Berenson-Allen Center For Noninvasive Brain Stimulation

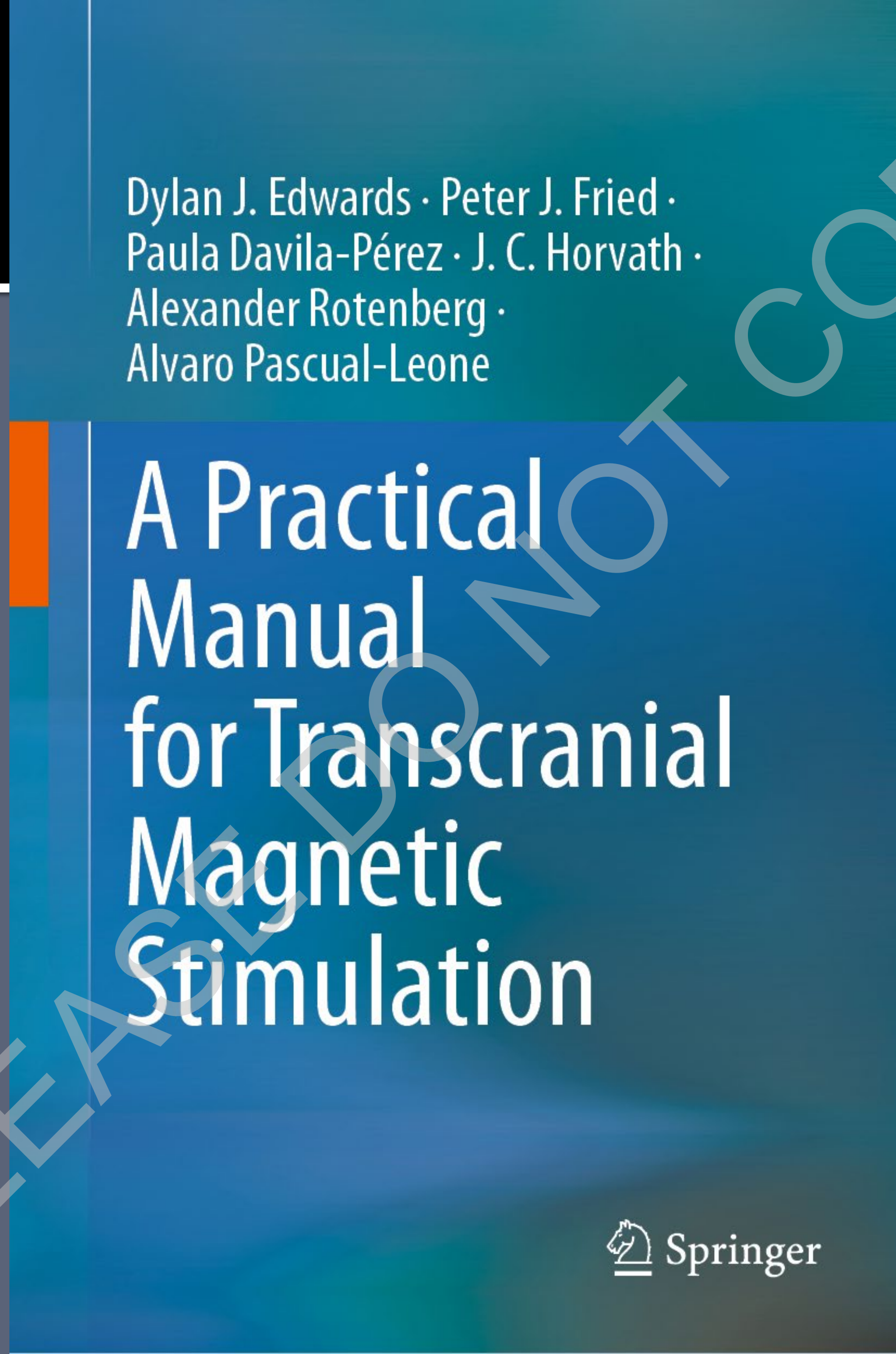
Intensive Course in Transcranial Magnetic Stimulation

State-Dependent Effects of Transcranial Magnetic Stimulation

"The cause of—and solution to—some of TMS's variability"

Peter J. Fried, Ph.D.

June 2025


Dylan J. Edwards · Peter J. Fried ·
Paula Davila-Pérez · J. C. Horvath ·
Alexander Rotenberg ·
Alvaro Pascual-Leone
A Practical Manual for Transcranial Magnetic Stimulation
Springer

Overview

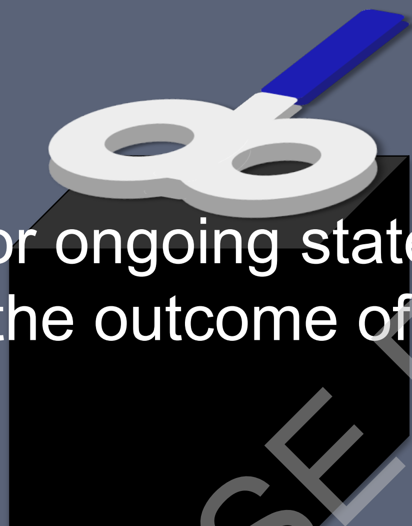
- What is ‘state-dependency’?
- Single Pulse TMS (specificity)
- Repetitive TMS (meta-plasticity, variability)
- Implications for study design

What is 'State-dependency'?

Input

Something
in the
middle

Output



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

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)

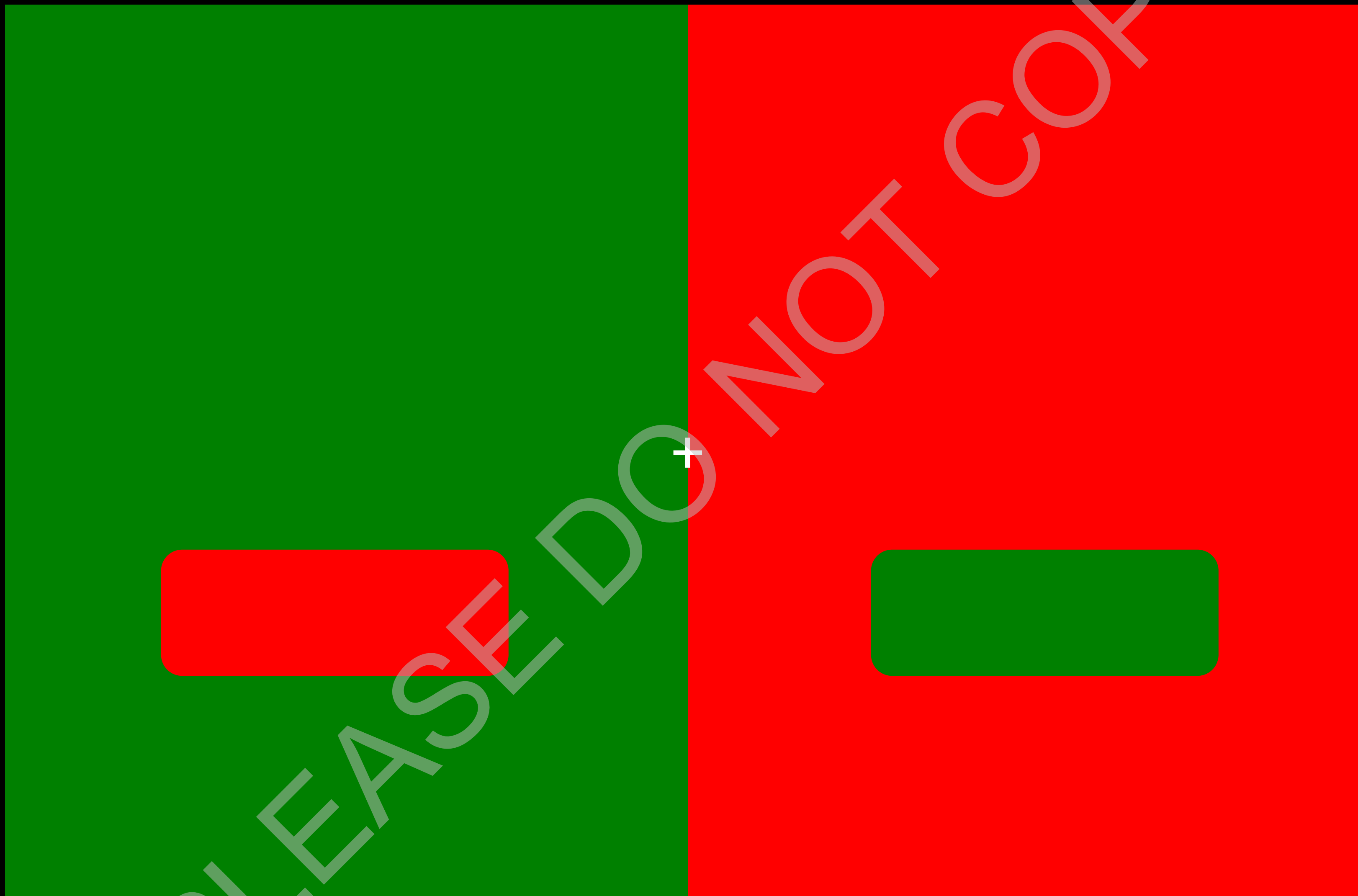
Overview

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

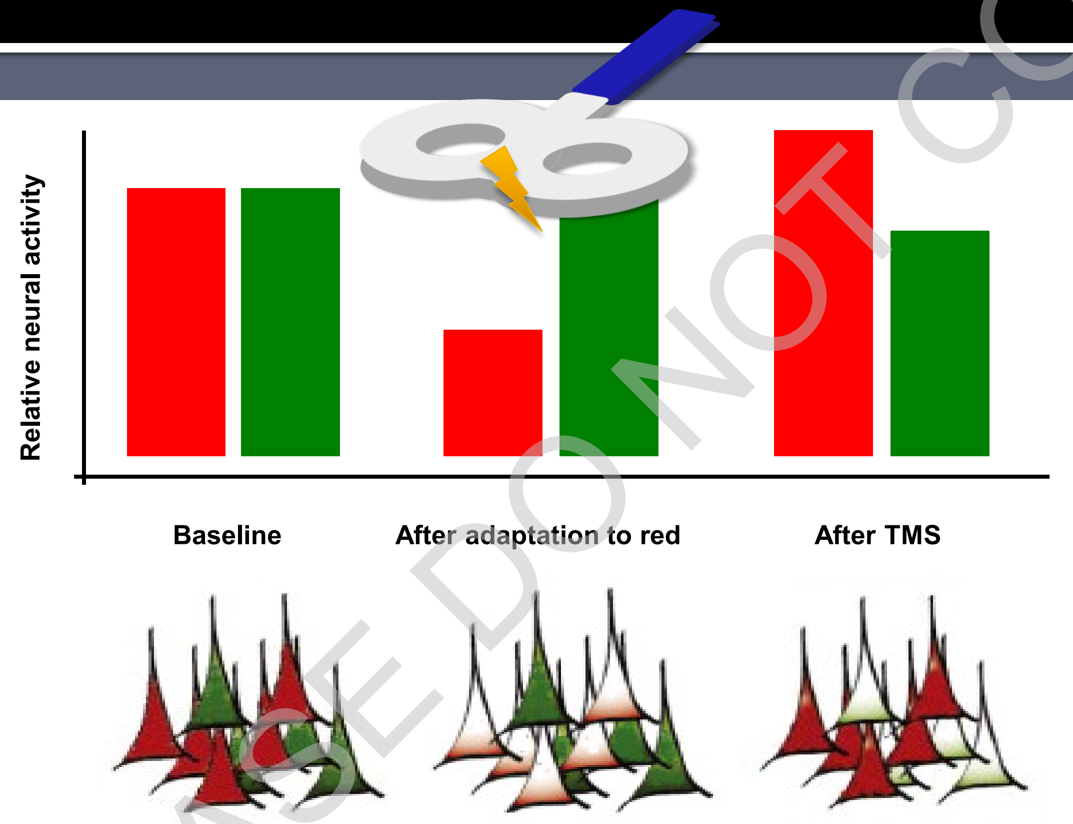
Adaptation & Priming

Adaptation:

Priming:

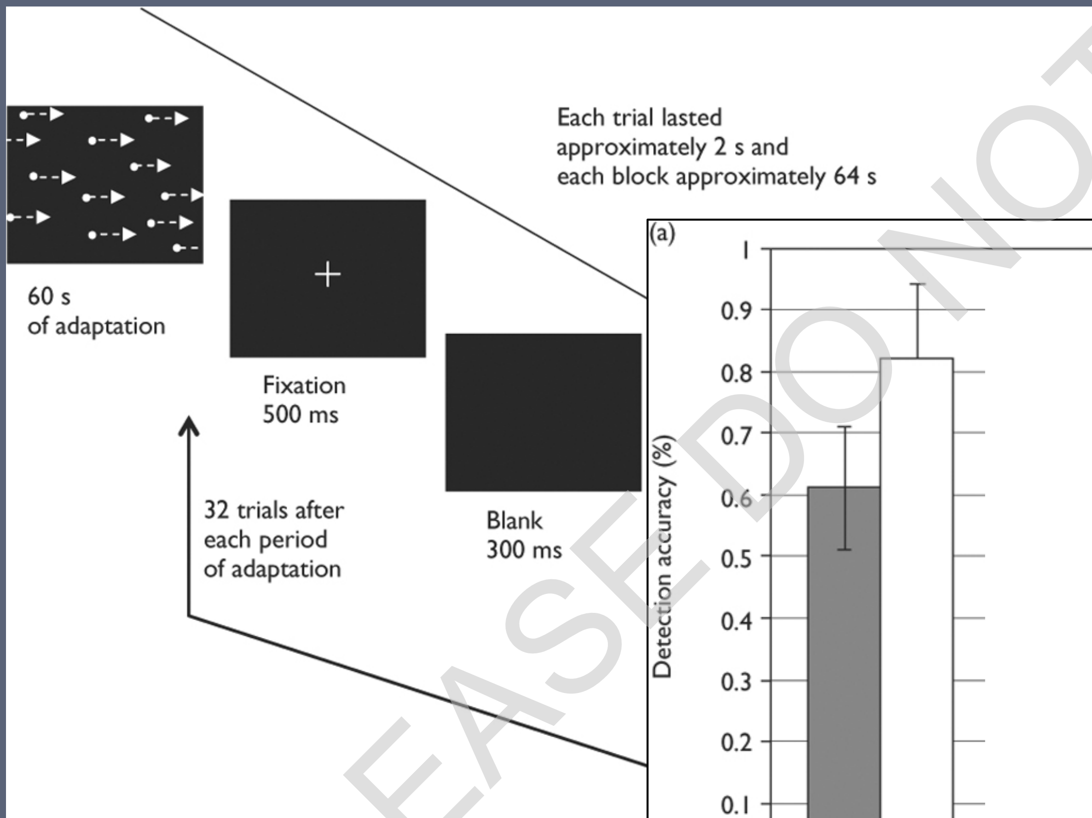


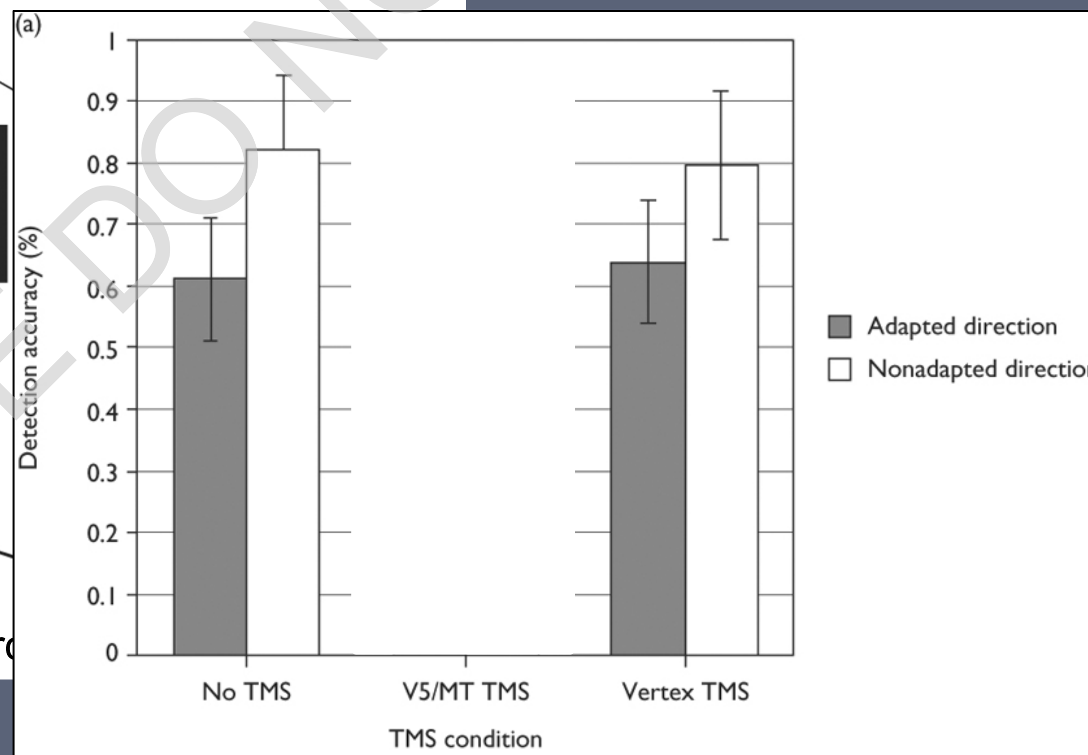
Color Adaptation: area V1



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

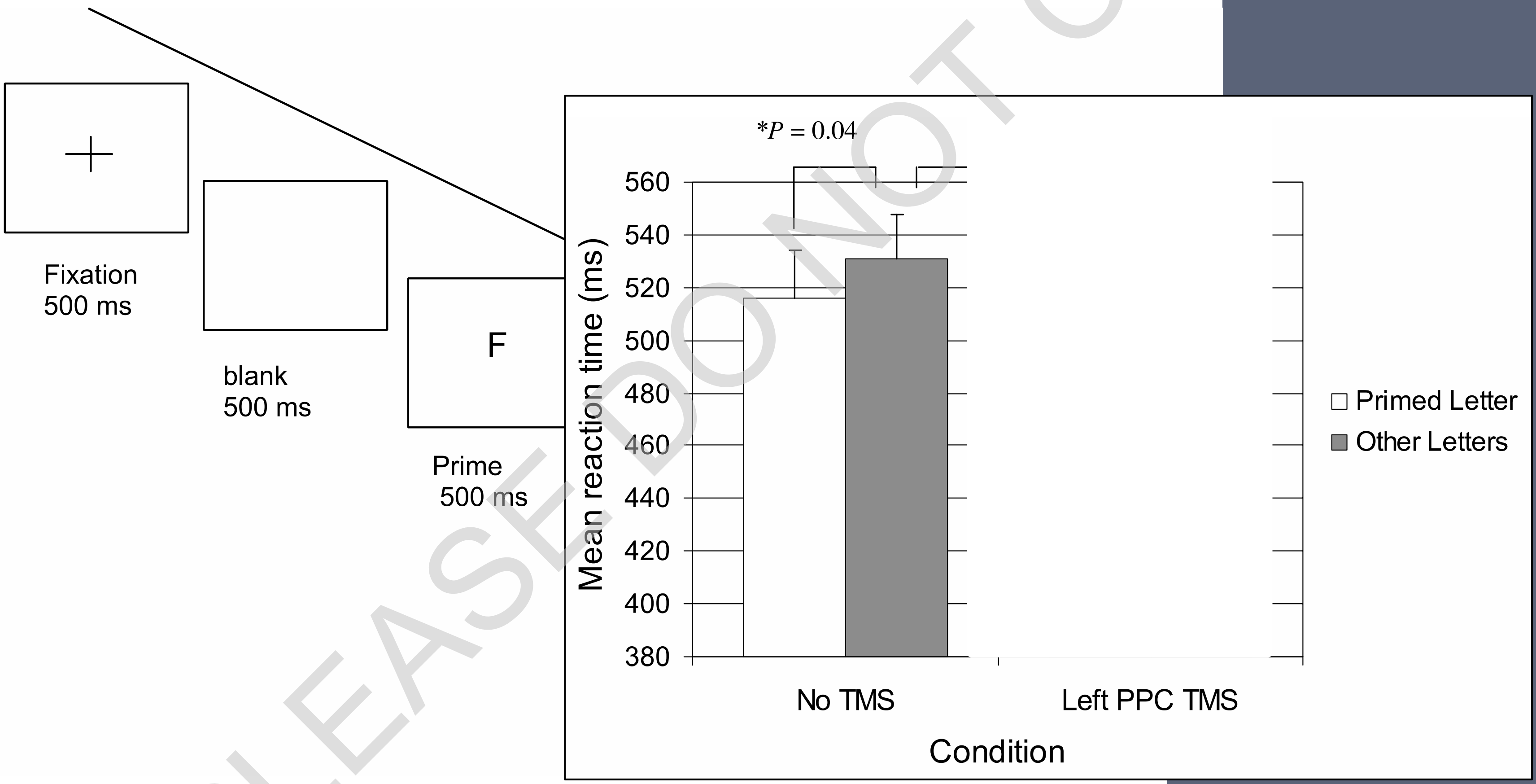
Motion Adaptation: area V5/MT





Cattaneo & Silvanto, 2008 (Neur

Letter Priming: left PPC

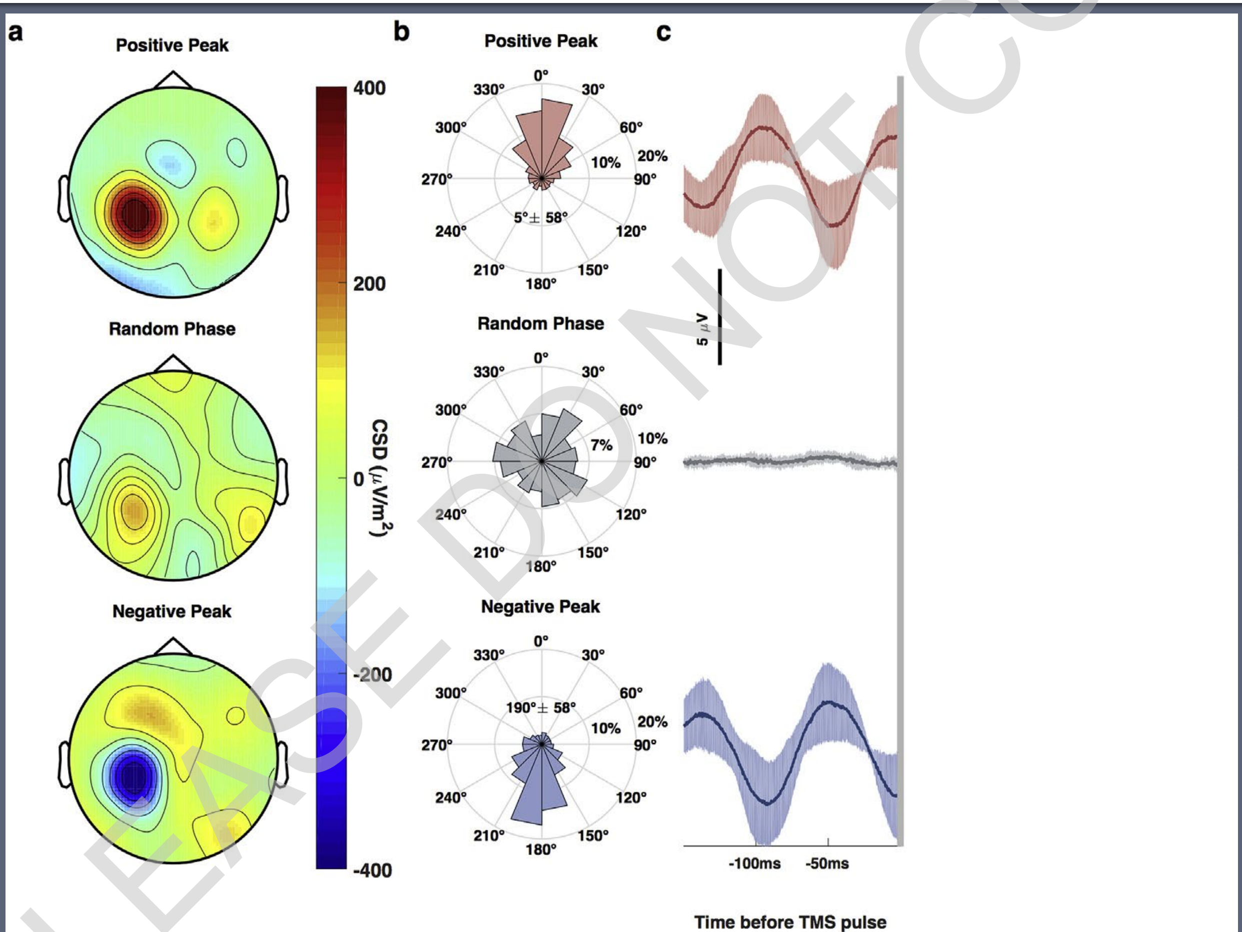


Cattaneo et al., 2008 (European Journal of Neuroscience)

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

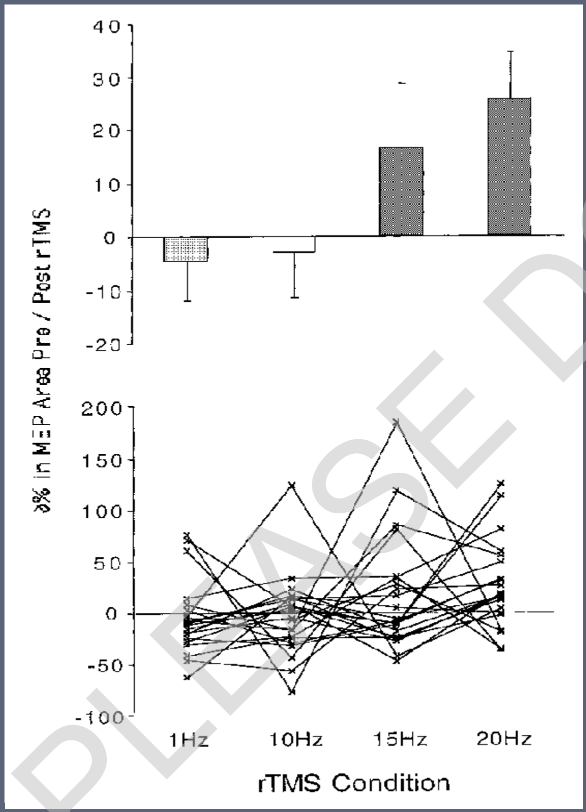
Exp Brain Res (2000) 133:425–430
DOI 10.1007/s002210000432

RESEARCH ARTICLE

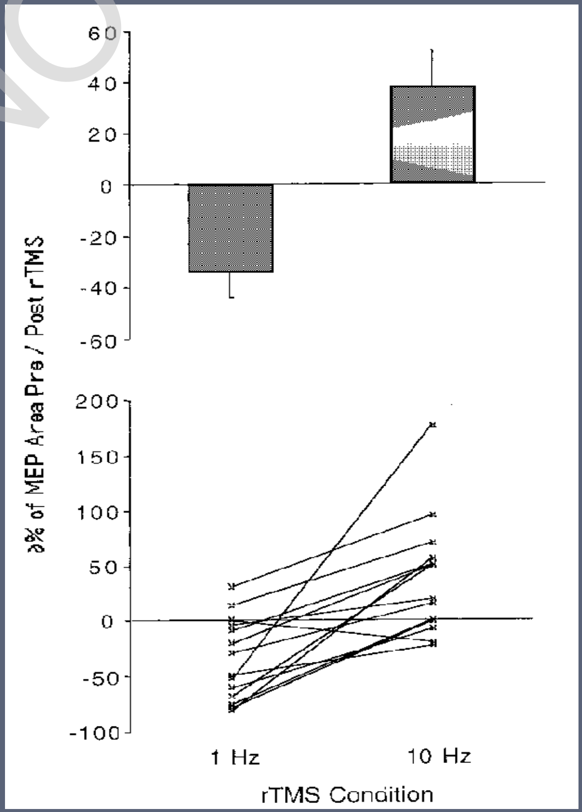
**Fumiko Maeda · Julian P. Keenan · Jose M. Tormos
Helge Topka · Alvaro Pascual-Leone**

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

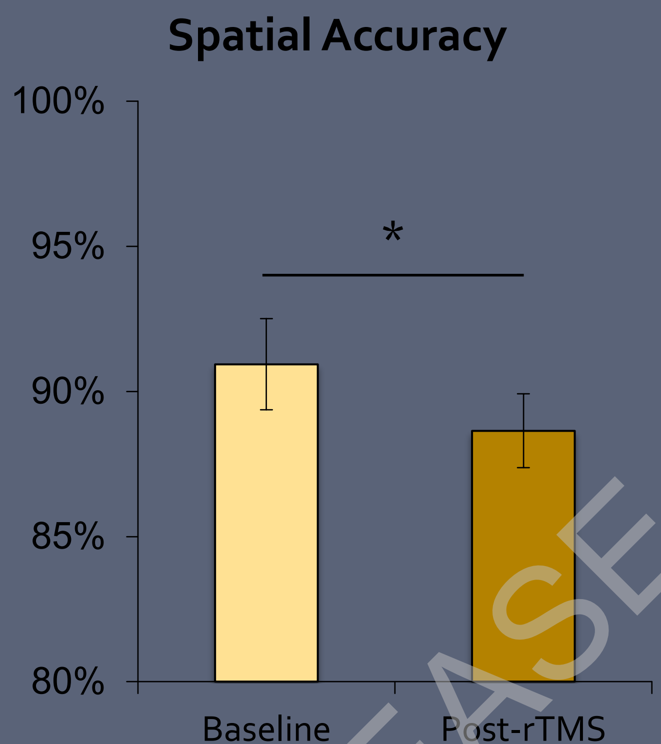
240 pulses

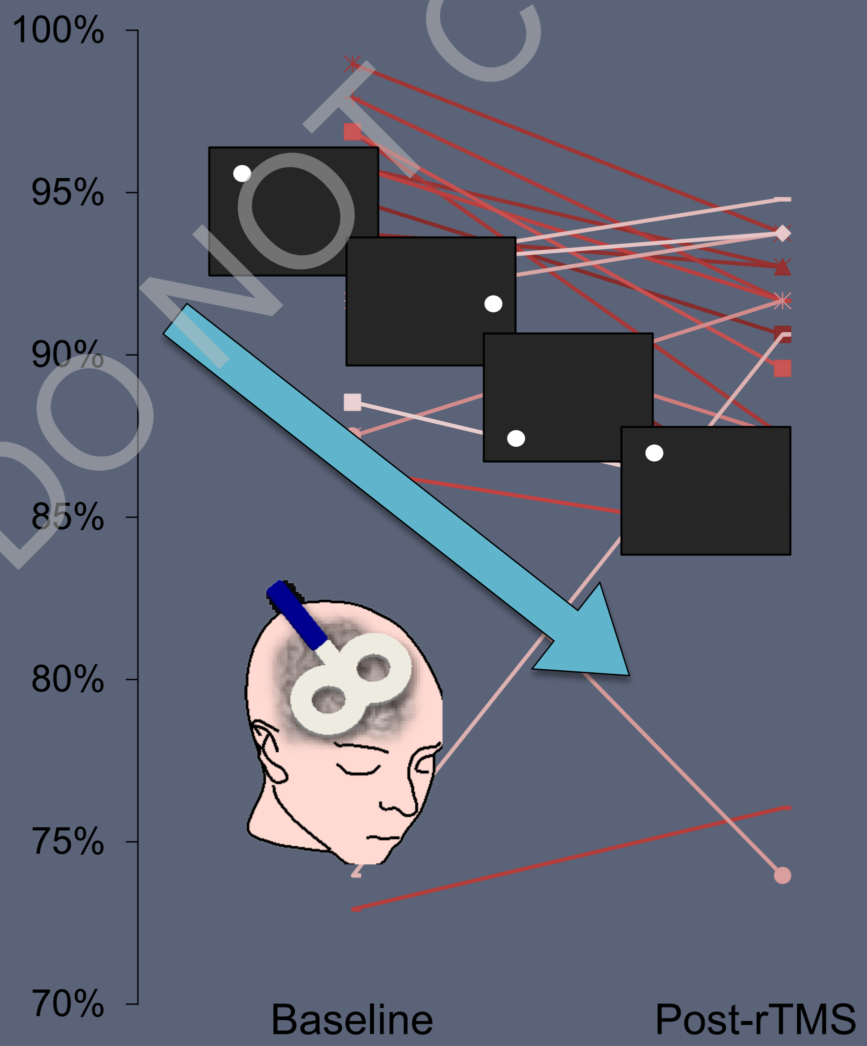


1600 pulses



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

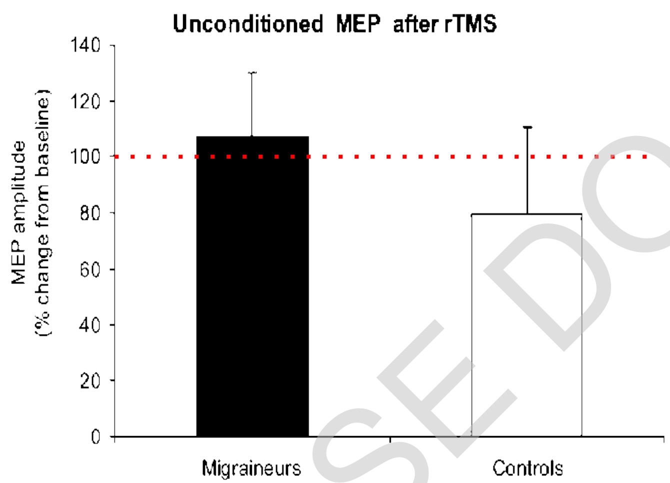
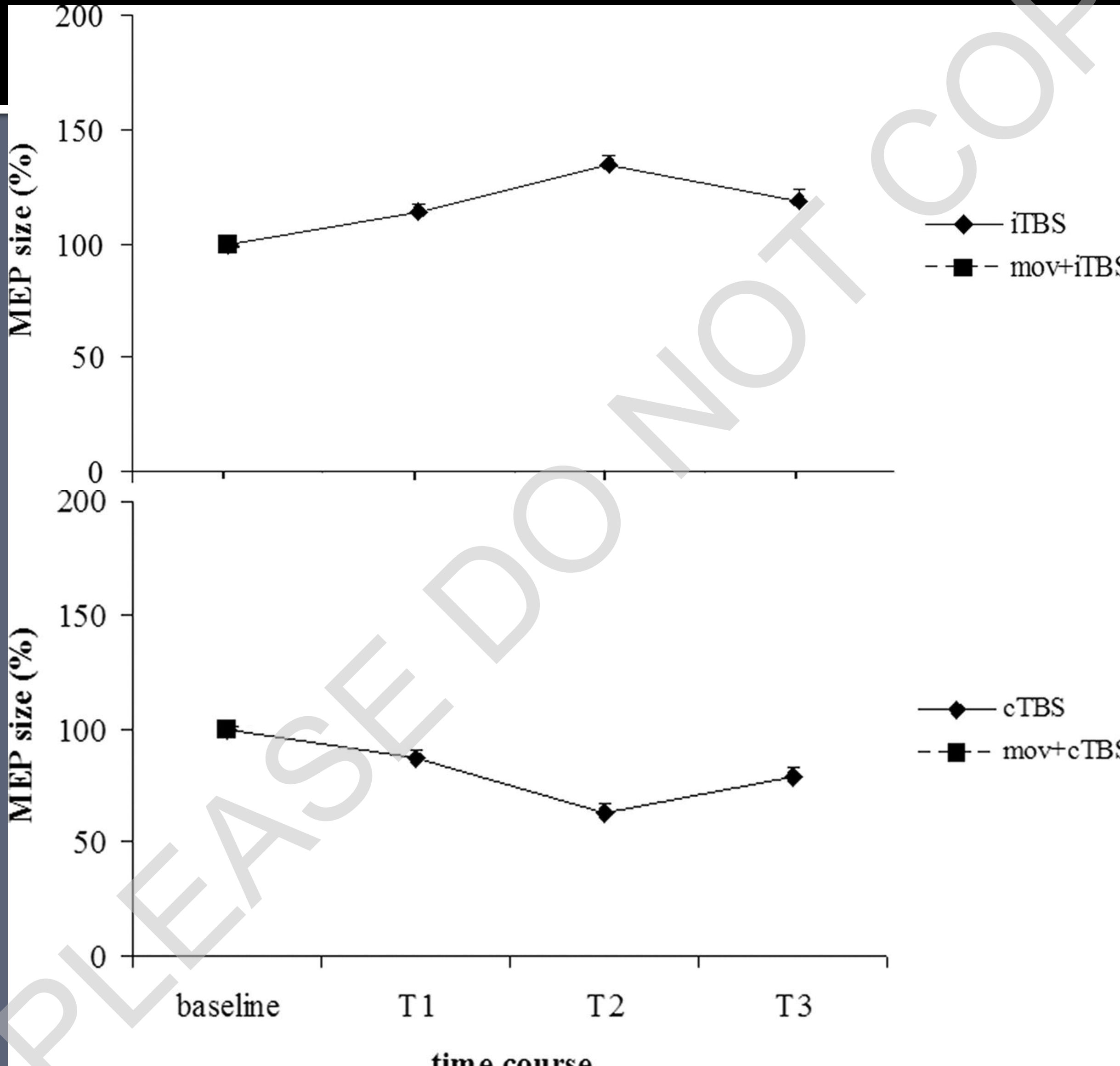


Fig. 1 Mean amplitude (±SD) of MEP to test stimulus alone after 1 Hz rTMS in migraineurs and controls (values are expressed as percentage of baseline MEP).

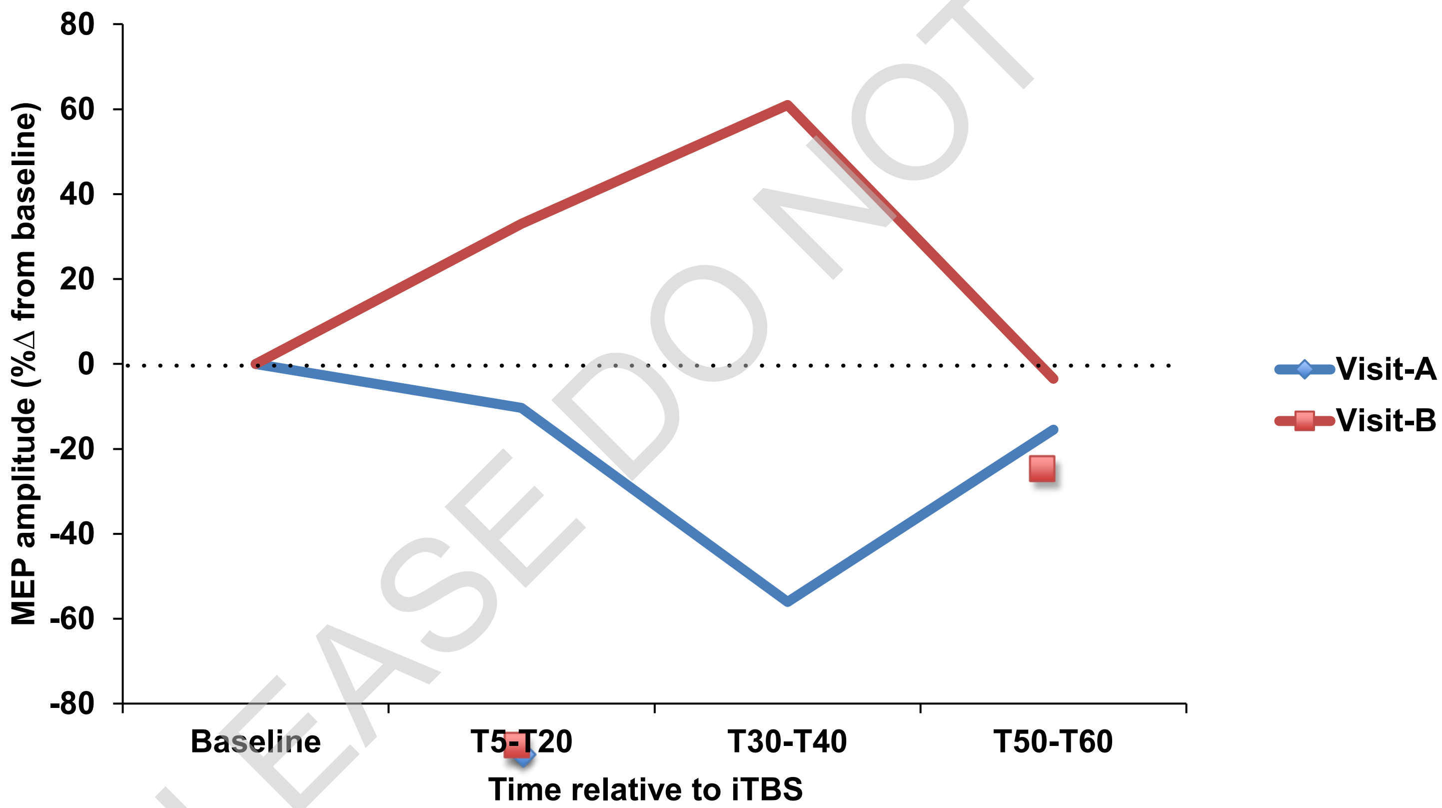
Brighina et al., 2005 (Experimental Brain Research)

Impact of physiological activity



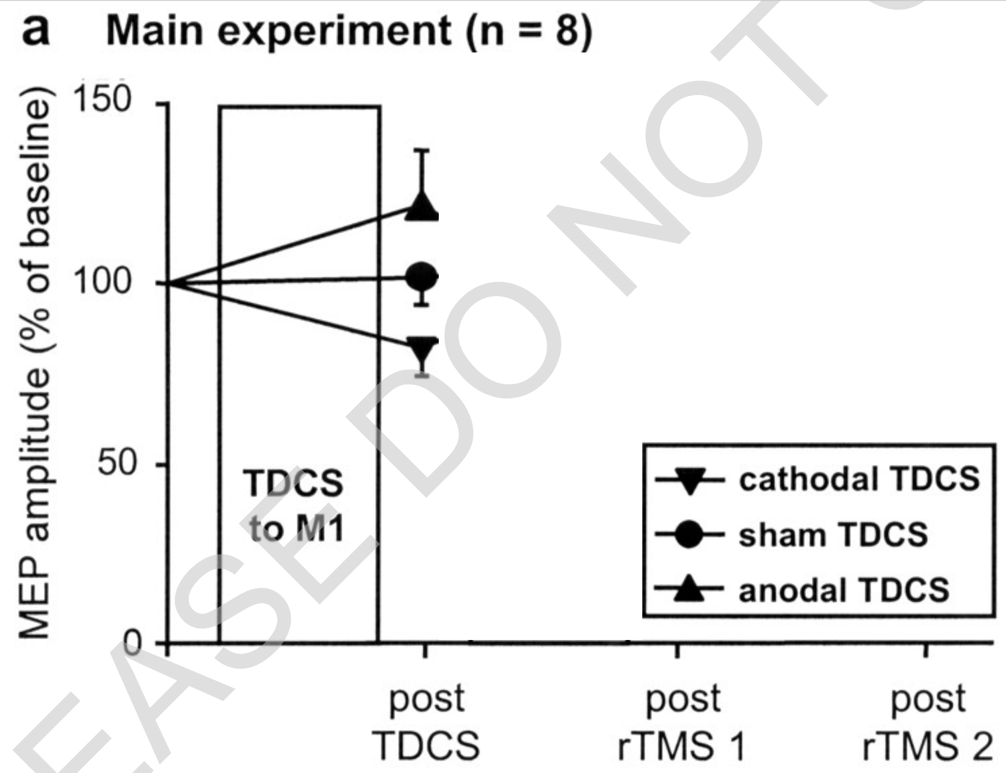
Iezzi E et al., 2008 (J Neurophysio)

Case example



Preconditioning rTMS with tDCS

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



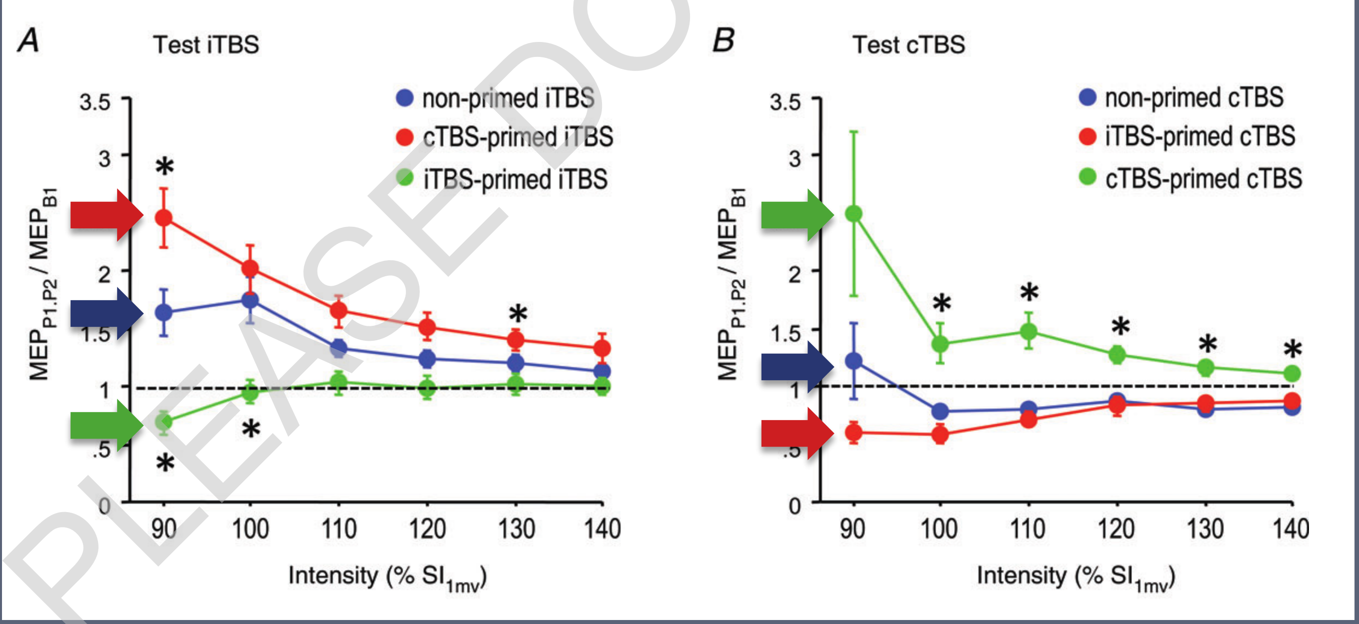
Siebner et al., 2004 (Journal of Neuroscience)

Preconditioning TBS with TBS

J Physiol 590.22 (2012) pp 5765–5781 5765

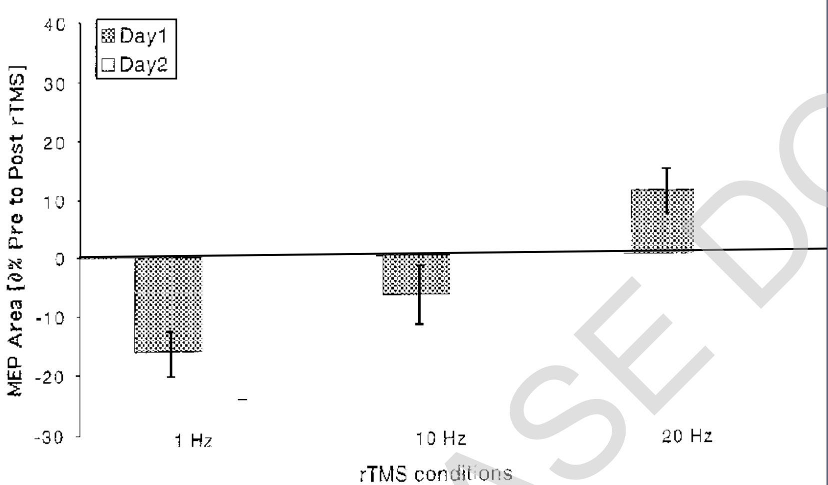
Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex

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



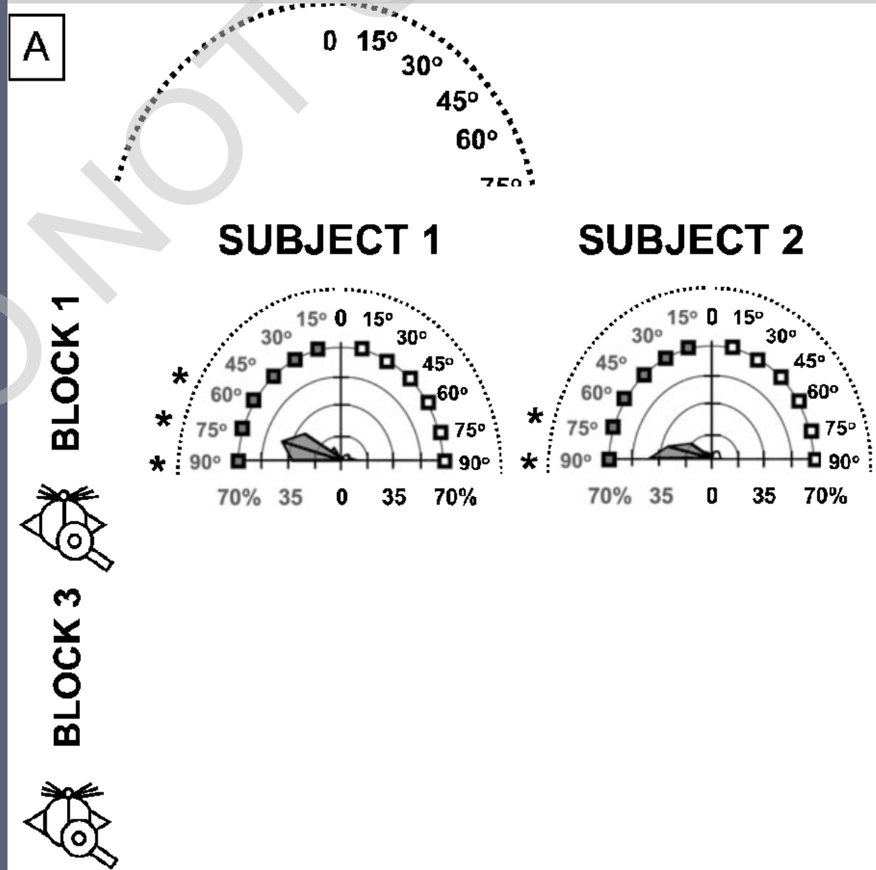
Meta-plasticity: Impact of Cumulative Sessions

Impact of rTMS on Motor-Evoked Potentials



Maeda et al., 2000 (Clinical Neurophysiology)

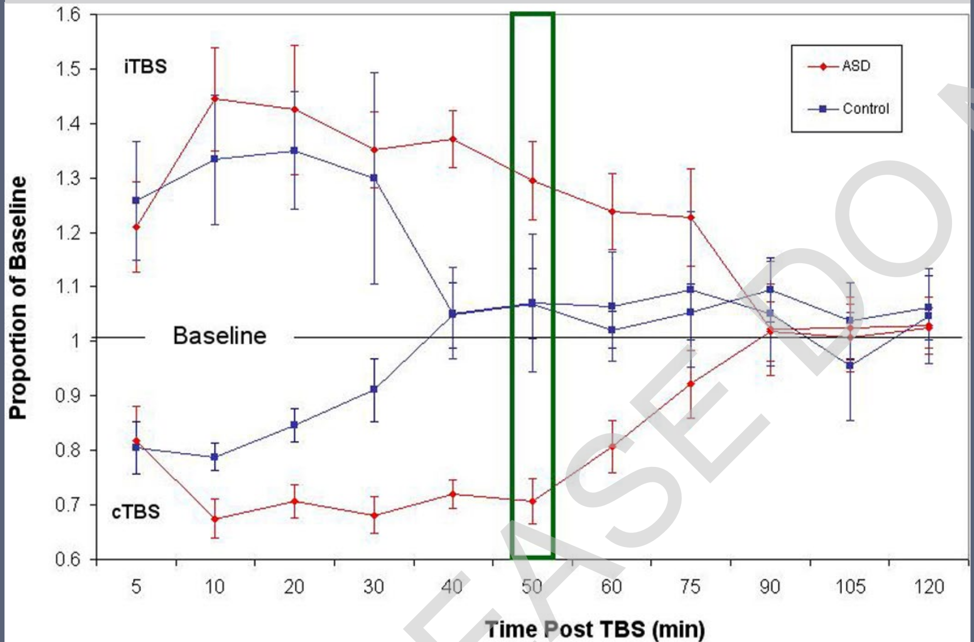
Impact of daily 1Hz rTMS on visuo-spatial detection



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

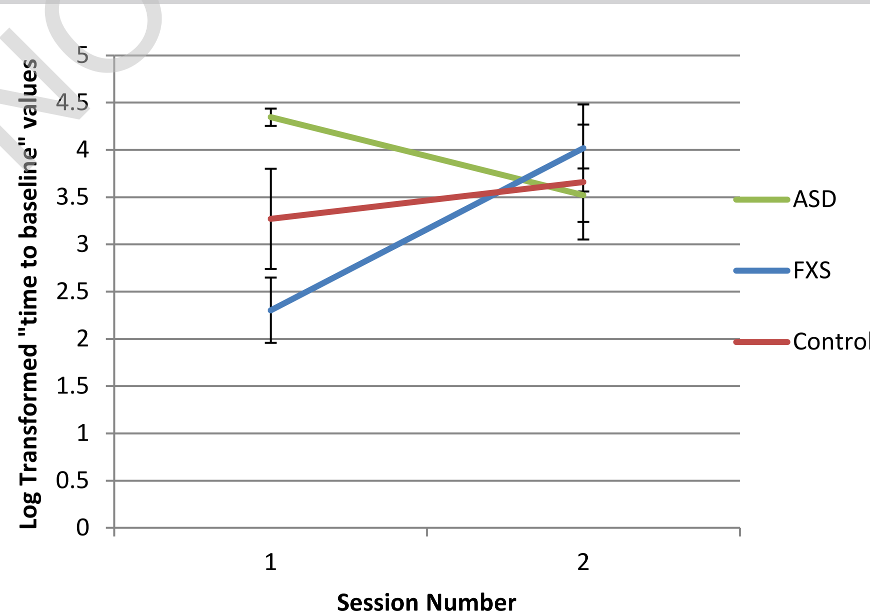
Altered Meta-plasticity in ASD

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



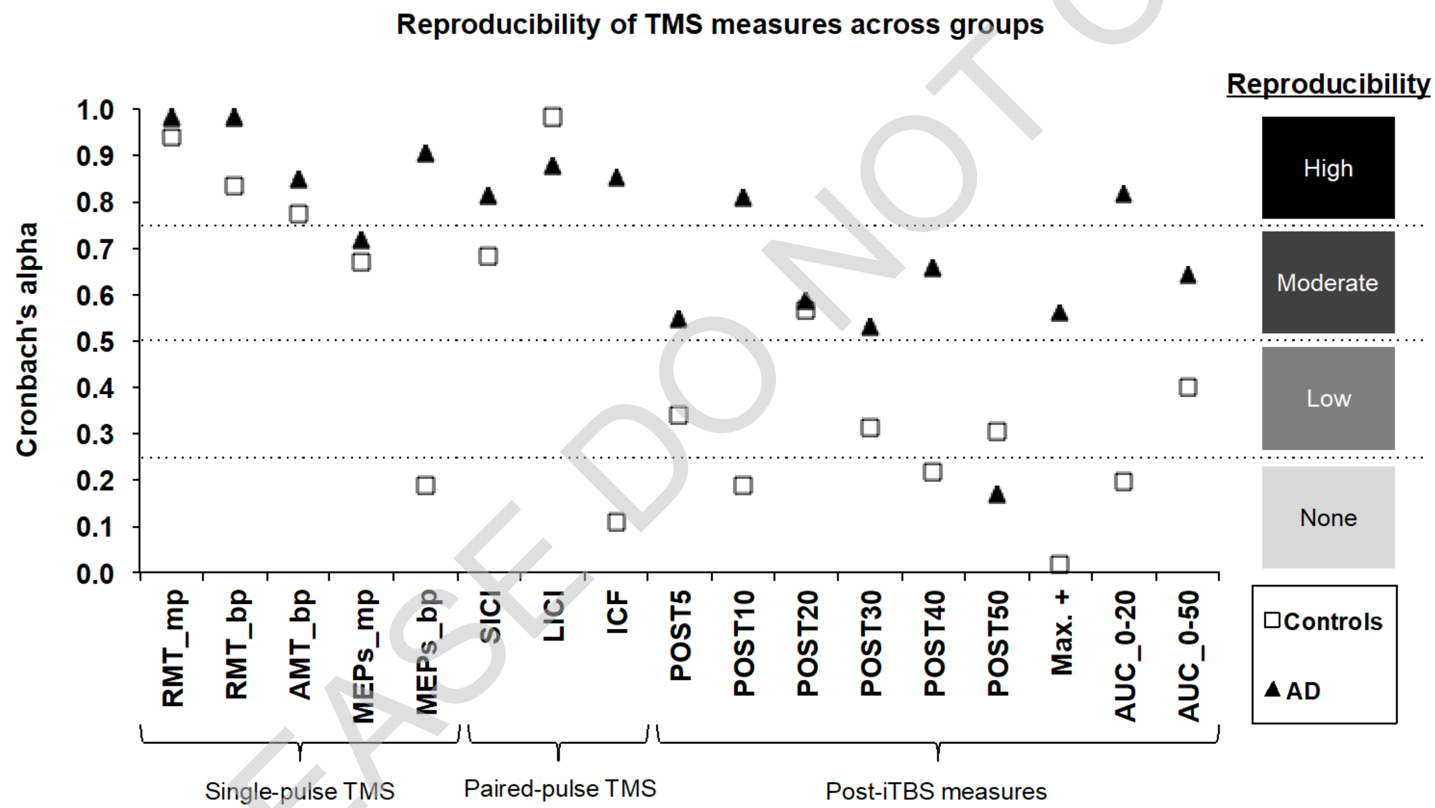
Oberman et al., 2012 (European Journal of Neuroscience)

Cumulative Impact of Back-to-Back TBS



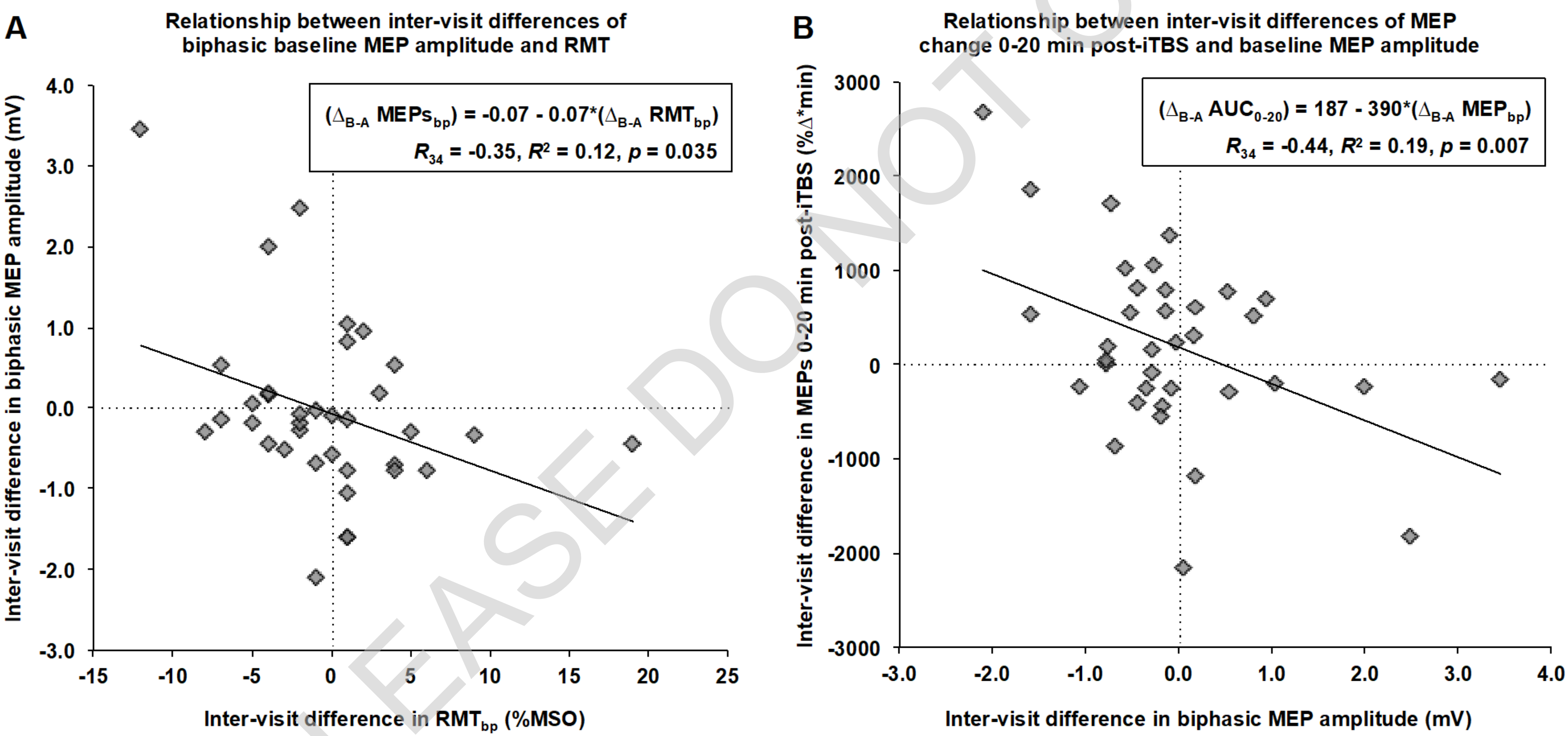
Oberman et al., 2016 (J Child Adolescent Psychopharm)

Reproducibility of TMS measures



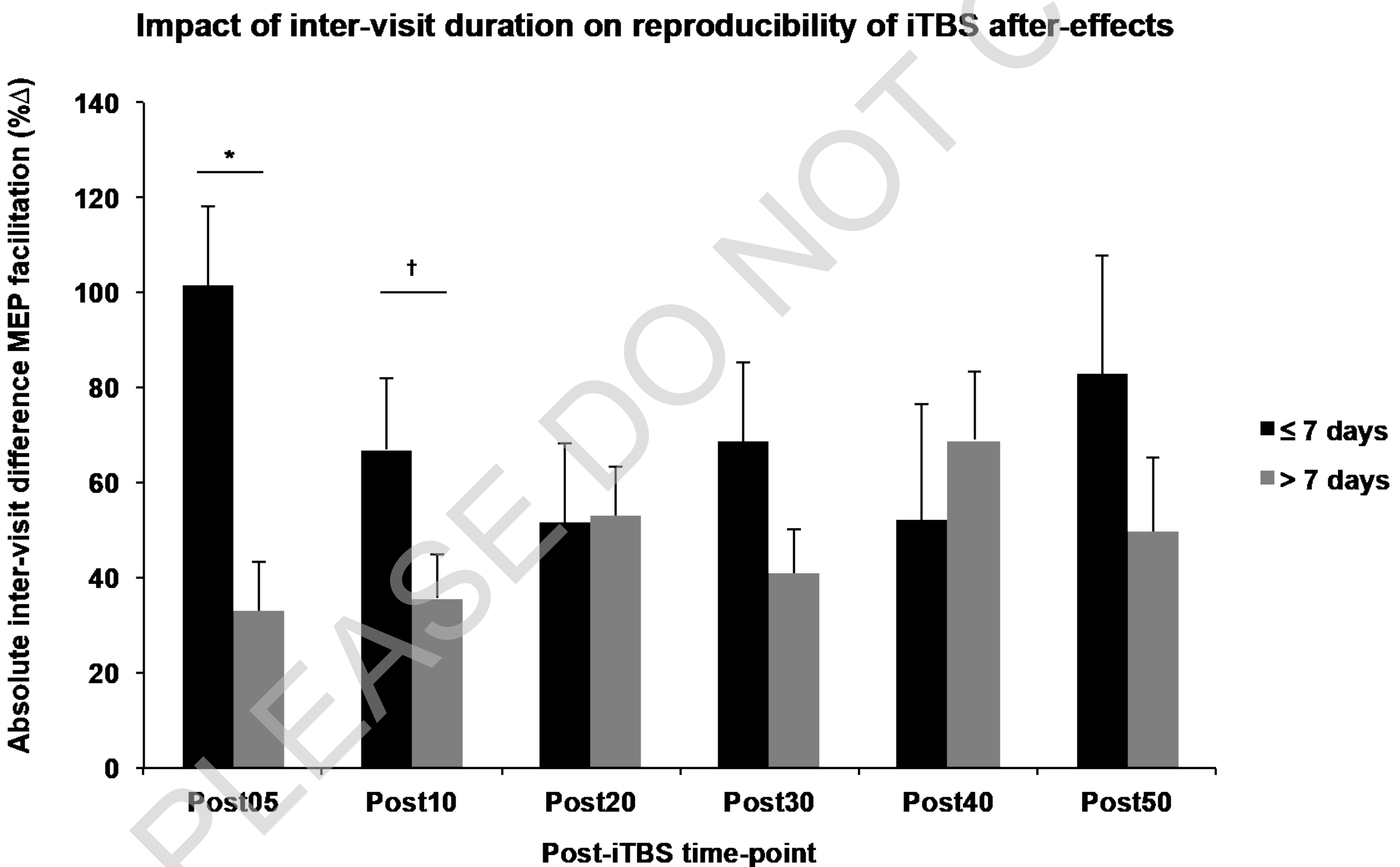
Fried et al., 2017 (Frontiers in Aging Neuroscience)

Factors that affect reproducibility



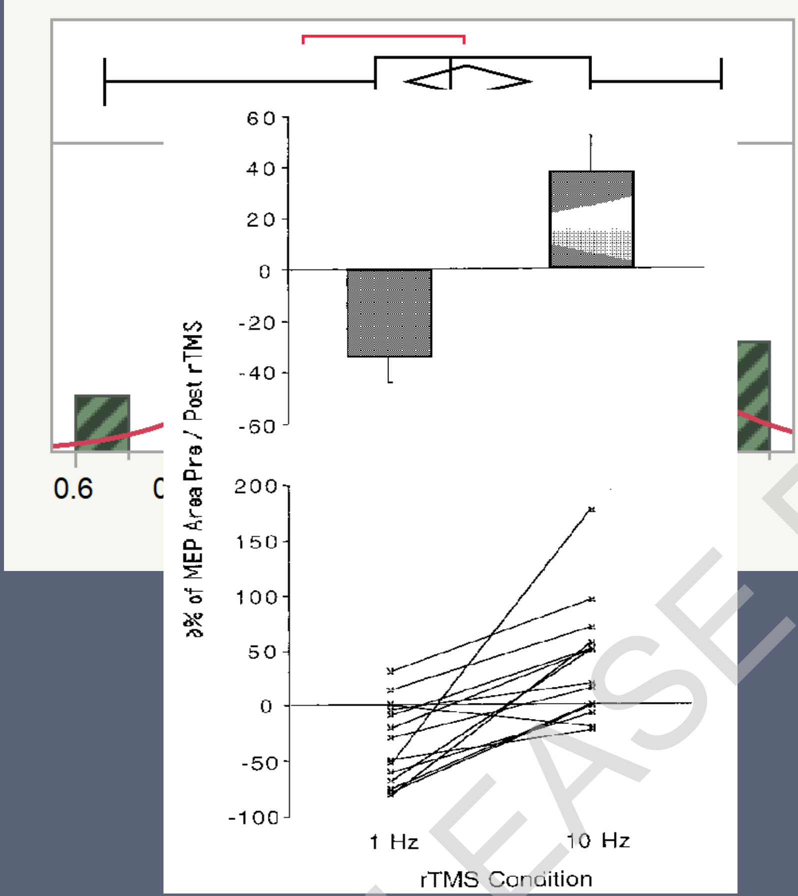
Fried et al., 2017 (Frontiers in Aging Neuroscience)

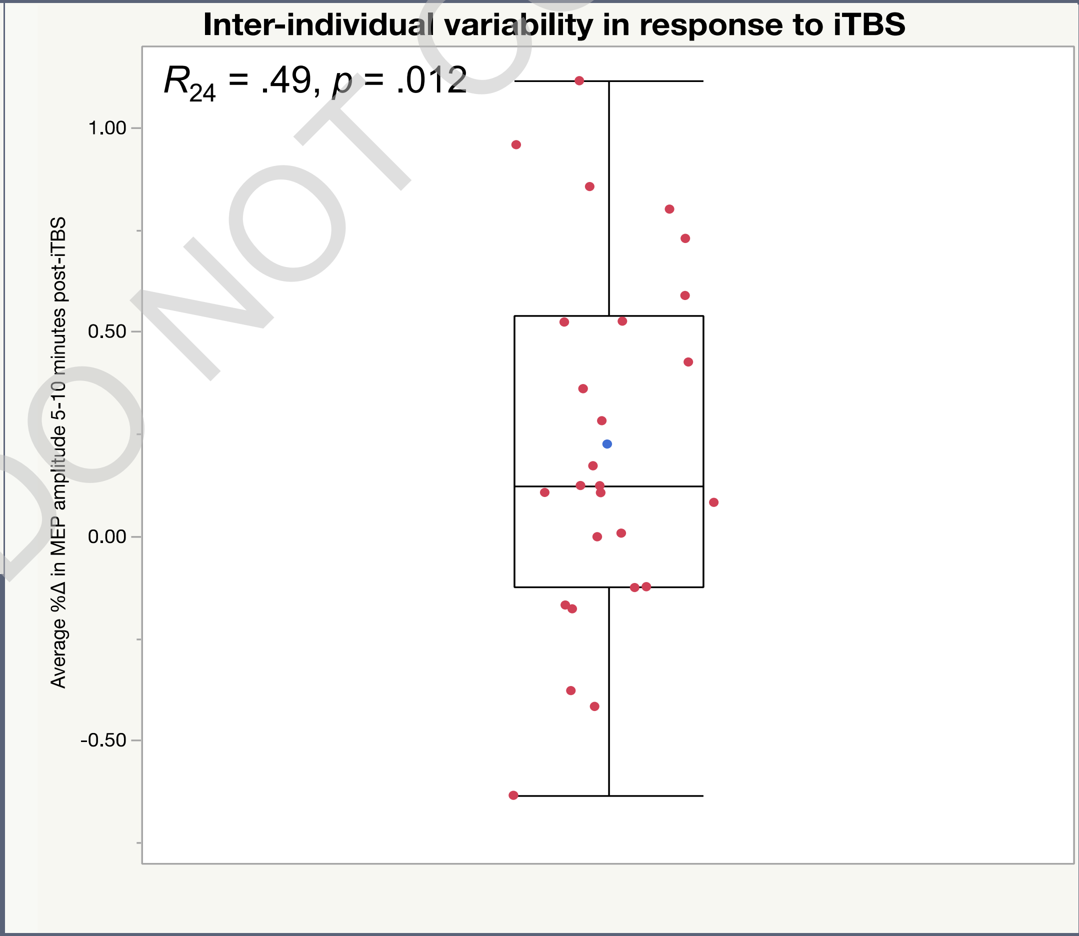
Factors that affect reproducibility



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

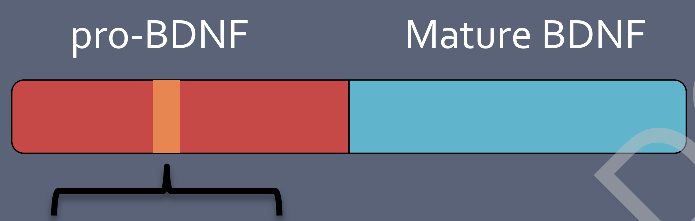
- Caffeine, Rx
- Prior stimulation
- Time of day
- Food intake
- Handedness
- Concomitant activity

Less Easy to Control

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

DNA

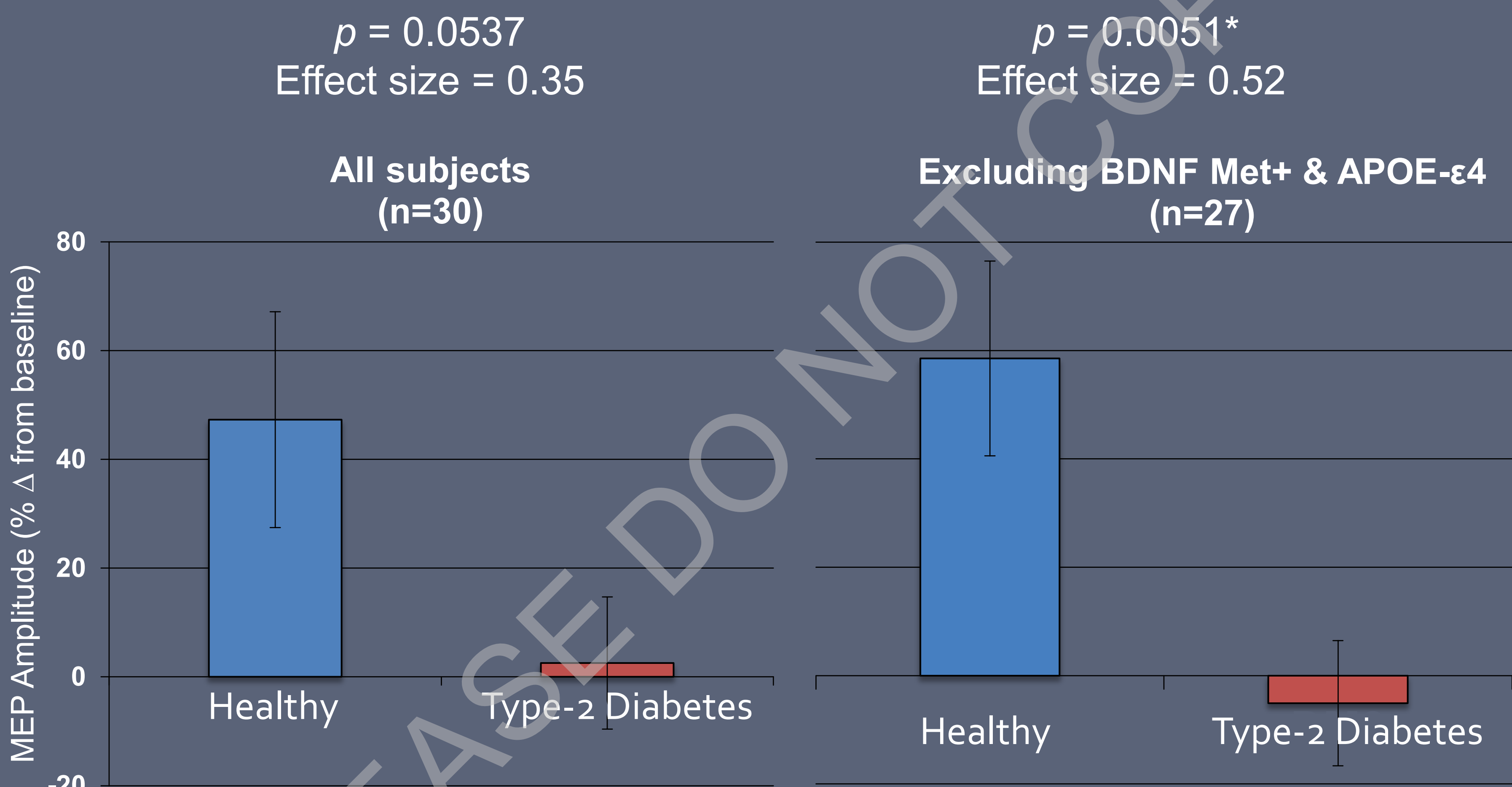
- Brain-derived neurotrophic factor (BDNF)
  - Modulates NMDAR-dependent plasticity
  - Activity-dependent release at synapses



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

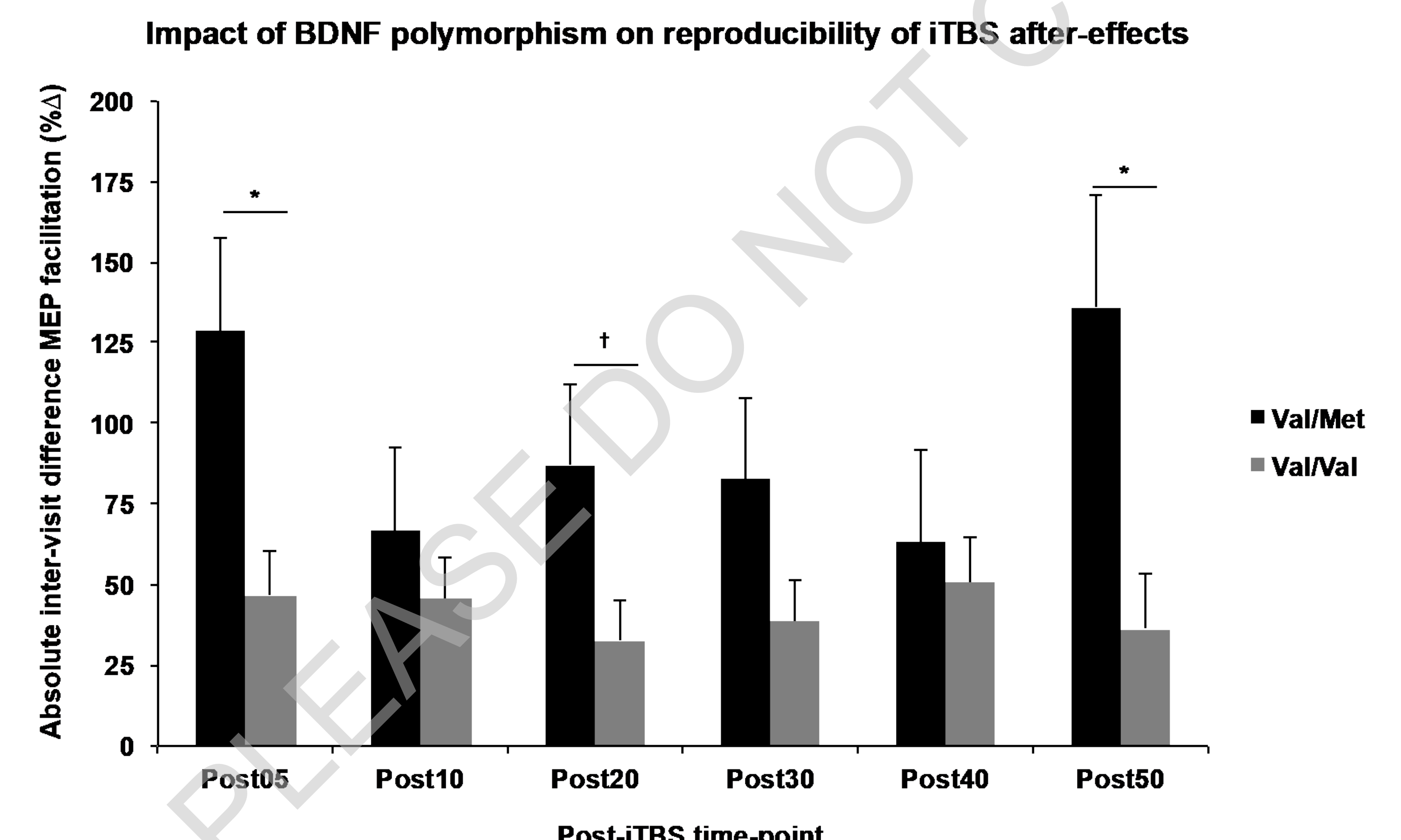
Single substitution of Guanine for Adenine results in an amino acid switch from Valine (Val) to Methionine (Met)

- 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

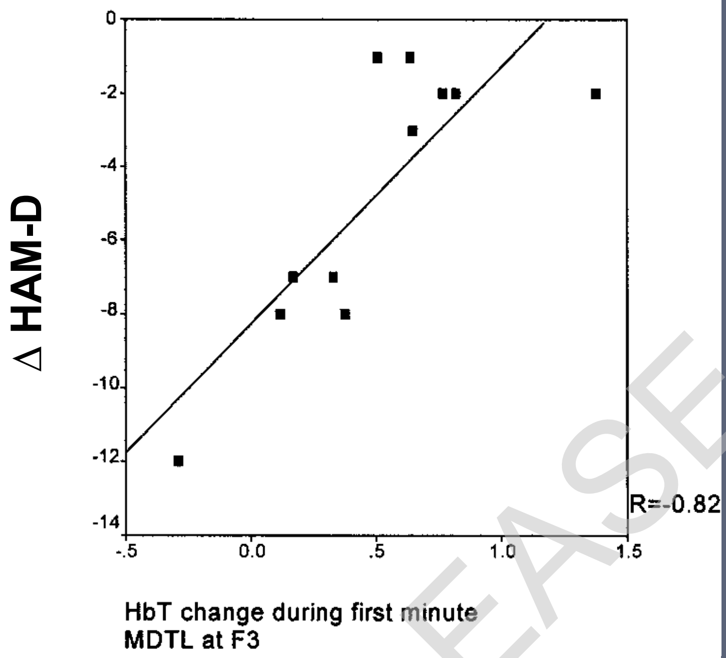


Fried et al., 2017 (Frontiers in Aging Neuroscience)

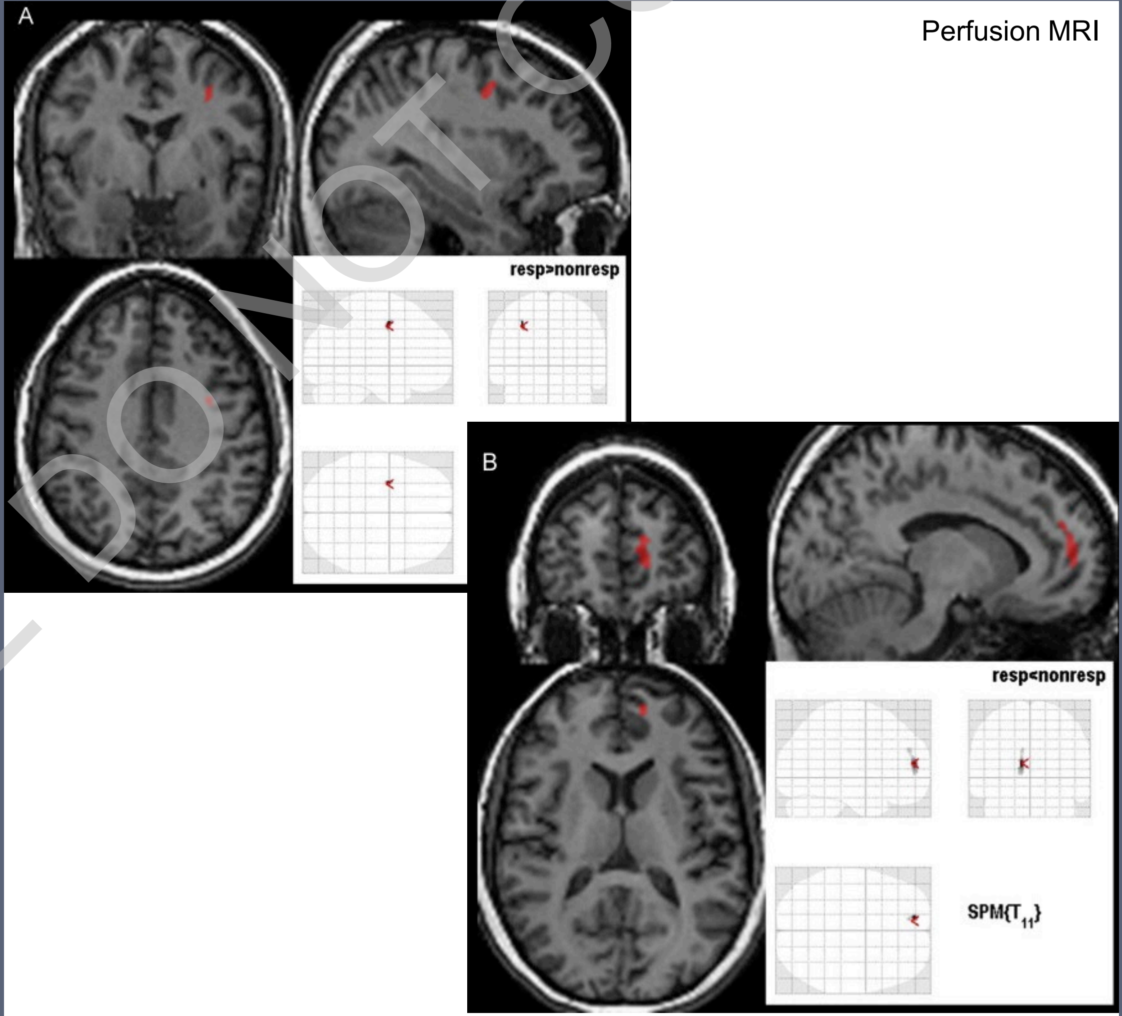
What to do? Follow the C's

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

Predicting Therapeutic Outcome: activity in single sites

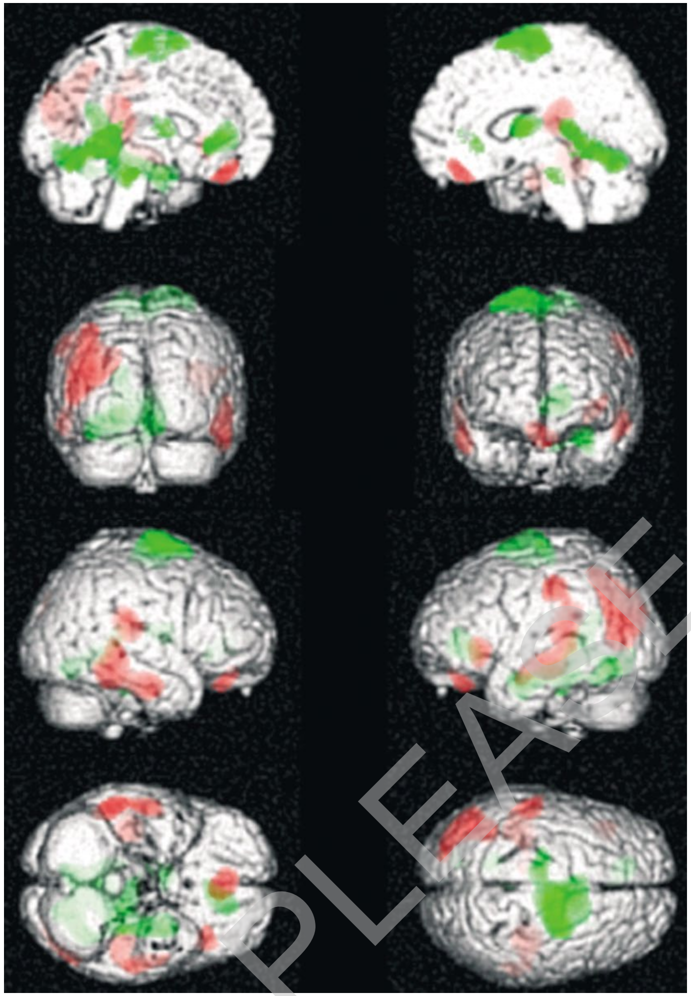


Eschweiler et al., 2000 (Psychiatry Res.: Neuroimaging)

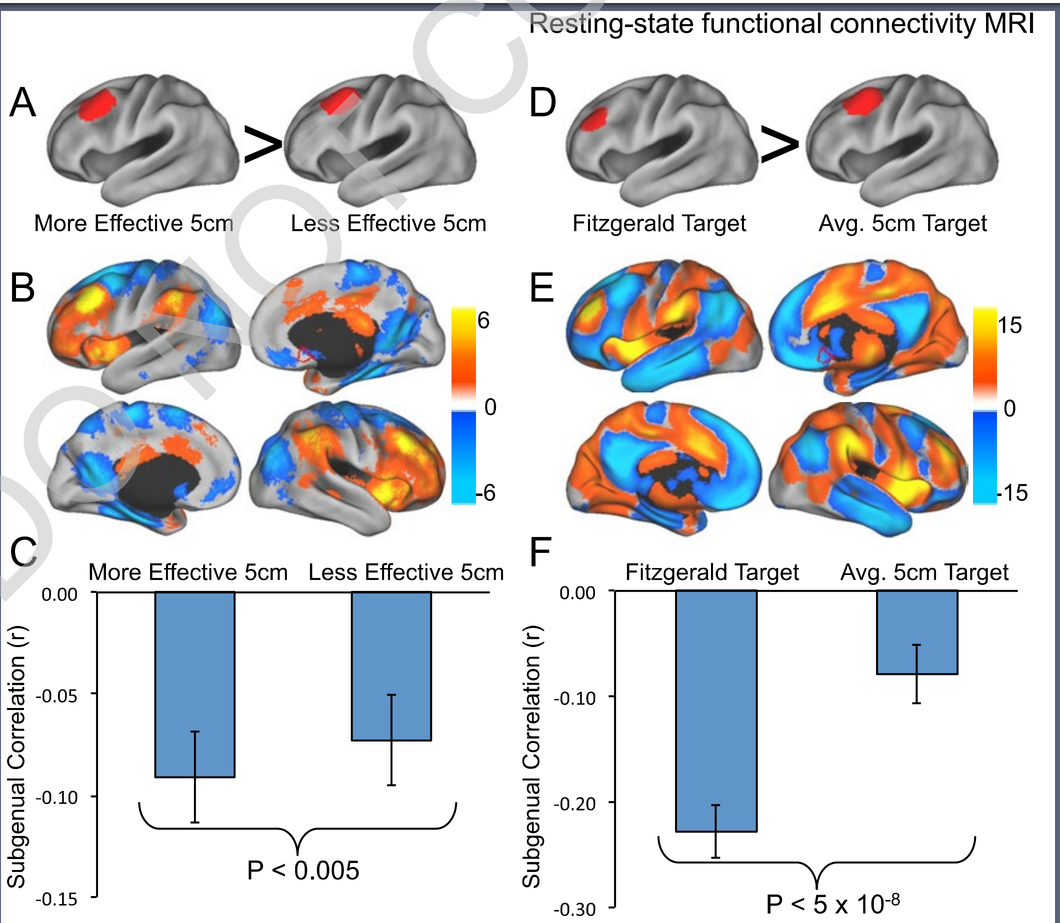


Weiduschat and Dubin, 2013 (J Affective Disorders)

Predicting Therapeutic Outcome: activity across networks

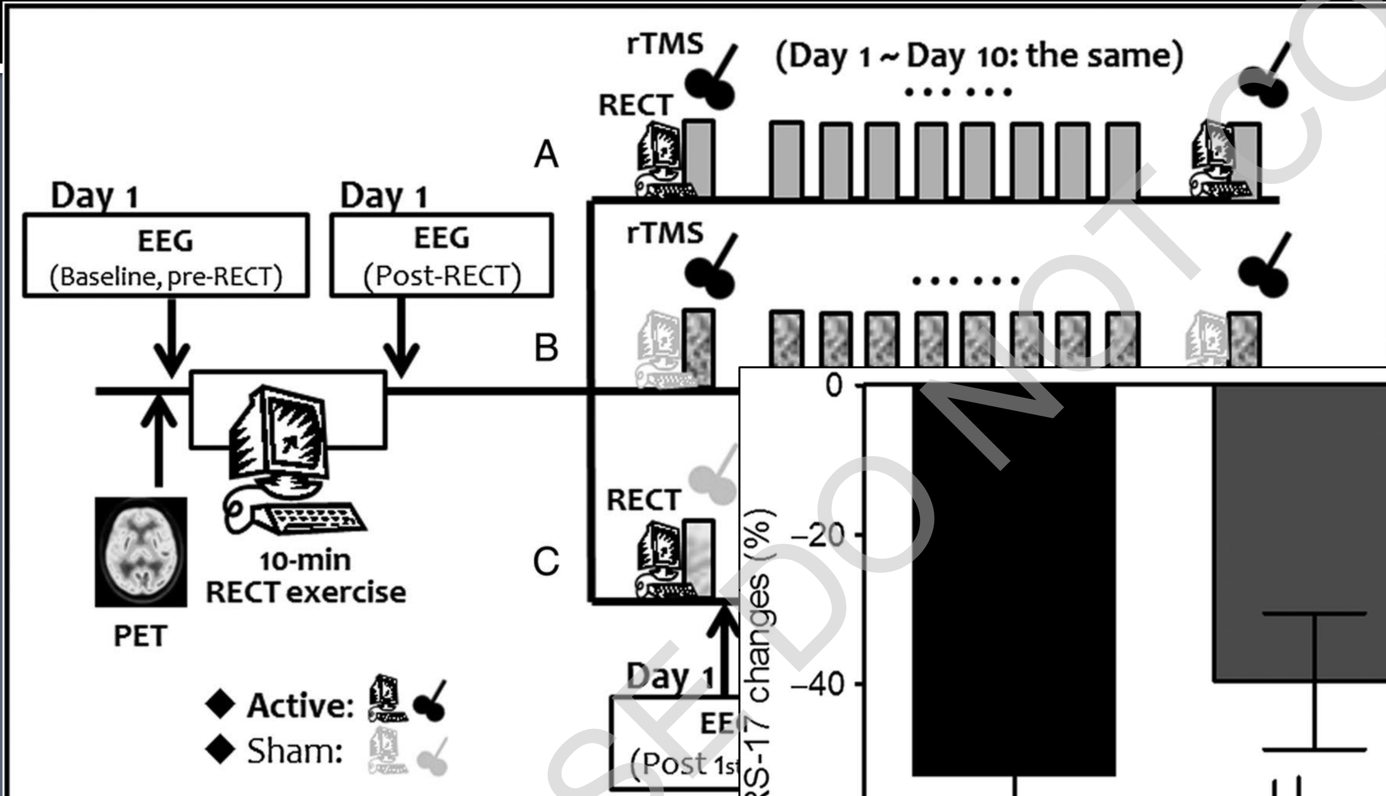


Mottaghy et al., 2002 (Psychiatry Res.: Neuroimaging)

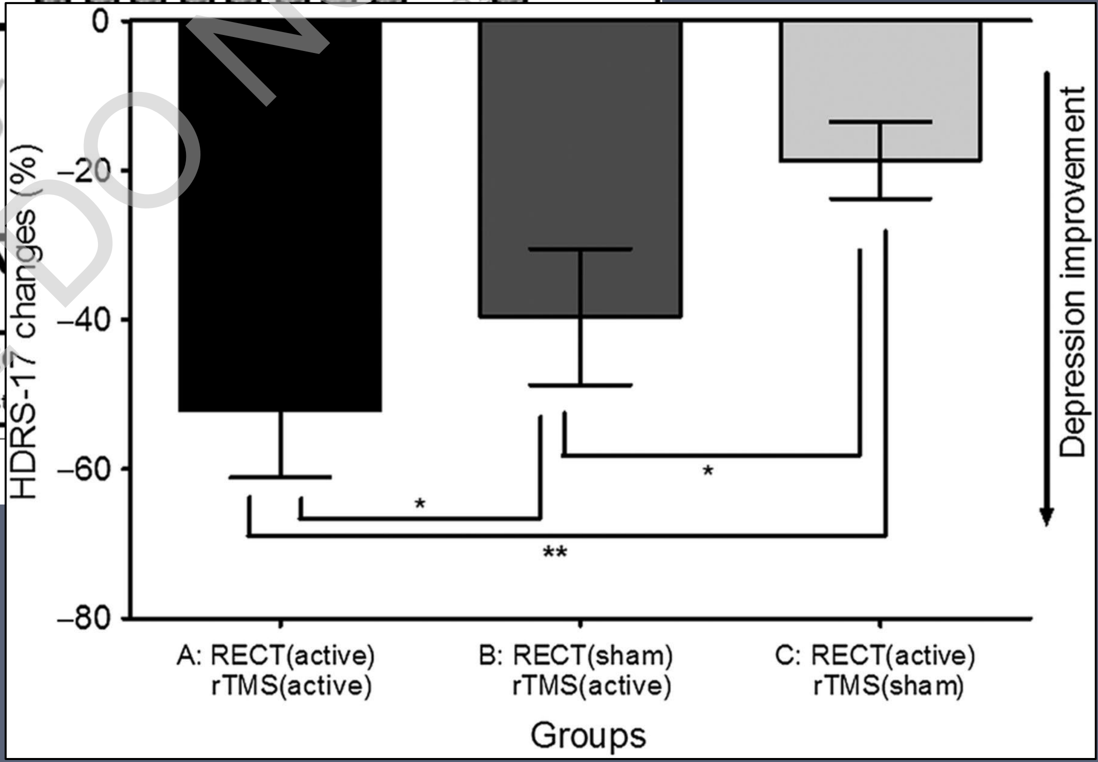


Fox et al., 2012 (Biological Psychiatry)

Changing brain state to improve efficacy



Li et al., 2016 (Cerebral Cortex)



Future Interventions

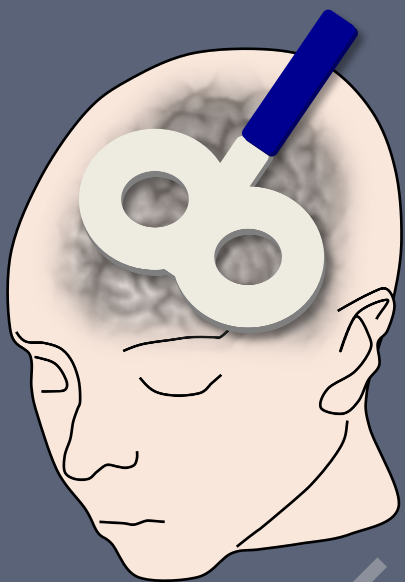
- Individualized targeting
  - Single node vs. network
- Prime sub-populations of neurons
  - Intrinsic vs. extrinsic engagement
- Assess efficacy online
  - Custom dose
- Leverage placebo effect

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



sham

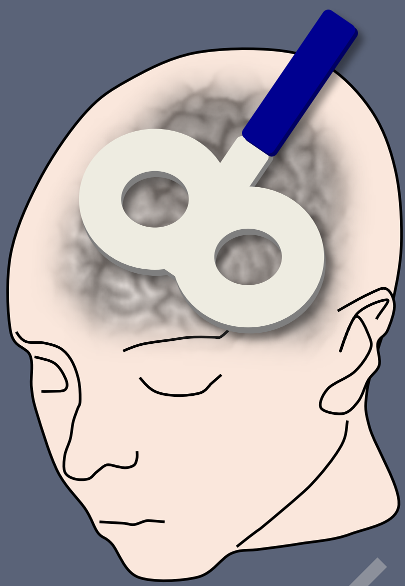
Pros:

Easy, fast, cheap
No switching coils
Similar sensations

Cons:

Might induce current
Won't fool non-naïve

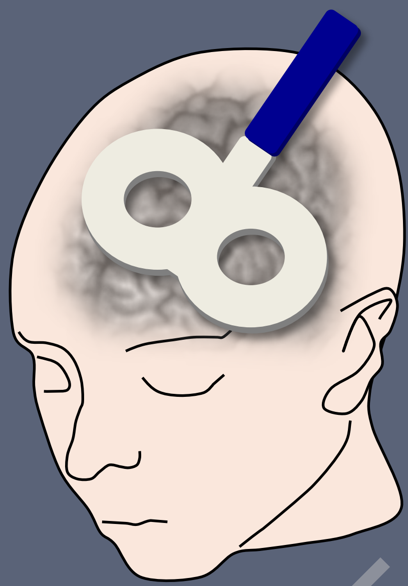
Option 2: Use "sham" Coil



Pros:
Similar look and feel
Tech getting better

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

Option 3: Active Control Site



Pros:

Easy, fast, cheap

Same sensations

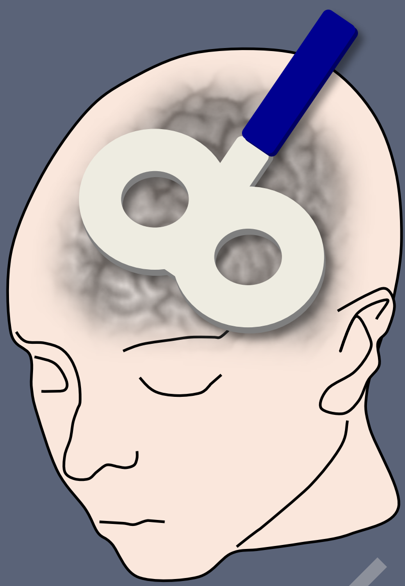
Cons:

Will control site have real effects?

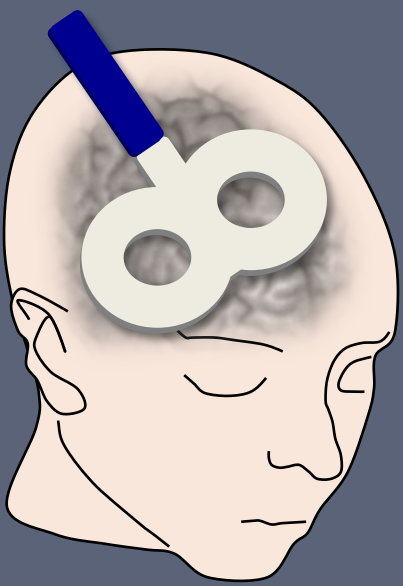
Laterality of sensations

Option 4: Double Dissociation

Left hemisphere



Right hemisphere



Pros:

Easy, fast, cheap
Same sensations
Greater explanatory power

Cons:

More difficult study design

So… Now what?