



Berenson-Allen Center
For Noninvasive Brain Stimulation

Intensive Course in Transcranial Magnetic Stimulation

State-Dependent Effects of Transcranial Magnetic Stimulation

“The cause of—and solution to—some of TMS’s variability”

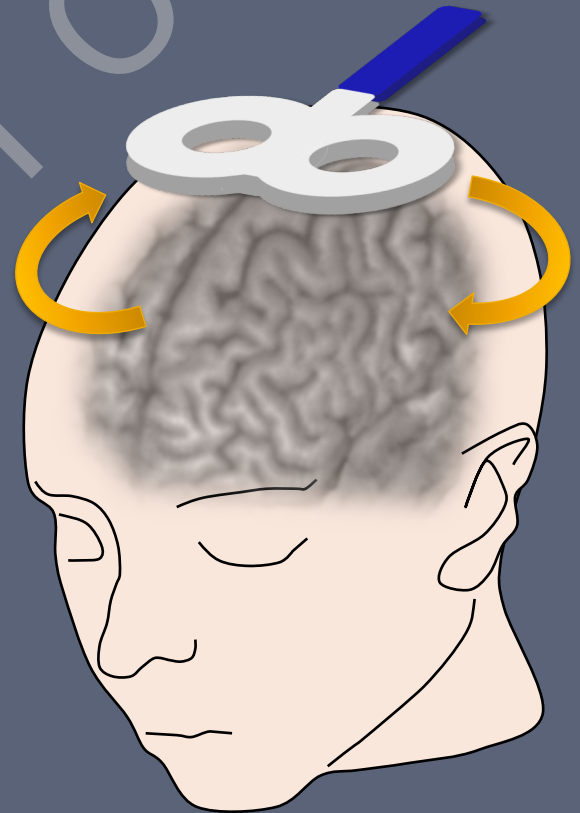
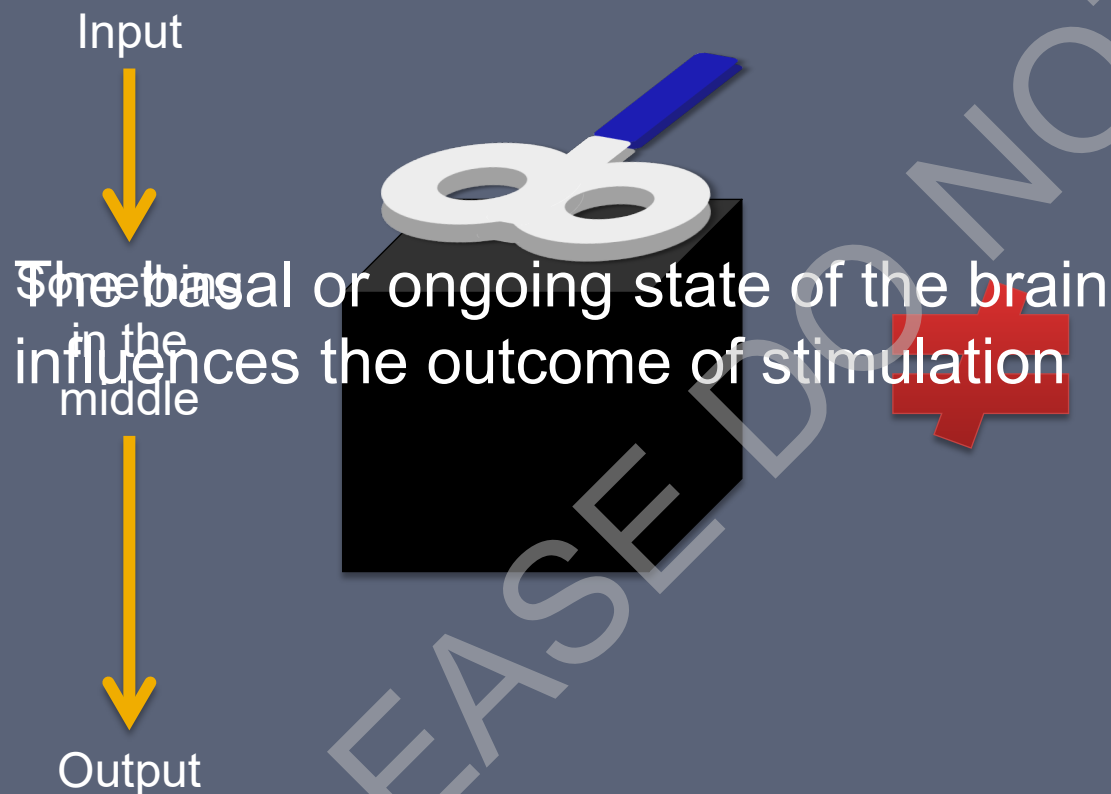
Peter J. Fried, Ph.D.

November 2025

Overview

- What is 'state-dependency'?
- Single Pulse TMS (specificity)
- Repetitive TMS (meta-plasticity, variability)
- Implications for study design

What is 'State-dependency'?



Paired-Pulse TMS

Test pulse
(alone)

Conditioning Pulse
+ Test Pulse

Intracortical
Inhibition
(ISI = 1-6ms)

Intracortical
Facilitation
(ISI = 8-30ms)

Modified from: Kobayashi & Pascual-Leone, 2003 (Lancet Neurology)

Overview

- What is 'state-dependency'?
- Single Pulse TMS (specificity)
 - Adaptation & Priming
- Repetitive TMS (meta-plasticity)
- Implications for study design

Adaptation & Priming

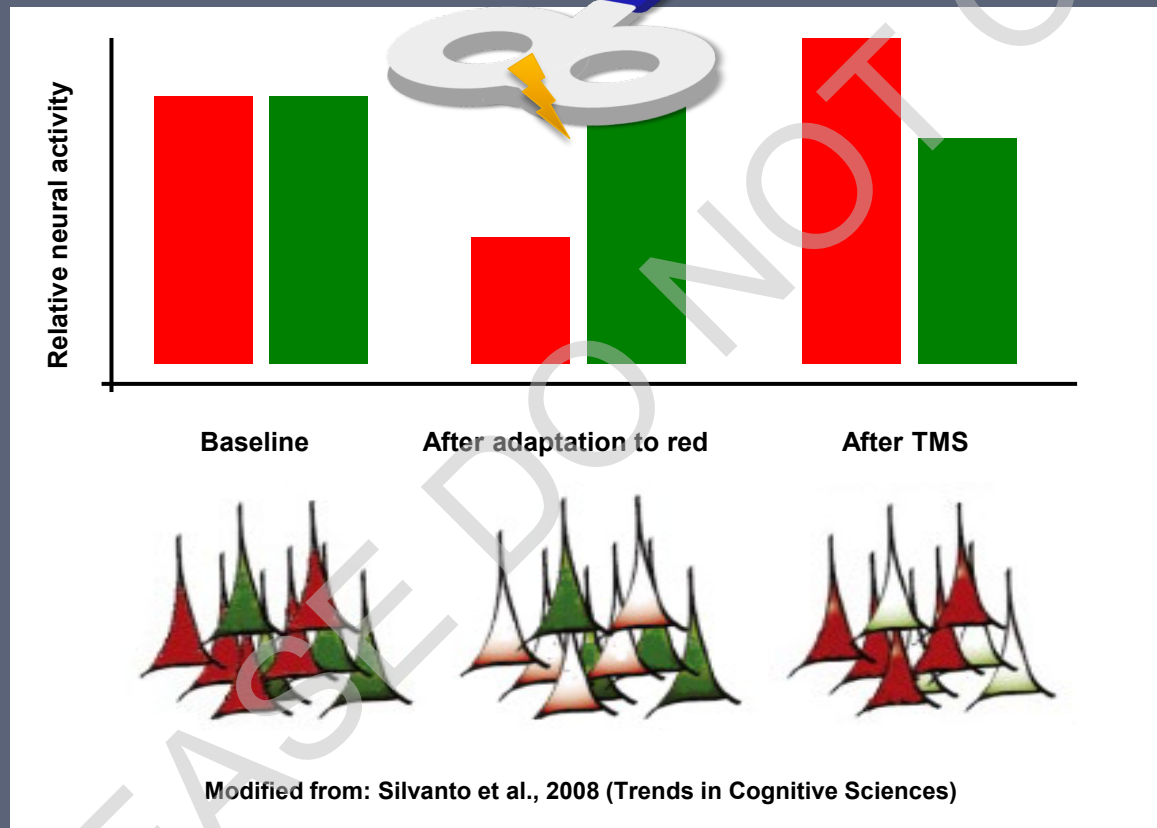
Adaptation:

Priming:

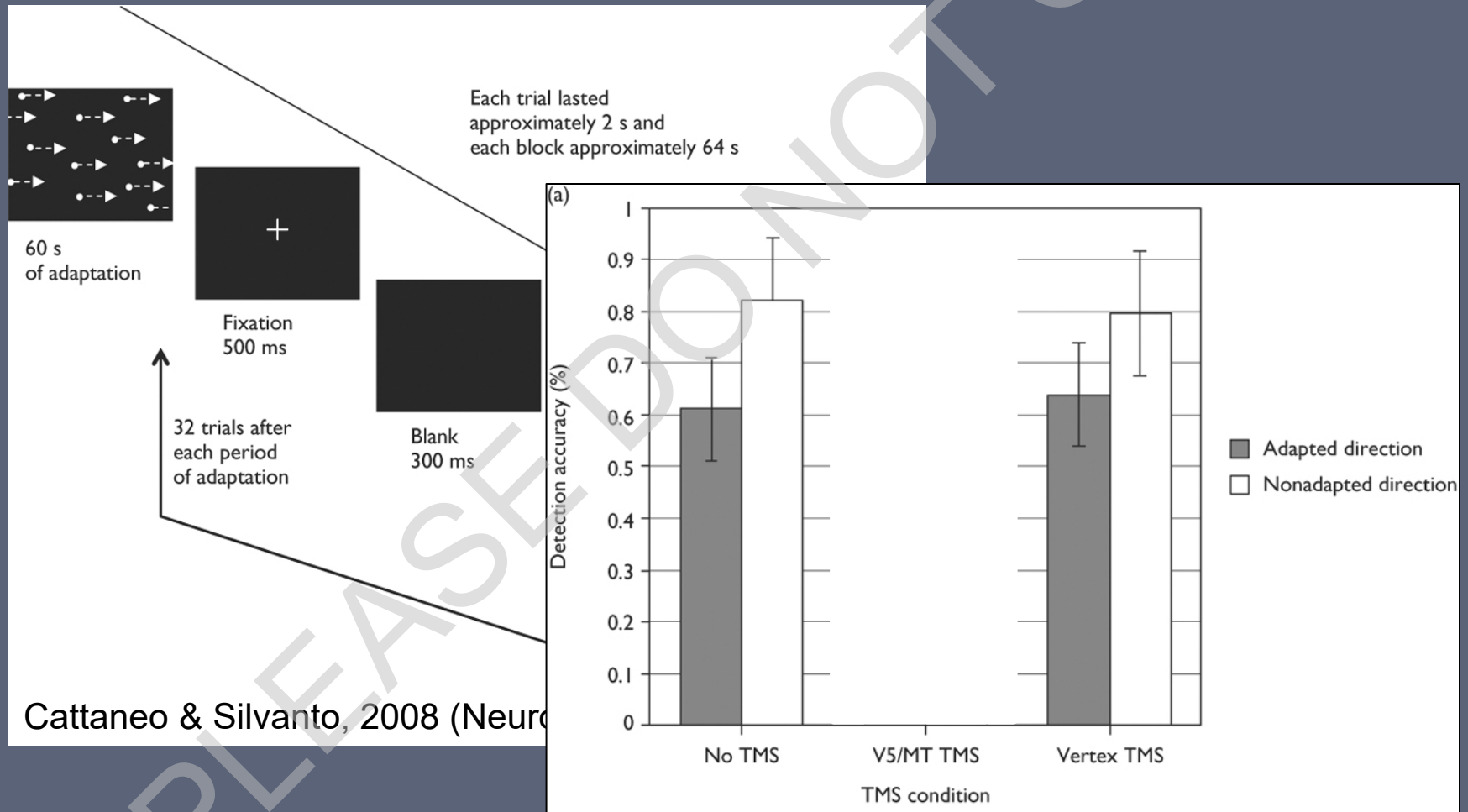




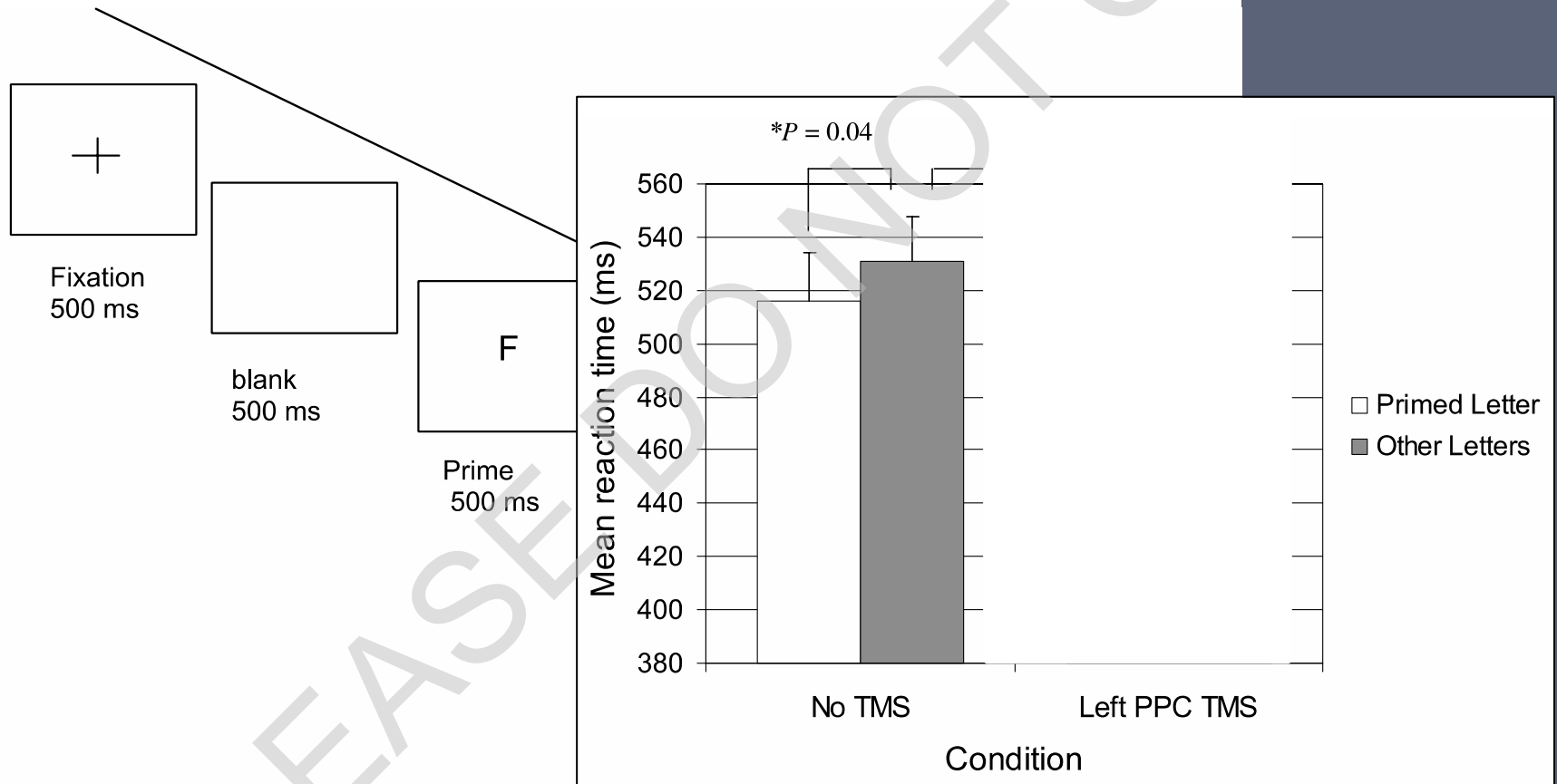
Color Adaptation: area V1



Motion Adaptation: area V5/MT



Letter Priming: left PPC

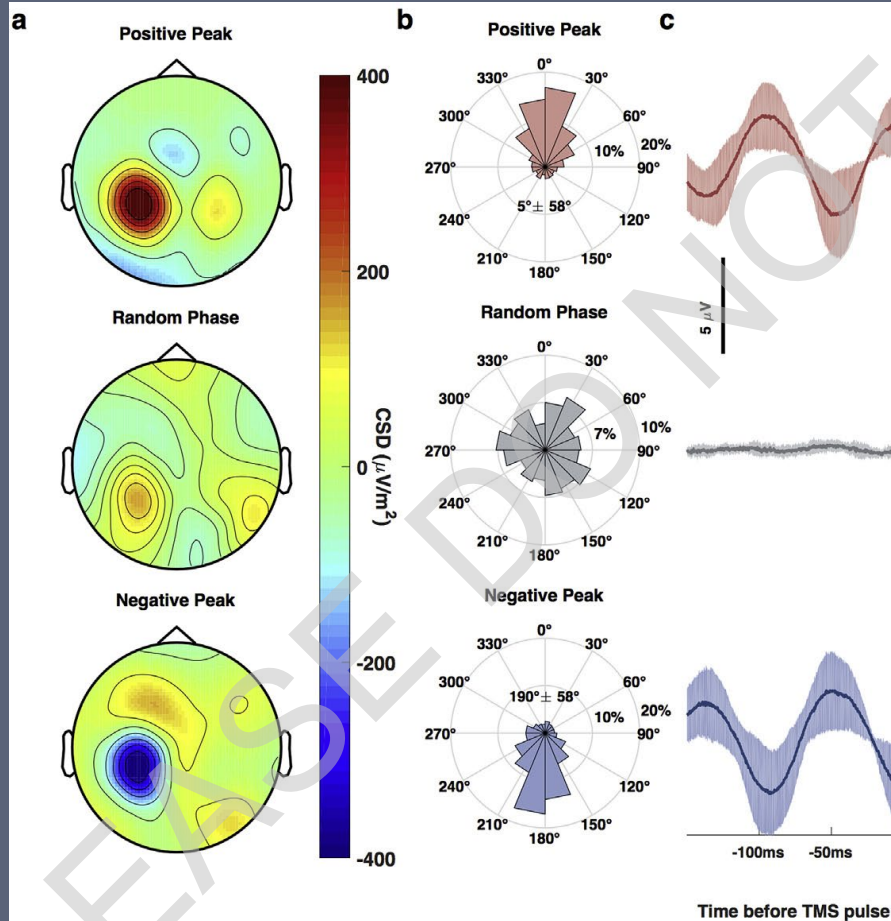


Cattaneo et al., 2008 (European Journal of Neuroscience)

Take Home – Adaptation/Priming

- ↓ neural activity = ↑ TMS susceptibility
- Adaptation/Priming can improve selectivity of TMS
- “Functionally independent, spatially overlapping populations of neurons”

Closed-loop EEG triggered TMS



Zrenner et al., 2018 (Brain Stimulation)

Overview

- What is 'state-dependency'?
- Single Pulse TMS (specificity)
- Repetitive TMS (meta-plasticity)
 - Inter-individual variability
 - Altered impact in disorders
 - Preconditioning, multiple sessions
- Implications for study design

Convention

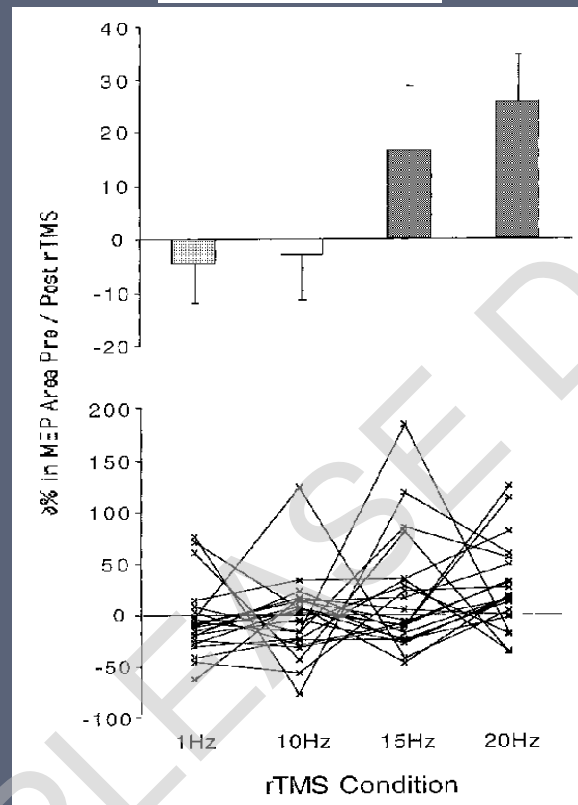
- ≥ 10 Hz rTMS / iTBS
- ~ 1 Hz rTMS / cTBS

RESEARCH ARTICLE

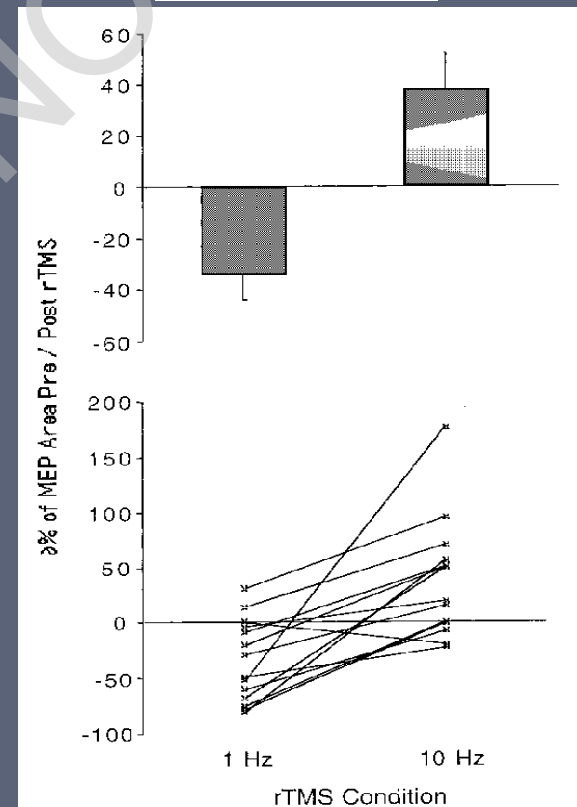
Fumiko Maeda · Julian P. Keenan · Jose M. Tormos
Helge Topka · Alvaro Pascual-Leone

Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability

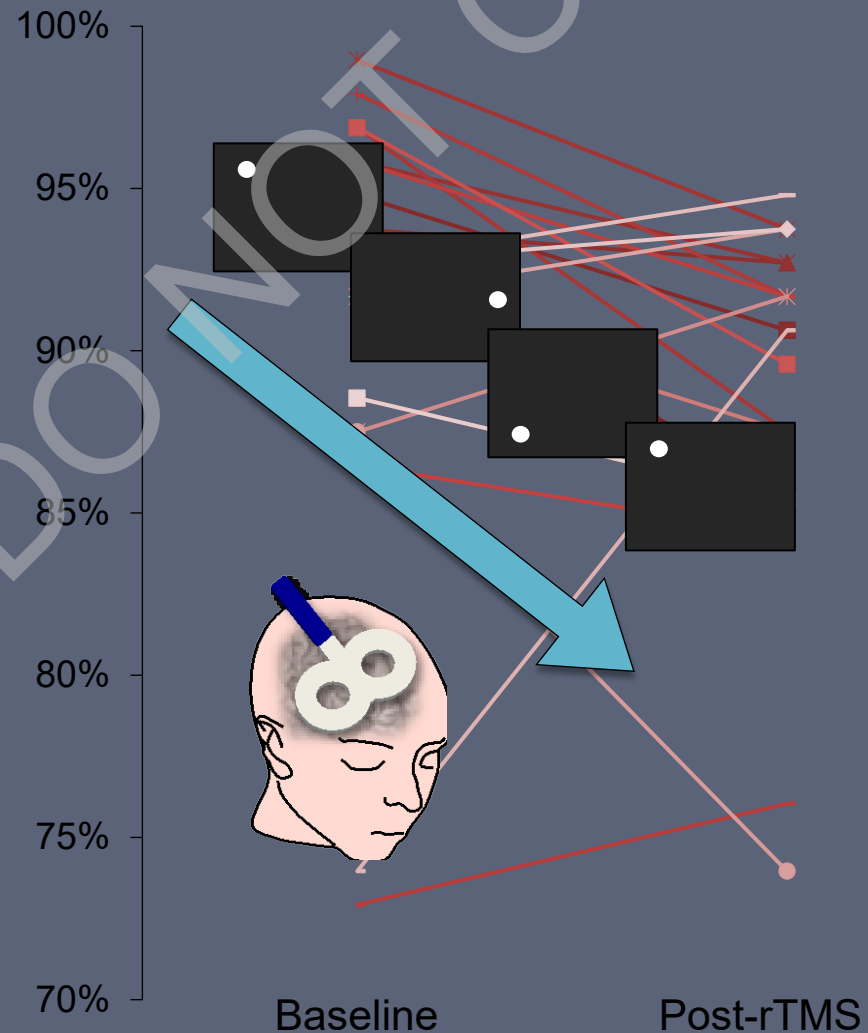
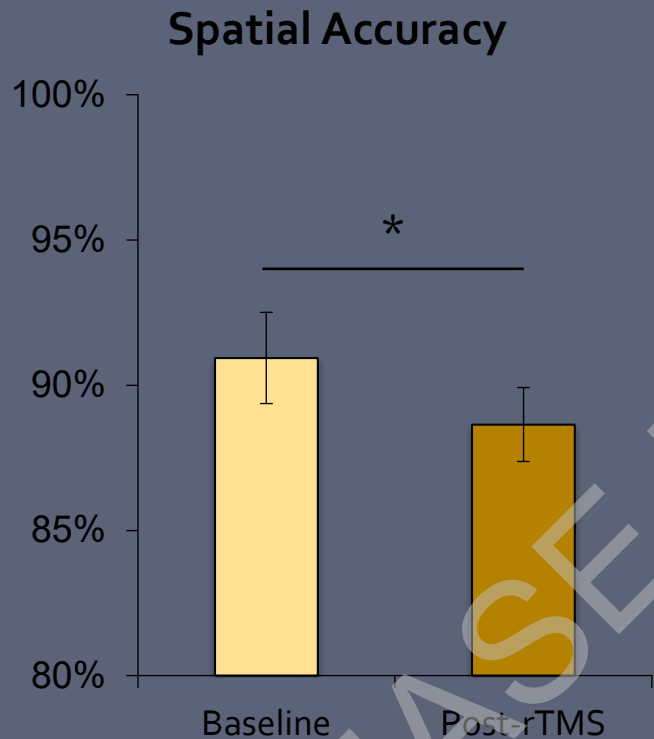
240 pulses



1600 pulses

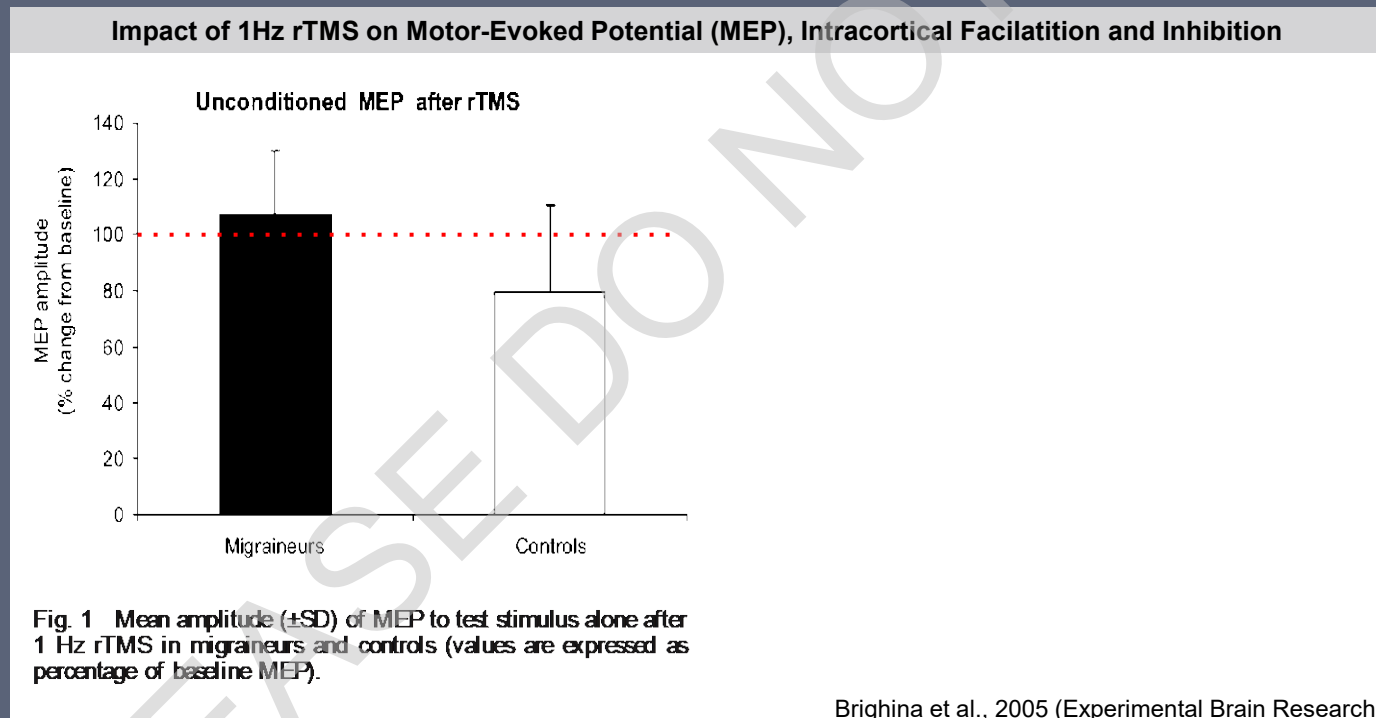


Variability in Cognitive Interventions

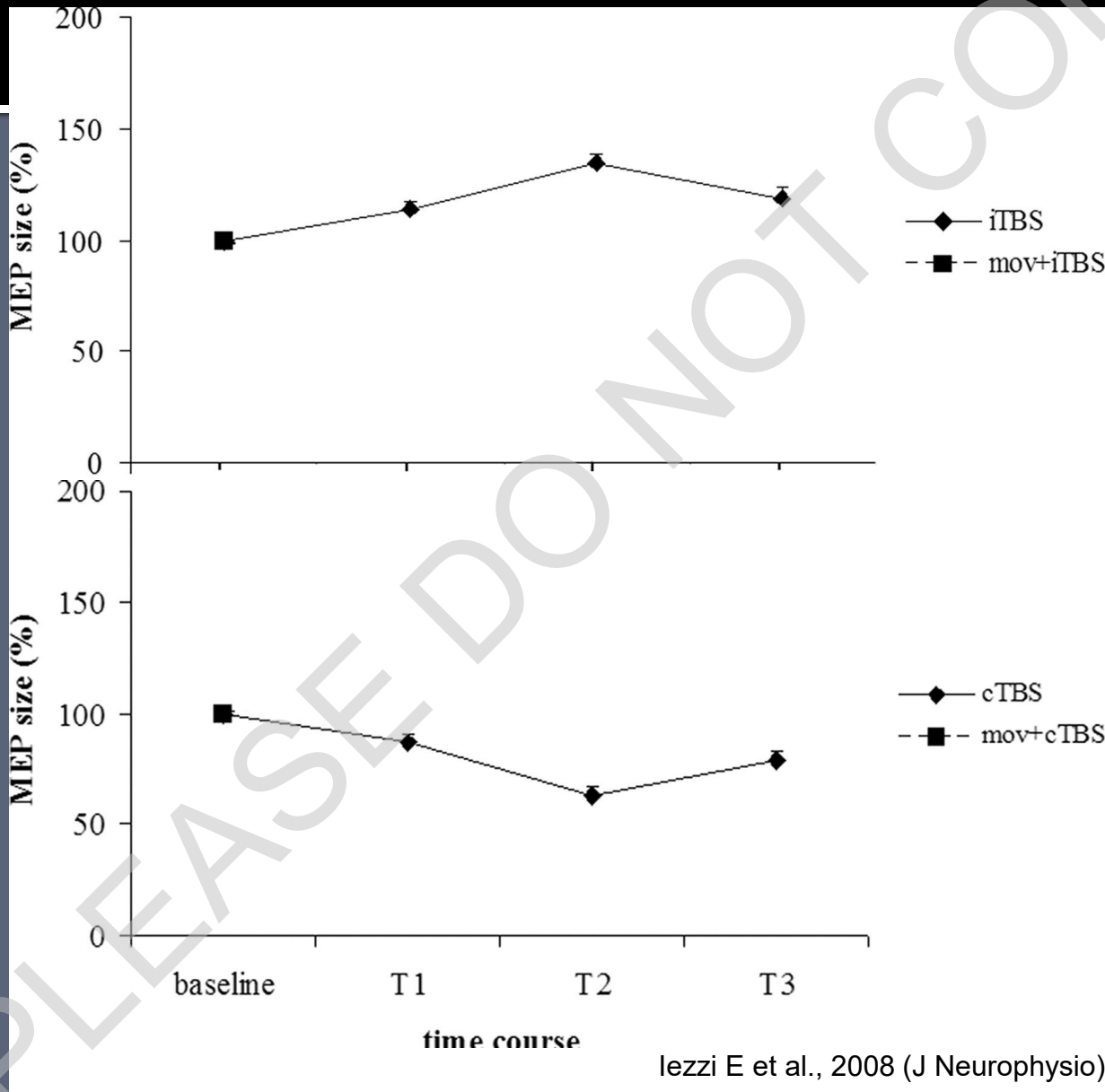


Modified from Fried et al., 2014

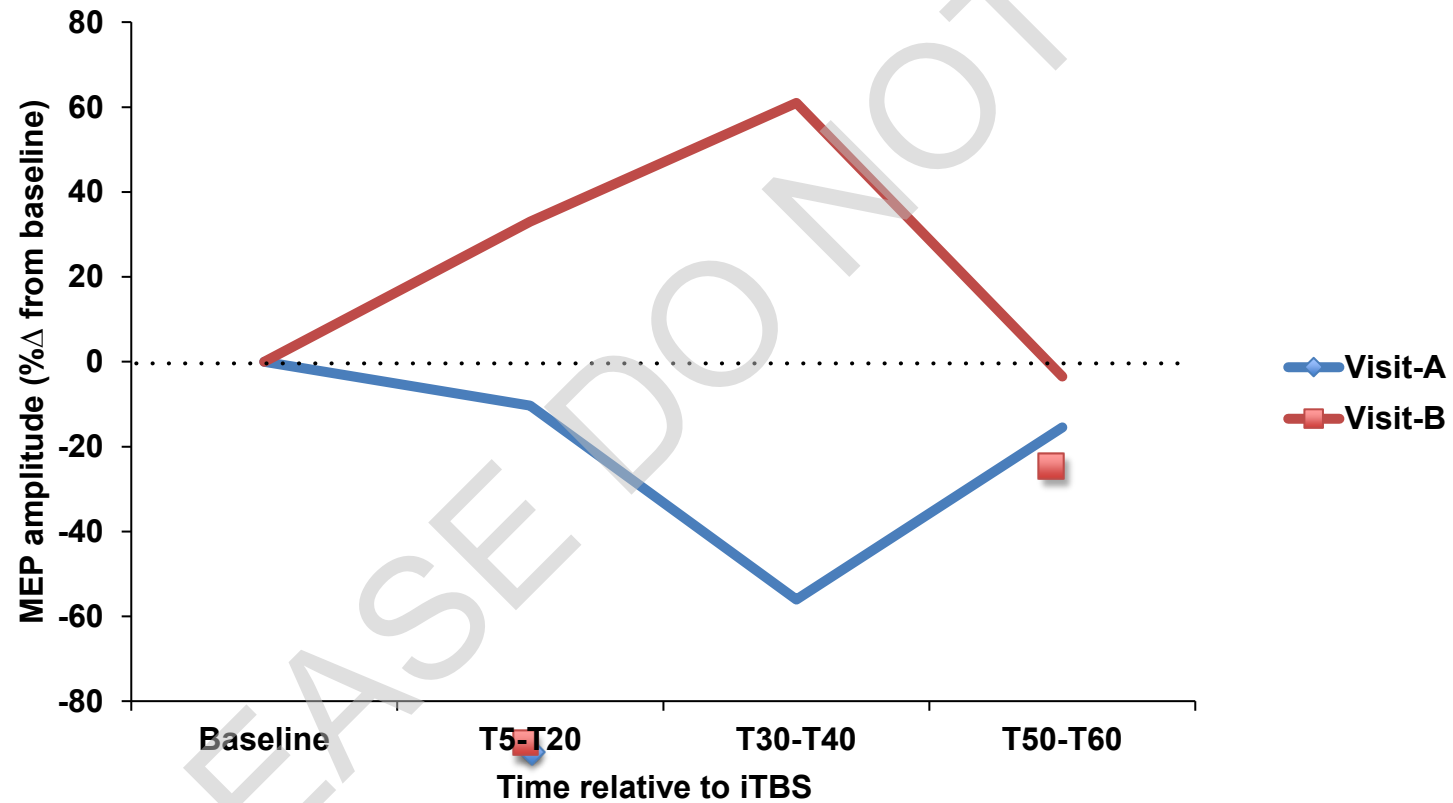
Altered response to rTMS in disease



Impact of physiological activity



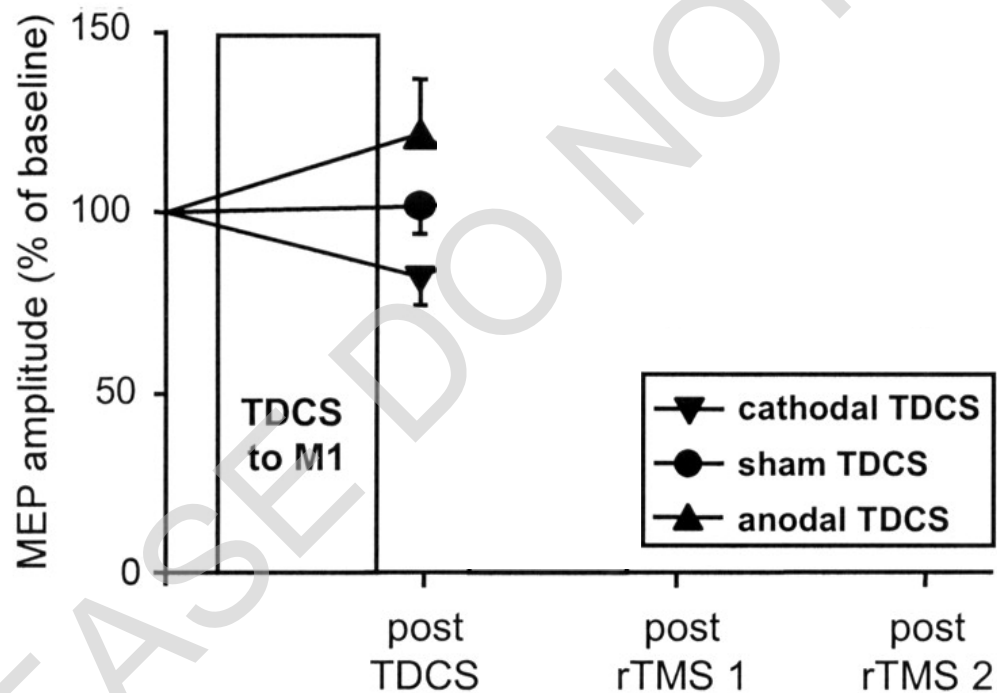
Case example



Preconditioning rTMS with tDCS

Impact of tDCS/rTMS on Motor-Evoked Potential (MEP) amplitude

a Main experiment (n = 8)



Siebnner et al., 2004 (Journal of Neuroscience)

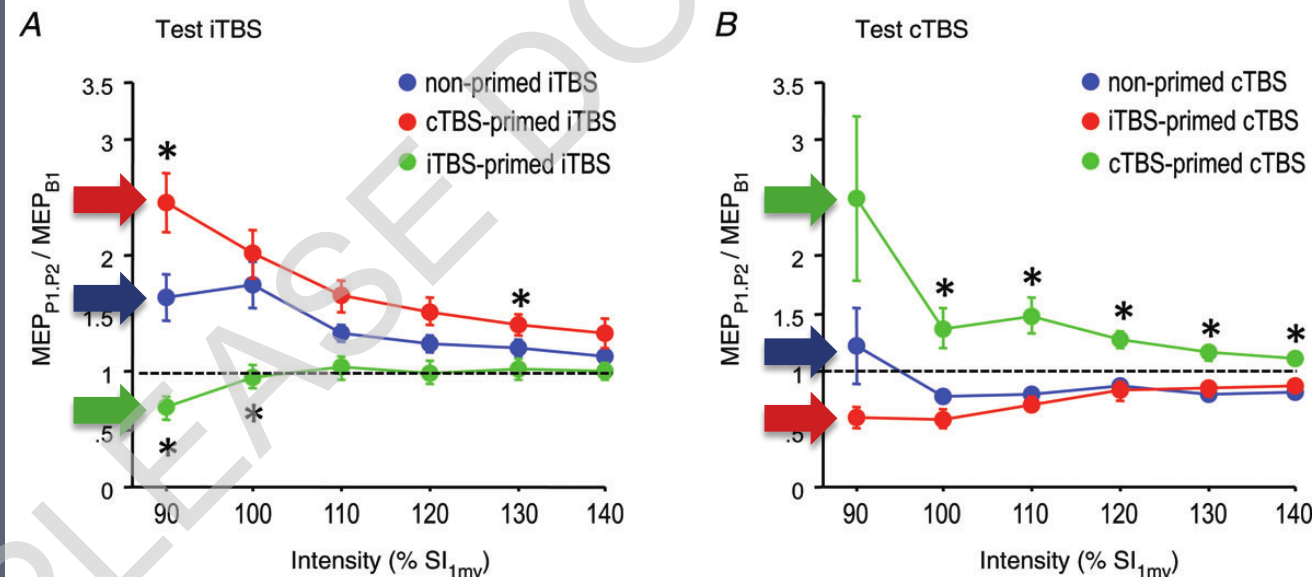
Preconditioning TBS with TBS

J Physiol 590.22 (2012) pp 5765–5781

5765

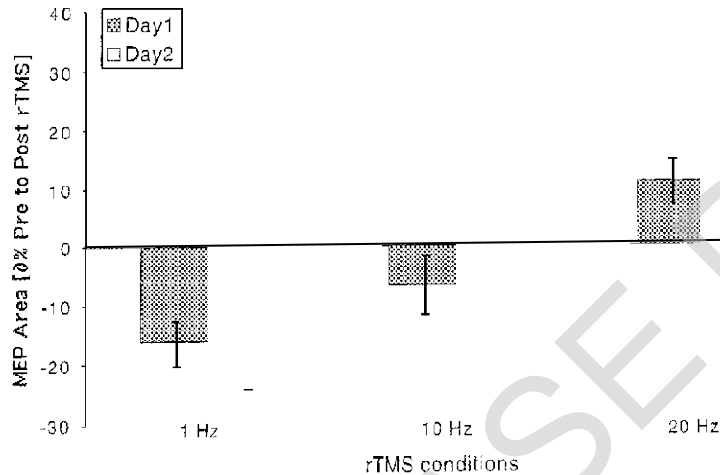
Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex

Takenobu Murakami¹, Florian Müller-Dahlhaus¹, Ming-Kuei Lu^{1,2} and Ulf Ziemann^{1,3}



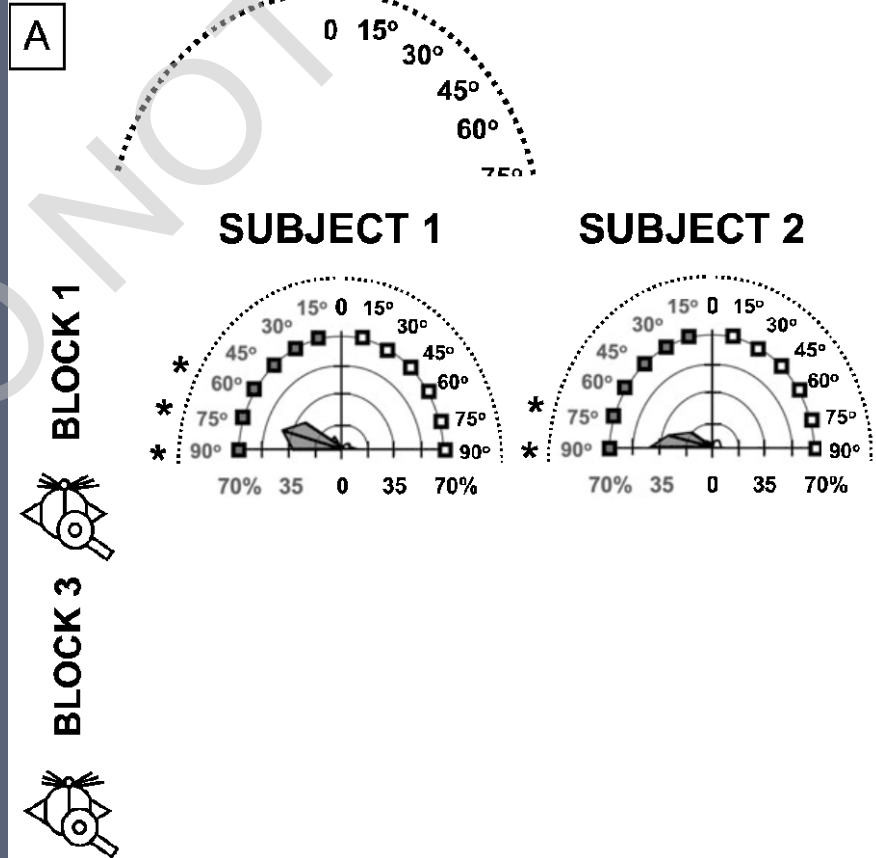
Meta-plasticity: Impact of Cumulative Sessions

Impact of rTMS on Motor-Evoked Potentials



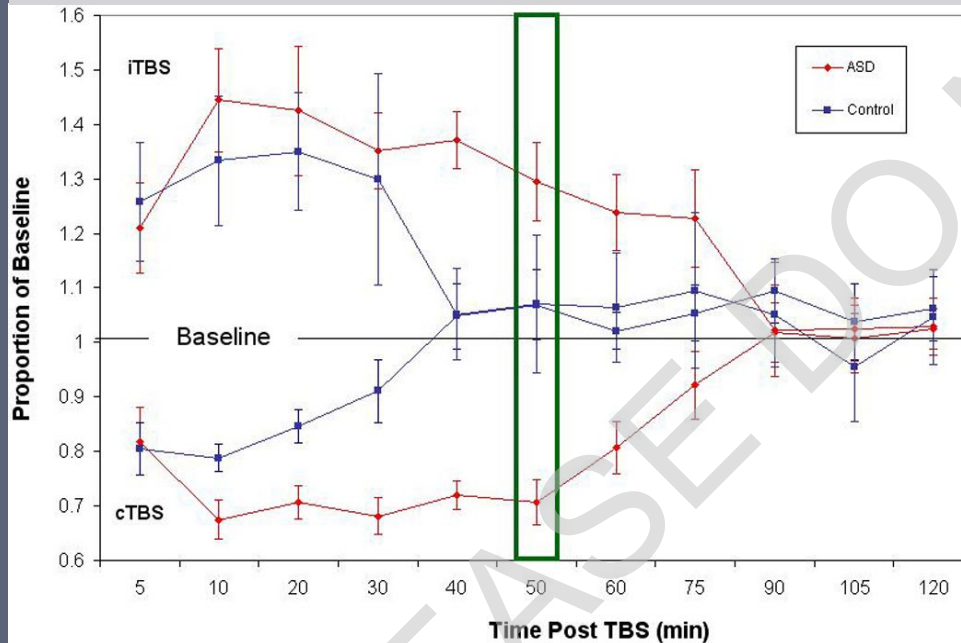
Maeda et al., 2000 (Clinical Neurophysiology)

Impact of daily 1Hz rTMS on visuo-spatial detection



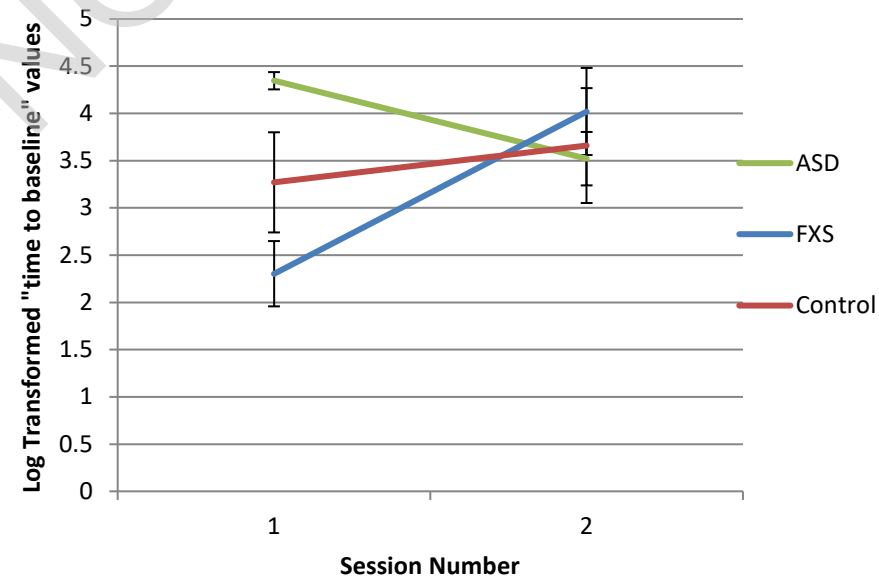
Altered Meta-plasticity in ASD

Impact of TBS on Motor-Evoked Potential (MEP) Amplitude



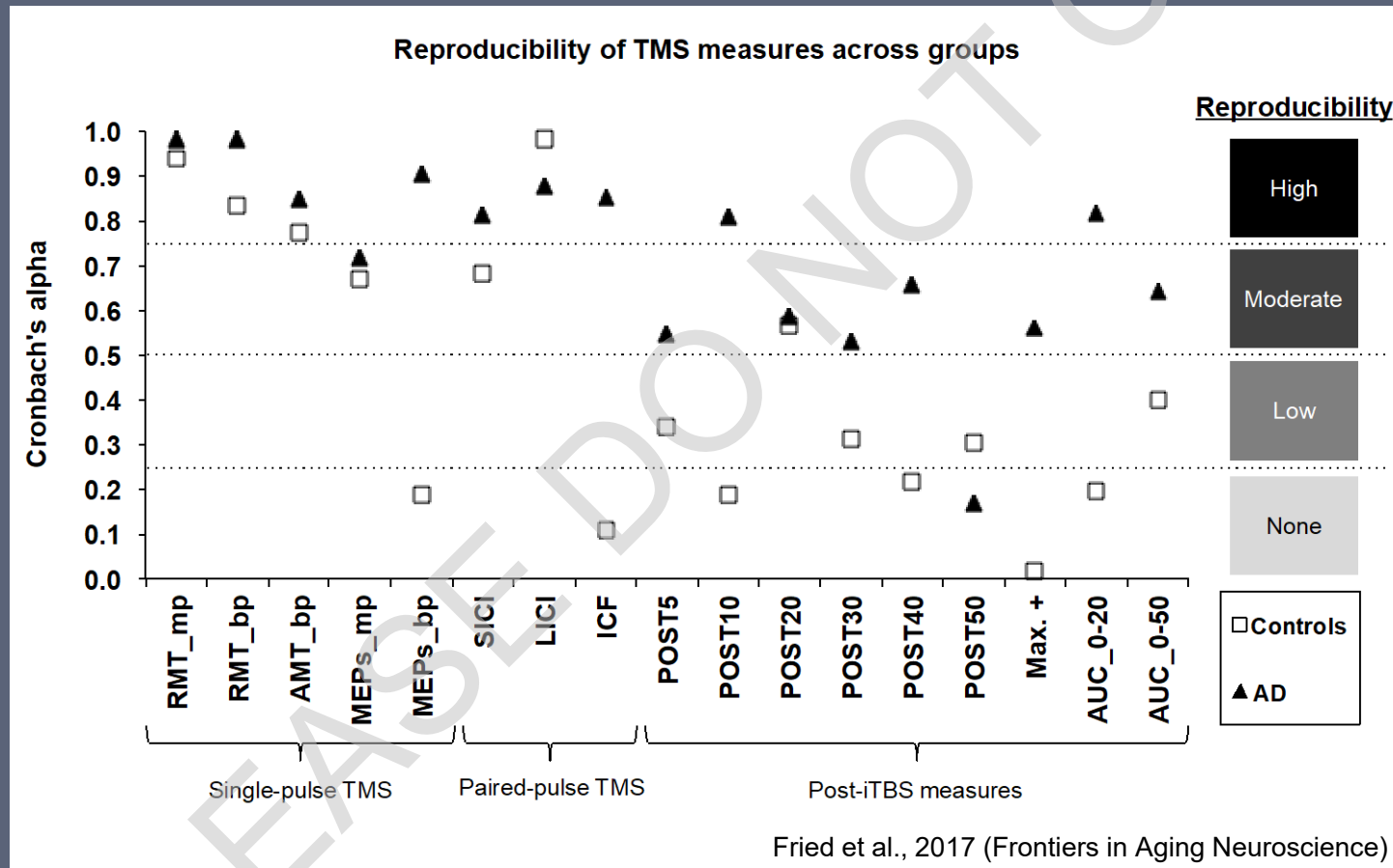
Oberman et al., 2012 (European Journal of Neuroscience)

Cumulative Impact of Back-to-Back TBS

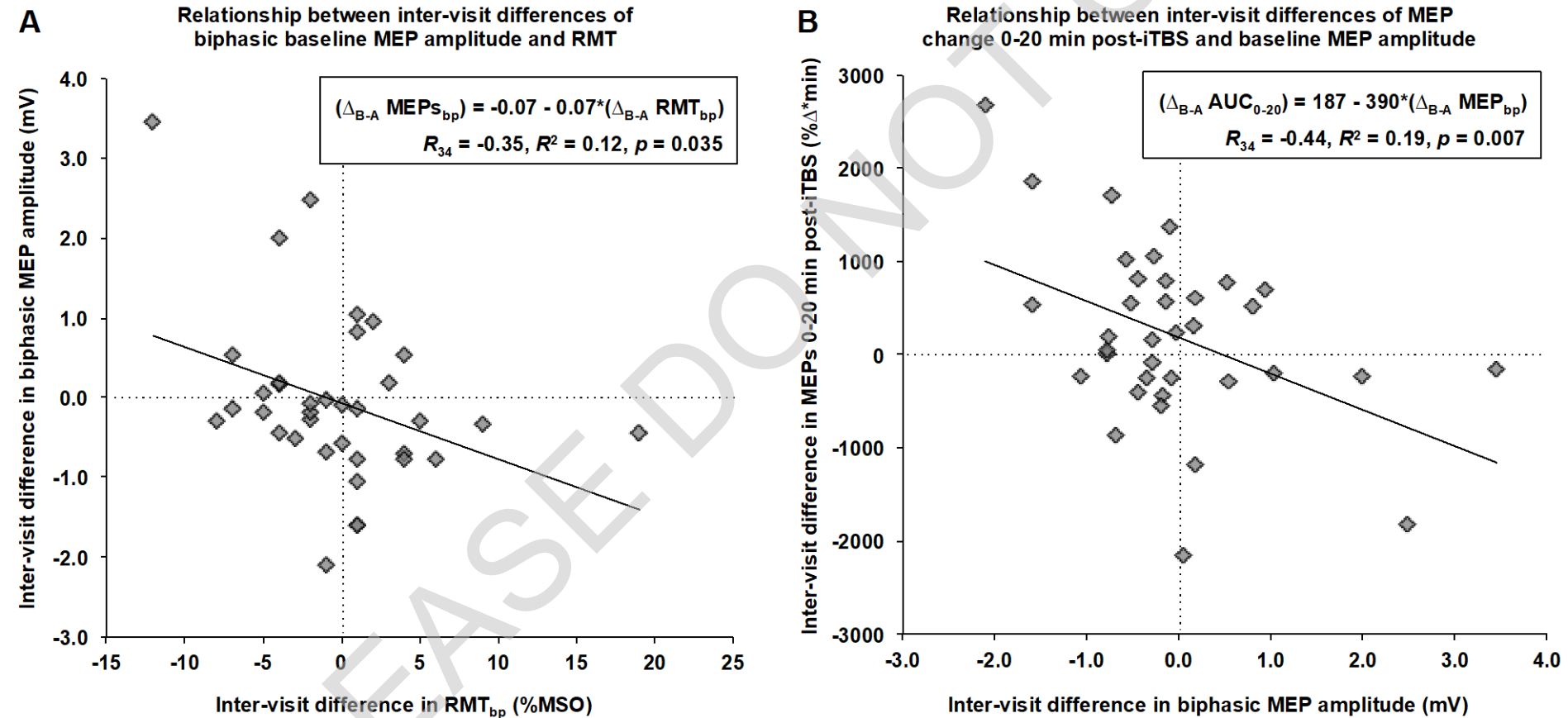


Oberman et al., 2016 (J Child Adolescent Psychopharm)

Reproducibility of TMS measures

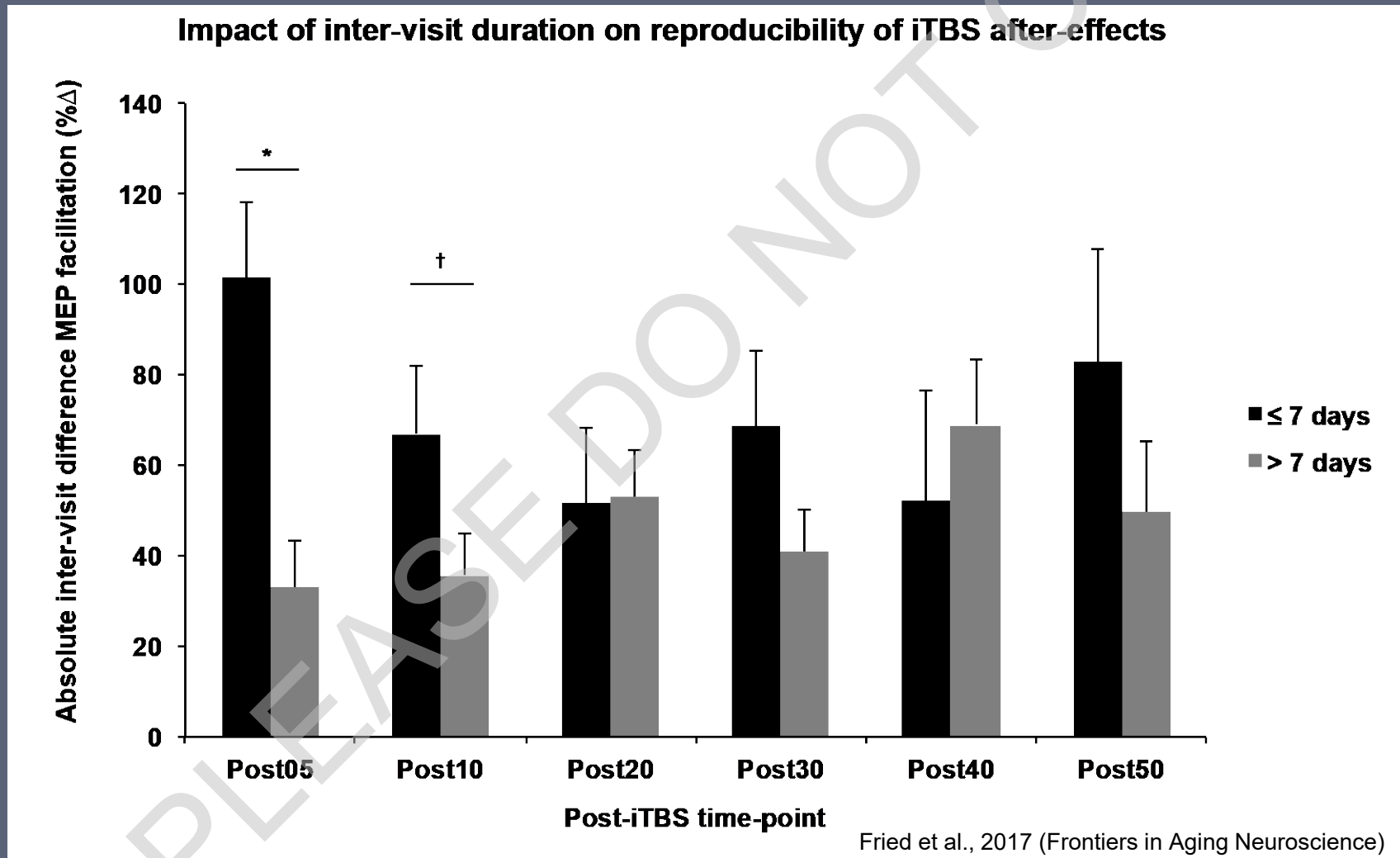


Factors that affect reproducibility

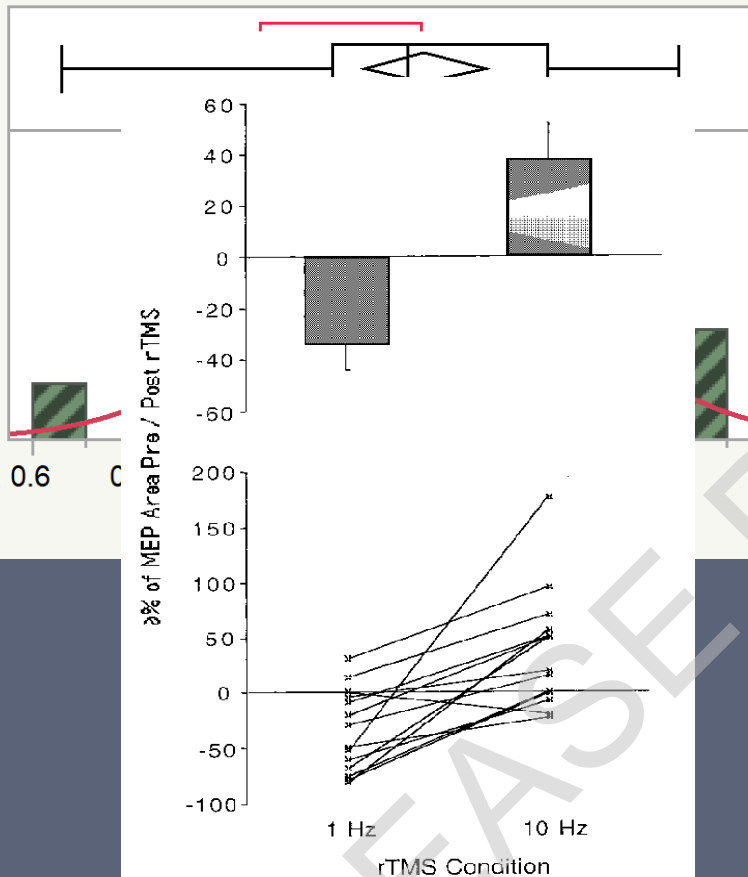


Fried et al., 2017 (Frontiers in Aging Neuroscience)

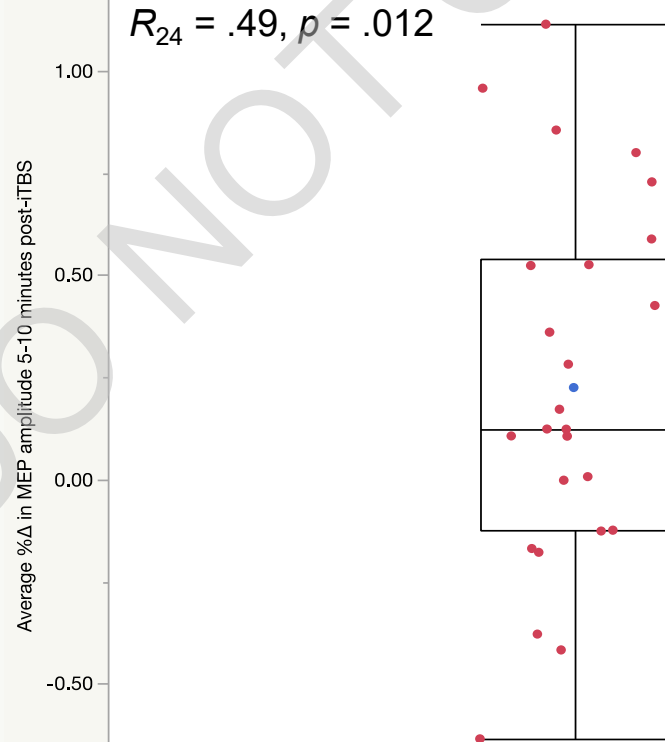
Factors that affect reproducibility



Variability due to study parameters



Inter-individual variability in response to iTBS



Unpublished data – do not share

Take Home – Variability in rTMS

- Impact of rTMS not absolute
 - Low/High Hz doesn't always suppress/enhance
 - Can be influenced by disorder
- Assess reliability/stability of outcome variable
- Presence of “homeostatic” forces
 - Very short interval ($\leq 1s$) $\rightarrow$ basis of rTMS
 - Back-to-back regimens $\rightarrow$ likely to interact
 - Daily sessions $\rightarrow$ build up facilitation
 - Meta-plastic effects might last up to a week

Overview

- What is 'state-dependency'?
- Single Pulse TMS (specificity)
- Repetitive TMS (meta-plasticity)
- Implications for study design
 - Confounds and approaches
 - Therapeutic efficacy
 - To sham or not to sham

Potential Confounds

Easy to control

- Caffeine, Rx
- Prior stimulation
- Time of day
- Food intake
- Handedness
- Concomitant activity

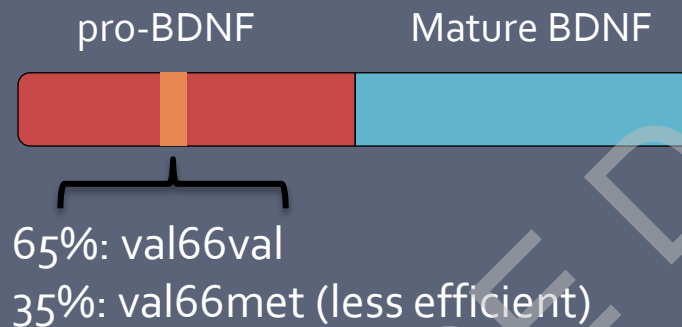
Less Easy to Control

- Amount of sleep
- Menstrual cycle
- Stress, mood
- Disease heterogeneity
- Baseline activity
- Expectation
- DNA

DNA

■ Brain-derived neurotrophic factor (BDNF)

- Modulates NMDAR-dependent plasticity
- Activity-dependent release at synapses



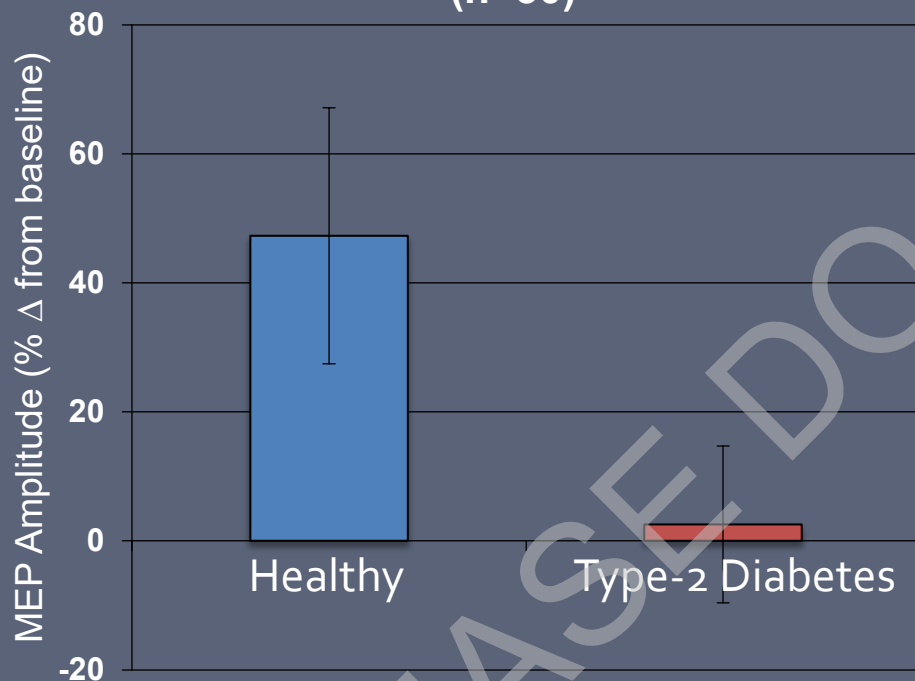
Single substitution of Guanine for Adenine results in an amino acid switch from Valine (Val) to Methionine (Met)

■ Apolipoprotein E (APOE)

- Produced by astrocytes, microglia (in CNS)
- Transports cholesterol & fat-soluble vitamins to neurons
- Three major isoforms:
 - ApoE2 (cys112, cys158): ~7%
 - ApoE3 (cys112, arg158): ~79%
 - ApoE4 (arg112, arg158): ~14%
 - E3,E4 & E4,E4: Higher risk for Alzheimer's disease

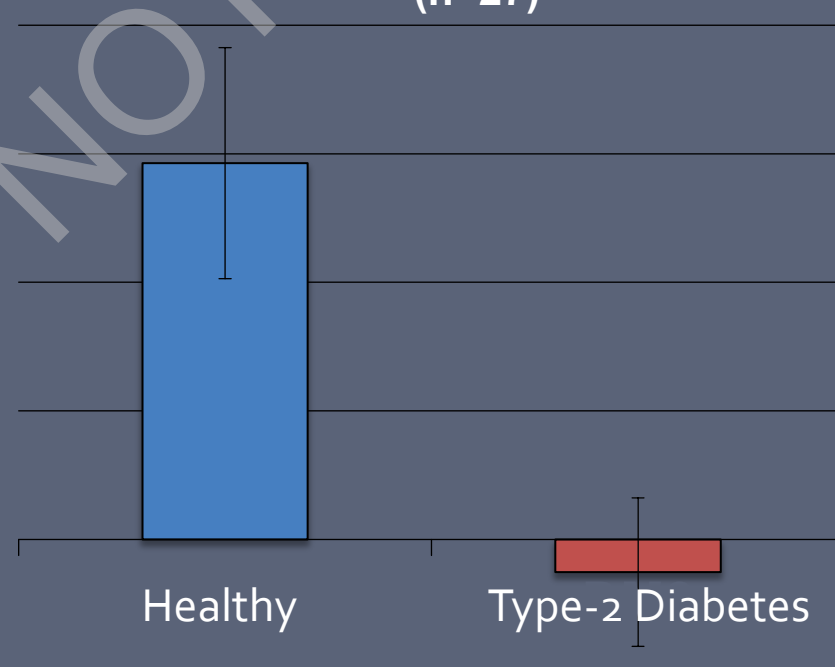
$p = 0.0537$
Effect size = 0.35

**All subjects
(n=30)**



$p = 0.0051^*$
Effect size = 0.52

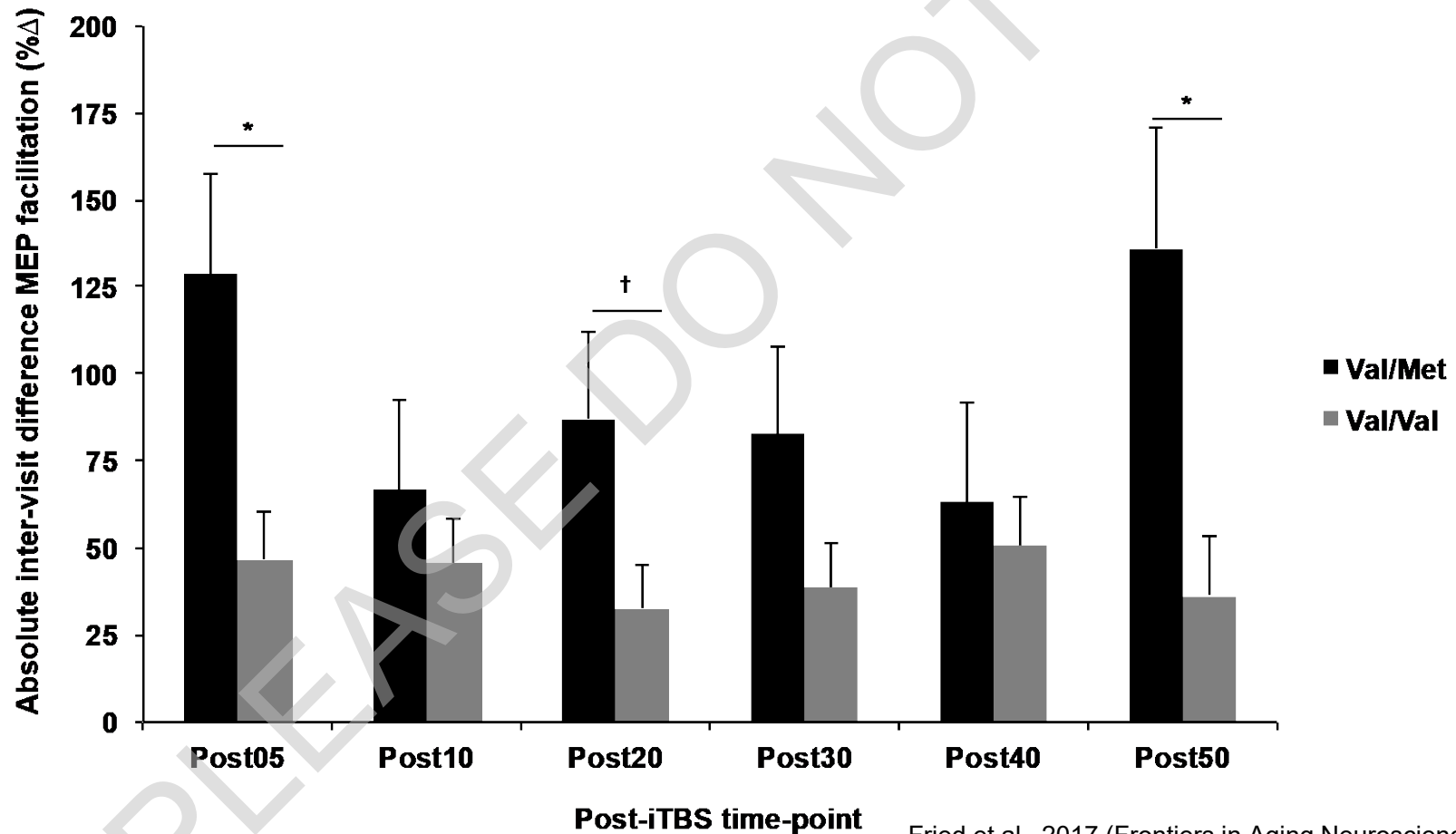
**Excluding BDNF Met+ & APOE- ϵ 4
(n=27)**



For full study, see Fried et al., 2017 (J Alzheimer's Disease)

Factors that affect reproducibility

Impact of BDNF polymorphism on reproducibility of iTBS after-effects

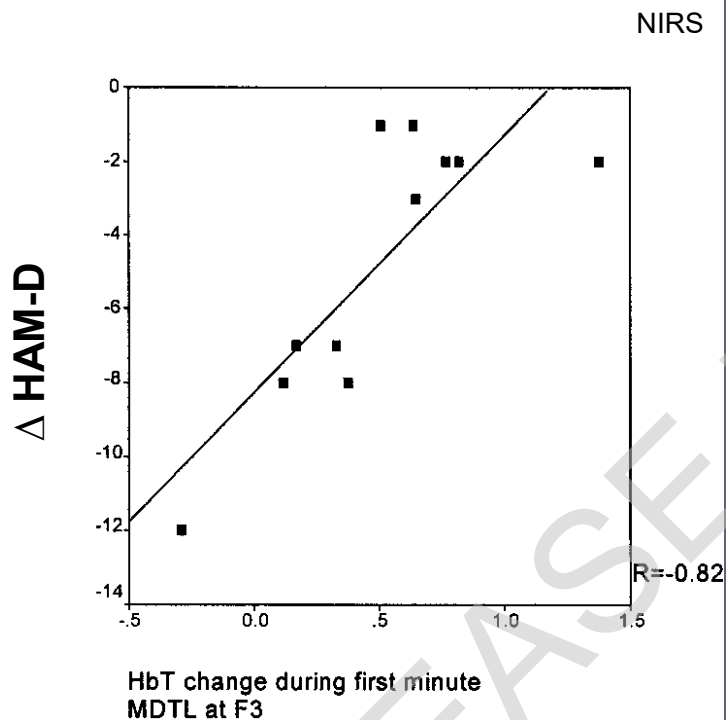


Fried et al., 2017 (Frontiers in Aging Neuroscience)

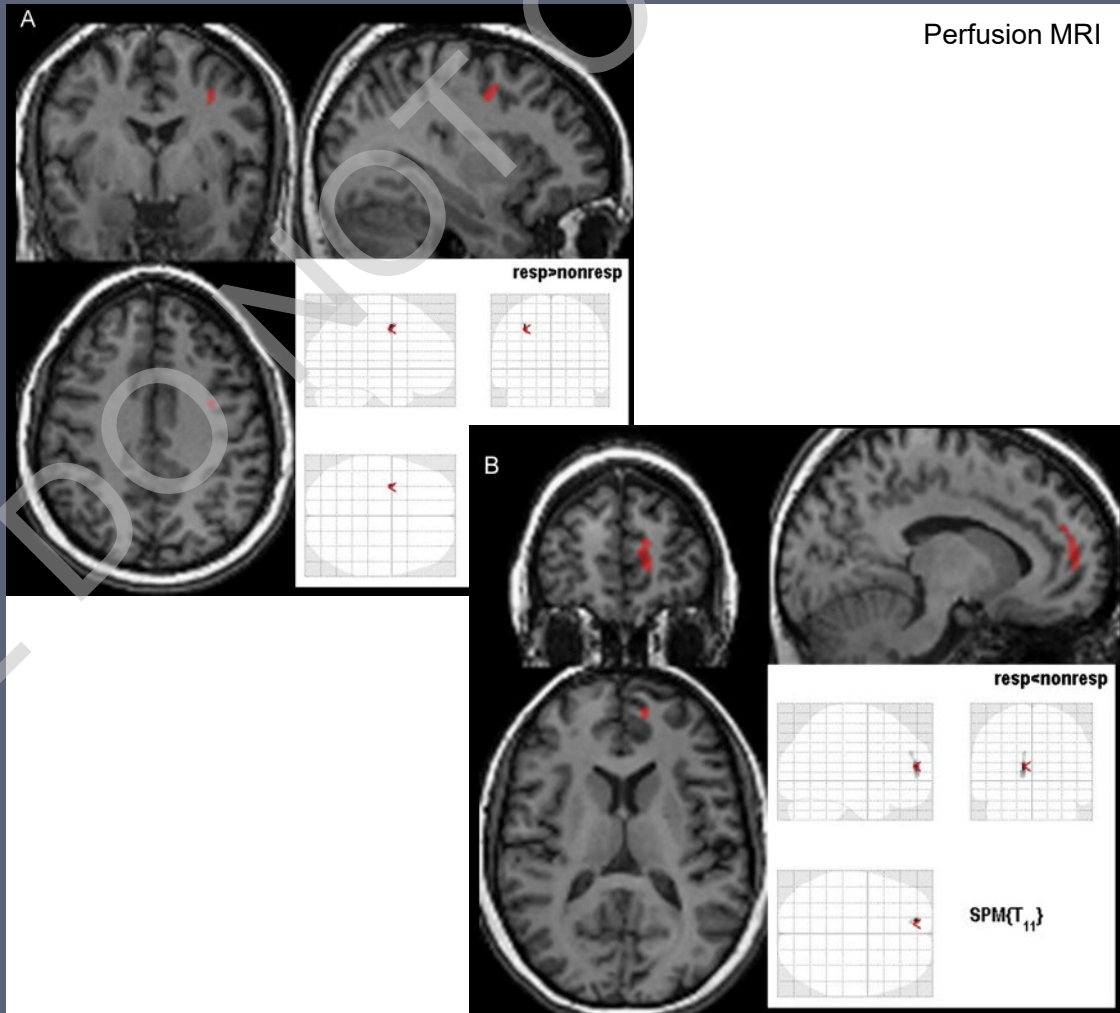
What to do? Follow the C's

- Collect / Correlate
- Control / Counter-balance
- Co-opt / Capitalize

Predicting Therapeutic Outcome: activity in single sites



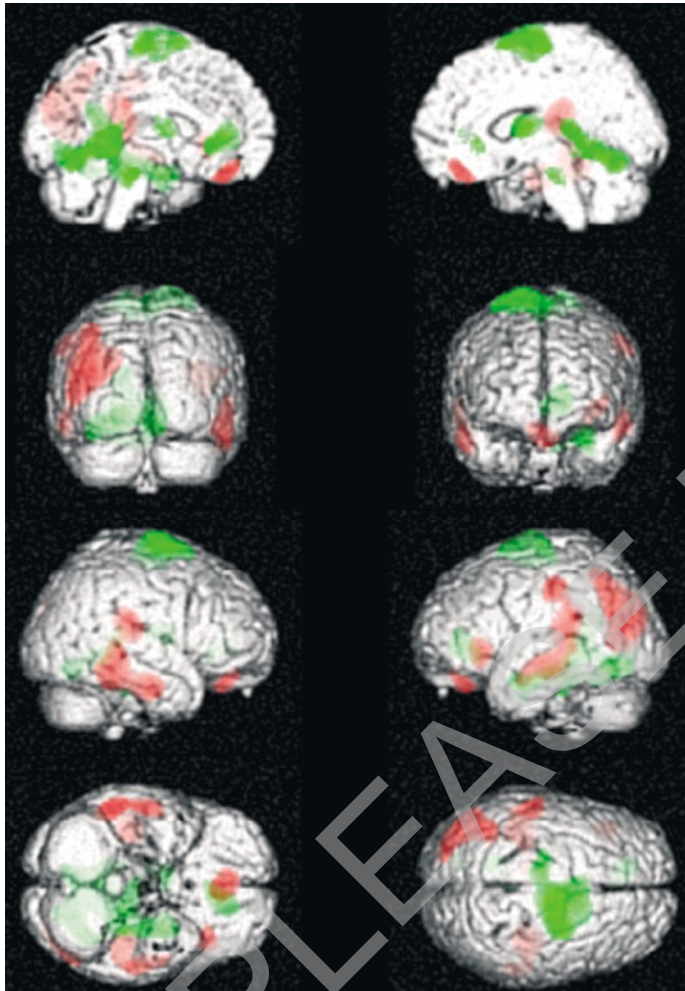
Eschweiler et al., 2000 (Psychiatry Res.: Neuroimaging)



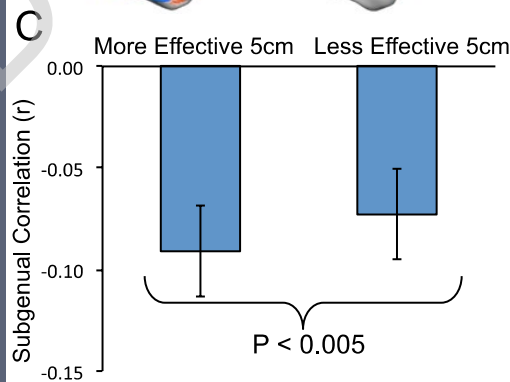
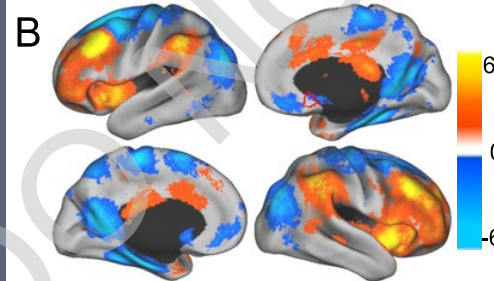
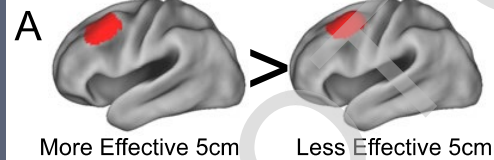
Weiduschat and Dubin, 2013 (J Affective Disorders)

Predicting Therapeutic Outcome: activity across networks

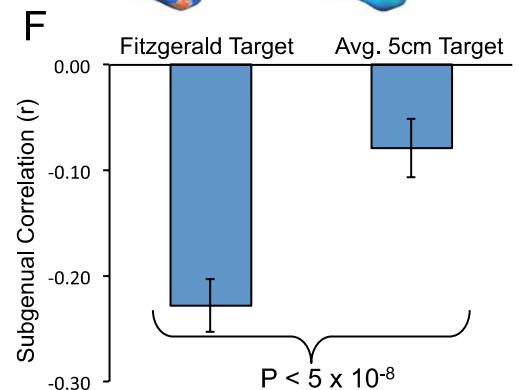
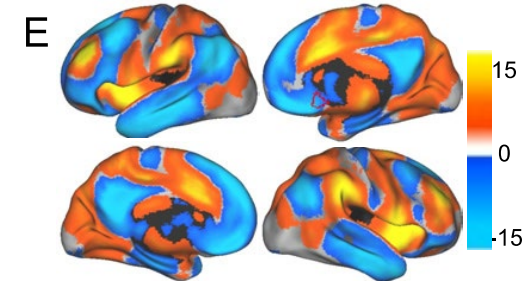
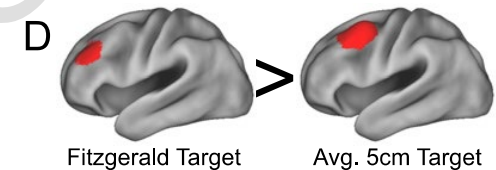
rCBF (SPECT)



Mottaghy et al., 2002 (Psychiatry Res.: Neuroimaging)

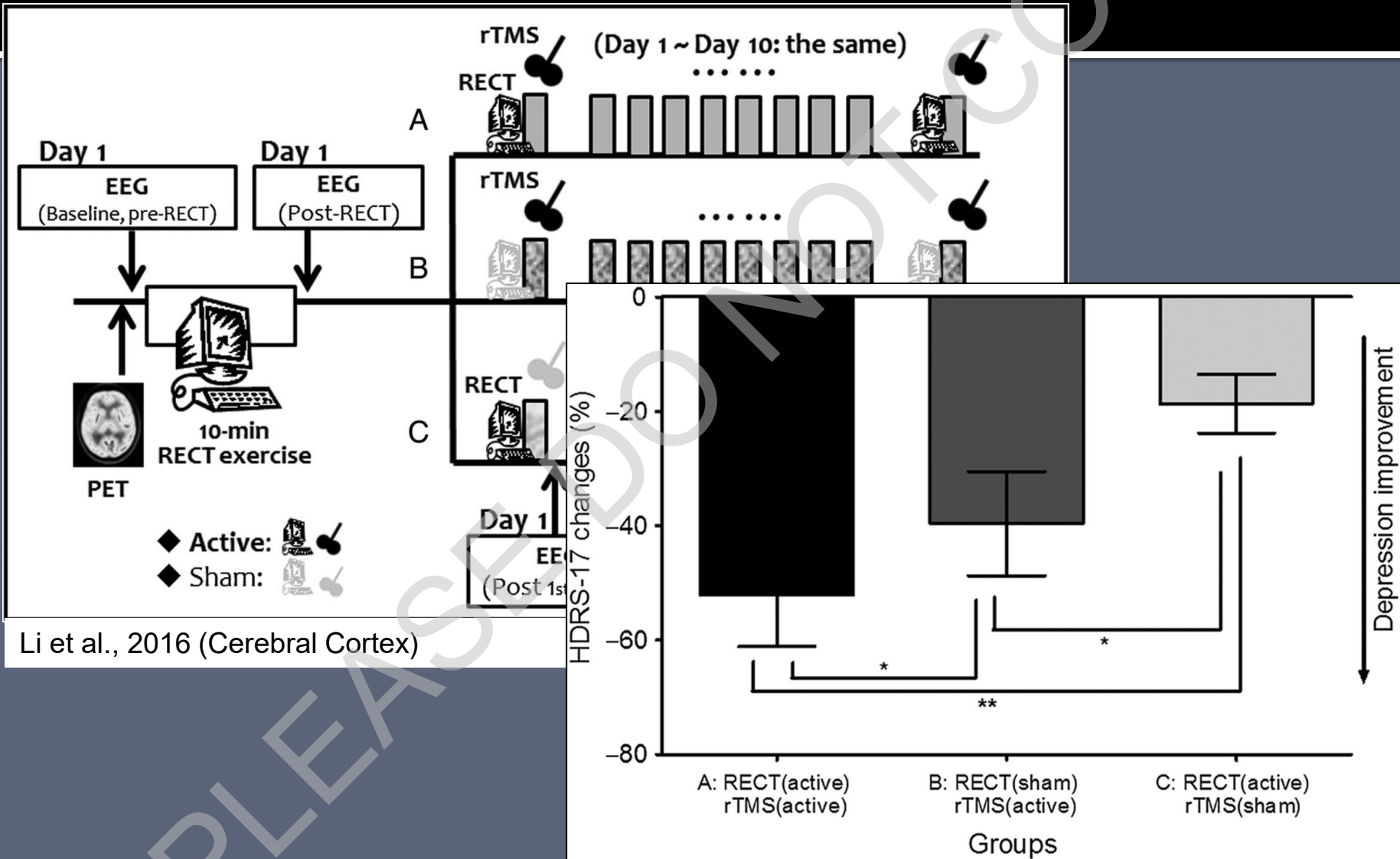


Resting-state functional connectivity MRI



Fox et al., 2012 (Biological Psychiatry)

Changing brain state to improve efficacy



Li et al., 2016 (Cerebral Cortex)

Future Interventions

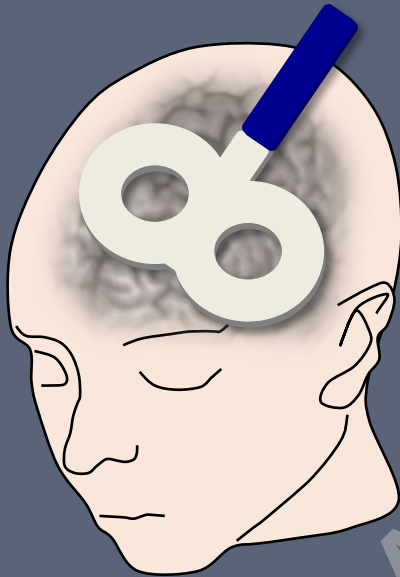
- Individualized targeting
 - Single node vs. network
- Prime sub-populations of neurons
 - Intrinsic vs. extrinsic engagement
- Assess efficacy online
 - Custom dose
- Leverage placebo effect

To Sham or Not to Sham...

- Only ~14% of randomized sham-controlled trials report blinding success (Broadbent et al. 2011, World J Bio Psychiatry)
- Patients correctly guessed Tx condition above chance (Berlim et al. 2013, Int J Neuropsychopharm)

Option 1: Tilt Coil 90°

real



Pros:

- Easy, fast, cheap
- No switching coils
- Similar sensations

Cons:

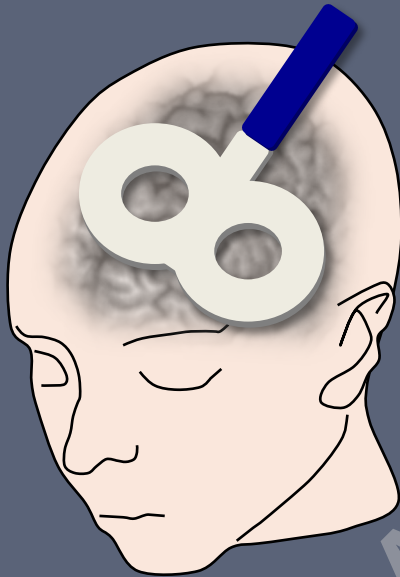
- Might induce current
- Won't fool non-naïve

sham



Option 2: Use “sham” Coil

real



Pros:

Similar look and feel
Tech getting better

Cons:

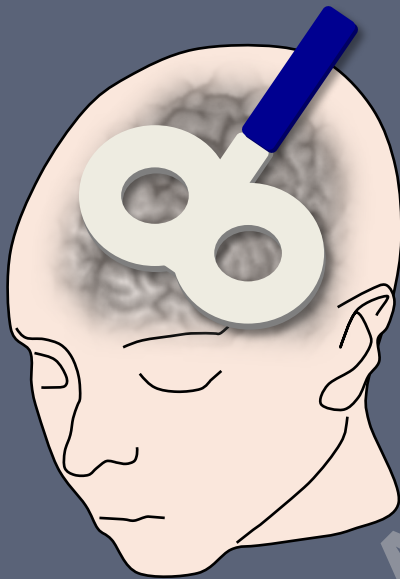
Slow, expensive
Must switch coils
Still doesn't feel the same

sham



Option 3: Active Control Site

real



Pros:

Easy, fast, cheap
Same sensations

Cons:

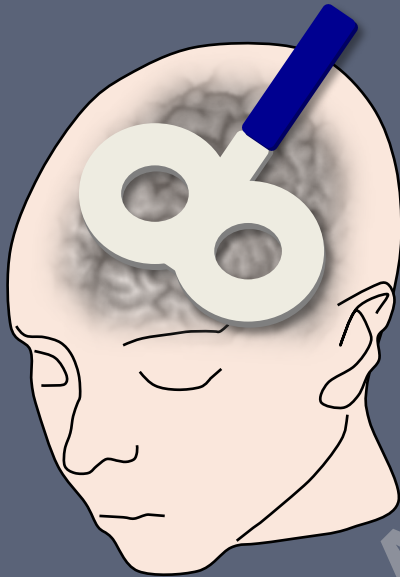
Will control site have
real effects?
Laterality of sensations

vertex



Option 4: Double Dissociation

Left hemisphere



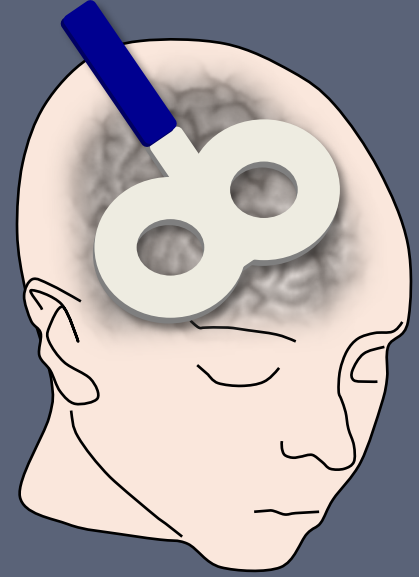
Pros:

Easy, fast, cheap
Same sensations
Greater explanatory
power

Cons:

More difficult study design

Right hemisphere



So... Now what?

