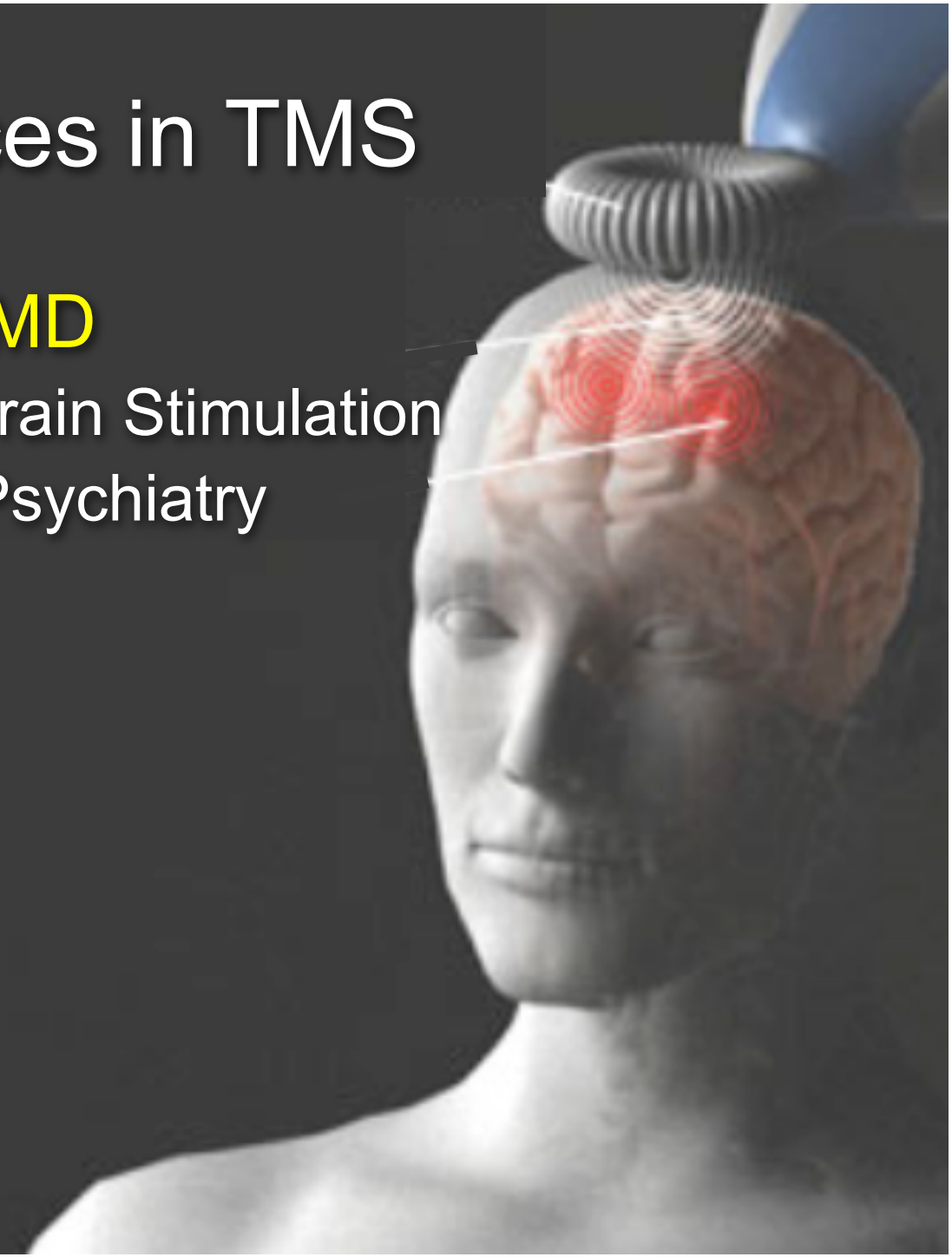
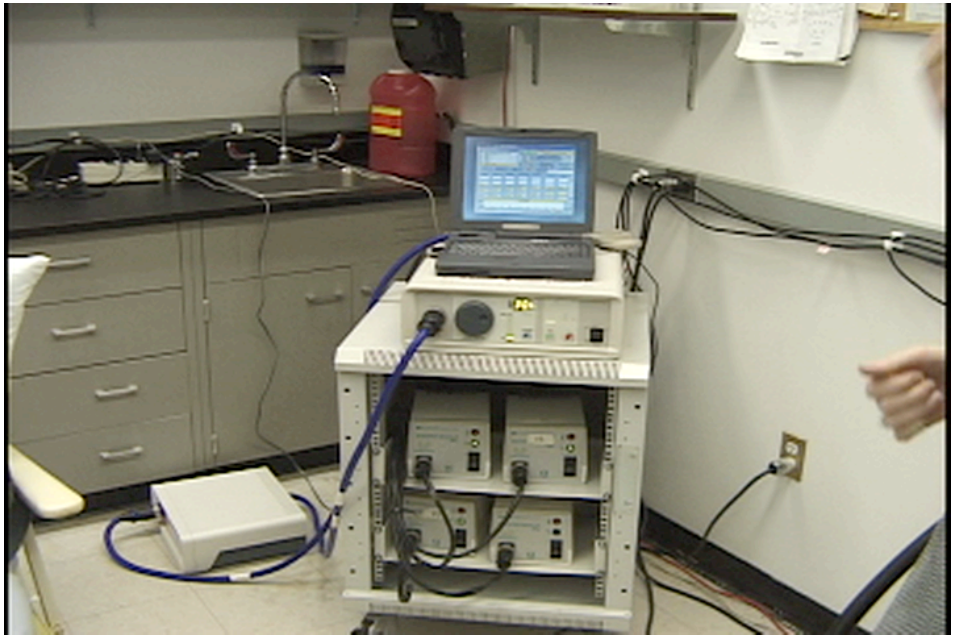
Recent Advances in TMS

Sarah H. Lisanby, MD
Director, Division of Brain Stimulation
Professor of Clinical Psychiatry
Columbia University



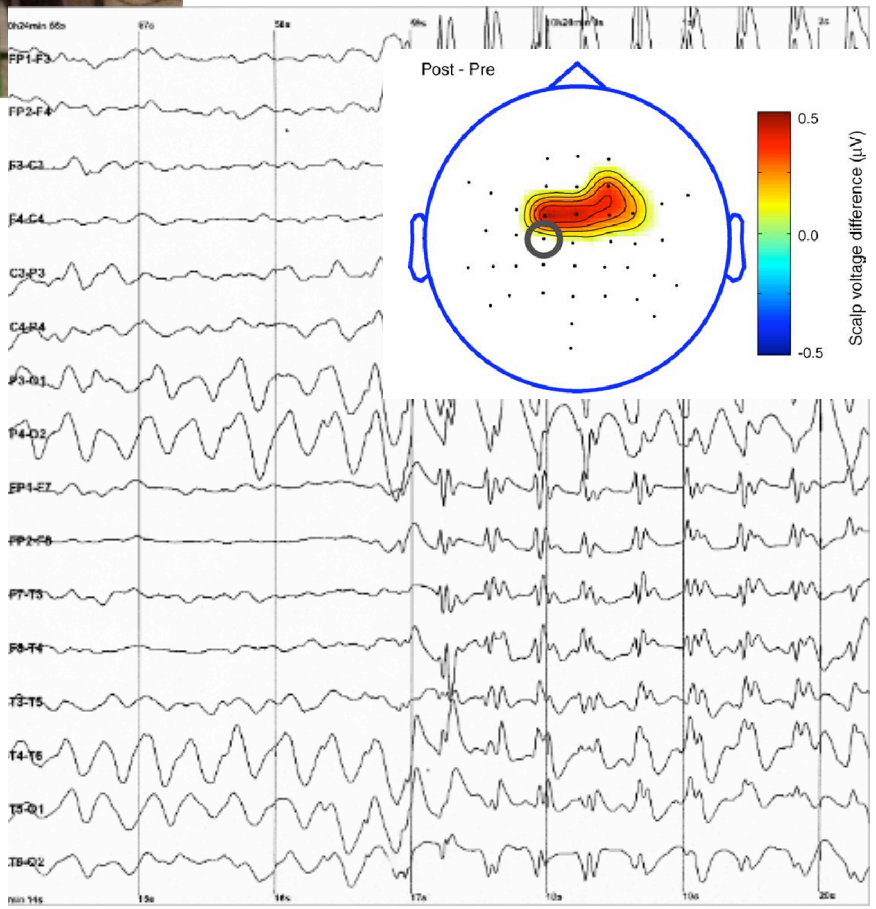


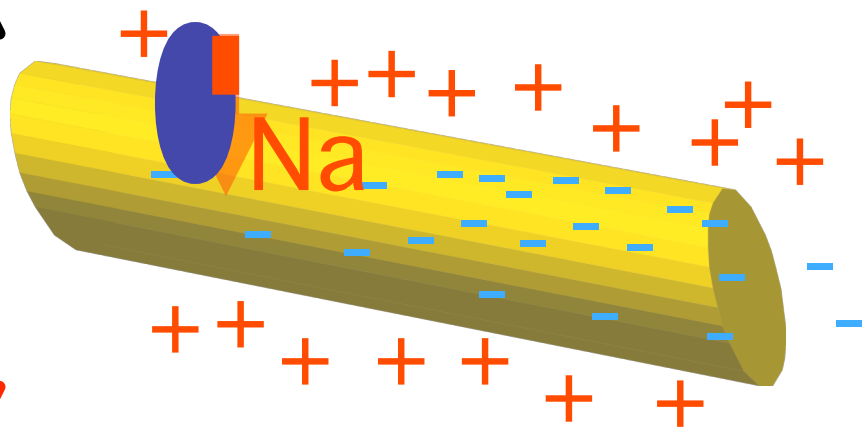
Outline

- TMS technology primer
- TMS Biomarkers
  - Techniques & measurement issues
- Examples

B field ------> MEG

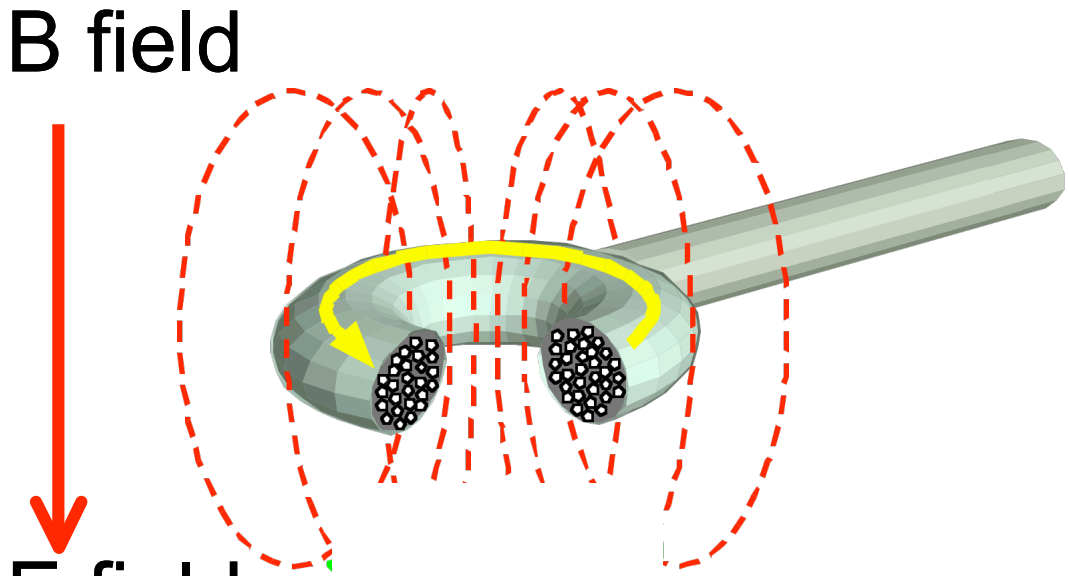
E field ------> EEG - ERP

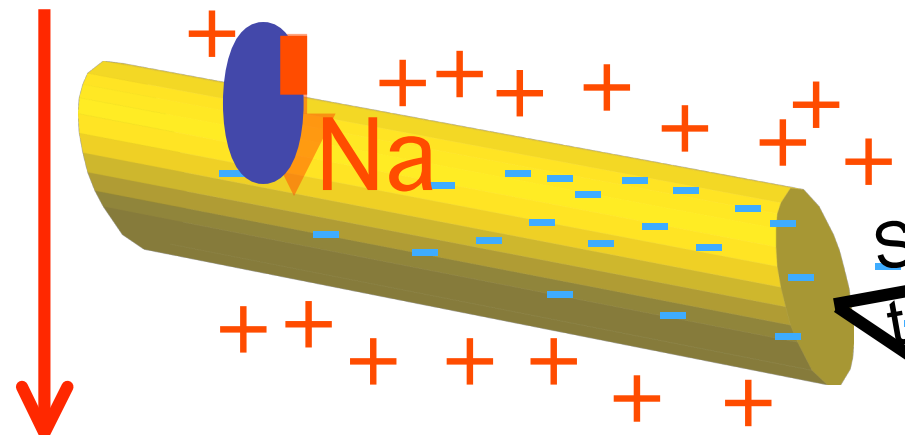




Neuronal depolarization

Mechanisms: Single Pulse TMS





Neuronal depolarization

Supra-threshold

Sub-threshold

Behavior

Transsynaptic action

Pre/post synaptic action

Neurotransmitter release

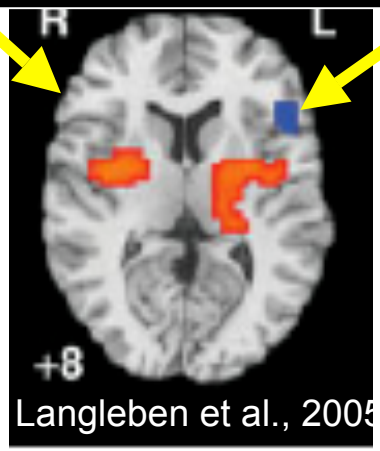
ICI / ICF

Strengths / Limitations

- Temporal precision
  - Pulse <1ms, but action can be lasting
- Spatial resolution
  - ~0.5 cm; has transsynaptic action but E-field cannot be focused at depth
- Tool to establish causality, with temporal and spatial precision
  - Test hypotheses generated by imaging and EEG
  - Absence of effect doesn't prove the area is uninvolved – may be methodological artifact
  - Interactions between illness/meds and TMS action

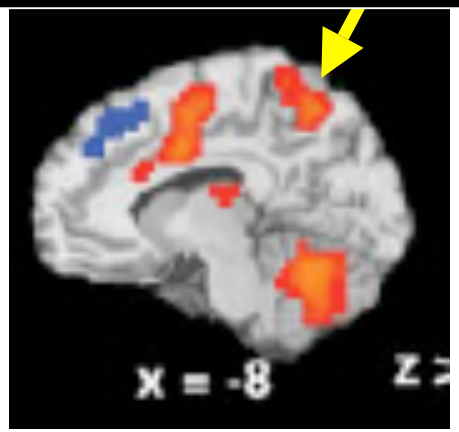
Acute TMS/Behavior Deception

- Spatial and temporal mapping of behavior-related circuitry
- Illustrates value of site and time specificity as control conditions
- But how can we know this isn't a methodological artifact?



Langleben et al., 2005

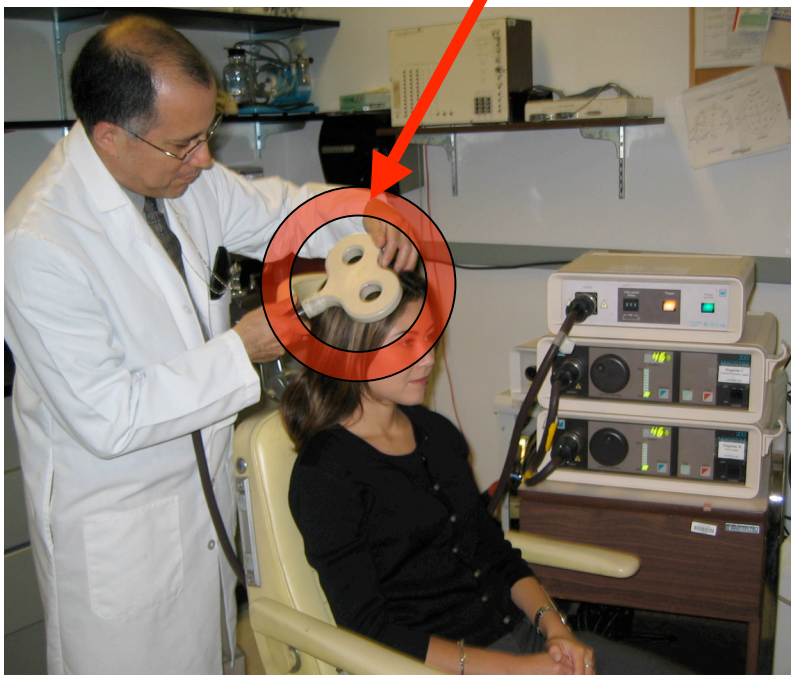
red: truth>lie
blue: lie>truth

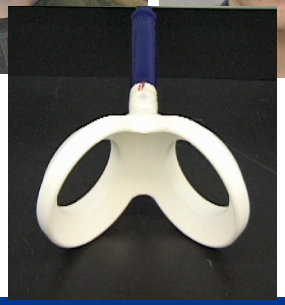


TMS Dosage Parameters

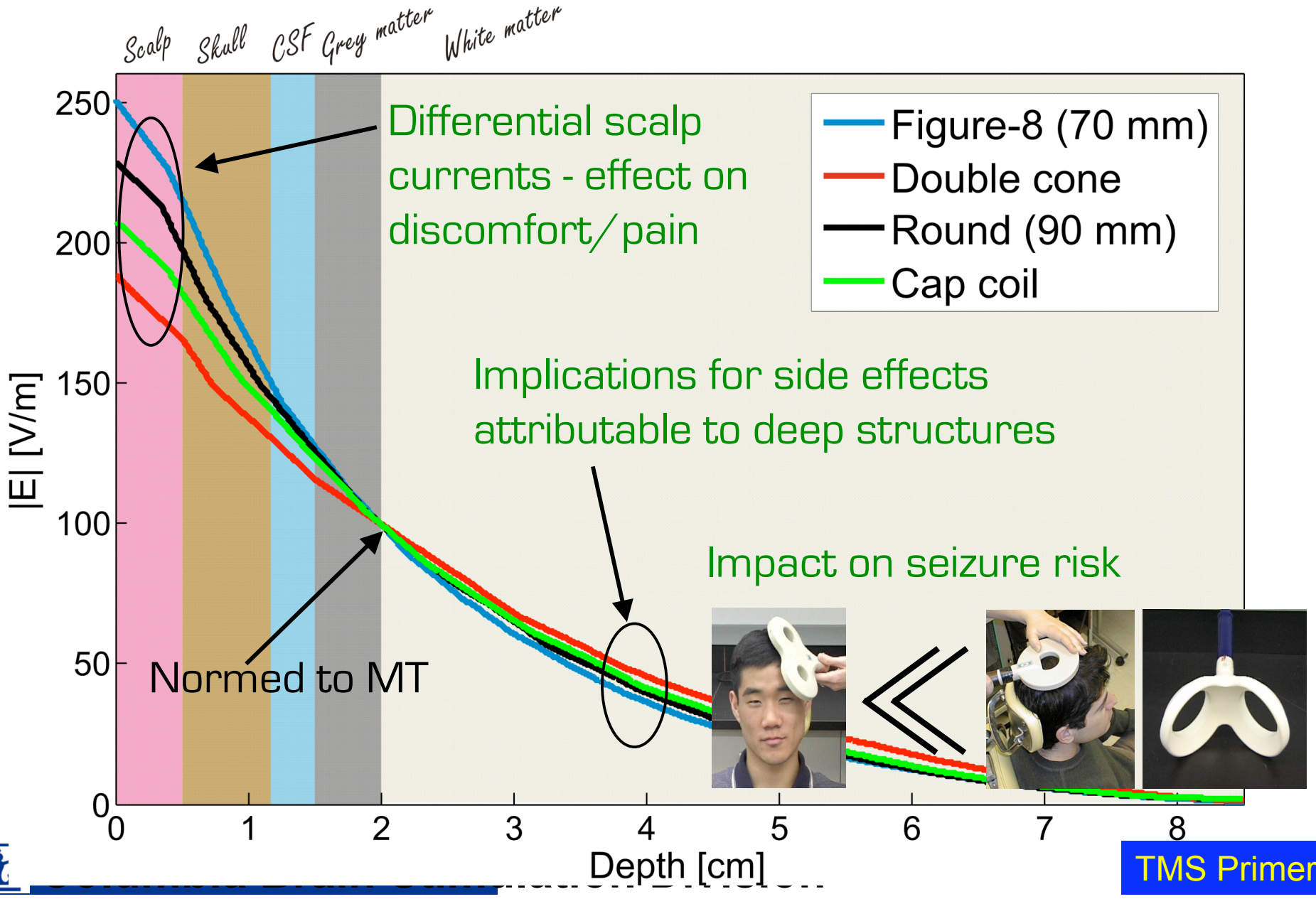
Orientation (current direction), Shape, Field distribution, Inductance (PW), Decay with distance

Coil

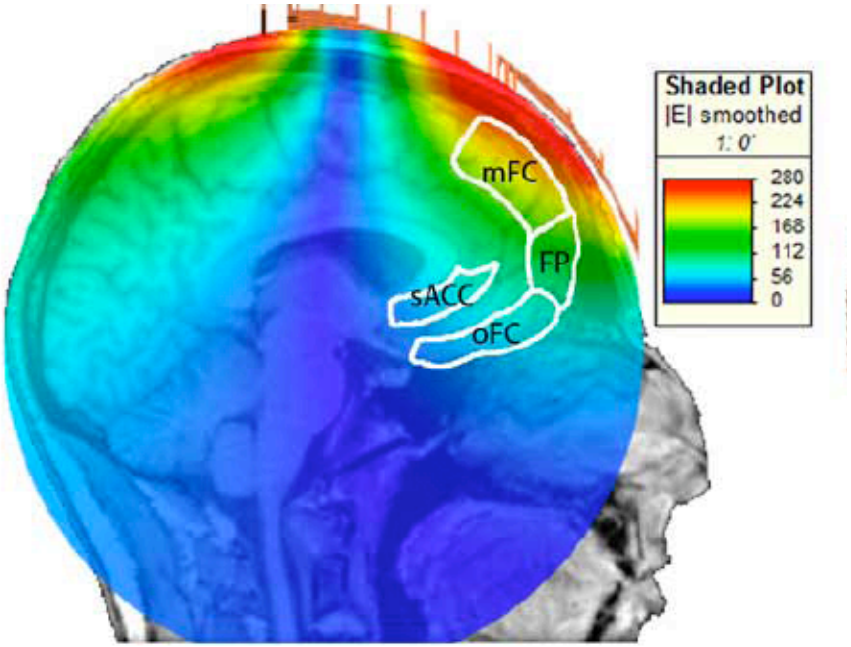




Field Drop-Off in Depth



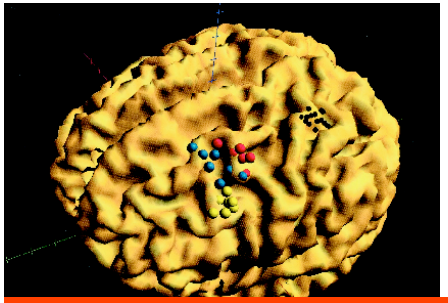
Depth versus Focality



Deng, Peterchev, Lisanby IEEE BME 2008

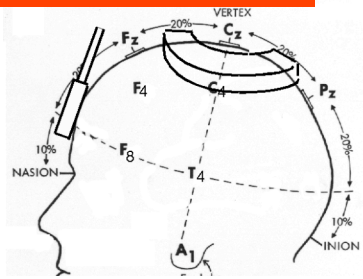
TMS Dosage Parameters

5cm Rule



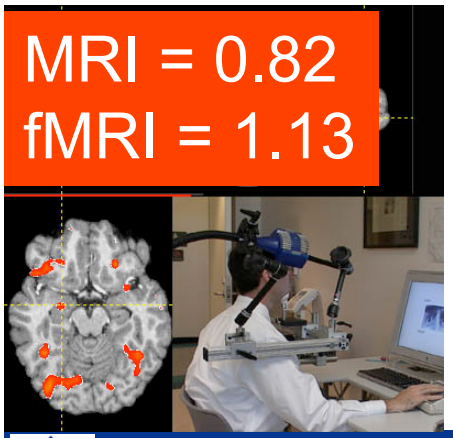
Effect size = 0.34

10-20



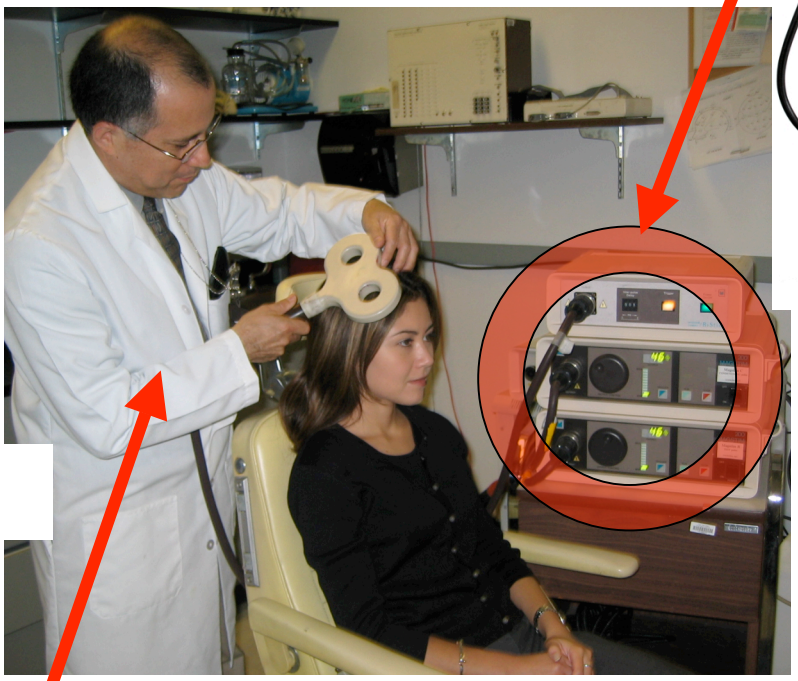
Frameless Stereotaxy

MRI = 0.82
fMRI = 1.13



Columbia University Brain Stimulation

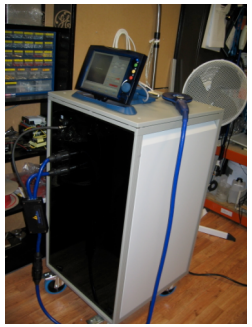
Device



Coil navigation systems

Higher frequencies

Magnetic Seizure Therapy

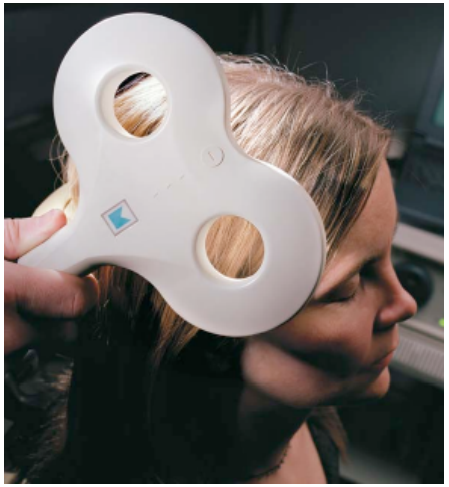


Sack et al. 2009

TMS = E-field

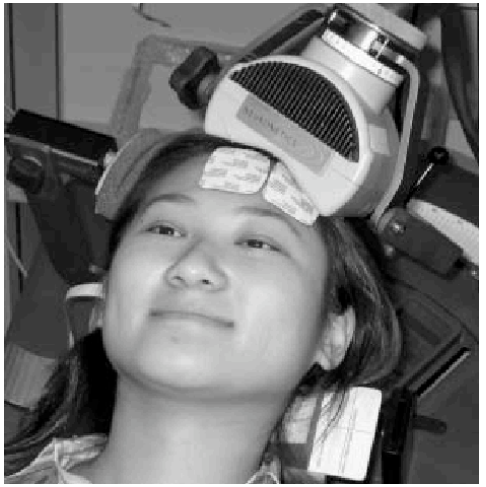
Implies risk of unblinding and somatosensory confounds on ERP and Oscillation effects

Coil Tilt
Sound



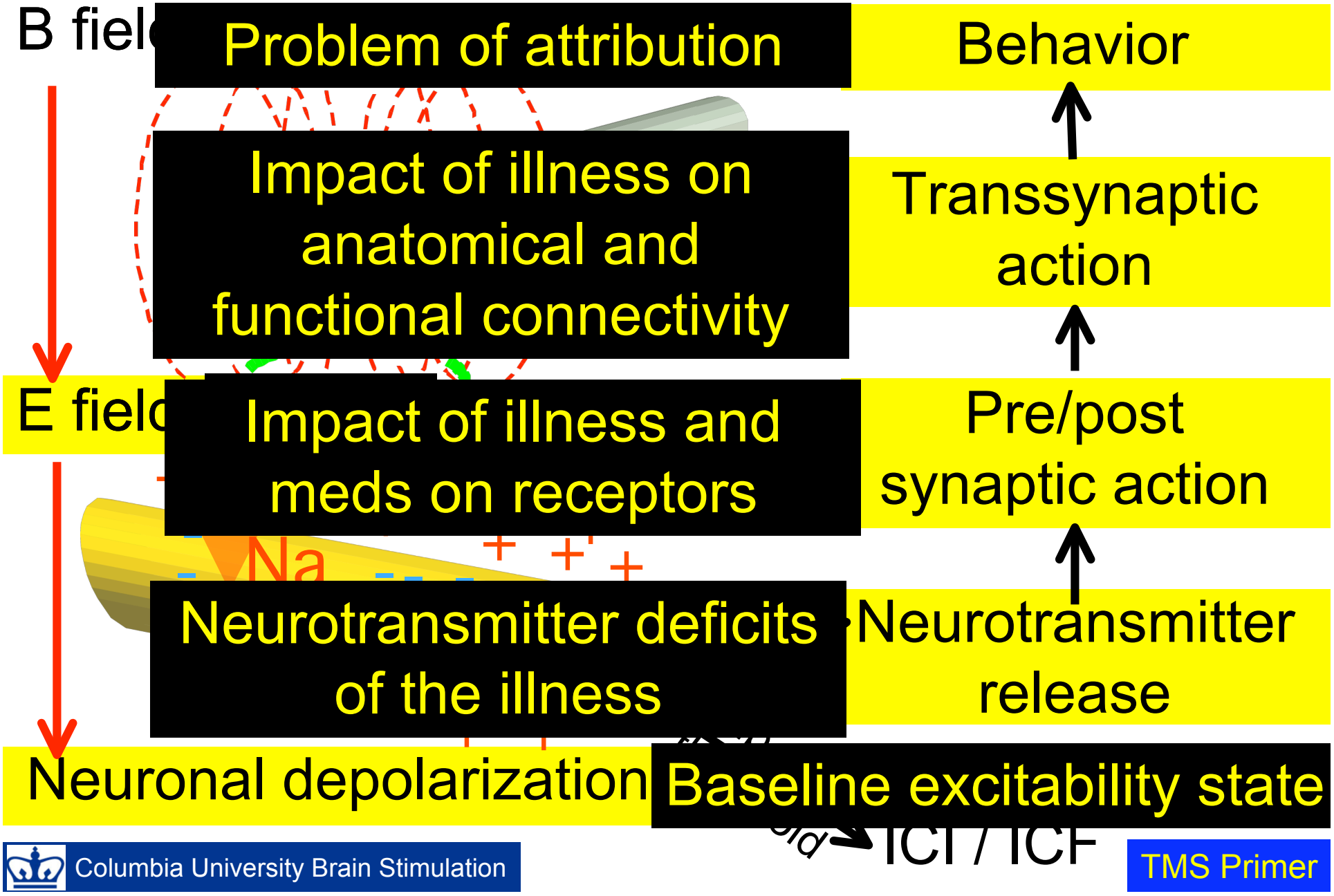
Metal Shield
Sound
Look

E-Field Cancellation:
Sound; Look
Dec. feel of active

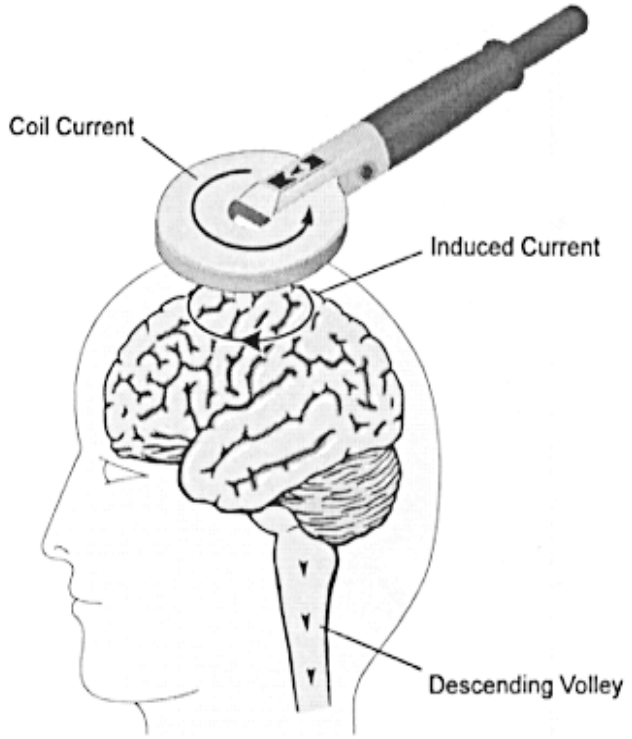


Scalp Stim:
Sound, Look,
Simulates feel of active

Confounds of Illness and Meds



Acute TMS/EMG Motor Circuitry



- Motor evoked potential (MEP) measures
  - Amplitude
  - Latency
  - Threshold
- Measures
  - CST integrity
  - Ion channel conductivity
  - Neuronal membrane excitability

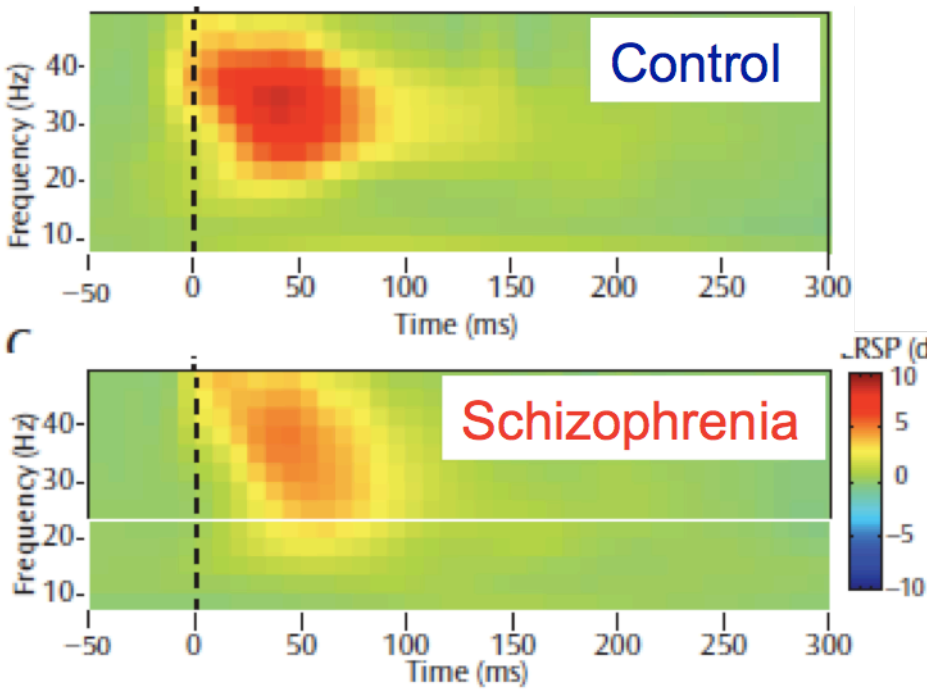
Tracks acute changes in cortical excitability

Reliable and reproducible

But limited to M1

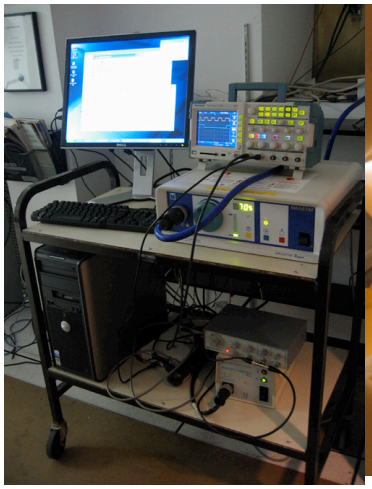
Acute | TMS/EEG | Cortical excitability

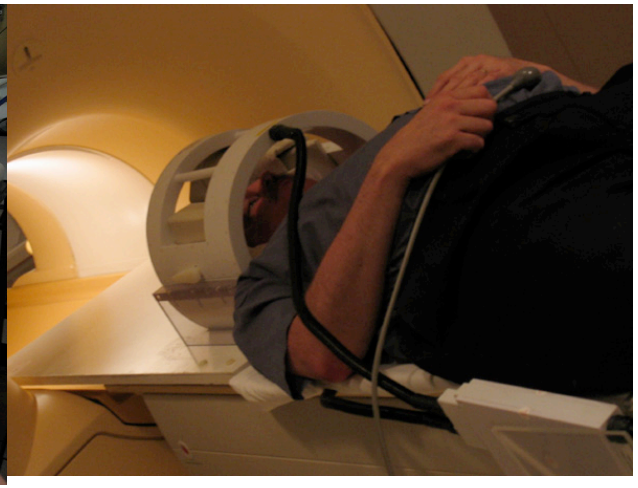
- Probe extra-motor cortical excitability
- Passive, task-independent
- Probe of ability to support neural oscillations – gamma
- Somatosensory confound

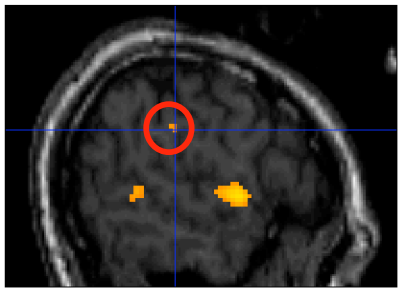


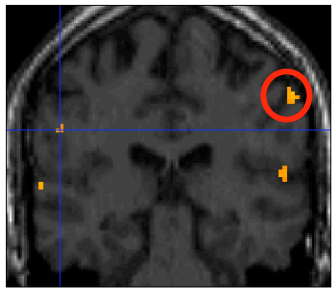
Mathalon & Ford. Am J Psych 2008
Ferrarelli et al. Am J Psych 2008

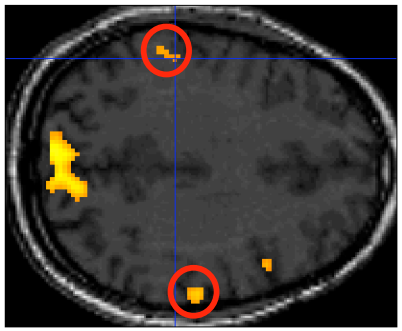
Acute TMS/fMRI Connectivity

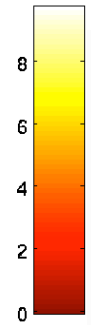


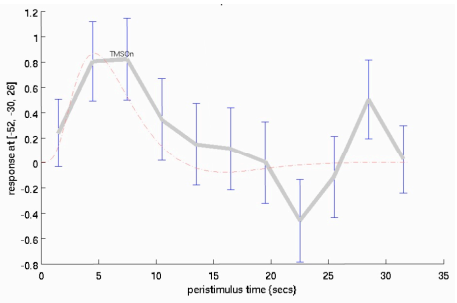










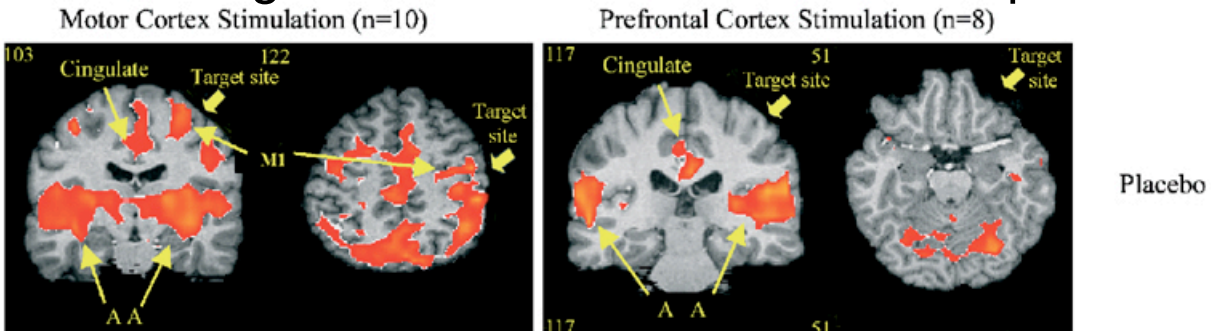


- TMS/fMRI interleaving
- Examine functional connectivity
- Probe pathophysiology
- Index of treatment effect
- Somatosensory confound

Concomitant Rx-Stimulation Interaction

- Interaction of TMS induced neurotransmitter release in presence of med-induced receptor blockade
- Impact of med on excitability

Effect of Lamotrigine on TMS-induced BOLD response



•Dissociation between med effect on MT and excitability of other brain regions.

•MT may not always track with drug effects on excitability.

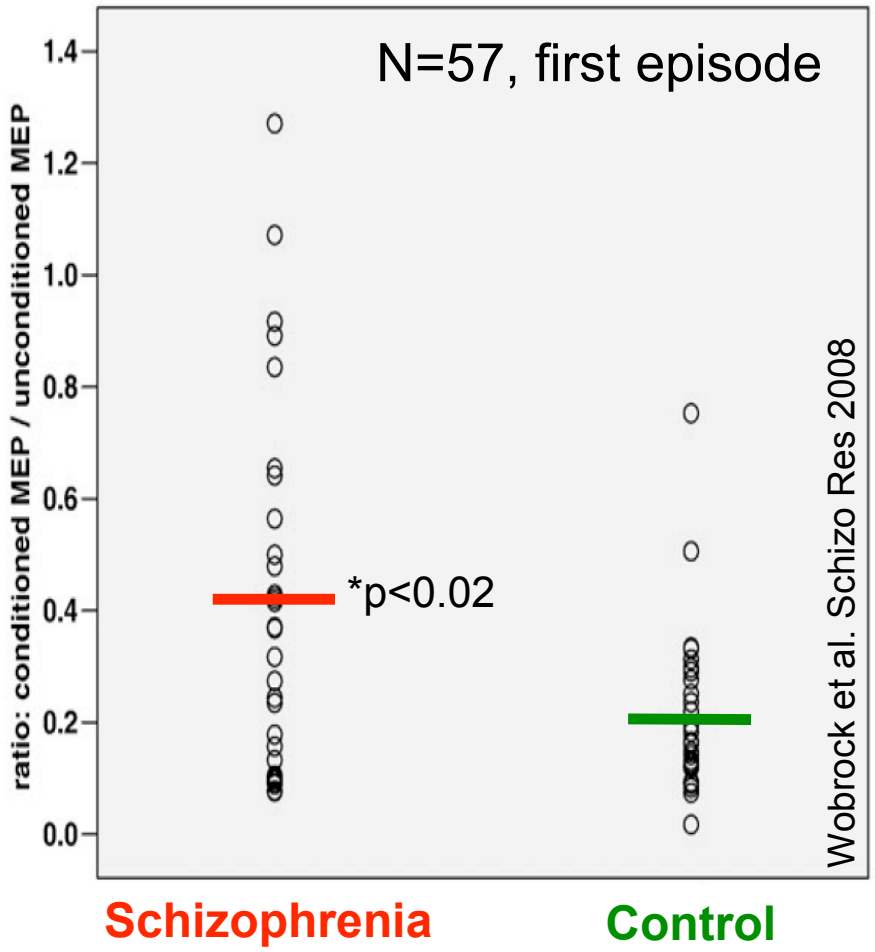
•Limitation in using MT as safety gauge and to individualize dosage

Decreas

nus
)o
luced
ses)

Acute ppTMS/EMG Motor Cortex GABA

- Abnormal in Schizophrenia

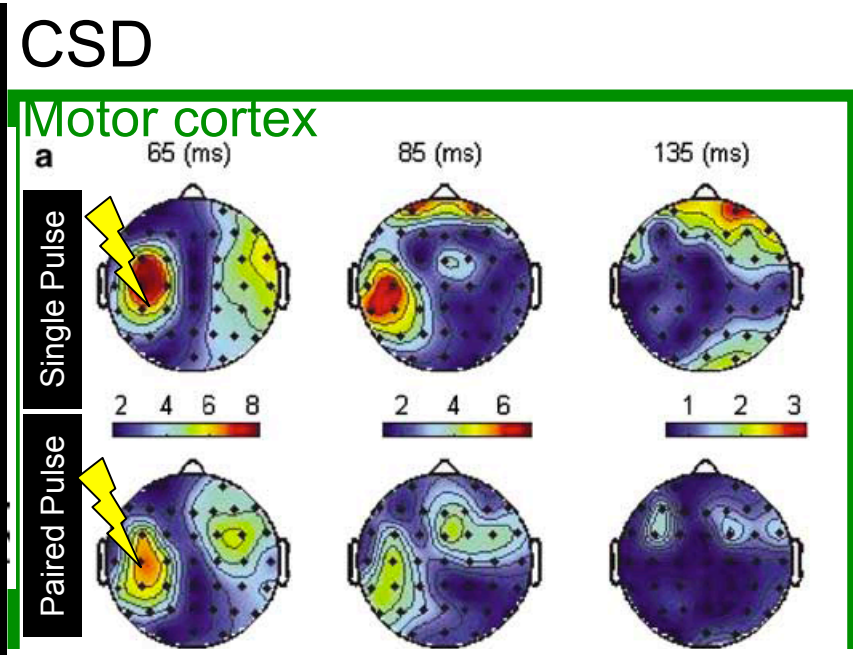


- In vivo measure of GABA function
- Tracks changes in response to intervention
- Pharmacological underpinnings well studied
- Reliability well established

- Intracortical Facilitation - NM

Acute | ppTMS/EEG | Cortical GABA

- Probe GABA function outside M1
- Examine functional connectivity
- Pharmacological underpinnings less studied
- Reliability less established



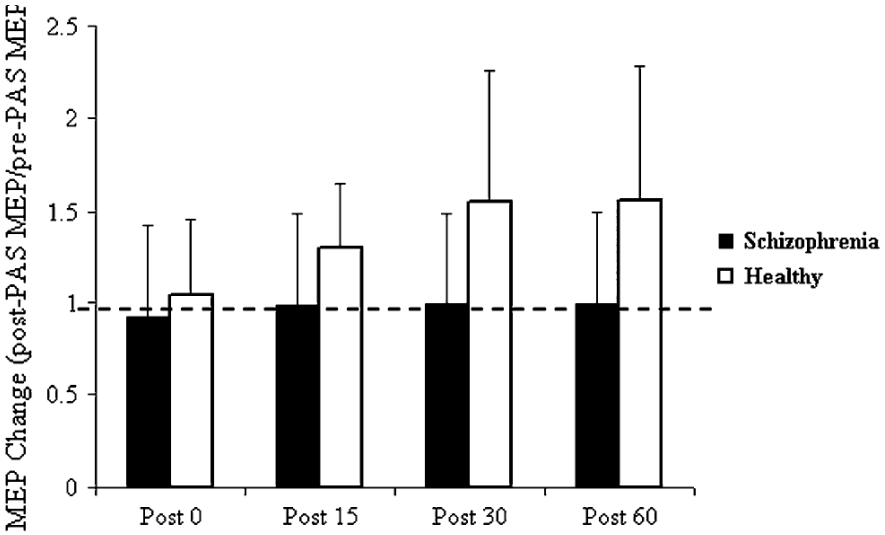
Daskalakis et al Neuropsychopharm 2008

Chronic PAS-TMS/EMG Synaptic Plasticity

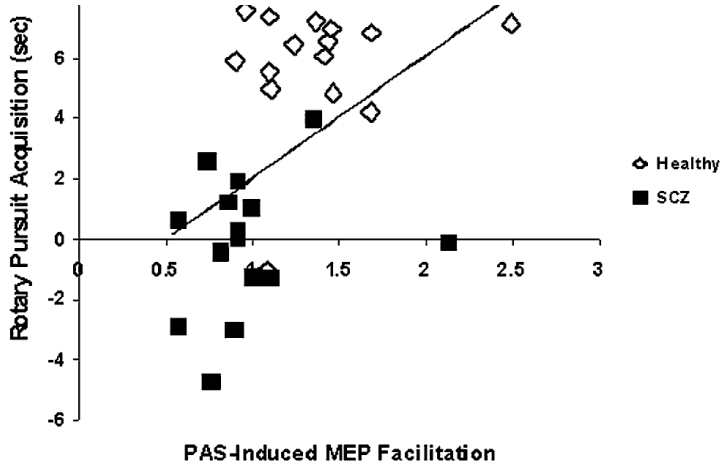
Probe corticospinal tract excitability to detect deficient synaptic plasticity in schizophrenia

Baseline Block 1 Block 2 Block 3

Deficient MEP enhancement

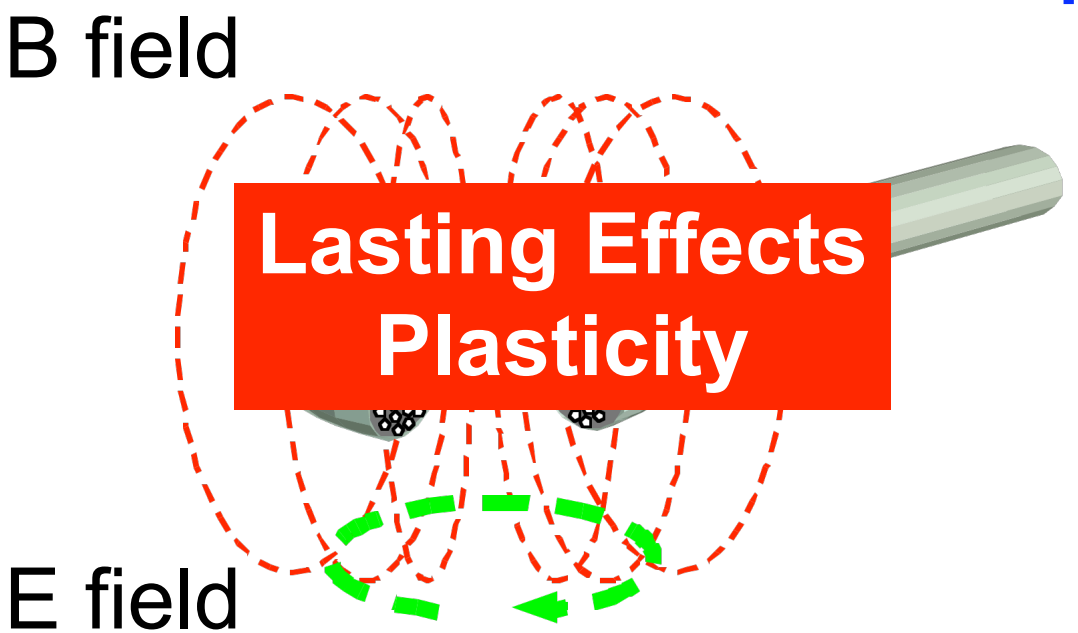


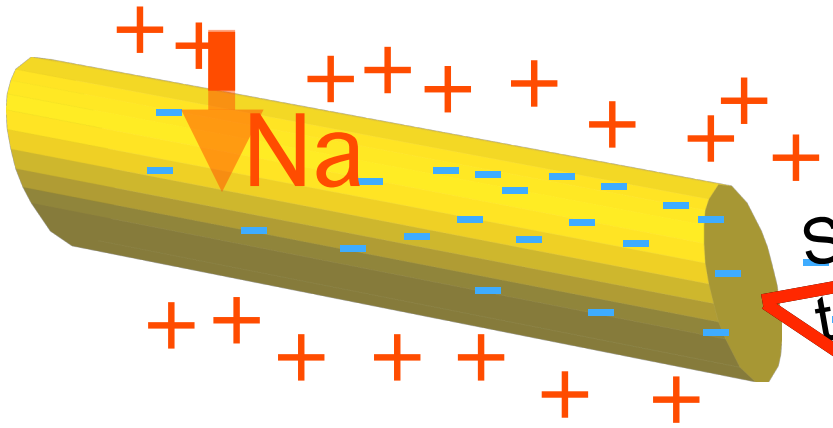
Plasticity correlates with skill learning



Frantseva et al Cerebral Cortex 2008

Mechanisms: Repetitive TMS





Supra-threshold

Sub-threshold

Behavior

Transsynaptic action

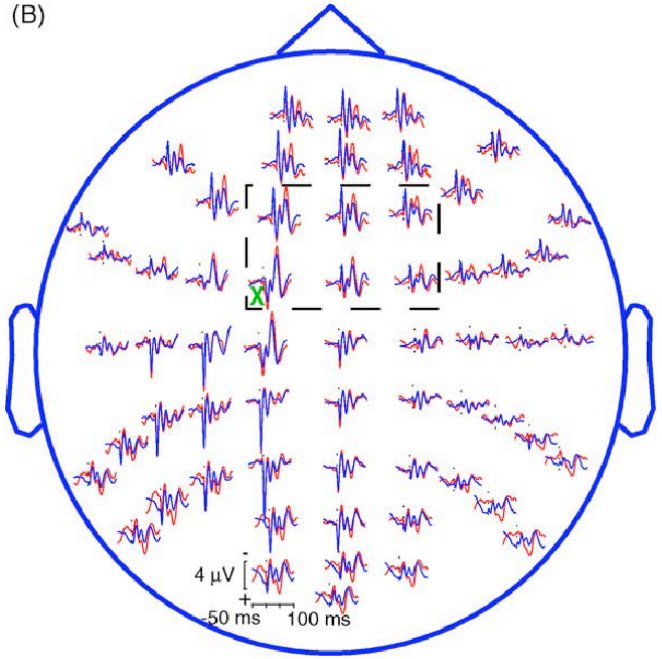
Pre/post synaptic action

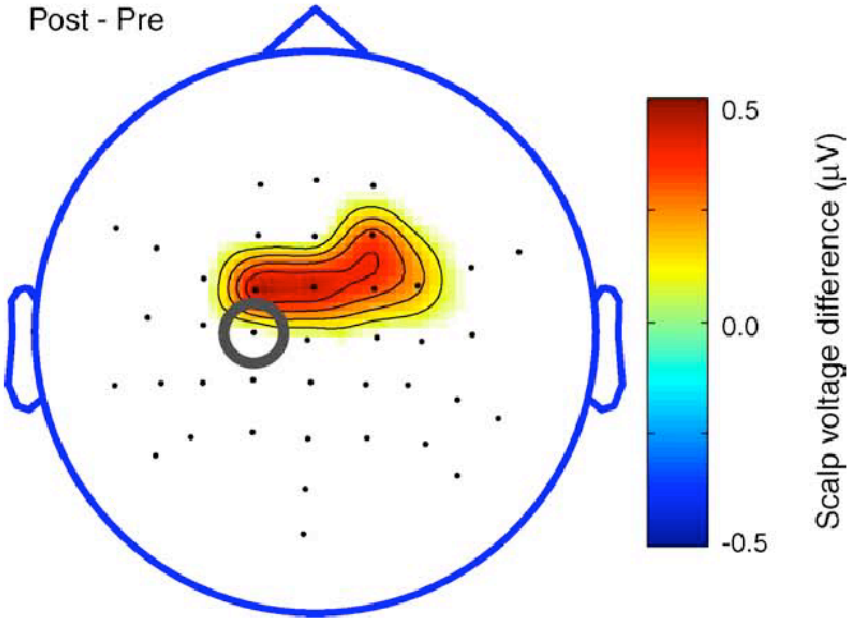
Neurotransmitter release

ICI / ICF

Mechanisms: Repetitive TMS

Tool to Modulate Cortical Plasticity and track dynamic changes in plasticity

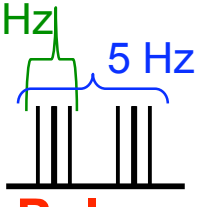


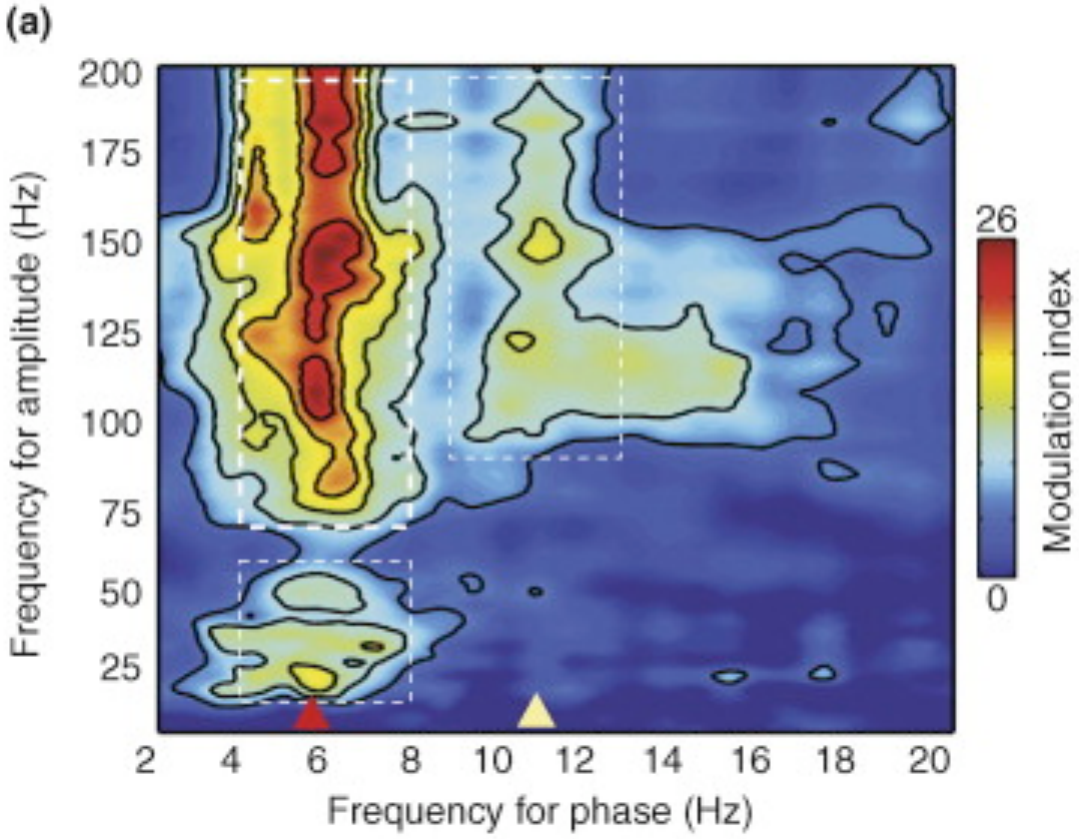


Esser et al., Brain Res Bul 2006;69:86-94

rTMS Dosage Parameters

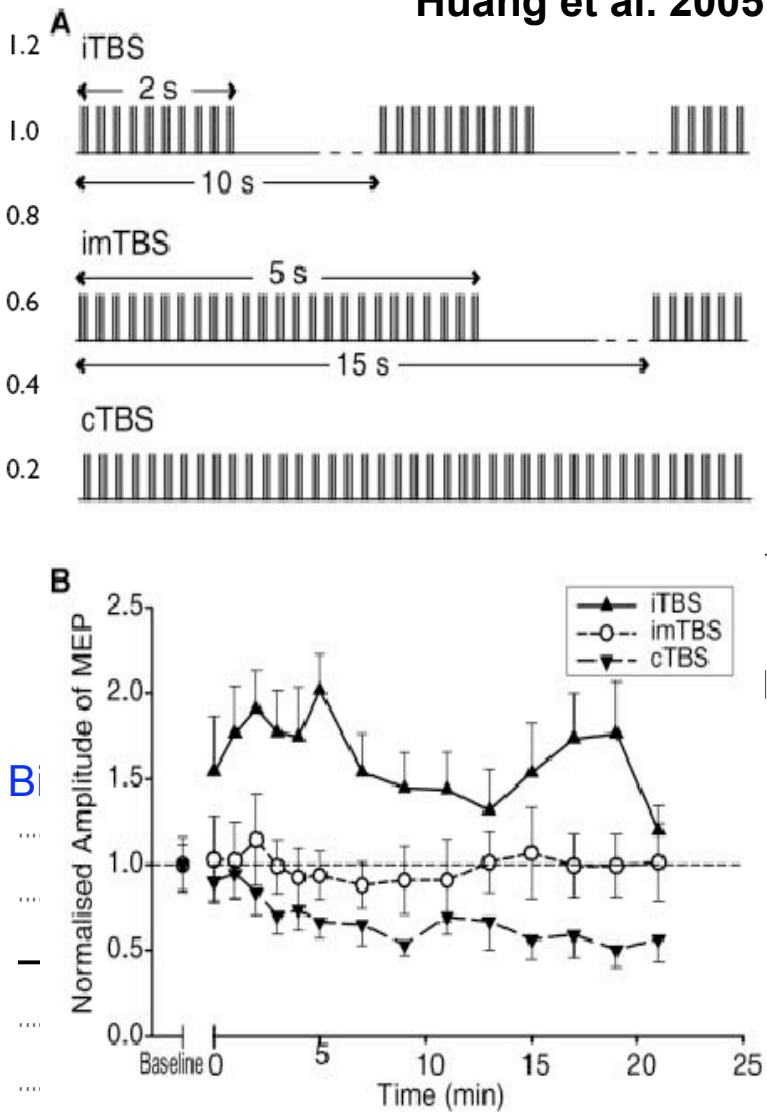
Simple/Compound Priming, Theta Burst





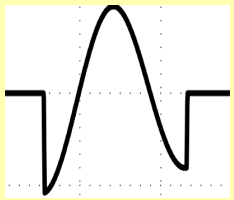
Theta-Gamma Phase Amplitude Coupling

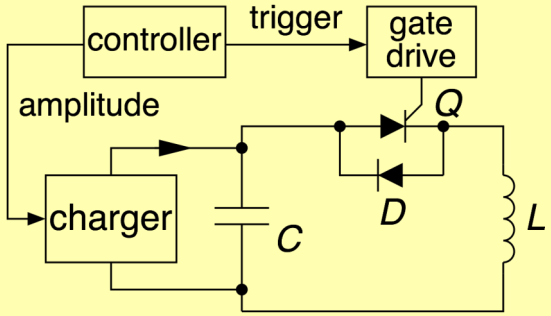
Huang et al. 2005



Controllable Pulse TMS (cTMS)

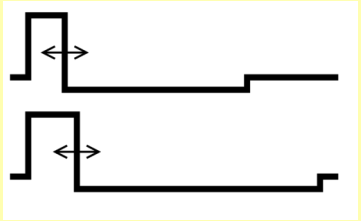
Conventional TMS



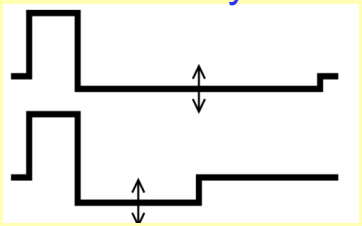


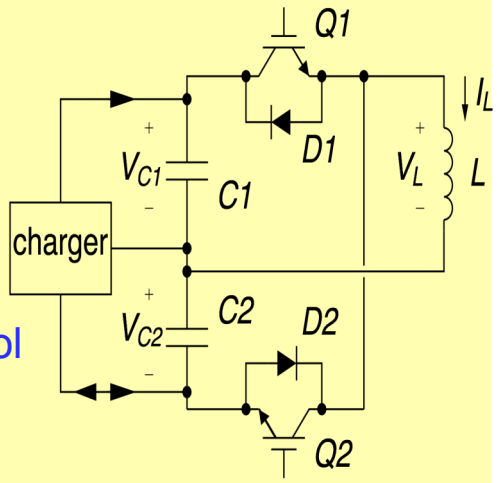
cTMS

Pulse width control



Directionality control



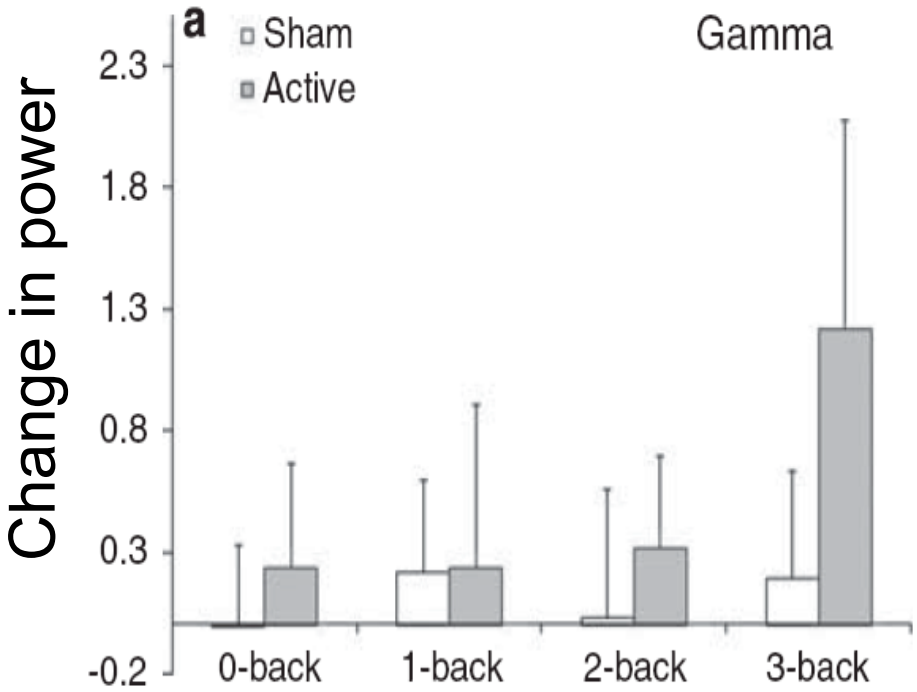


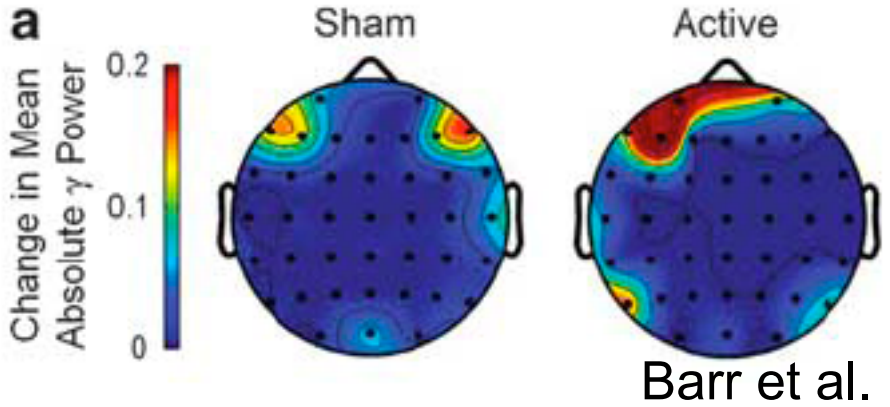
- Novel circuit topology
- User control of shape, width, directionality
- High frequency unidirectional rTMS
- *Novel biomarker – first in vivo assessment of neuronal membrane time constant*

Peterchev, Jalinous, & Lisanby 2008

Acute | rTMS/EEG/Behavior | Gamma

- Focal induction of gamma oscillations
- Permits assessment of functional role of neural oscillations
- But no impact on behavior, so unclear relevance

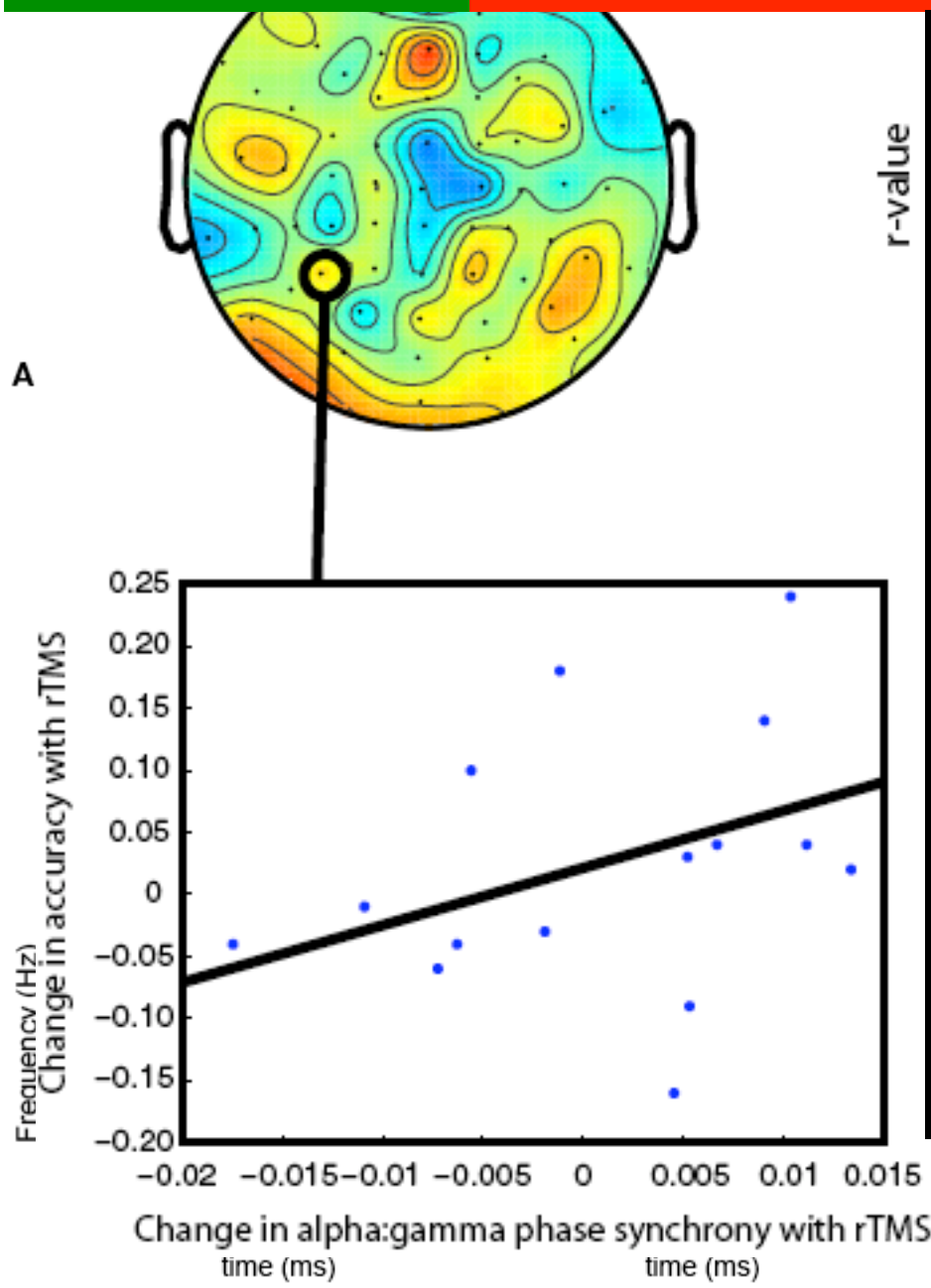




Barr et al.

Neuropsychopharmacology (2009) 34, 2359–2367

Acute rTMS/EEG/Behavior Alpha-Gamma



- Behavioral and physiological effects of TMS vary across individuals
- Is this variance noise or meaningful signal?

rTMS-Induced Change in Alpha-band Power (dB)

Hamidi et al. 2009

Example

Individual Differences in "Cognitive Reserve"

- The ability to maintain performance despite aging and/or dementia
  - Neural Reserve
    - Normally occurring brain networks that are efficient and resilient to task demands
  - Neural Compensation
    - Alternate networks recruited due to inability to utilize healthy networks.

A new paradigm to study cognitive reserve and resilience

- Identify individual differences in network expression associated with working memory performance
  - Validate that network with fMRI-guided TMS (Luber et al, 2007)
- Model cognitive reserve in healthy subjects via sleep deprivation induced memory impairment
  - Identify cognitive reserve network (Habeck et al 2005)
  - Test network using fMRI-guided TMS to remediate function (Luber et al., 2008)
- Intervention development to prevent WM impairment
  - Attempt to prevent the development of WM impairments (Luber et al., in preparation)

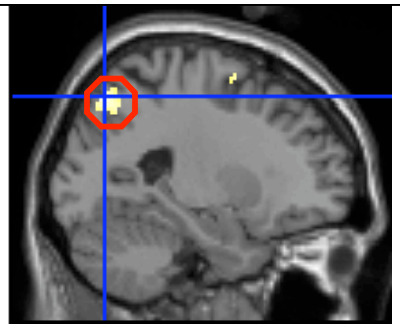
Modulating Cognition

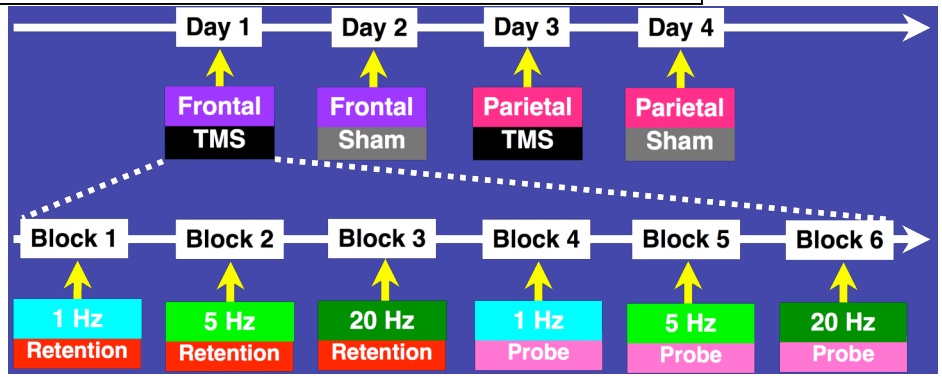
Research Report

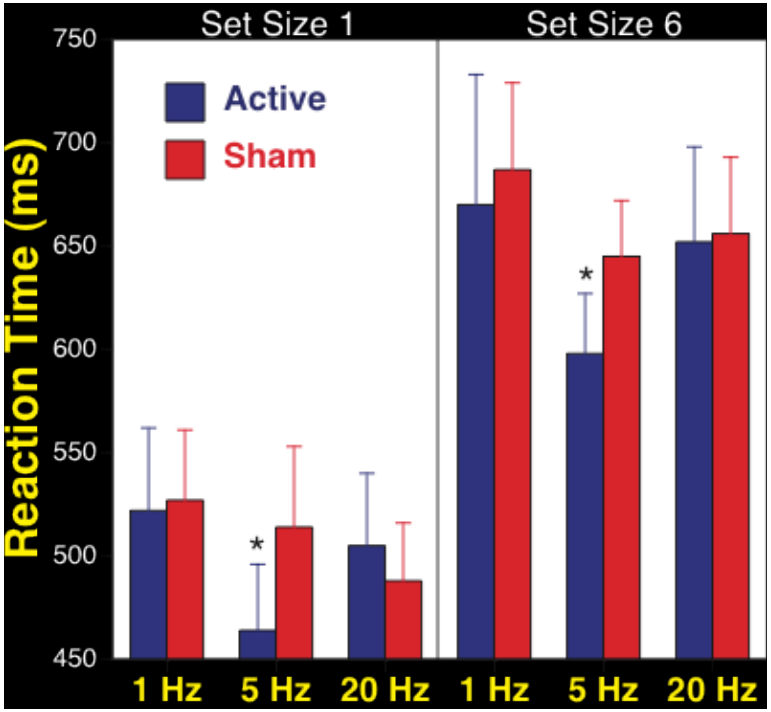
Brain Research 2007; 1128: 120-129

Facilitation of performance in a working memory task with rTMS stimulation of the precuneus: Frequency- and time-dependent effects

B. Luber[a,b,*], L.H. Kinnunen[a], B.C. Rakitin[c,d], R. Ellsasser[a], Y. Stern[c,d], S.H. Lisanby[a,b]





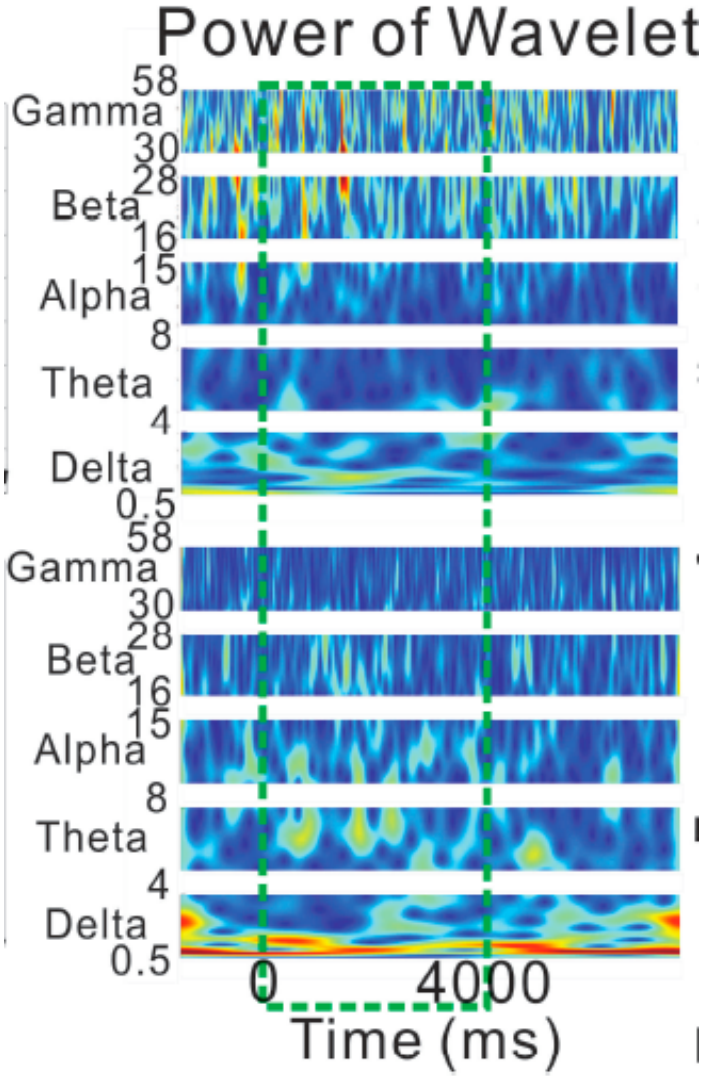


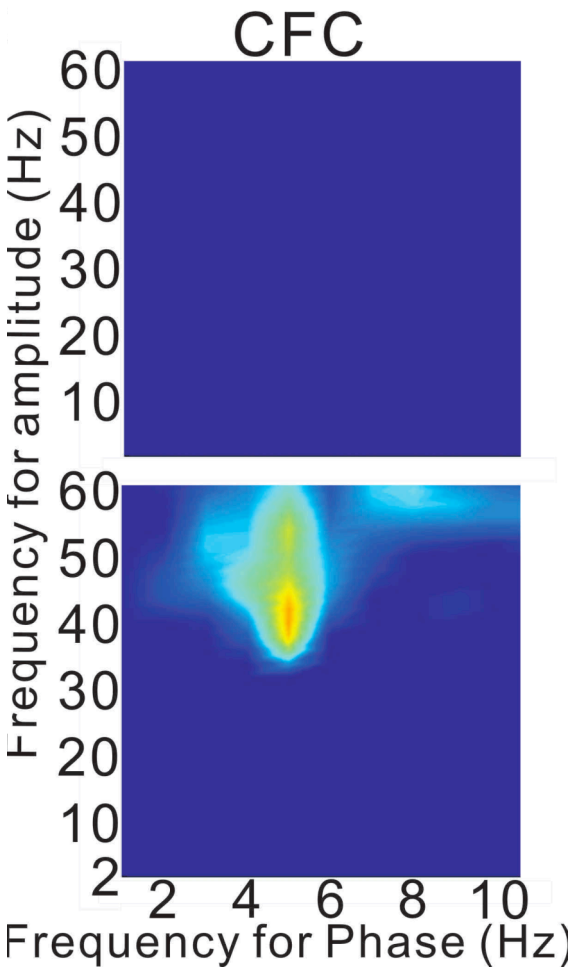
- Dose-finding study, within-subject cross-over, n=44 healthy subjects
- 5 Hz TMS to precuneus reduced RT by 50 ms
- Replicated (n=21), phase-dependent effect

Example

Theta Modulation of Gamma as Mechanisms for TMS WM Enhancement?

Modulating Cognition





Chen et al. 2009

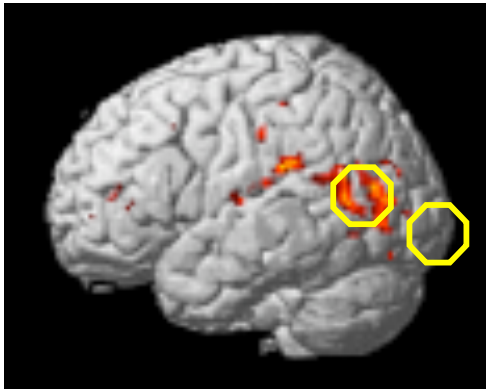
Example

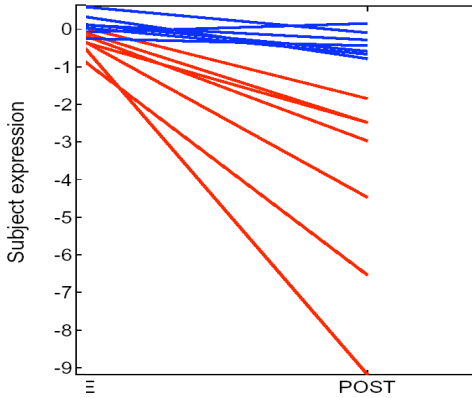
Remediation of sleep-deprivation induced working memory impairment with fMRI-guided TMS: Testing the role of resilience-associated cortical networks

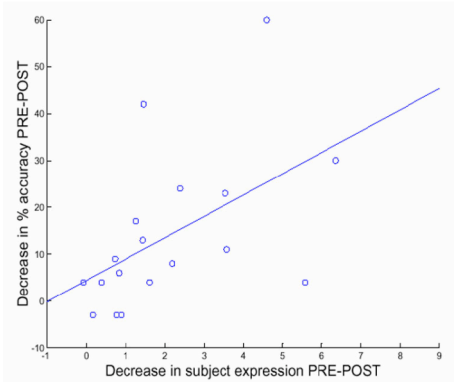
Luber, B., Stanford, A.D., Bulow, P., Nguyen, T., Rakitin, B.C., Habeck, C., Basner, R., Stern, Y., Lisanby, S.H.

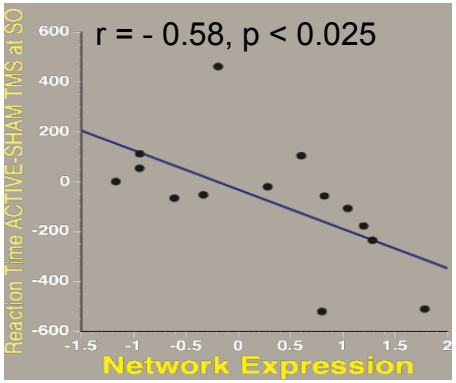
Remediating Cognition

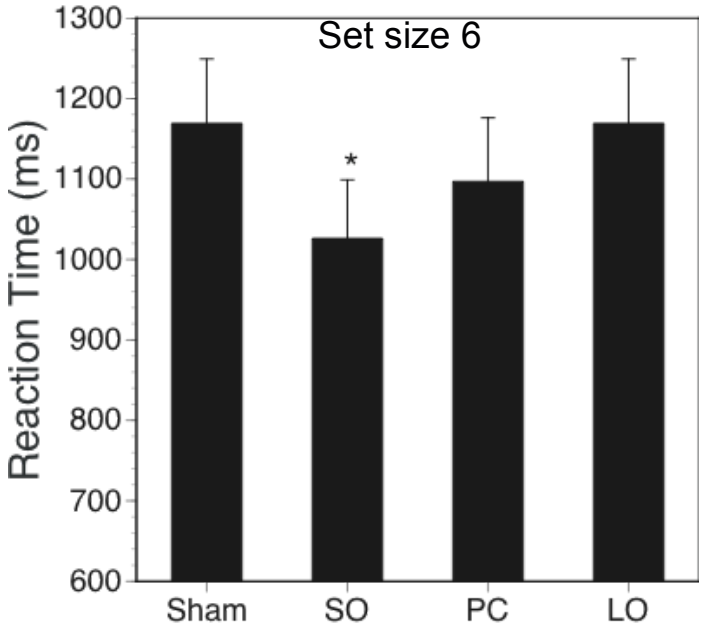
Cerebral Cortex, 2008









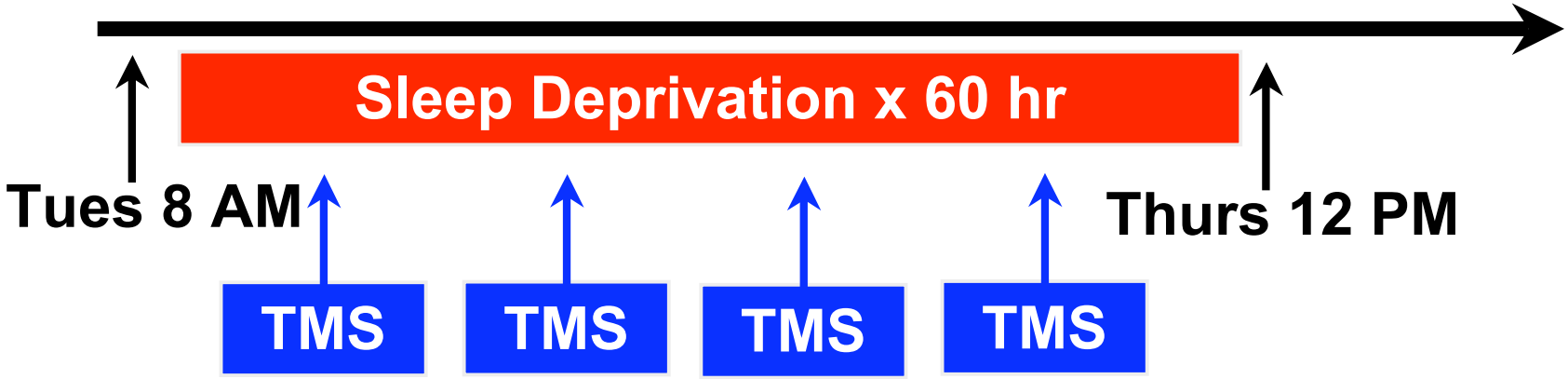


- Sleep deprived 60 hrs, N=15
- Within-subject cross-over
- 5 Hz TMS to superior occipital gyrus reduced RT by 143 ms
- Effect specific to sleep deprived state, not seen in sleep replete
- Degree of improvement correlated with network expression

Example

TMS Intervention Trial

Remediating Cognition



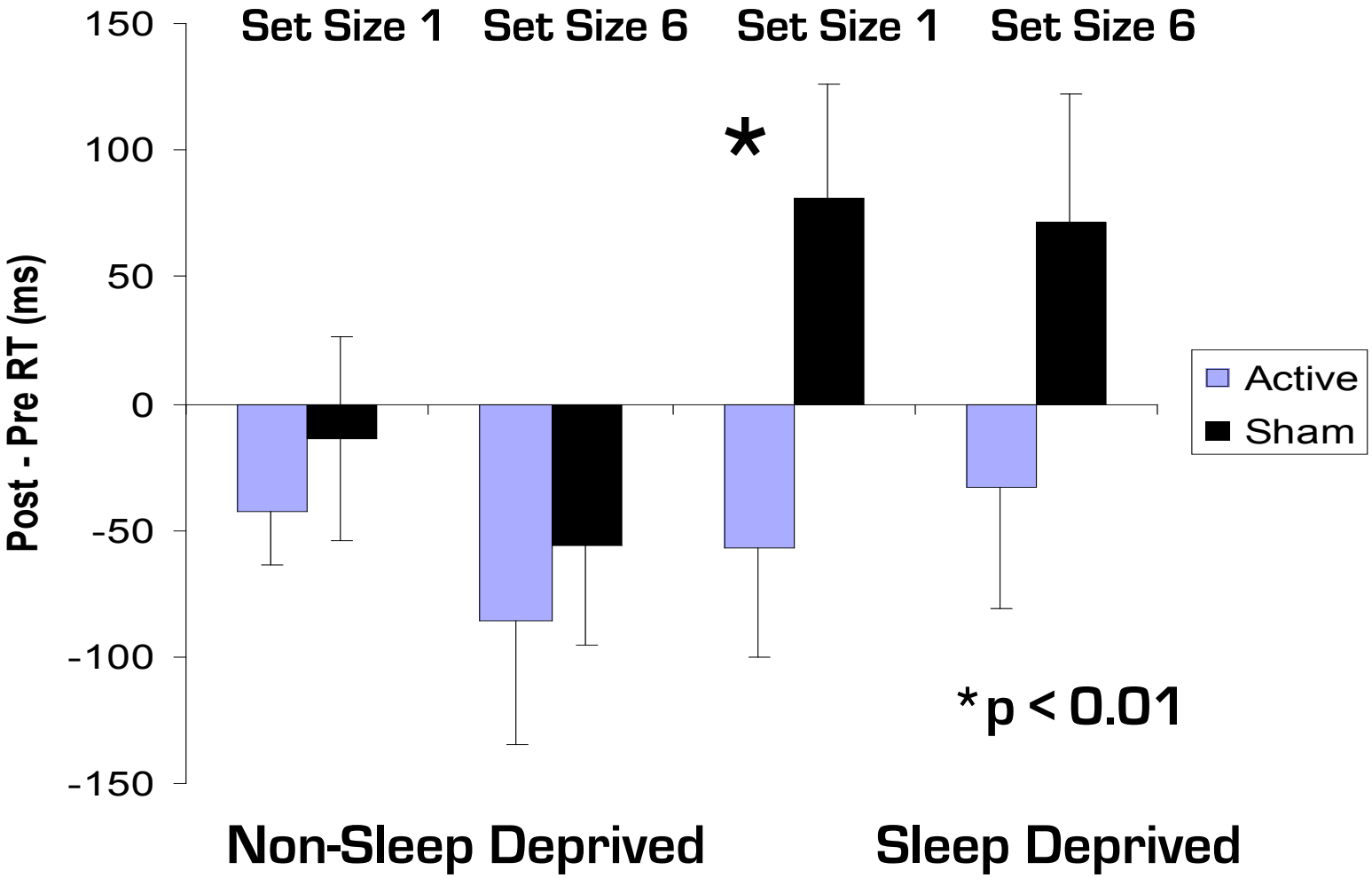
- TMS during during task performance to entrain network utilization and block performance decrements before they occur.
- 5 Hz rTMS 100 % MT, 7s, ITI 25 s, retention phase of DMS task, superior occipital gyrus
- Sham-controlled randomized trial

Luber et al. In preparation

Example

Remediating Cognition

Active TMS prevented decline in WM performance with sleep deprivation

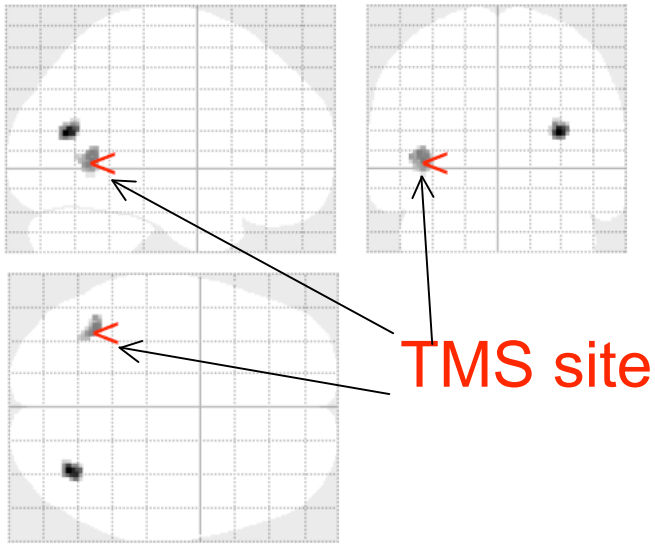


Luber et al. In preparation

Example

TMS Effects on Network Expression

Remediating Cognition



- fMRI – Multivariate linear model analysis
- Network distinguishes active and sham groups
- 2 regions, left occipito/temporo/parietal and right parahippomcapal gyrus.

- Illustrates power of coupling TMS with fMRI modeling of individual differences
- Confirmation of reserve associated networks
- Suggests TMS effects on behavior achieved via modulation of network expression

Luber et al. In preparation

Example

What we know

What we don't know

- Exact mechanisms of action
- Interactions between TMS mechanisms, illness, and med effects
- Optimal techniques to probe and remediate cognition

Future Directions

- Refined targeting of cortical regions
  - E-field shaping with specialized coils
- Refined targeting of transsynaptic action
  - Structural (DTI) and functional (fMRI, EP) connectivity
- Optimized dosing via intermediate biomarkers
  - To achieve specific physiological effects
- Validated methods to individualize dosage outside M1

Columbia University Medical Center

New York State Psychiatric Institute

Brain Stim and Therapeutic Modulation Division

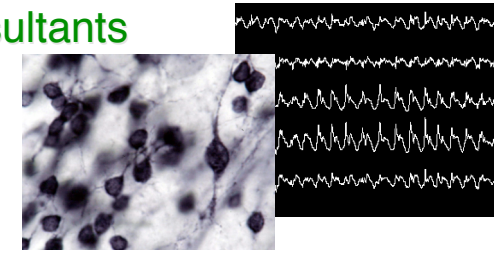
Division Chief- S. H. Lisanby, MD

Faculty - Fortunato Battaglia, MD
Peter Bulow, MD
Yael Cycowicz, PhD
Kathleen Friel, P
Reza Jalinous, PhD
Bruce Luber, PhD
Antonio Mantovani, MD, PhD
Shawn McClintock, PhD
Angel Peterchev, PhD
Joan Prudic, MD
Charles Schroeder, PhD
Alexandra Sporn, MD
Arielle Stanford, MD

Fellows / Students - Julien Besle, PhD
Ming Chen, PhD; Zhi Deng, MS
Won He Le, MD
Stefan Rowny, MD

RA/RC – Bruce Bassie, Sarah Bellovin-Weiss, Lis Bernhardt, Jenny Bress, Seth Disner, Niko Reyes, Greg Westin

Collaborators and Consultants
Victoria Arango, PhD
Peter Balsam, PhD
Truman Brown, PhD
Andrew J Dwork, MD
Klaus Ebmeier, MD
Brian Fallon, MD
Joy Hirsch, PhD
Mustafa Husain, MD
Larry Kegeles, MD, PhD
George Kirov, MD
Jim Leckman, MD
Dolores Malaspina, MD
Bente Pakkenberg, MD
Brad Peterson, MD
Alan Scott, MD
Dikoma Shungu, PhD
Blair Simpson, MD
Yaakov Stern, PhD
Herbert Terrace, PhD
Mark Underwood, PhD
Tor Wager, PhD



Nursing / Social Work-
Linda Fitzsimmons, MSN, RN; Alley Karyat, RN; Nancy Turret, MSW

Administrators-
Letecia Latif, Rosa Jou-Zang

Grants-
R01s MH060884; MH069895
K23 MH076976; K12
NBIB R21 EB005855
NIDA, DARPA, NYSTAR
NARSAD, Stanley, AFAR
Dana, Lieber Center
UK Medical Research Council
Tourette Syndrome Assoc
Neuronetics, Cyberonics, ANS

Equipment Support-
Magstim, MagVentures