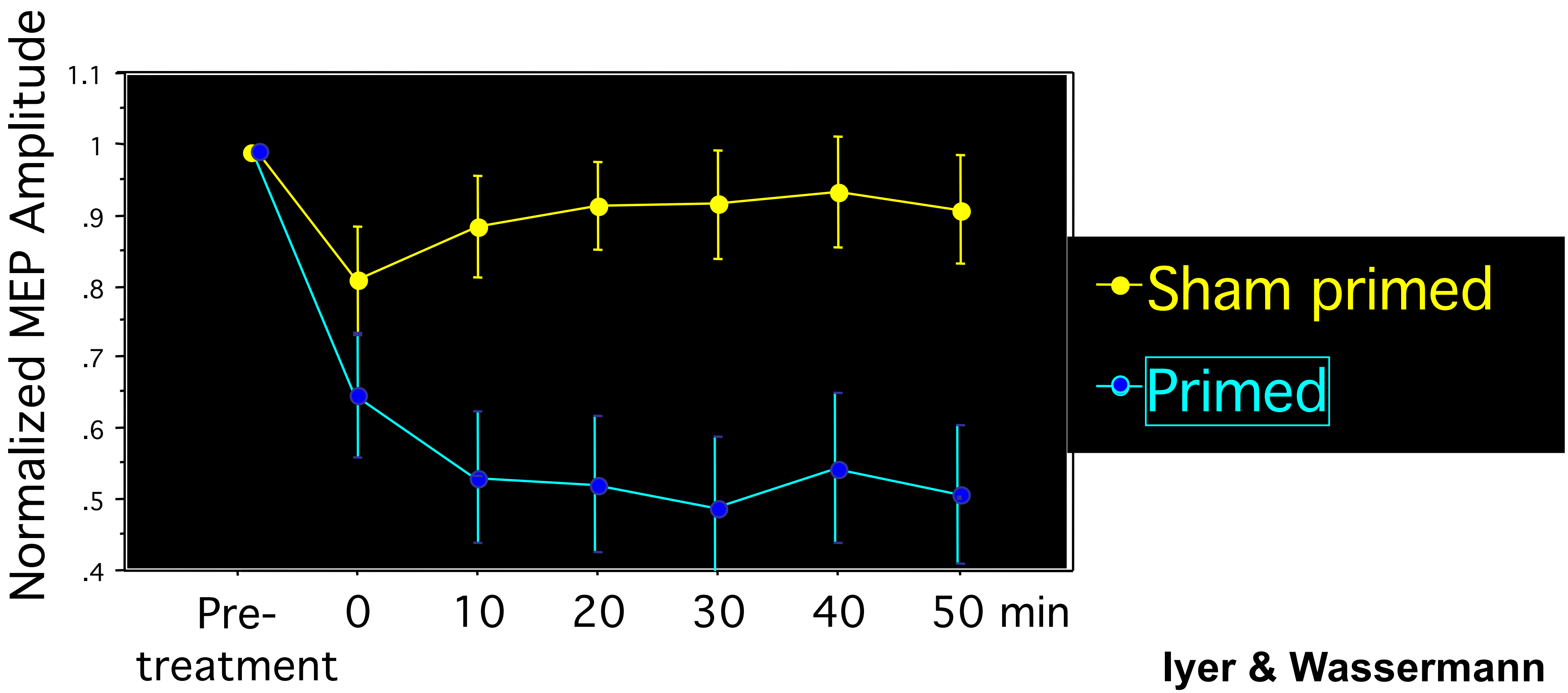


5 pulses at 10 Hz (but not 5 or 20 Hz) immediately prior to trials enhanced target detection

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

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

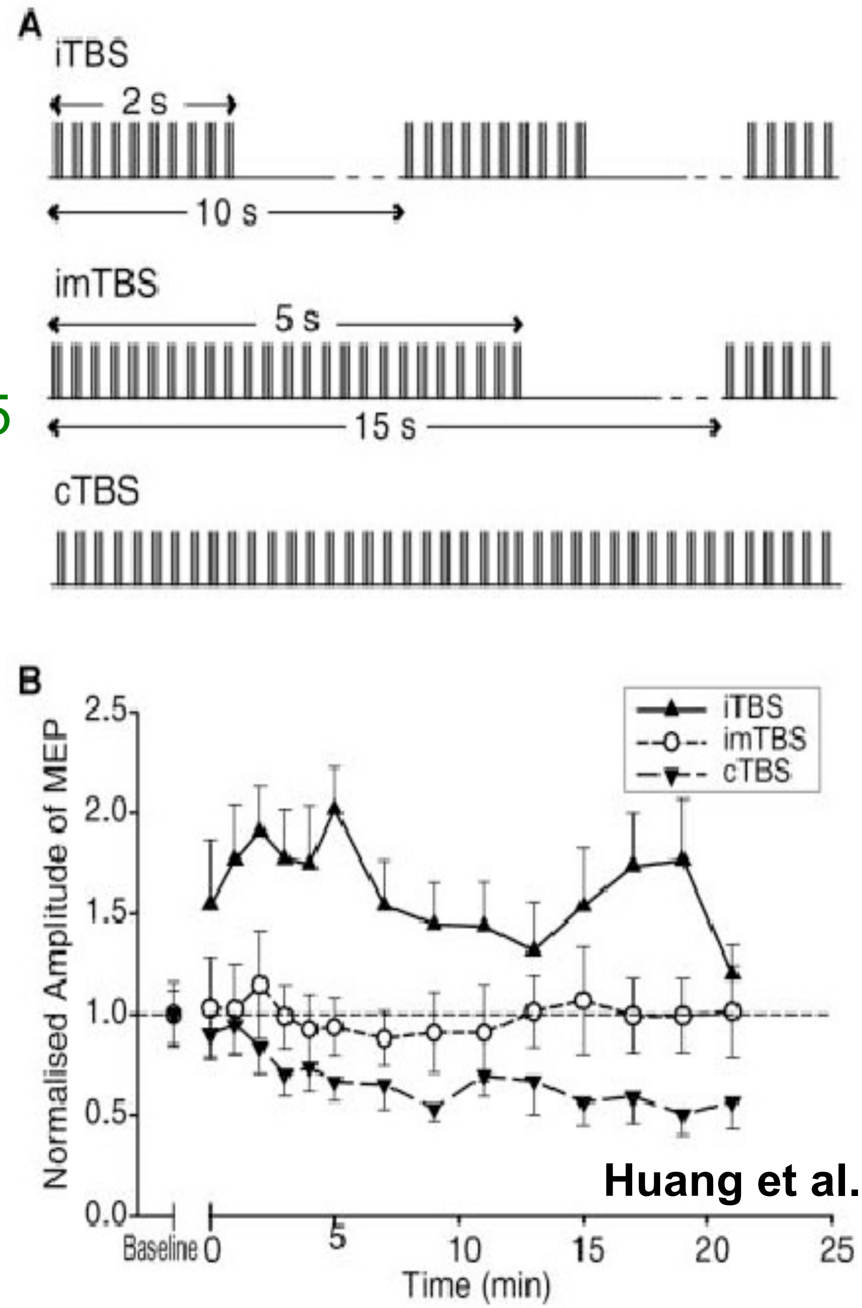
Baseline MEP → **6 Hz Priming or Sham** → **1 Hz rTMS x 10 min** → **Repeat MEP**



Iyer & Wassermann

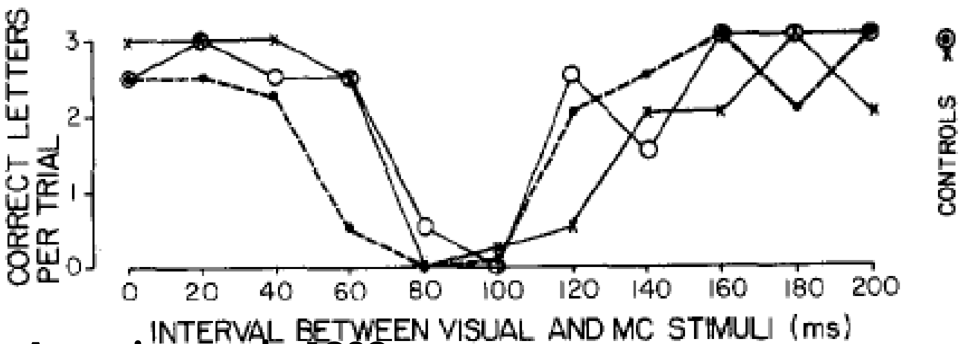
Interaction of Frequency, Duration and ITI

- 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

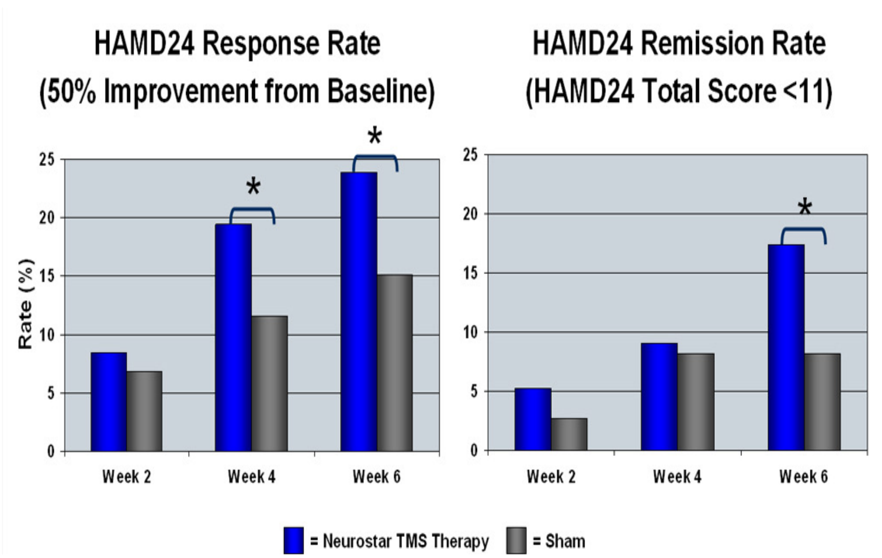


Huang et al. 2005

Duration: Cumulative effects



Amassian et al., 1989



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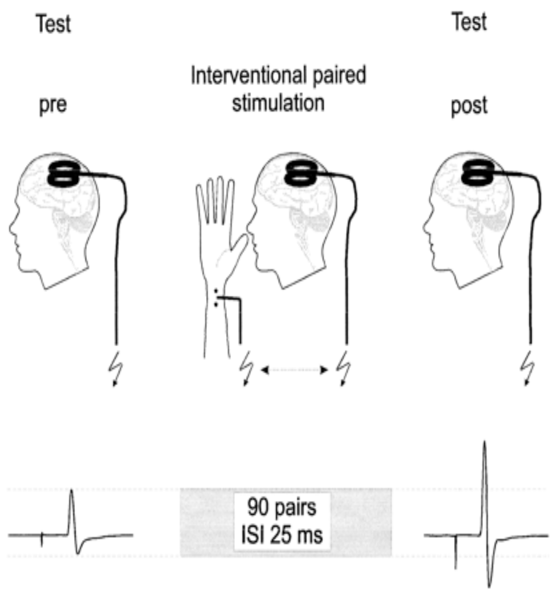
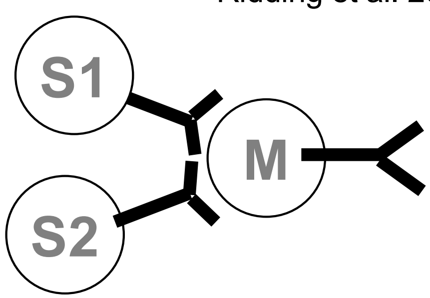
- Lasting effects - Modulation
  - Neuroplasticity
    - Synaptic efficacy, LTP/LTD
    - Modulation of cortical excitability
    - Modulation of functional connectivity

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

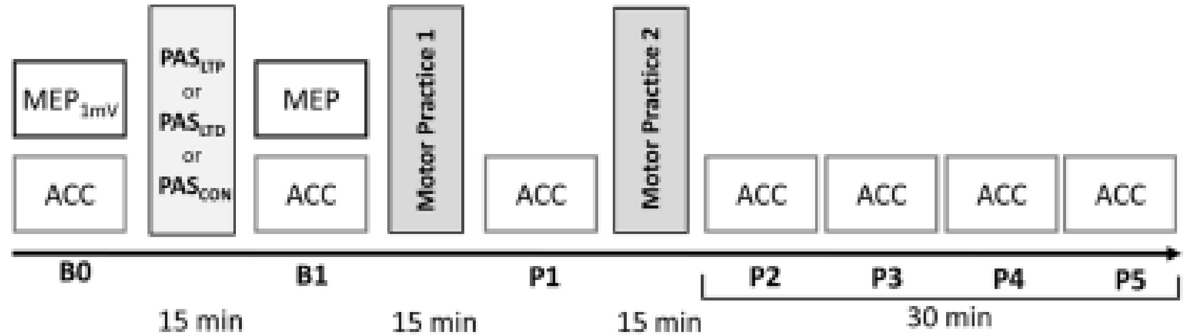
Paired Associated Stimulation (PAS)

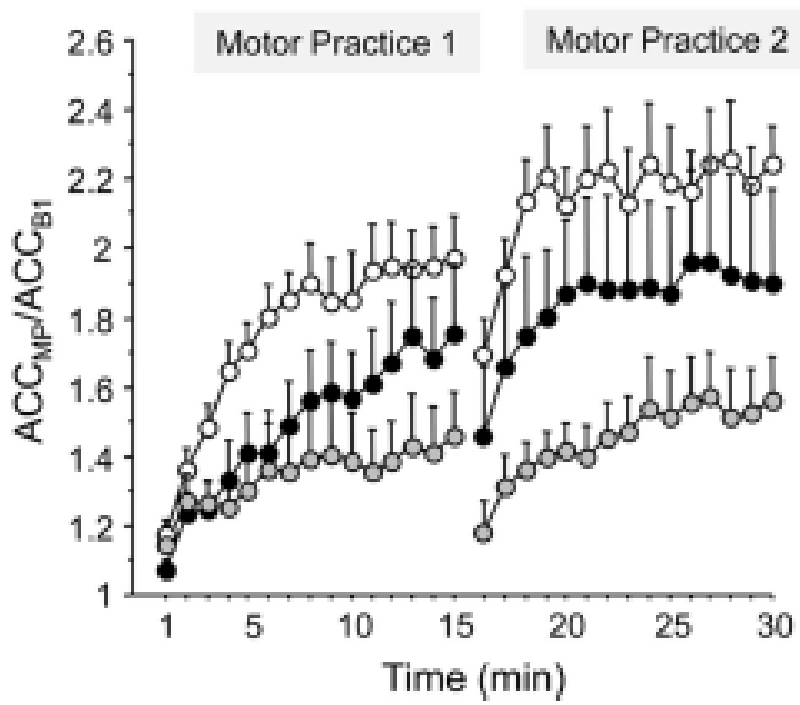


Stefan et al. 2000;
Ridding et al. 2001



Synaptic coincidence:
Hebbian plasticity

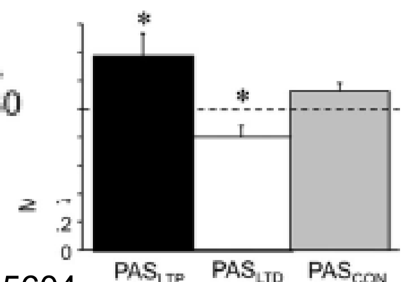




LTP PAS
(N20+2ms)

Control PAS
(N20+100 ms)

LDP PAS (N20-5ms)

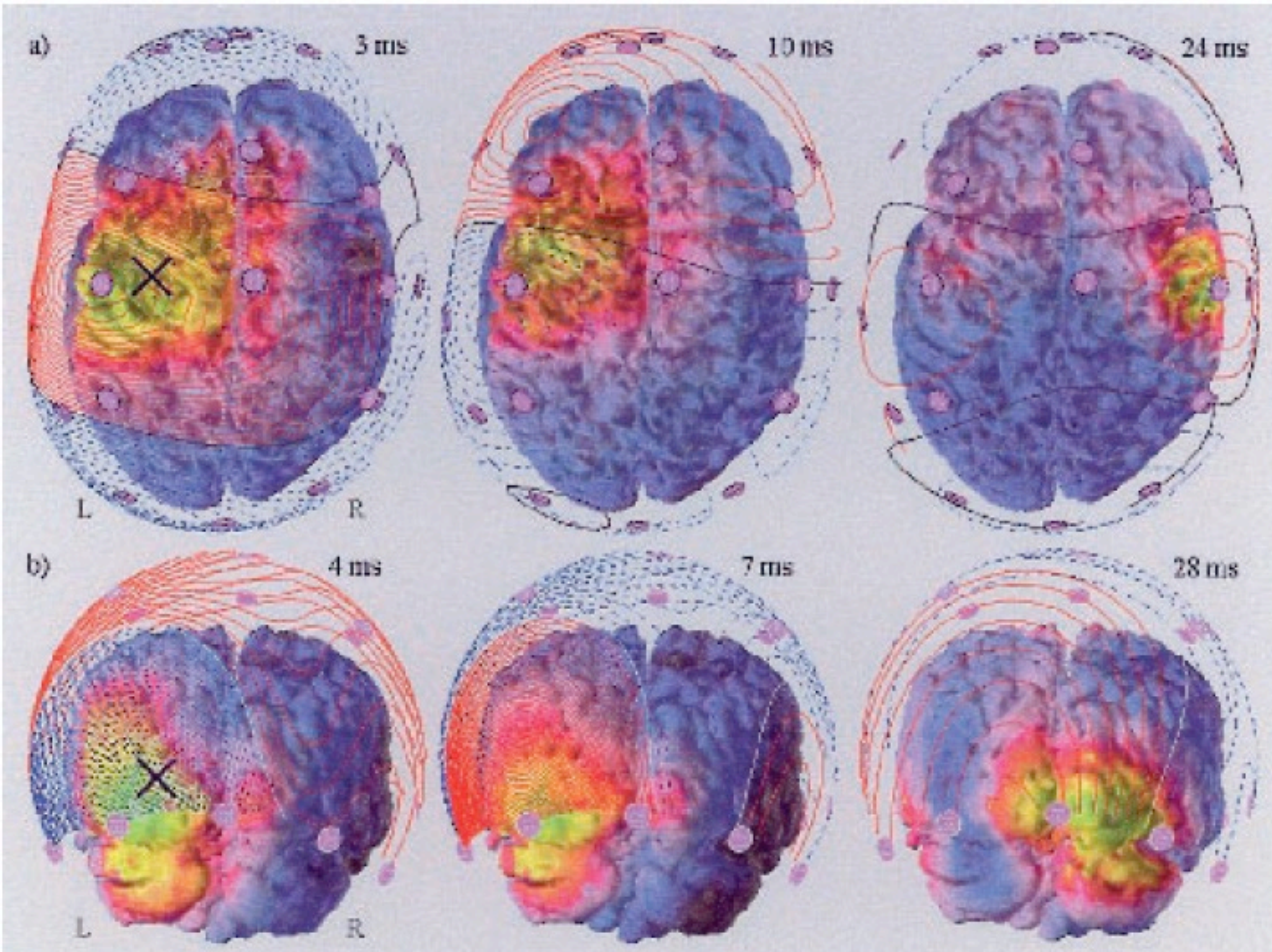


Jung and Ziemann 2009 J Neurosci 29: 5597-5604

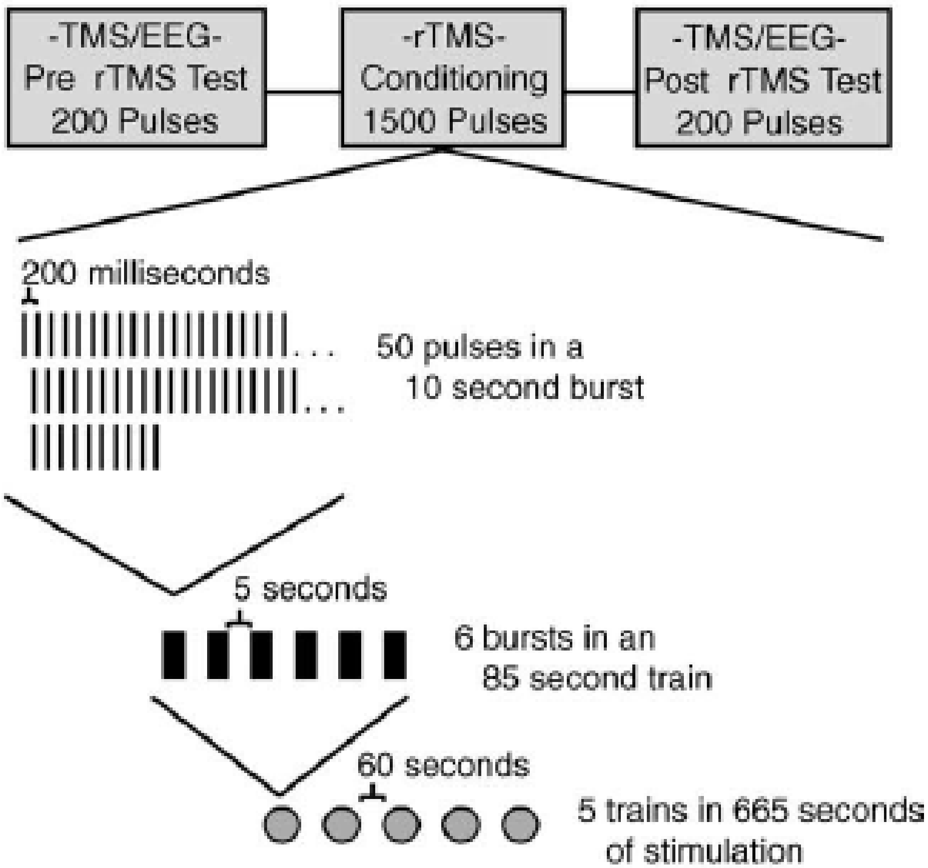
Exploring the spatio-temporal dynamics of brain networks with simultaneous TMS-EEG

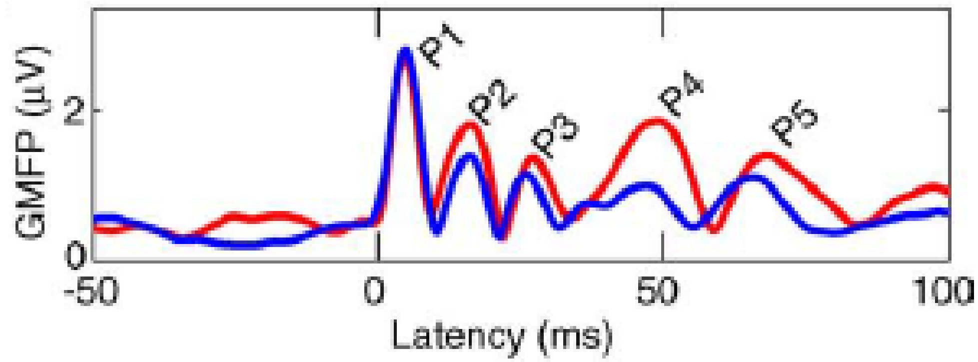
-Changes in topographic EEG activity due to TMS pulses

Illmoniemi et al., 1997



Observing LTP-like effects using simultaneous TMS/EEG



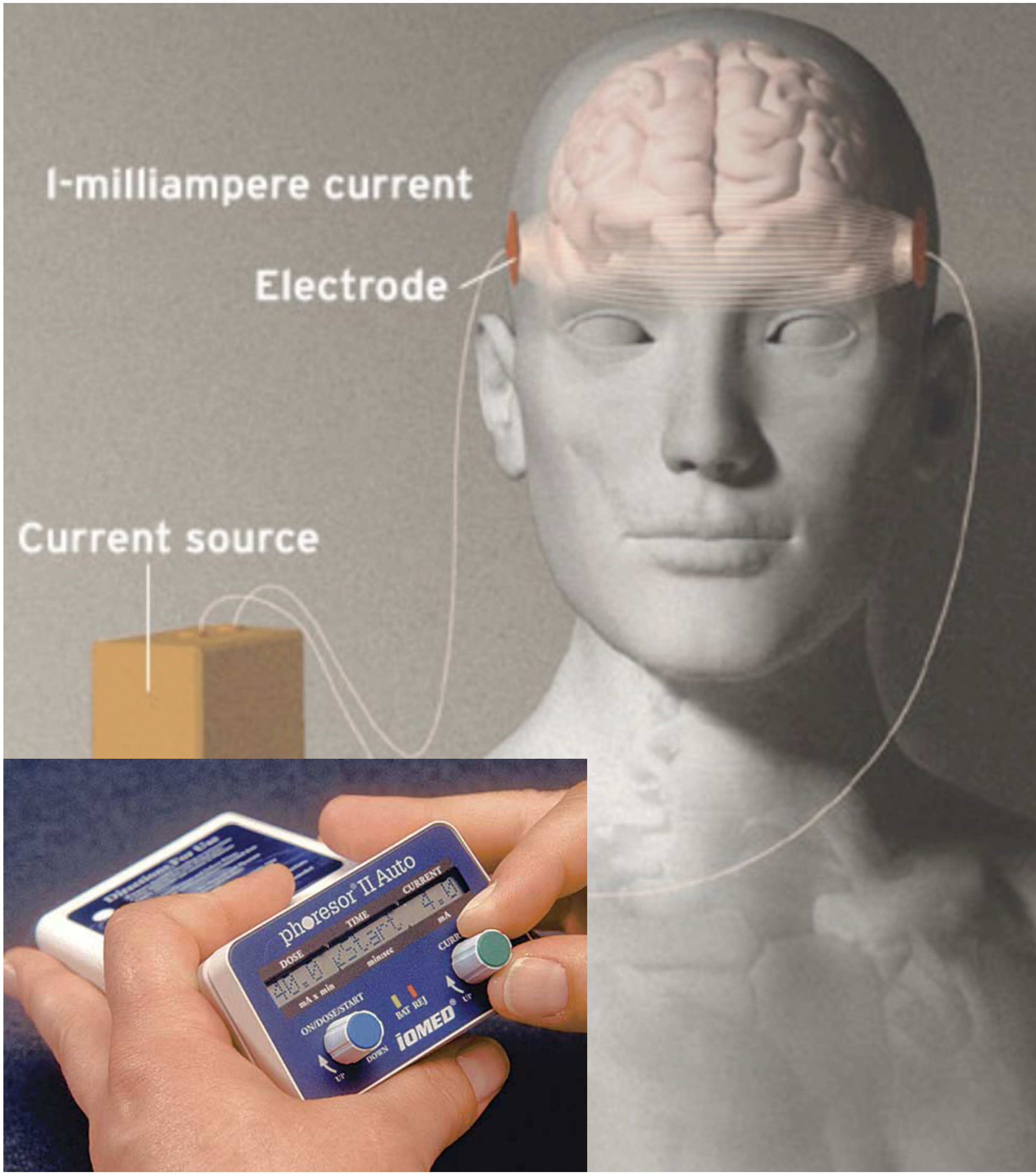


5 Hz conditioning rTMS results in enhanced amplitudes of TMS evoked potentials (TEPs)

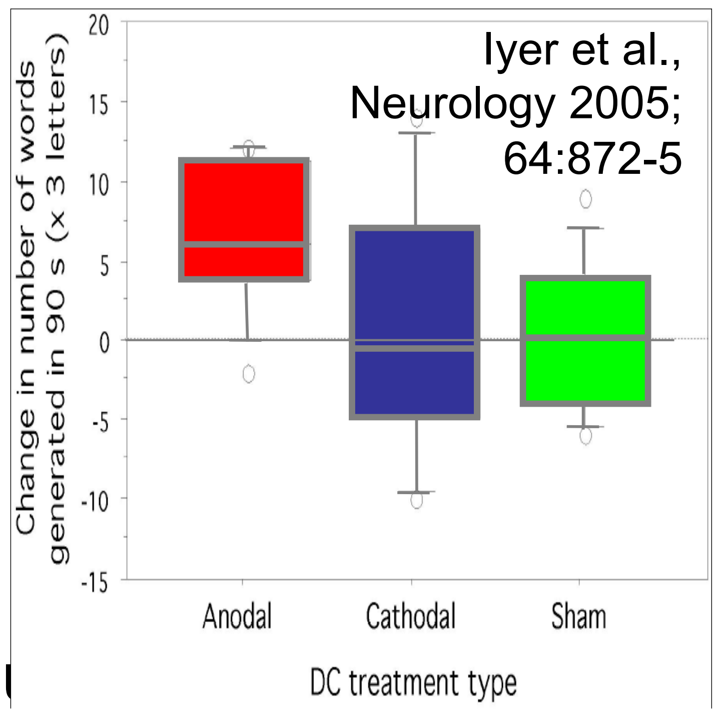
Global averaged EEG power across 64 electrodes

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

Transcranial Direct Current Stimulation



- Direct current (1 mA) polarizes cortex
- Anodal facilitates, Cathodal inhibits
- Effects last hrs
- Safe, painless
- Enhances verbal fluency, word recall, recovery of function post stroke
- Cheap, portable



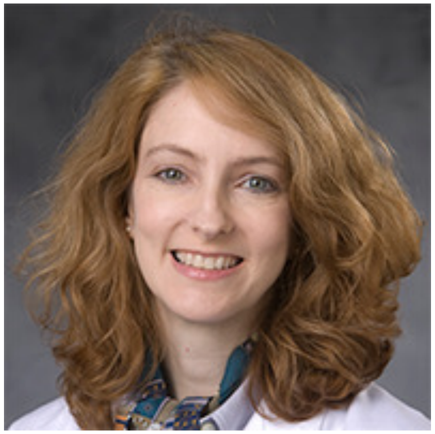
TMS-tDCS Strengths / Limitations

- Temporal precision
  - TMS: Pulse <1ms, useful complement to imaging & EEG; can modulate frequencies
  - tDCS: low resolution: offline, pre-post changes
- Spatial resolution
  - TMS: ~0.5 cm; has transsynaptic action but E-field cannot be focused at depth
  - tDCS: low resolution (although can be improved)
- Mechanisms of action
  - Both are tools to establish causality, to test hypotheses generated by imaging and EEG
  - But TMS has a larger range of effects: a better toolbox

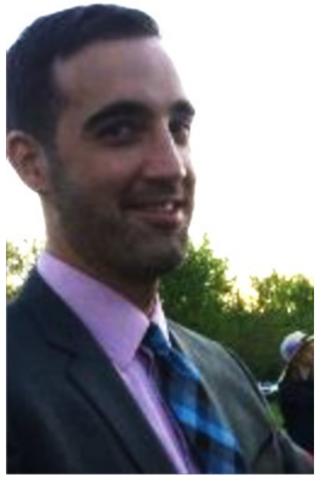
Summary: State of the art and the future

- 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

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



Lisanby, MD



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