
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"



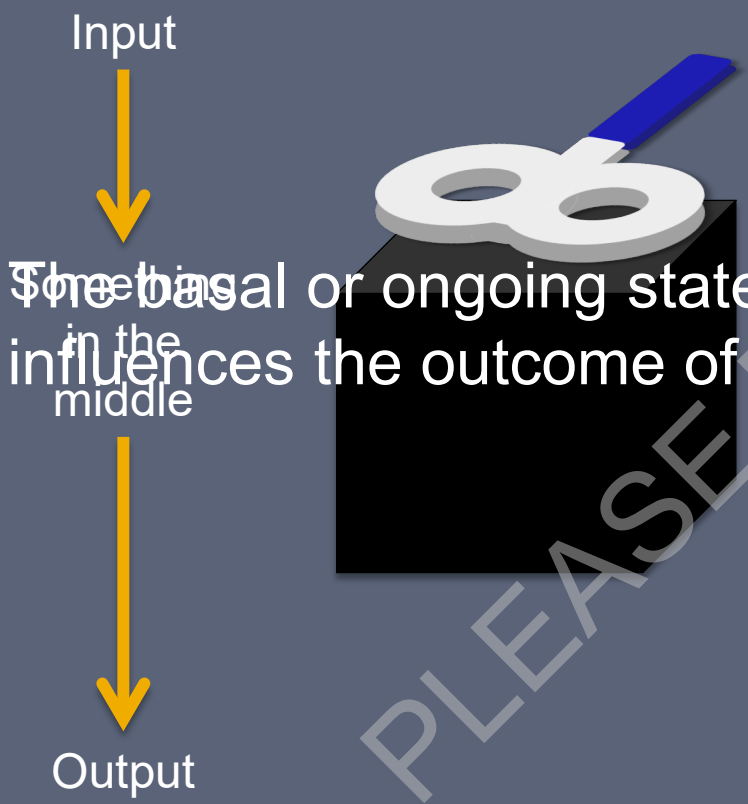
Peter J. Fried, Ph.D.

January 2024

# Overview

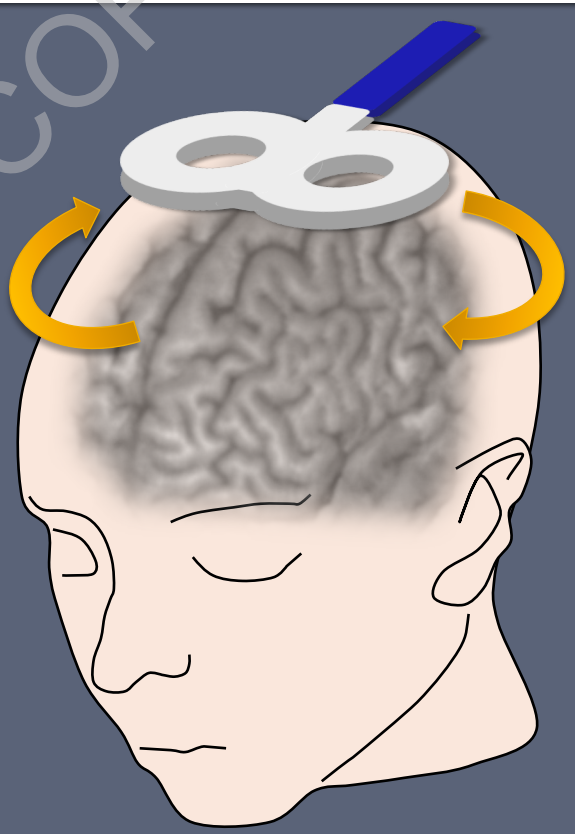
- What is 'state-dependency'?
- Single Pulse TMS (specificity)
- Repetitive TMS (meta-plasticity, variability)
- Implications for study design

# What is 'State-dependency'?






The basal or ongoing state of the brain influences the outcome of stimulation



# Paired-Pulse TMS




Intracortical Inhibition (ISI = 1-6ms)

Intracortical Facilitation (ISI = 8-30ms)

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

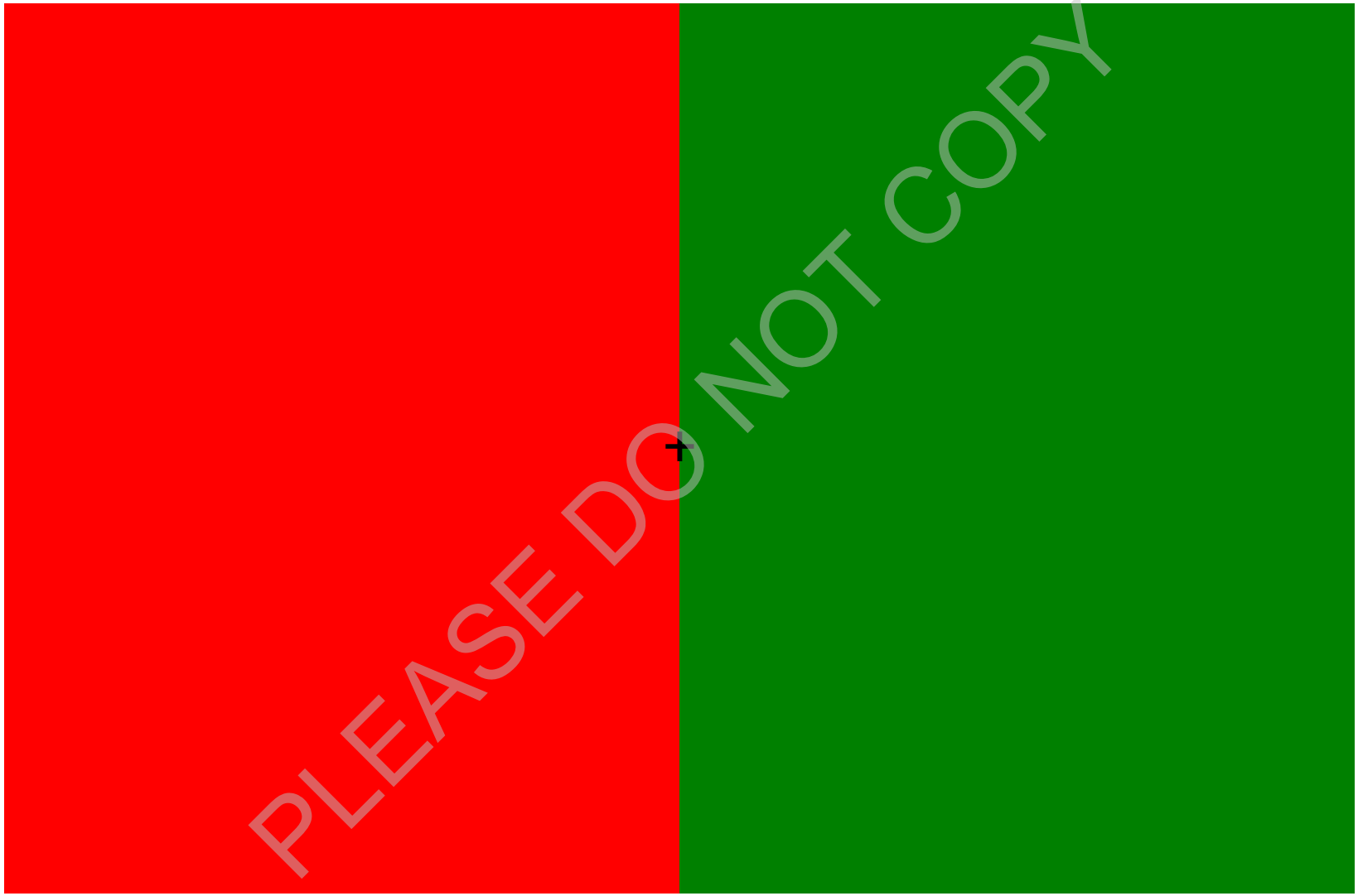
# Overview

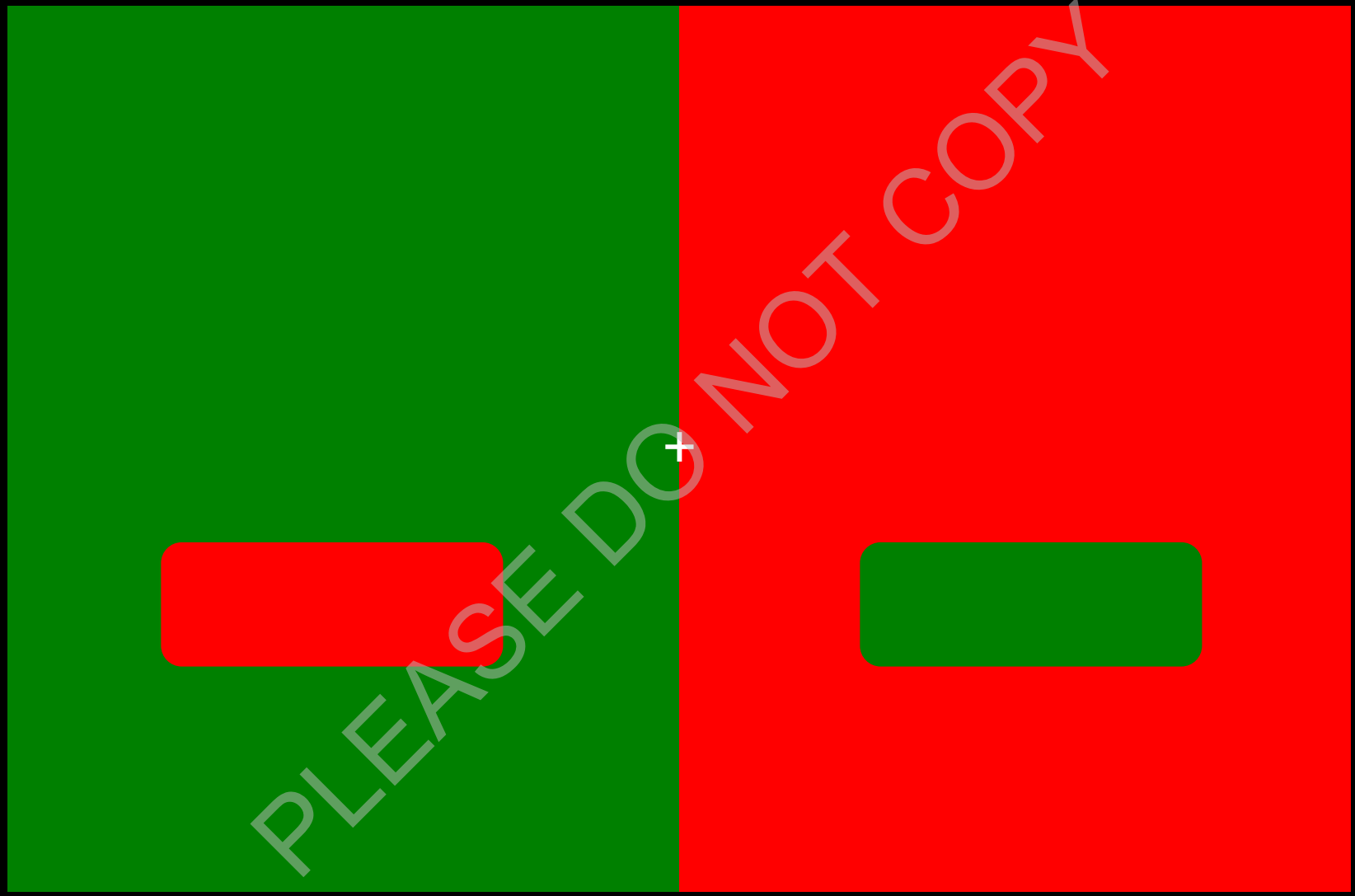
- What is 'state-dependency'?
- Single Pulse TMS (specificity)
  - Adaptation & Priming
- Repetitive TMS (meta-plasticity)
- Implications for study design

# Adaptation & Priming

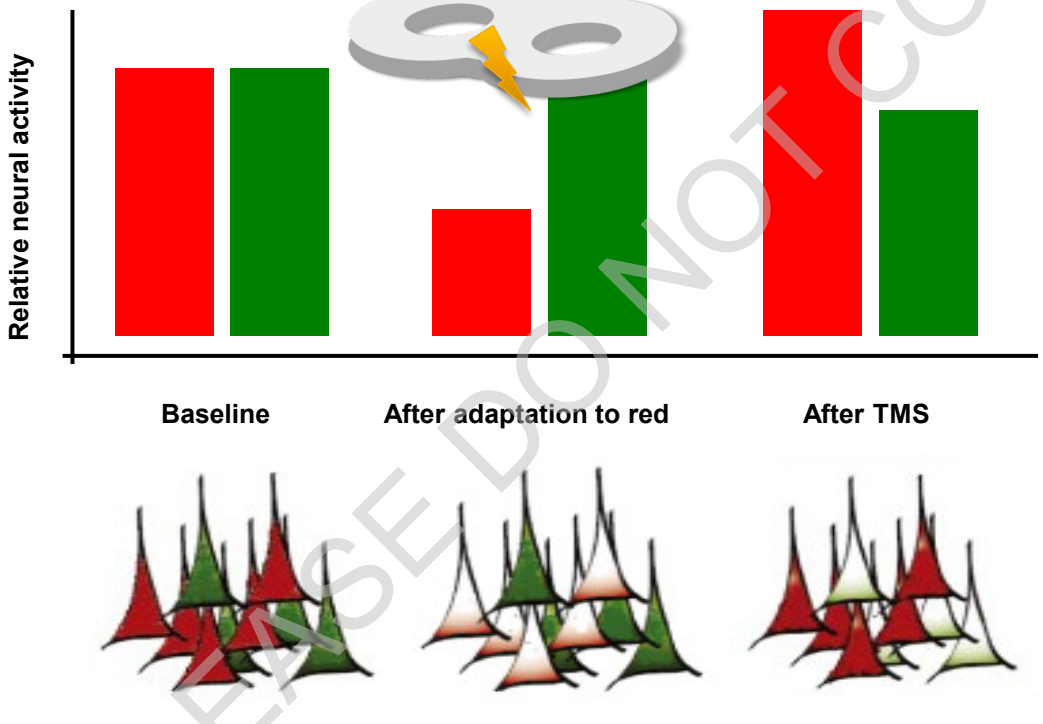
Adaptation:

Priming:



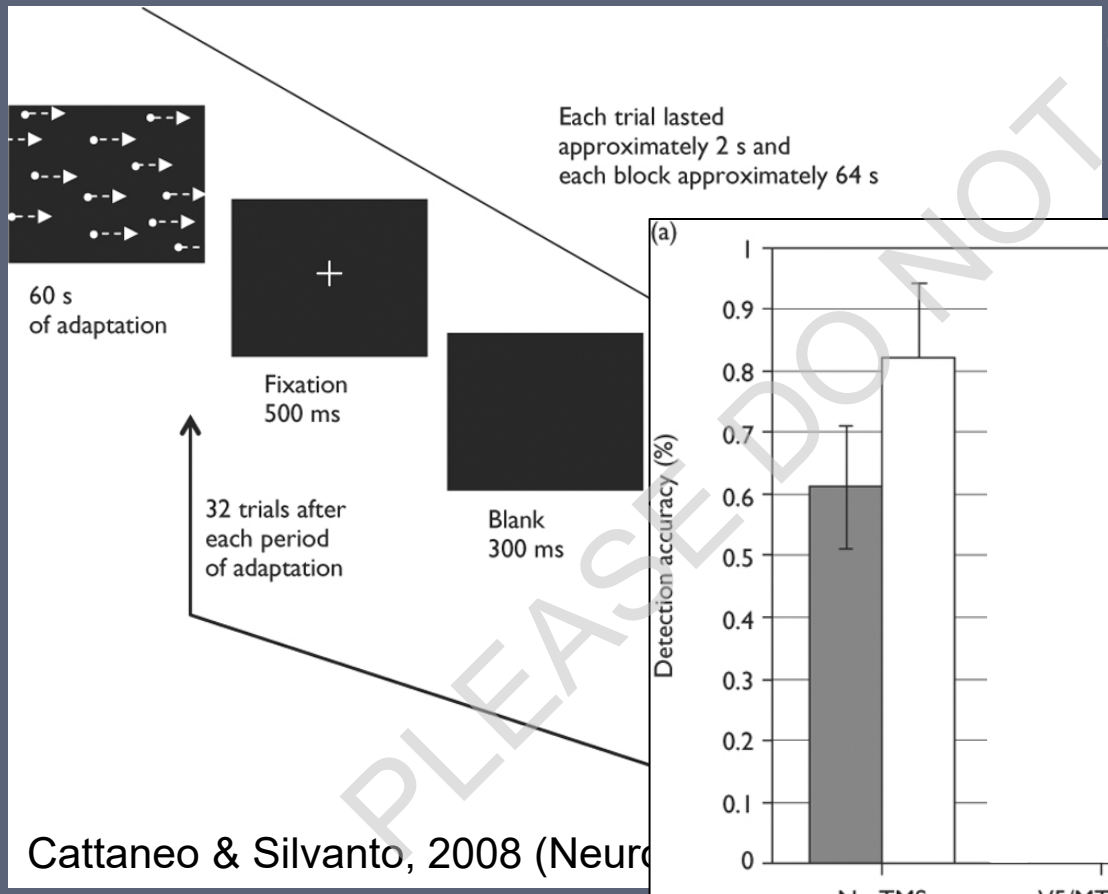

PLEASE DO NOT COPY

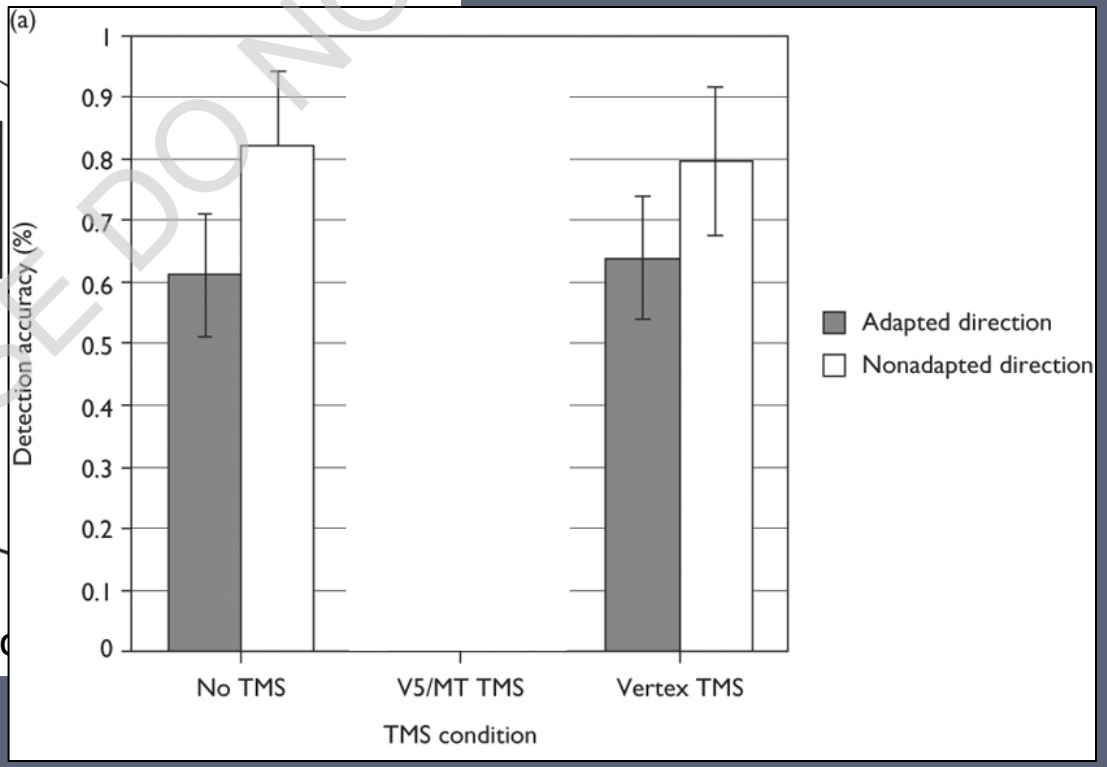
# Color Adaptation: area V1




Modified from: Silvanto et al., 2008 (Trends in Cognitive Sciences)

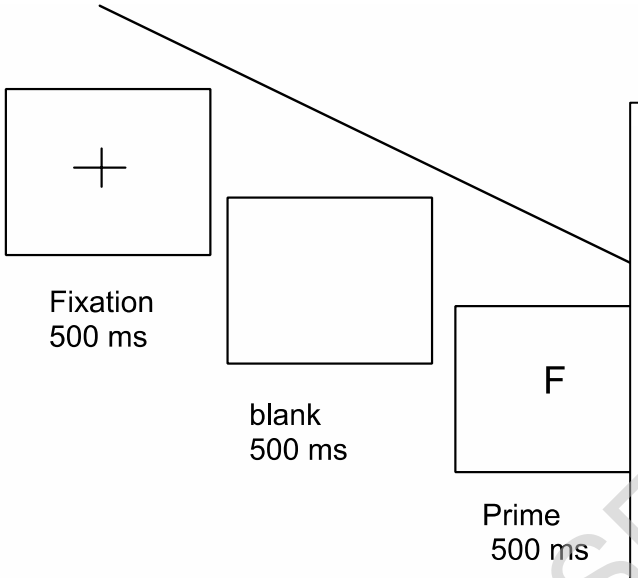
# Motion Adaptation: area V5/MT

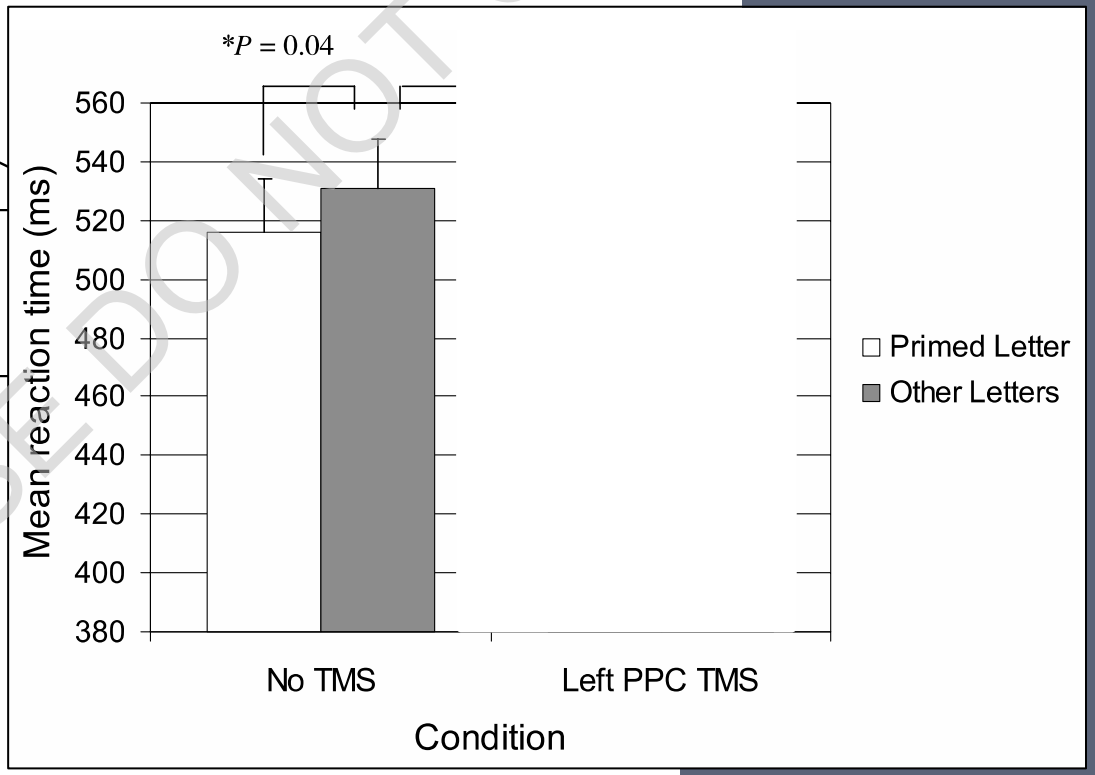



Cattaneo & Silvanto, 2008 (Neuro

# Letter Priming: left PPC



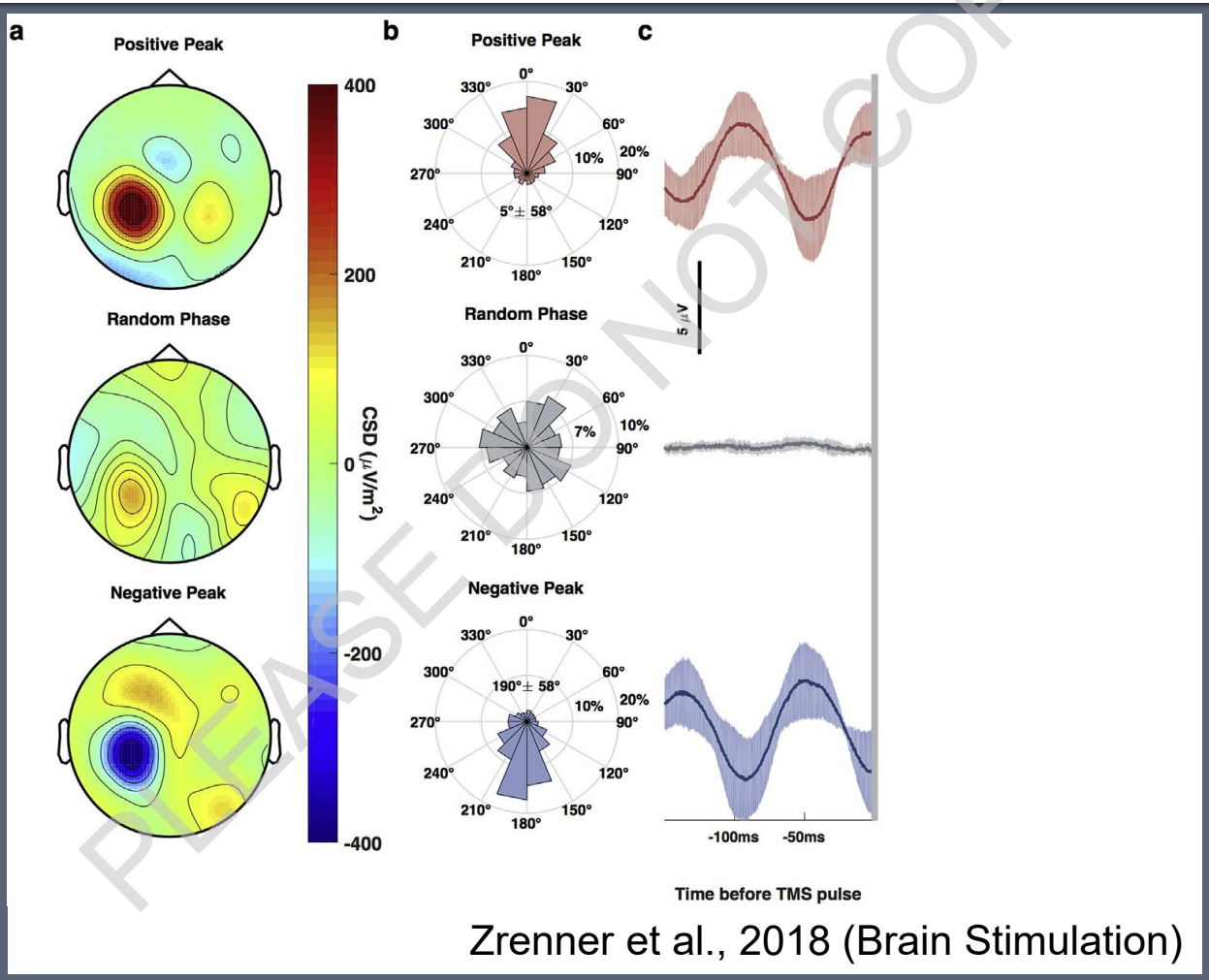




Cattaneo et al., 2008 (European Journal of Neuroscience)

# 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

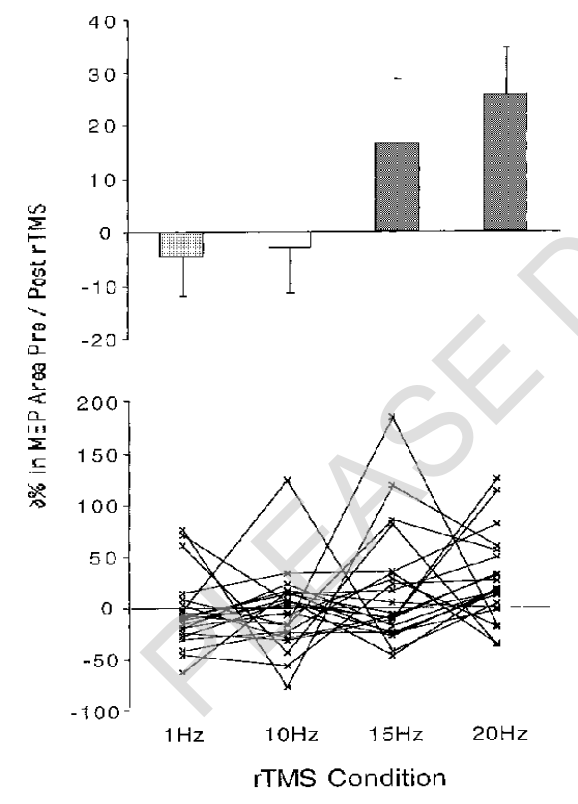
Exp Brain Res (2000) 133:425–430
DOI 10.1007/s002210000432

RESEARCH ARTICLE

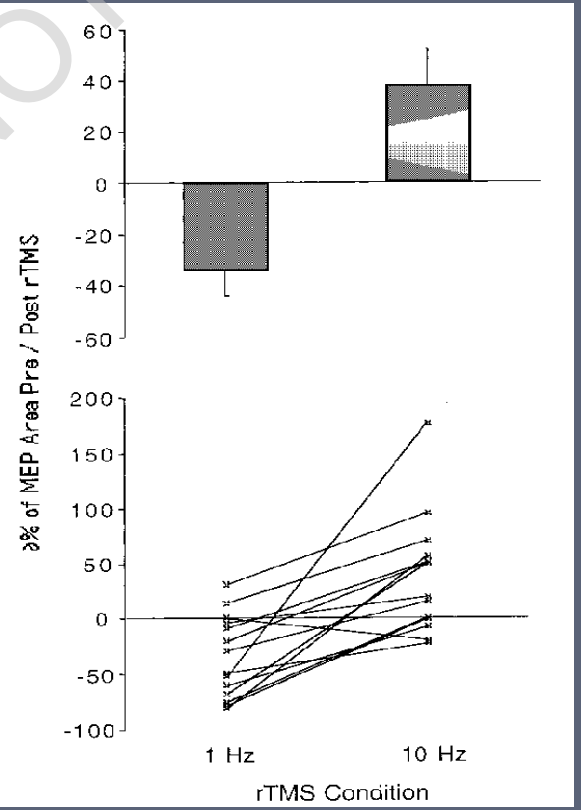
Fumiko Maeda · Julian P. Keenan · Jose M. Tormos
Helge Topka · Alvaro Pascual-Leone

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

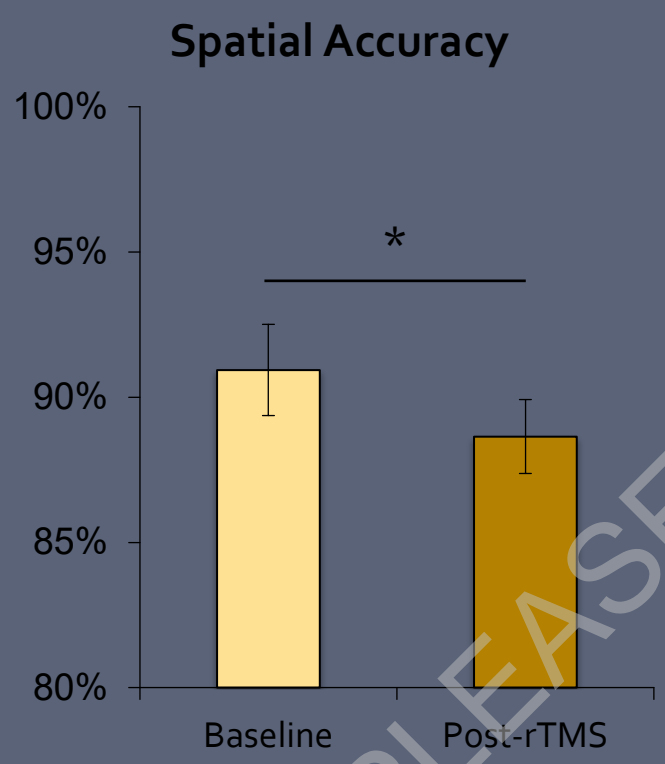
240 pulses

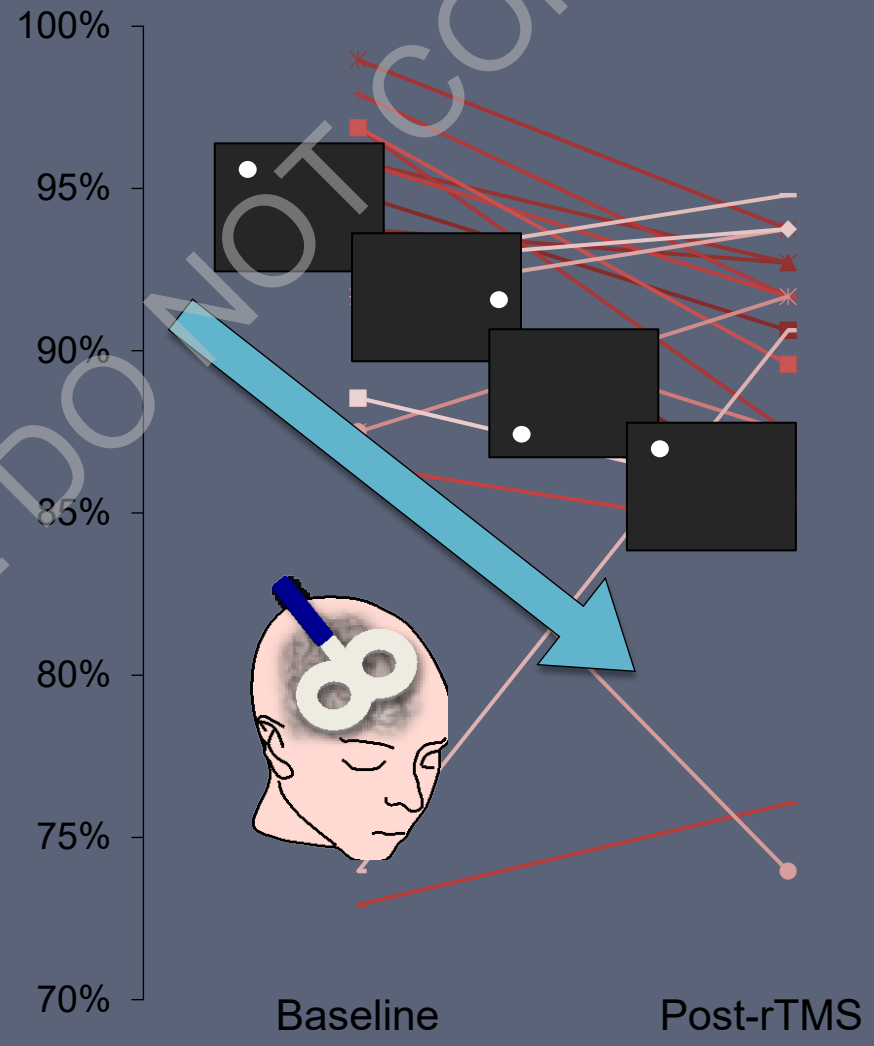



1600 pulses



# Variability in Cognitive Interventions






Modified from Fried et al., 2014

# Altered response to rTMS in disease

**Impact of 1Hz rTMS on Motor-Evoked Potential (MEP), Intracortical Facilatition and Inhibition**

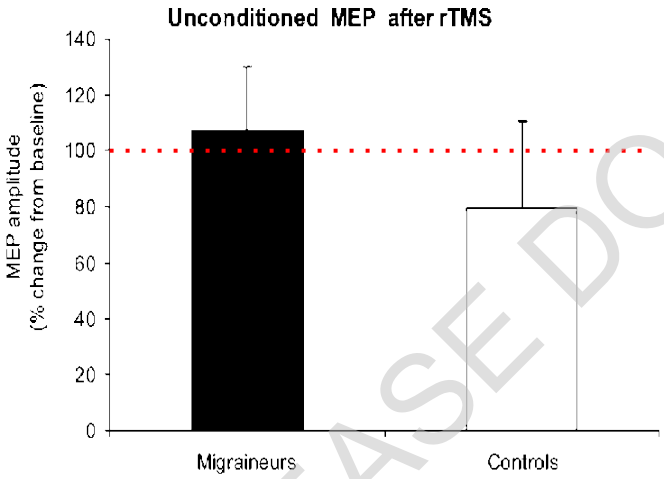
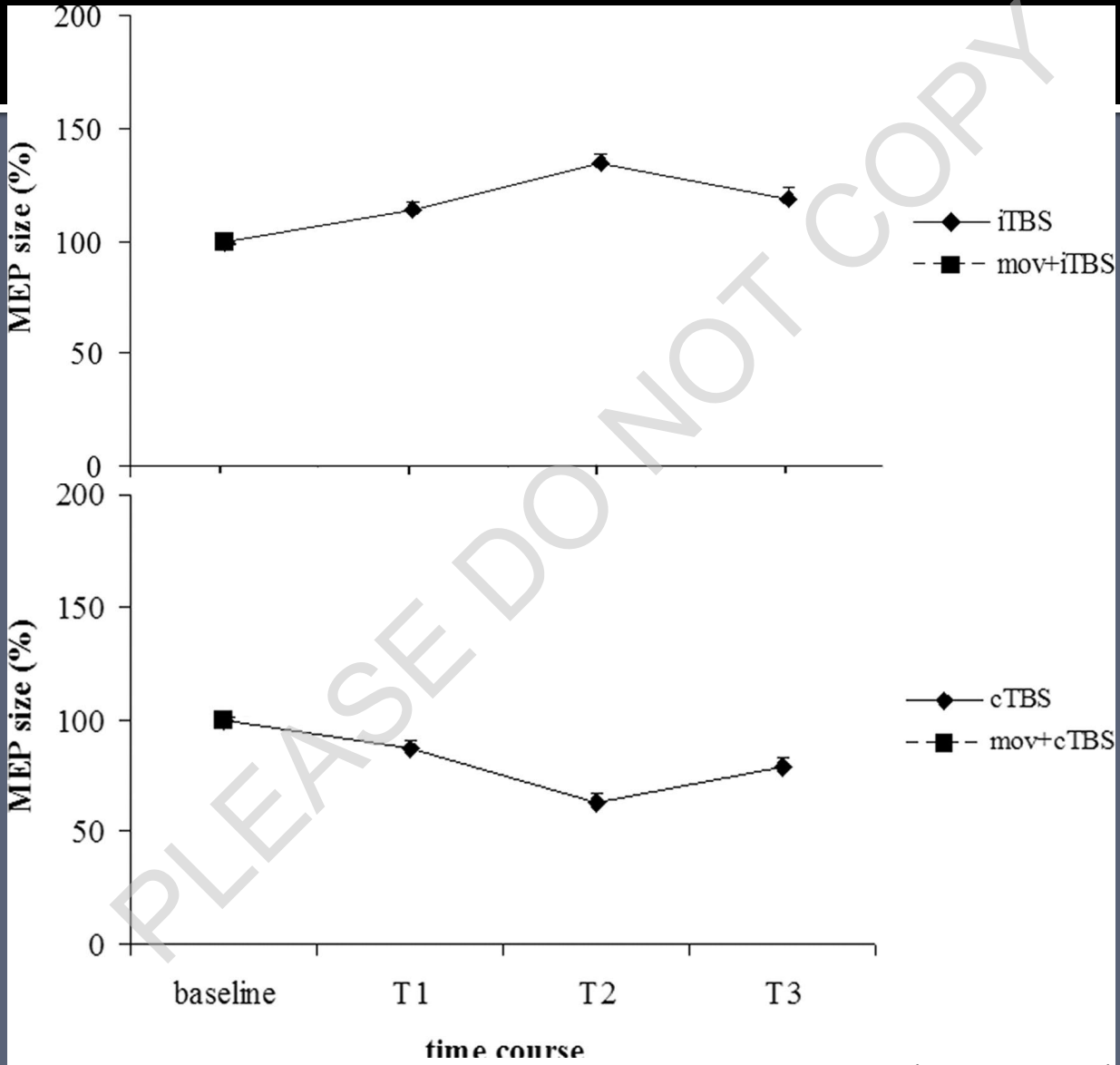



Fig. 1 Mean amplitude (±SD) of MEP to test stimulus alone after 1 Hz rTMS in migraineurs and controls (values are expressed as percentage of baseline MEP).

Brighina et al., 2005 (Experimental Brain Research)

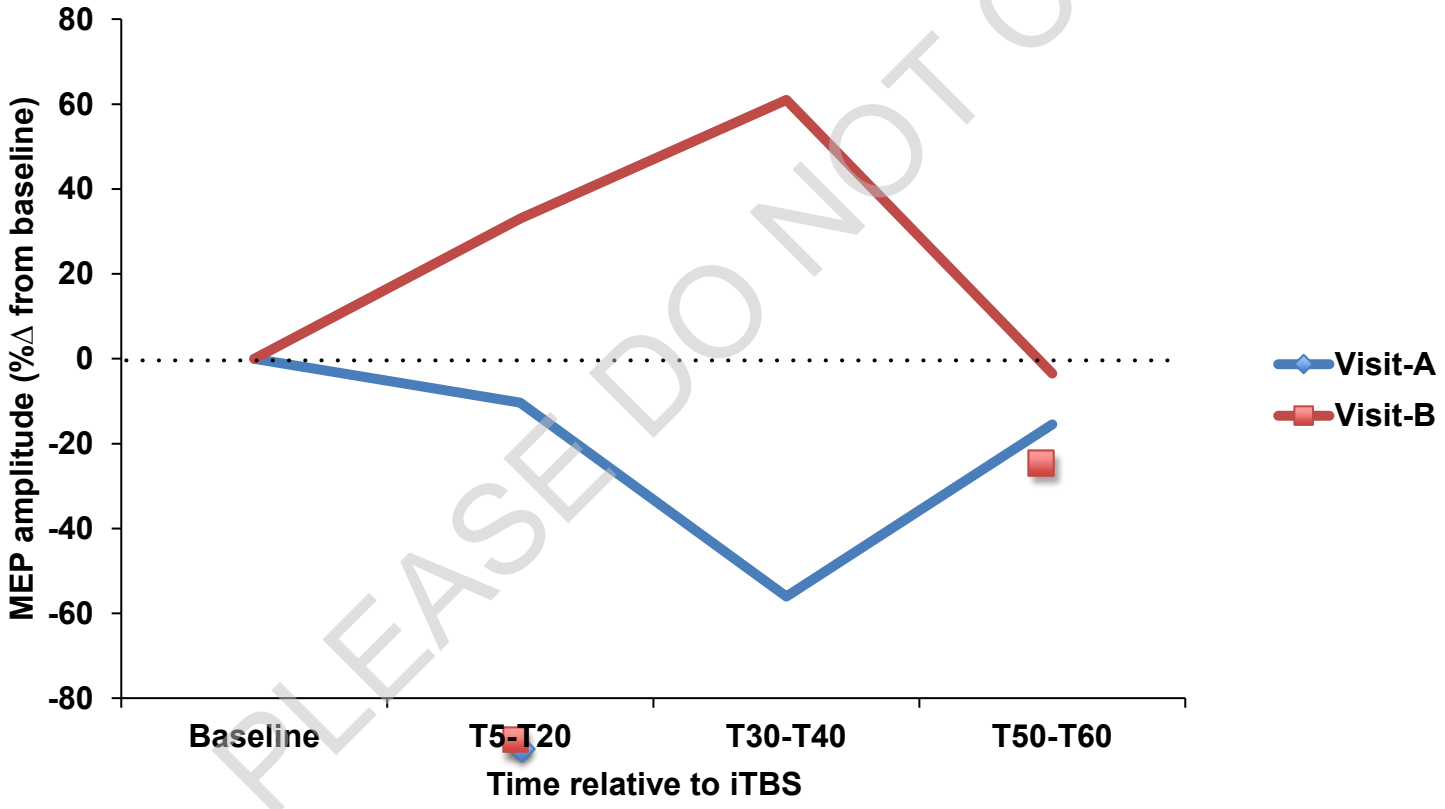
# Impact of physiological activity





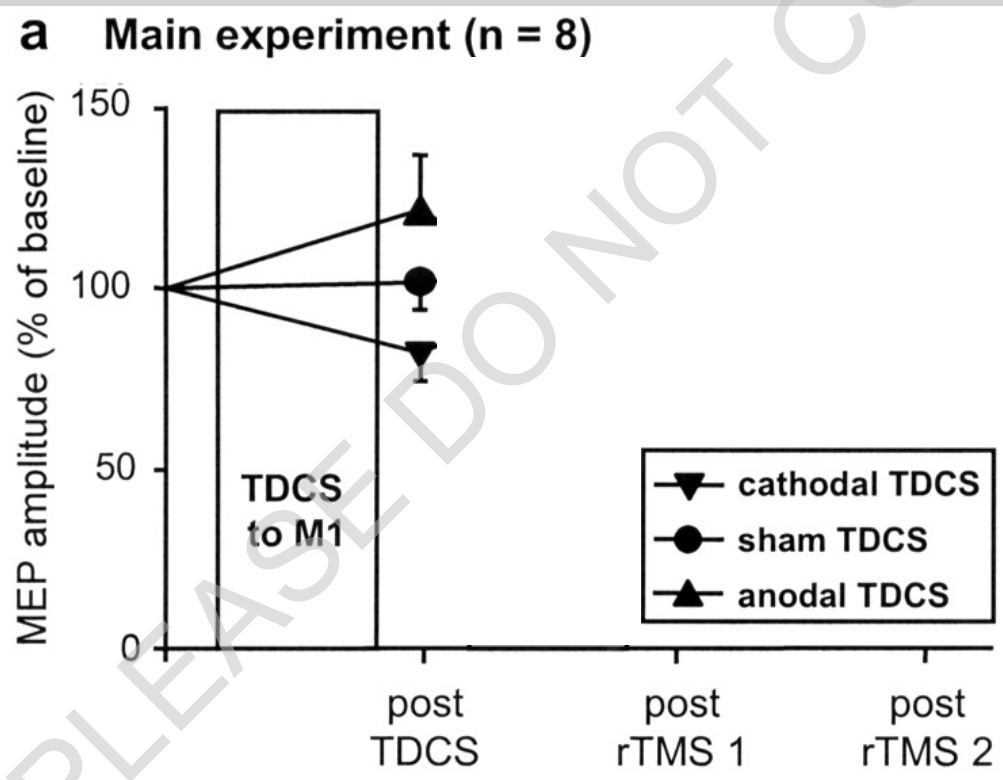

Iezzi E et al., 2008 (J Neurophysio)

# Case example



# Preconditioning rTMS with tDCS

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




Siebner et al., 2004 (Journal of Neuroscience)

# Preconditioning TBS with TBS

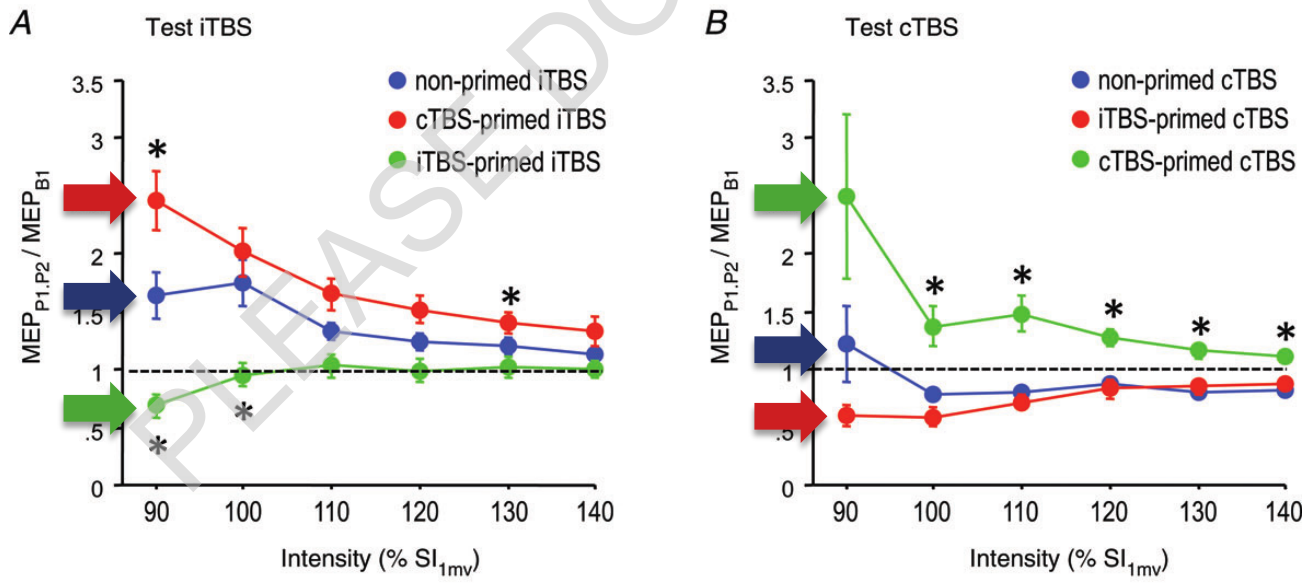
*J Physiol* 590.22 (2012) pp 5765–5781



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

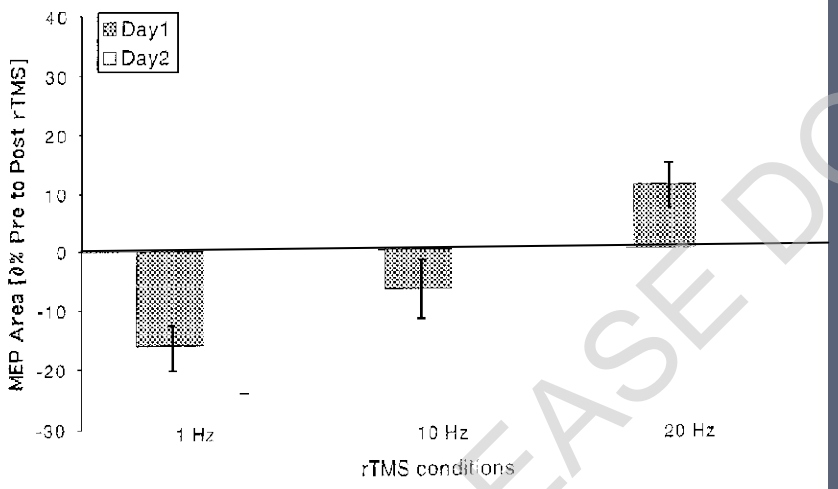
Takenobu Murakami[1], Florian Müller-Dahlhaus[1], Ming-Kuei Lu[1,2] and Ulf Ziemann[1,3]





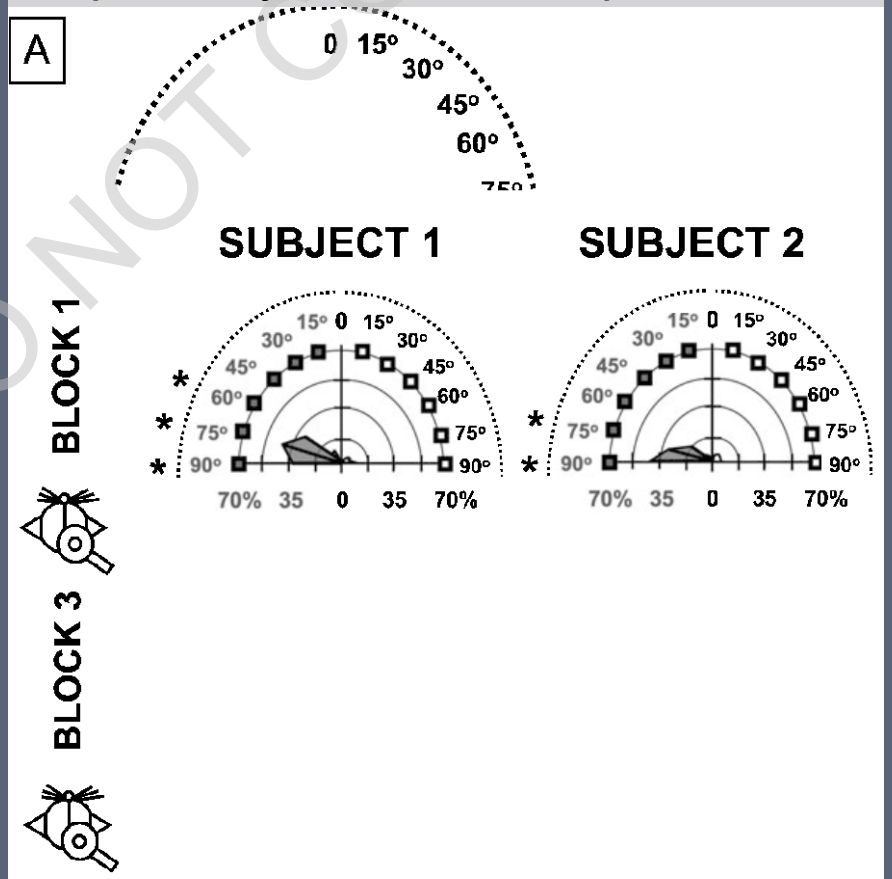
# Meta-plasticity: Impact of Cumulative Sessions

**Impact of rTMS on Motor-Evoked Potentials**




Maeda et al., 2000 (Clinical Neurophysiology)

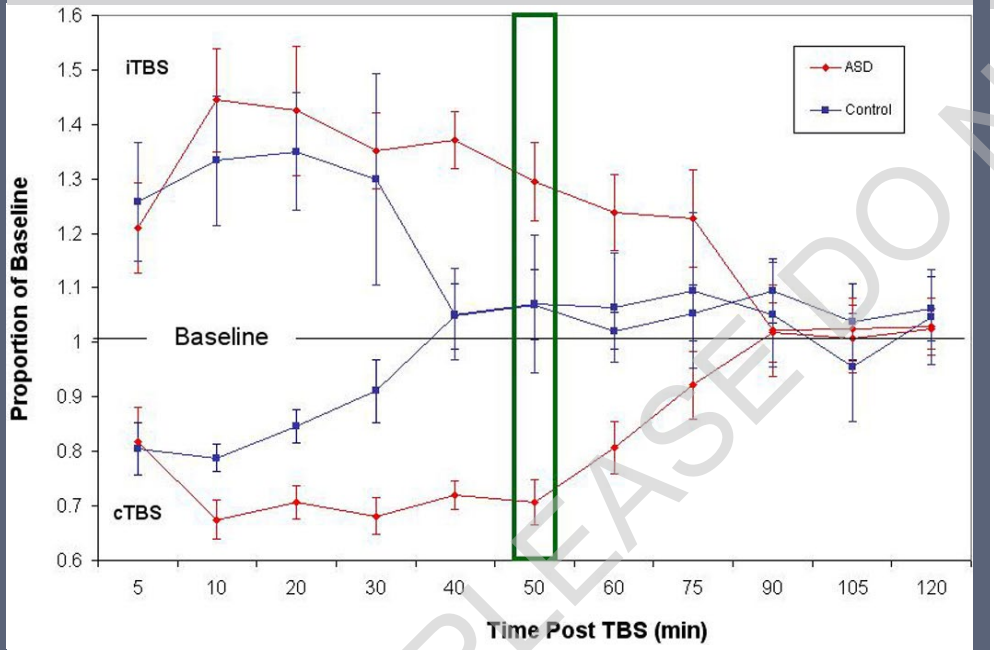
**Impact of daily 1Hz rTMS on visuo-spatial detection**




Valero-Cabré et al., 2008 (European Journal of Neuroscience)

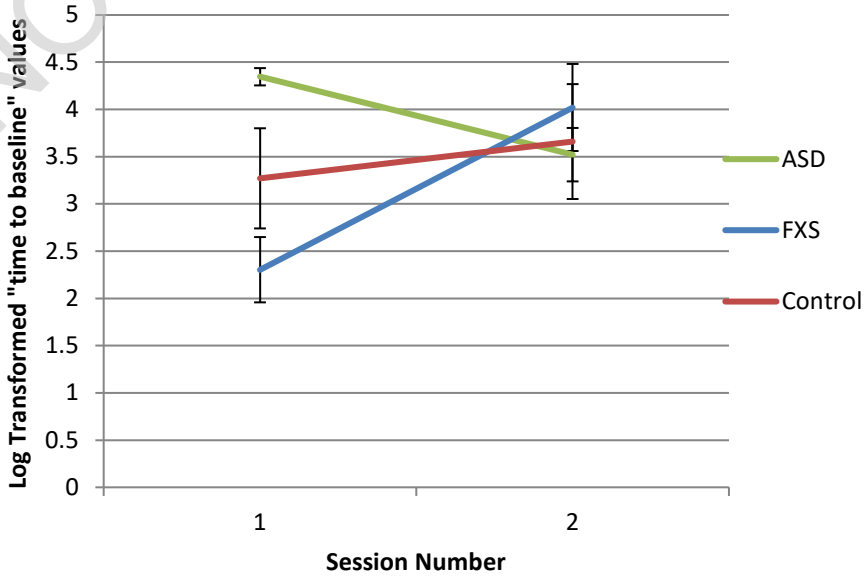
# Altered Meta-plasticity in ASD

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



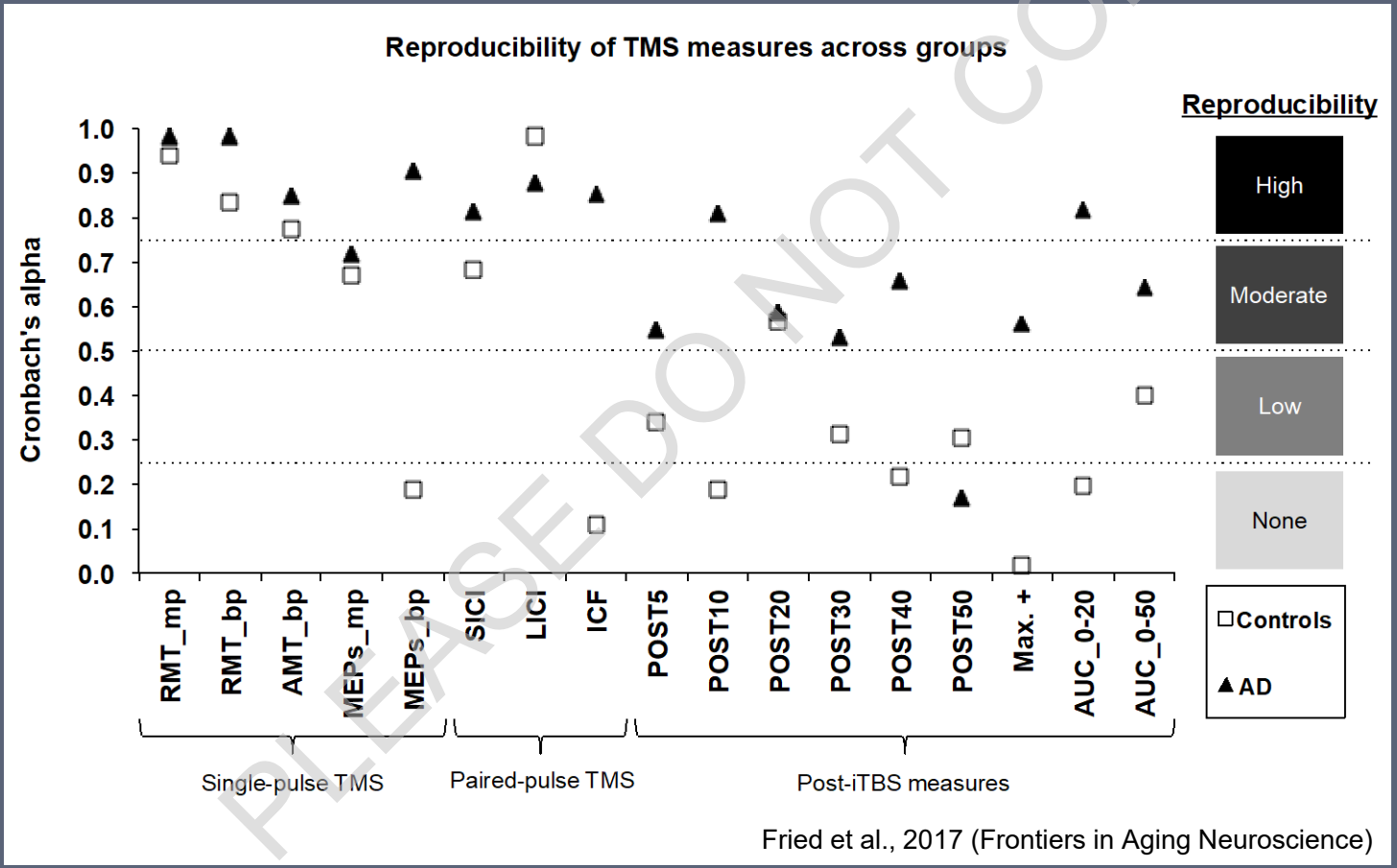

Oberman et al., 2012 (European Journal of Neuroscience)

**Cumulative Impact of Back-to-Back TBS**



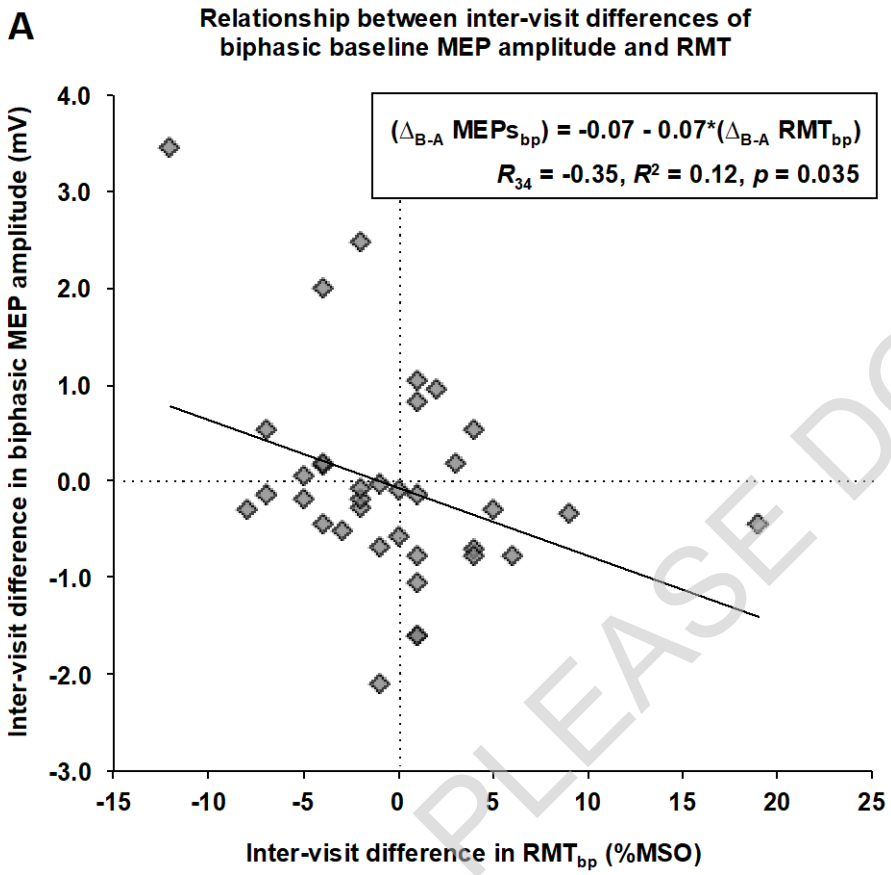

Oberman et al., 2016 (J Child Adolescent Psychopharm)

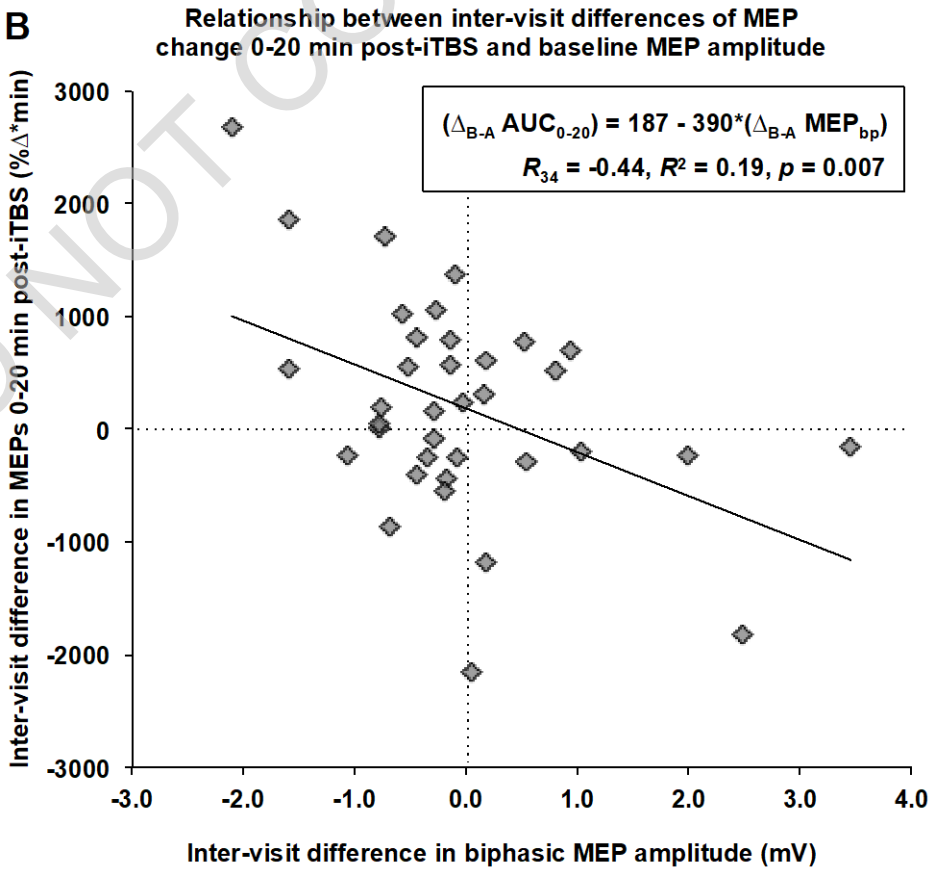
# Reproducibility of TMS measures




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

# Factors that affect reproducibility






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

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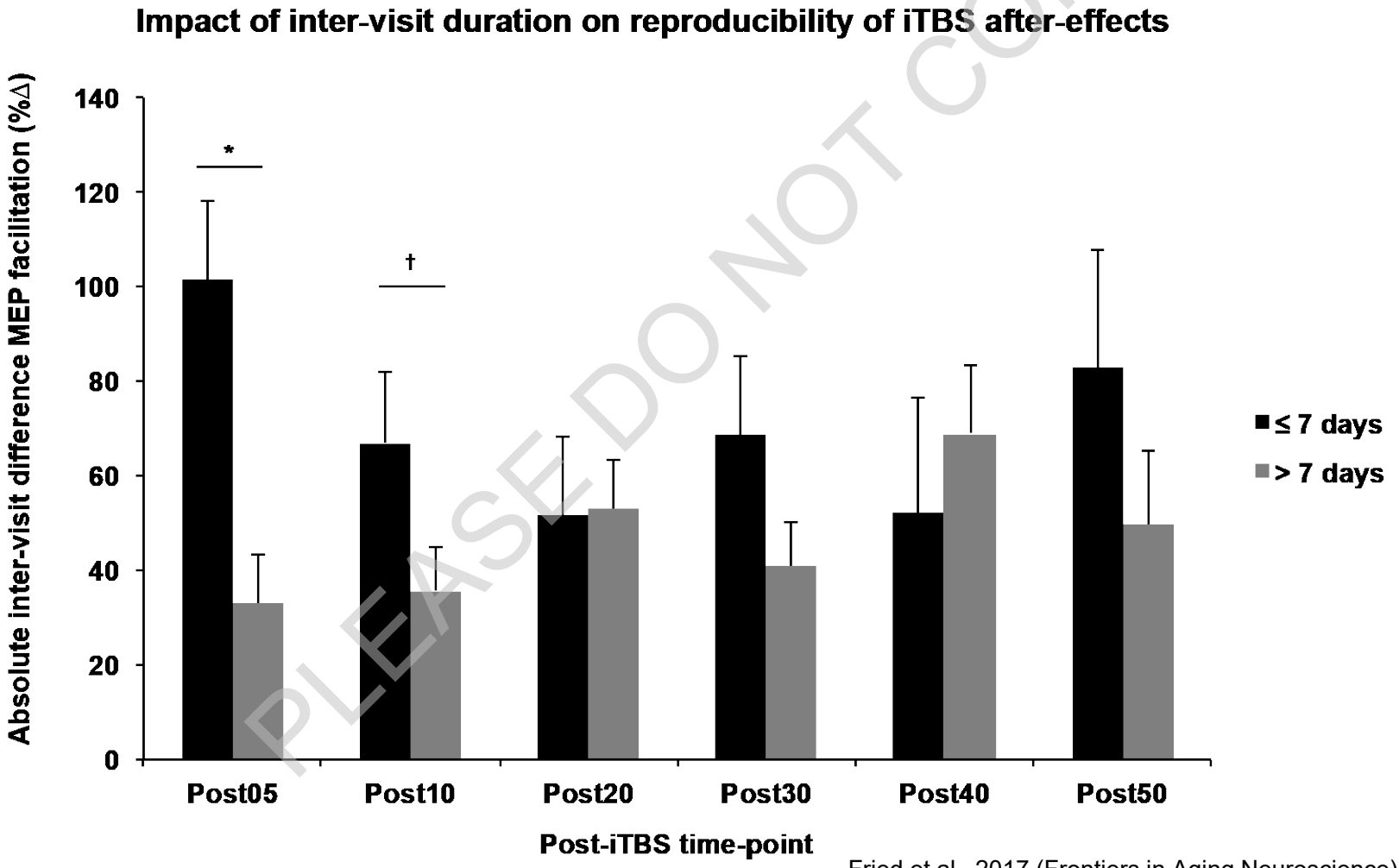
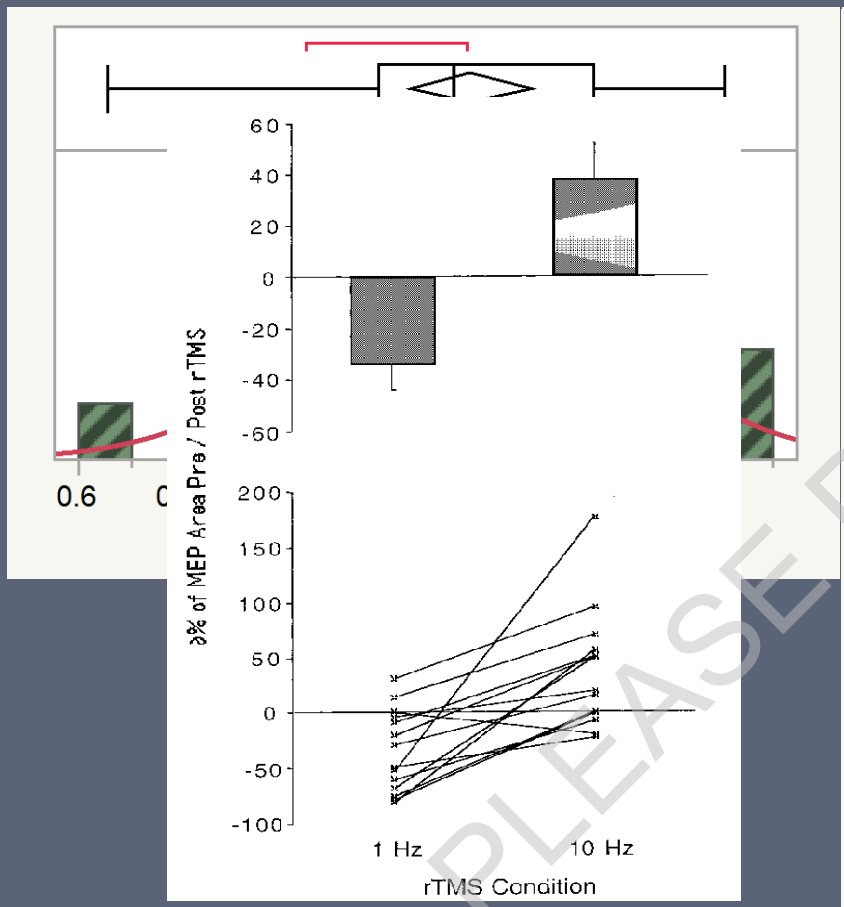
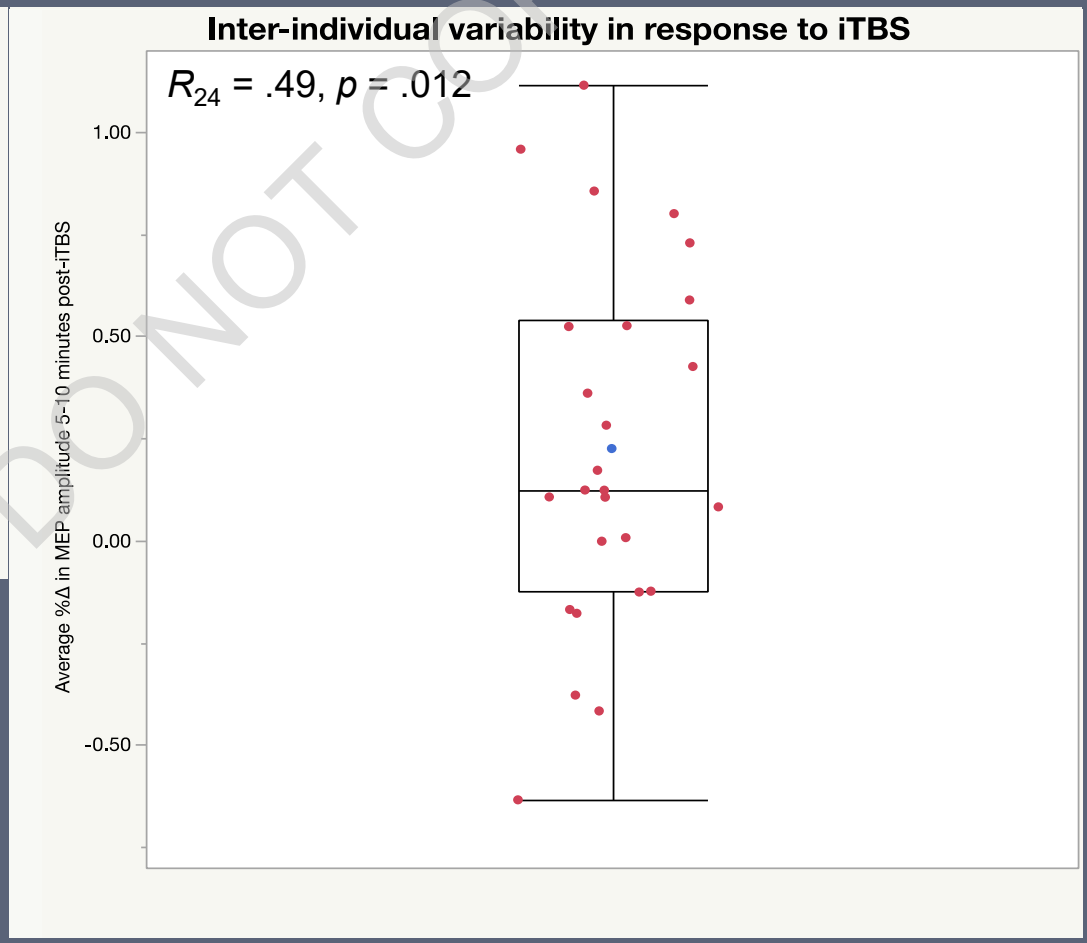



Fried et al., 2017 (Frontiers in Aging Neuroscience)

# Variability due to study parameters






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 (≤ 1s) → basis of rTMS
  - Back-to-back regimens → likely to interact
  - Daily sessions → 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

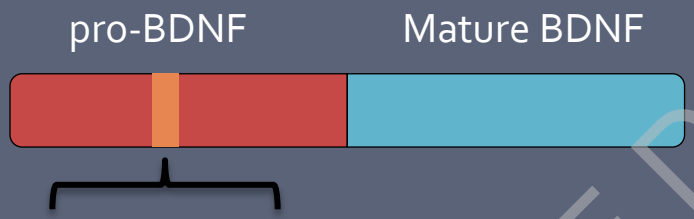
- Caffeine, Rx
- Prior stimulation
- Time of day
- Food intake
- Handedness
- Concomitant activity

Less Easy to Control

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

# DNA

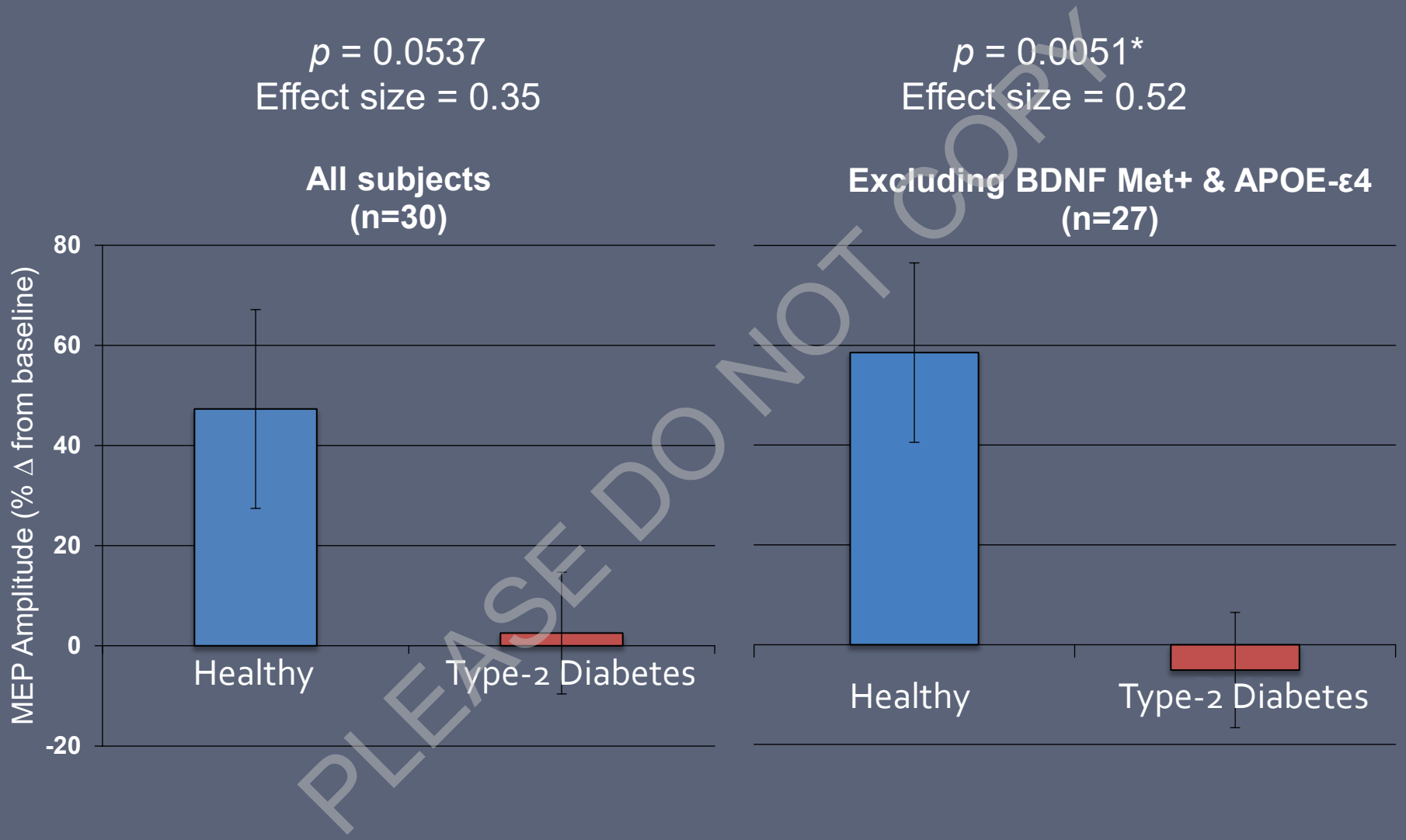
- Brain-derived neurotrophic factor (BDNF)
  - Modulates NMDAR-dependent plasticity
  - Activity-dependent release at synapses




65%: val66val
35%: val66met (less efficient)

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

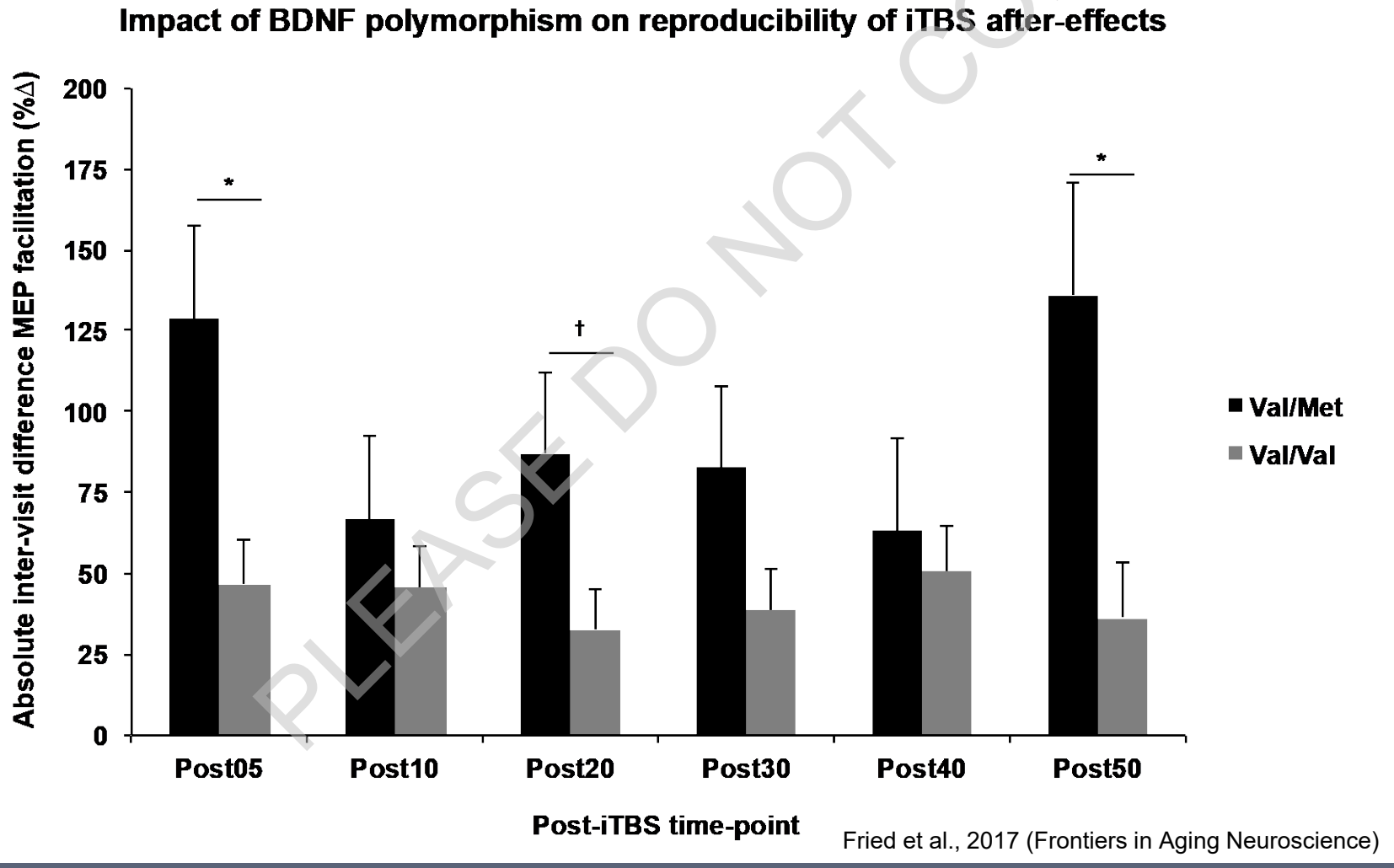
- Apolipoprotein E (APOE)
  - Produced by astrocytes, microglia (in CNS)
  - Transports cholesterol & fat-soluble vitamins to neurons
  - Three major isoforms:
    - ApoE2 (cys112, cys158): ~7%
    - ApoE3 (cys112, arg158): ~79%
    - ApoE4 (arg112, arg158): ~14%
      - E3,E4 & E4,E4: Higher risk for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






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

# Factors that affect reproducibility



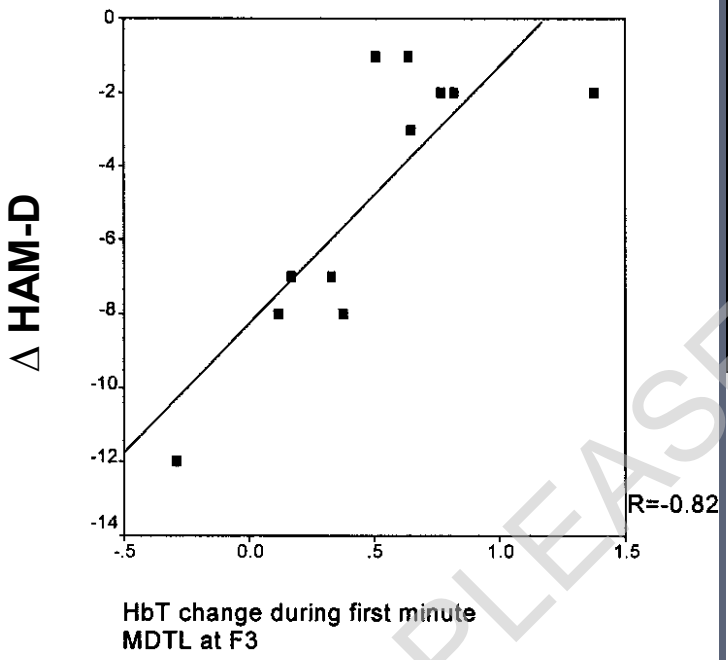

Fried et al., 2017 (Frontiers in Aging Neuroscience)

# What to do? Follow the C's

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

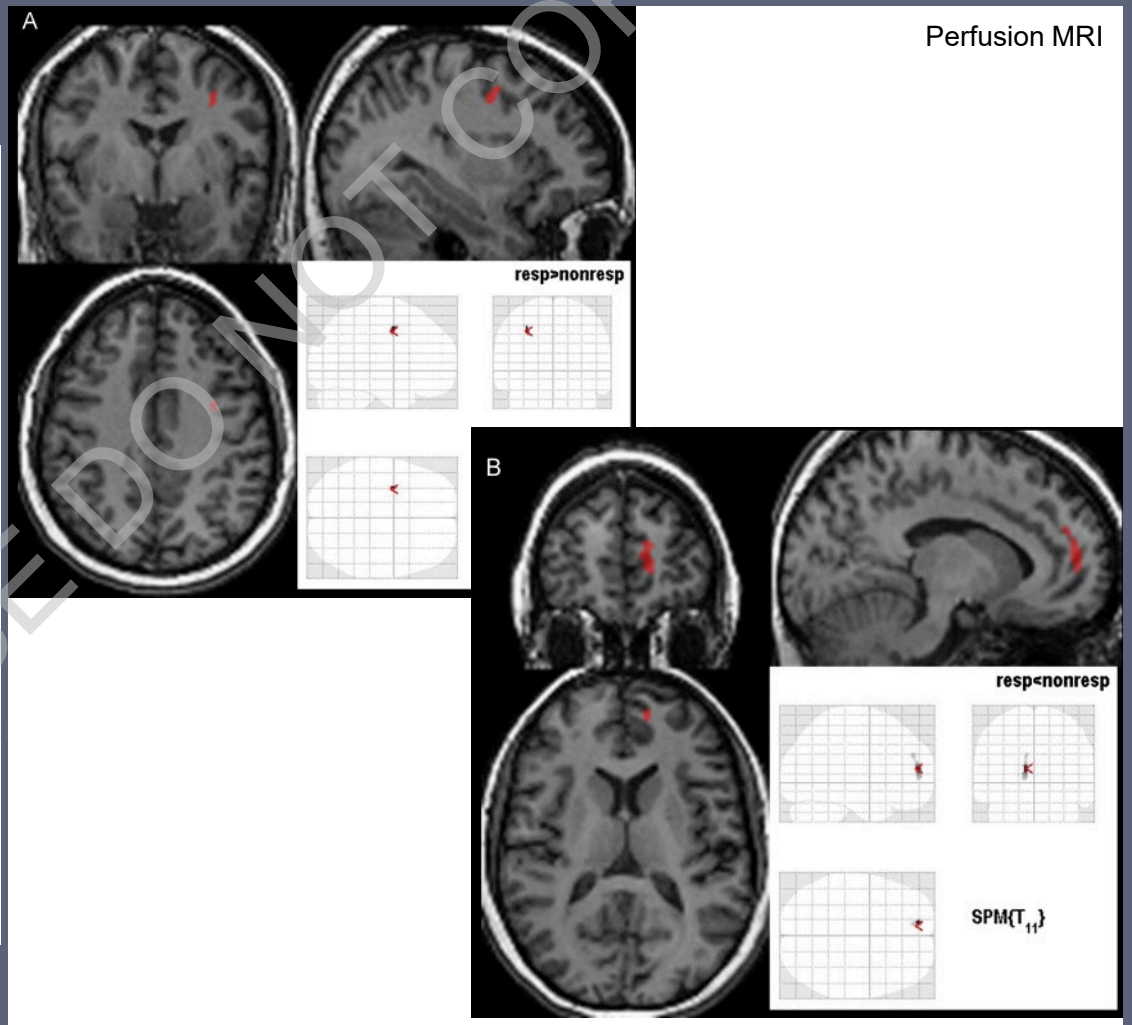
# Predicting Therapeutic Outcome: activity in single sites

NIRS




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

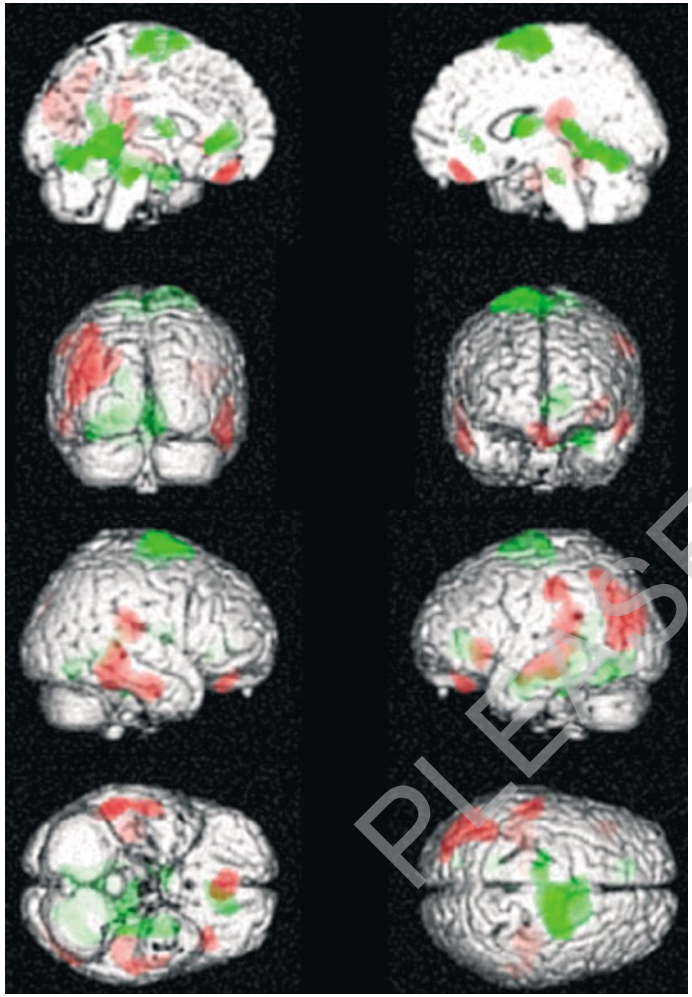
Perfusion MRI




Weiduschat and Dubin, 2013 (J Affective Disorders)

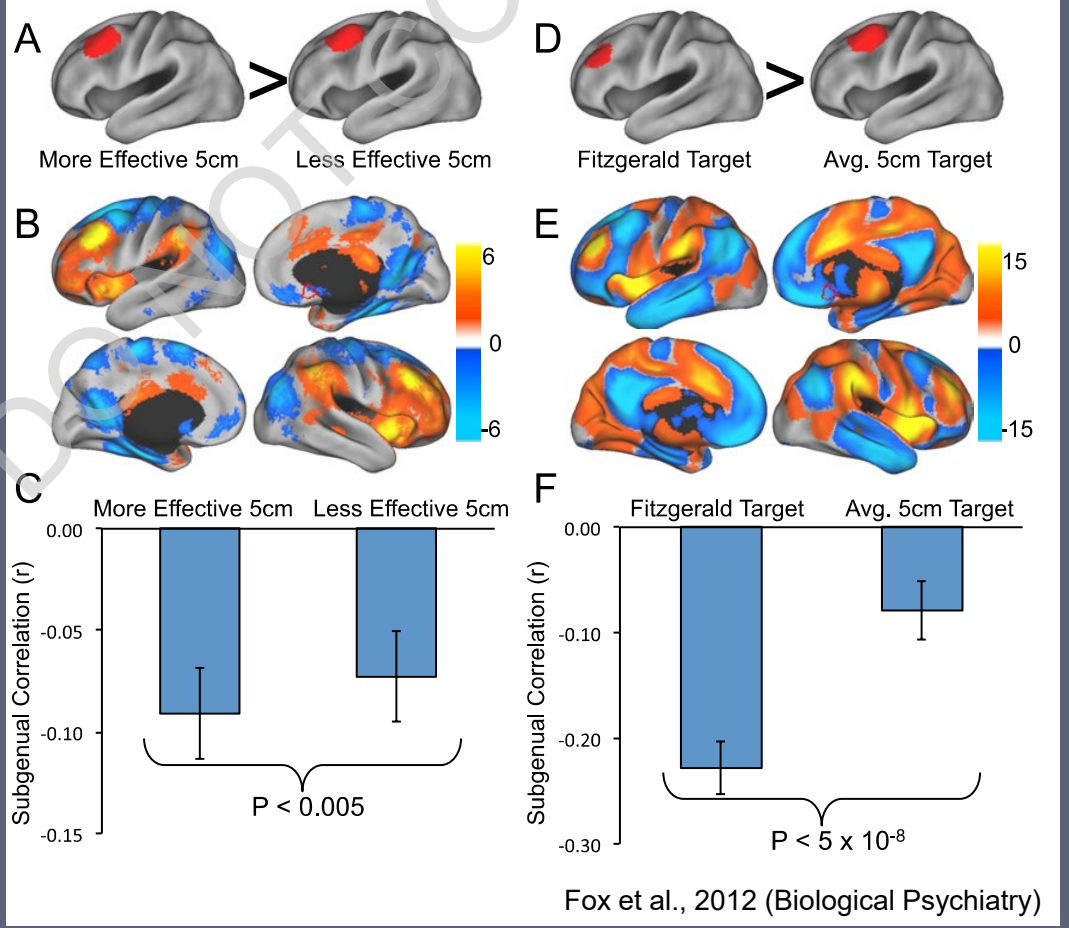
# Predicting Therapeutic Outcome: activity across networks

rCBF (SPECT)



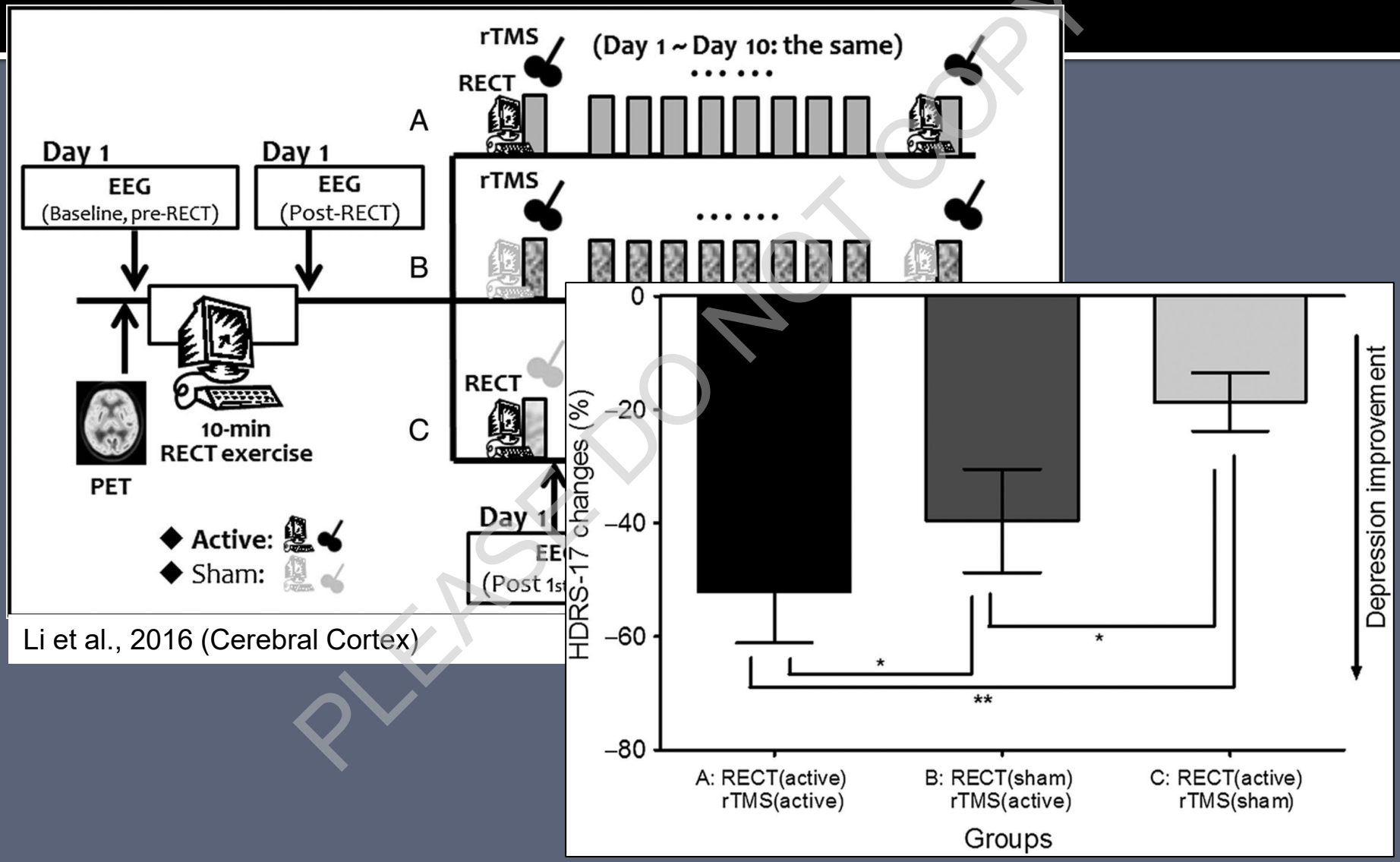
Mottaghy et al., 2002 (Psychiatry Res.: Neuroimaging)

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

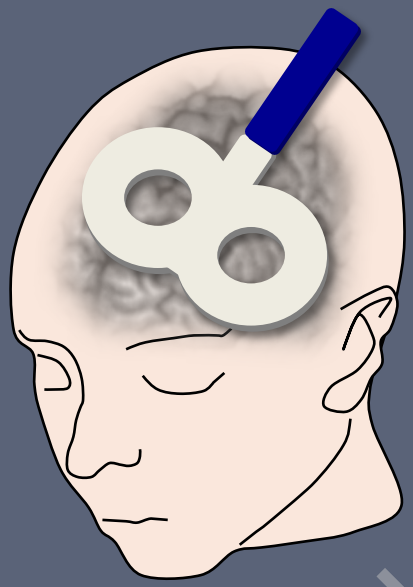
- Individualized targeting
  - Single node vs. network
- Prime sub-populations of neurons
  - Intrinsic vs. extrinsic engagement
- Assess efficacy online
  - Custom dose
- Leverage placebo effect

# 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

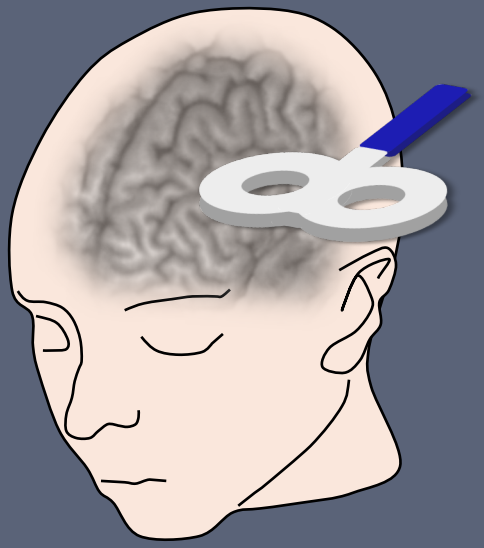
Similar sensations

Cons:

Might induce current

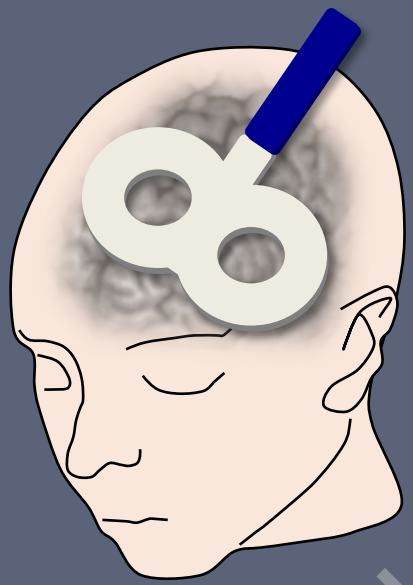
Won't fool non-naïve

sham



# Option 2: Use "sham" Coil

real



Pros:

Similar look and feel

Tech getting better

Cons:

Slow, expensive

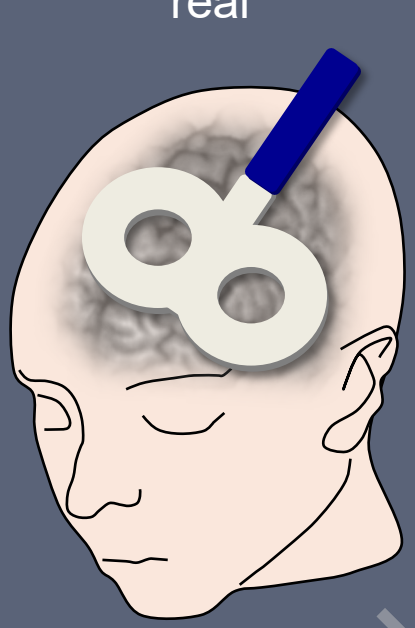
Must switch coils

Still doesn't feel the same

sham

# Option 3: Active Control Site

real



Pros:

Easy, fast, cheap

Same sensations

Cons:

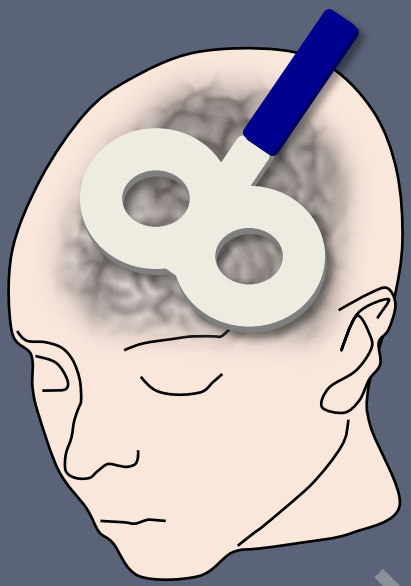
Will control site have real effects?

Laterality of sensations

vertex

# Option 4: Double Dissociation

Left hemisphere



Pros:

Easy, fast, cheap

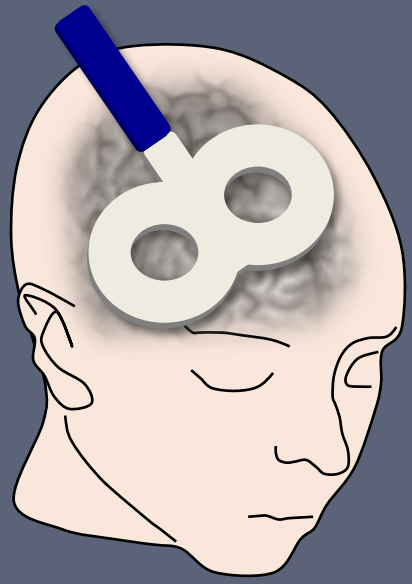
Same sensations

Greater explanatory power

Cons:

More difficult study design

Right hemisphere



# So… Now what?