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

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Peter J. Fried, Ph.D.

February 2026

Overview

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

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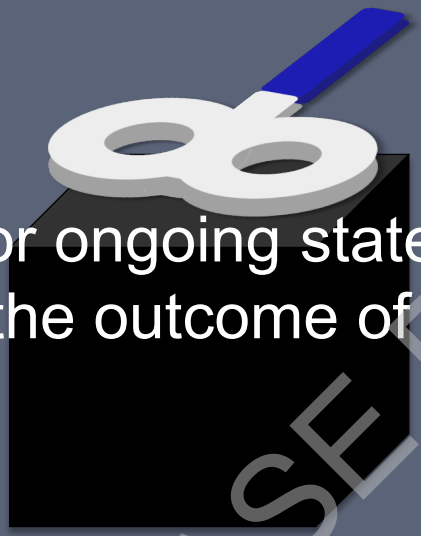
What is 'State-dependency'?

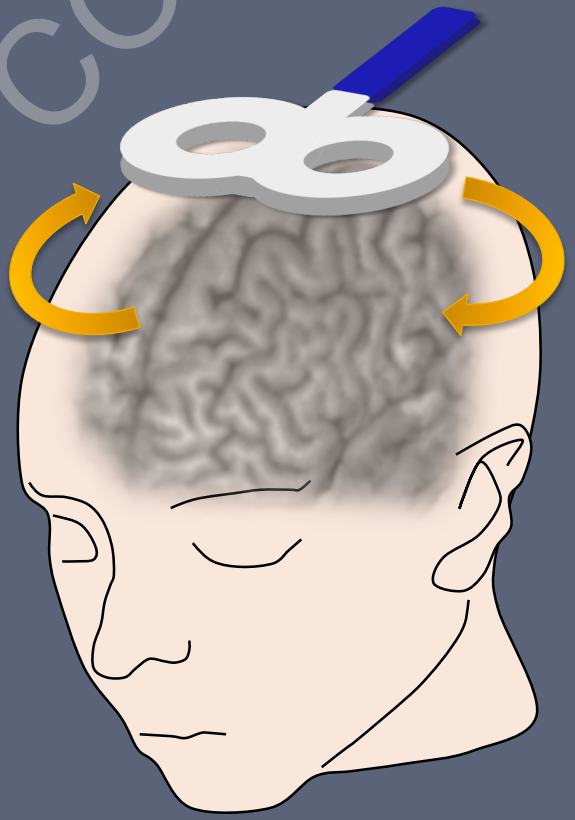
Input

Something in the middle

Output



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



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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)

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Overview

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

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Adaptation & Priming

Adaptation:

Priming:

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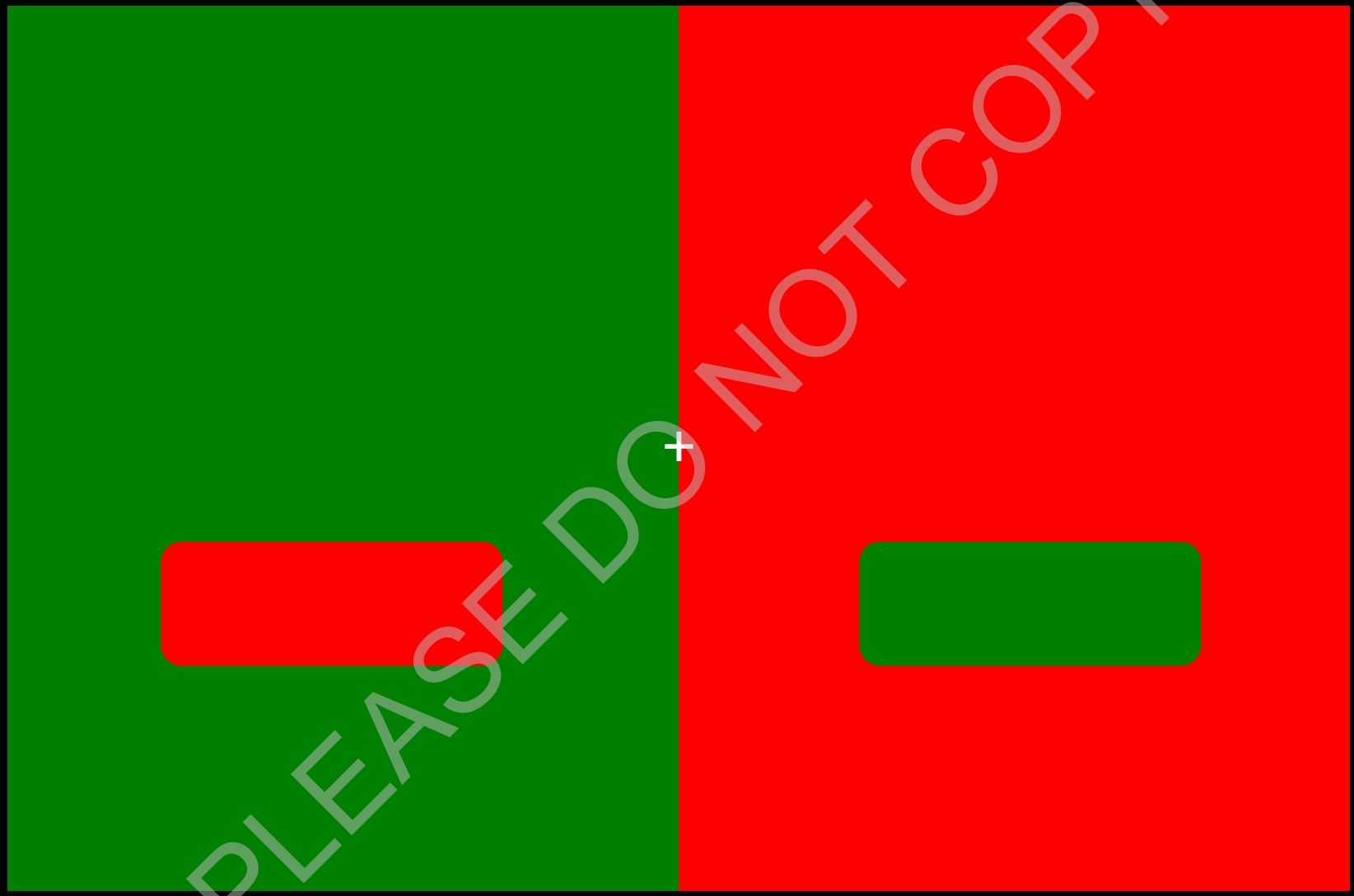

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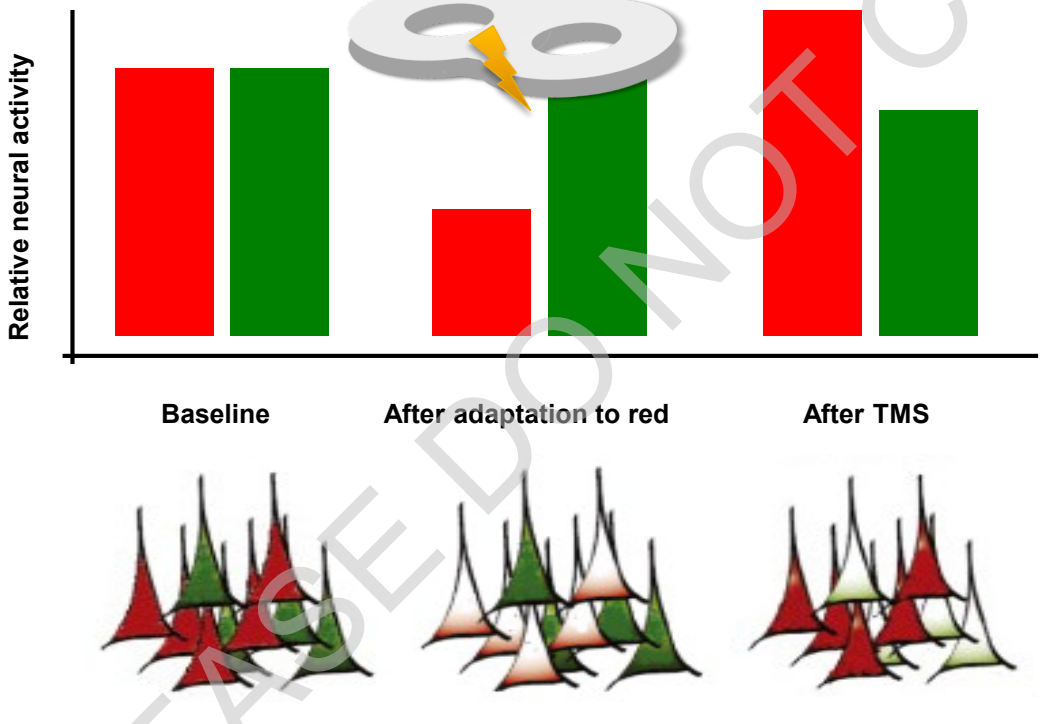
Color Adaptation: area V1



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

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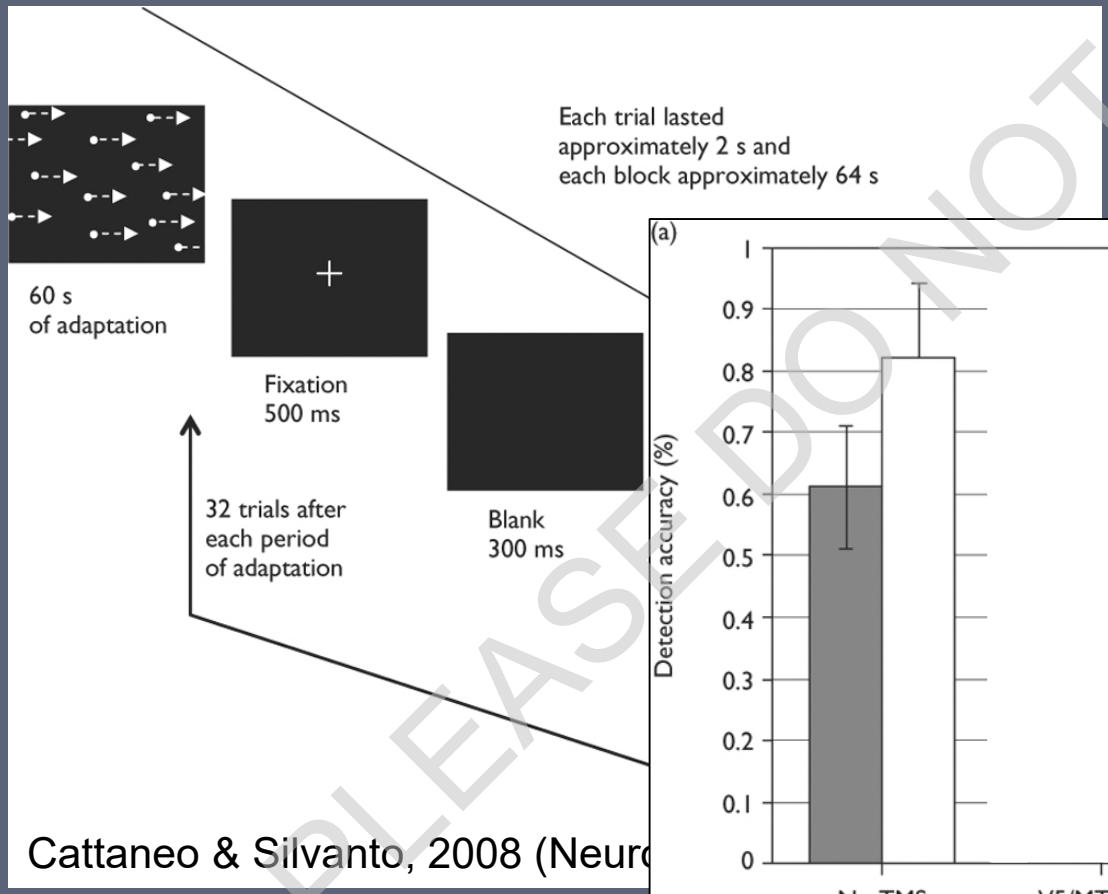
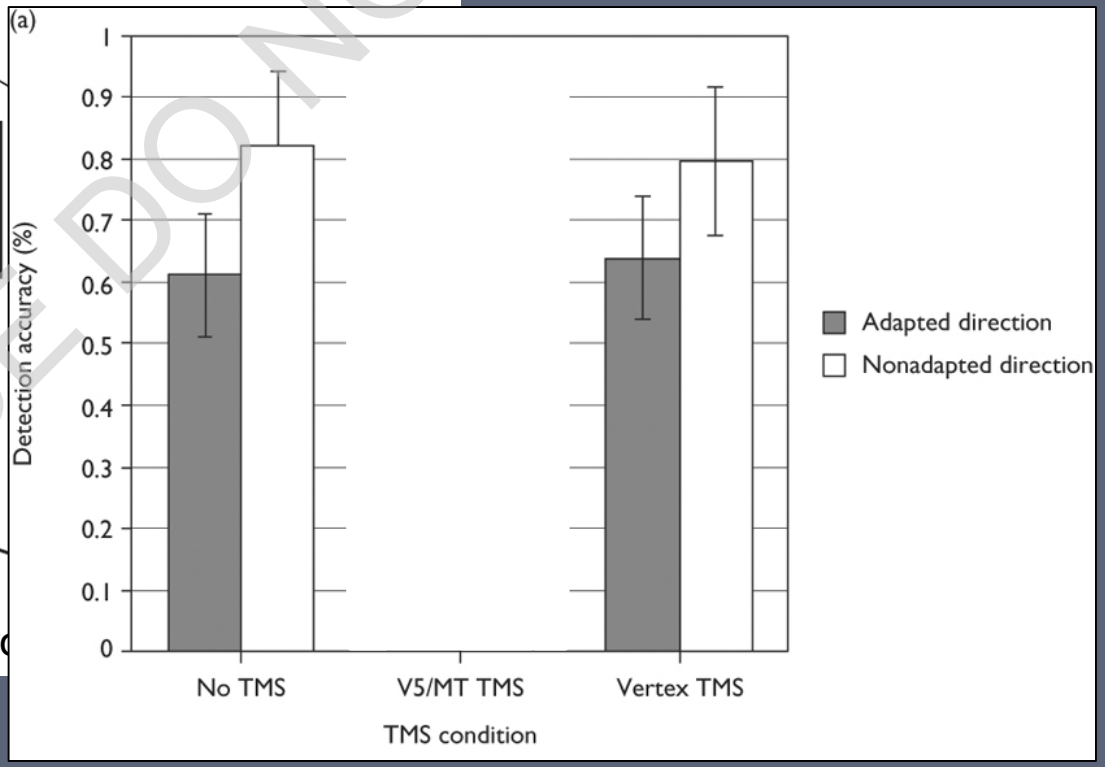
Motion Adaptation: area V5/MT





Cattaneo & Silvanto, 2008 (Neuro

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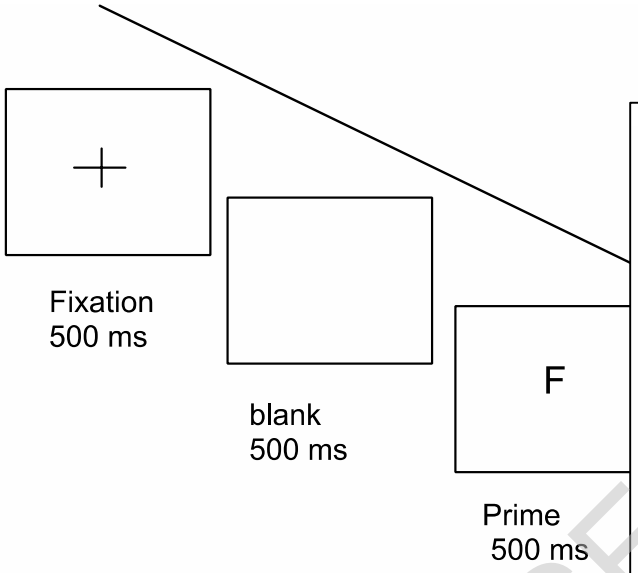
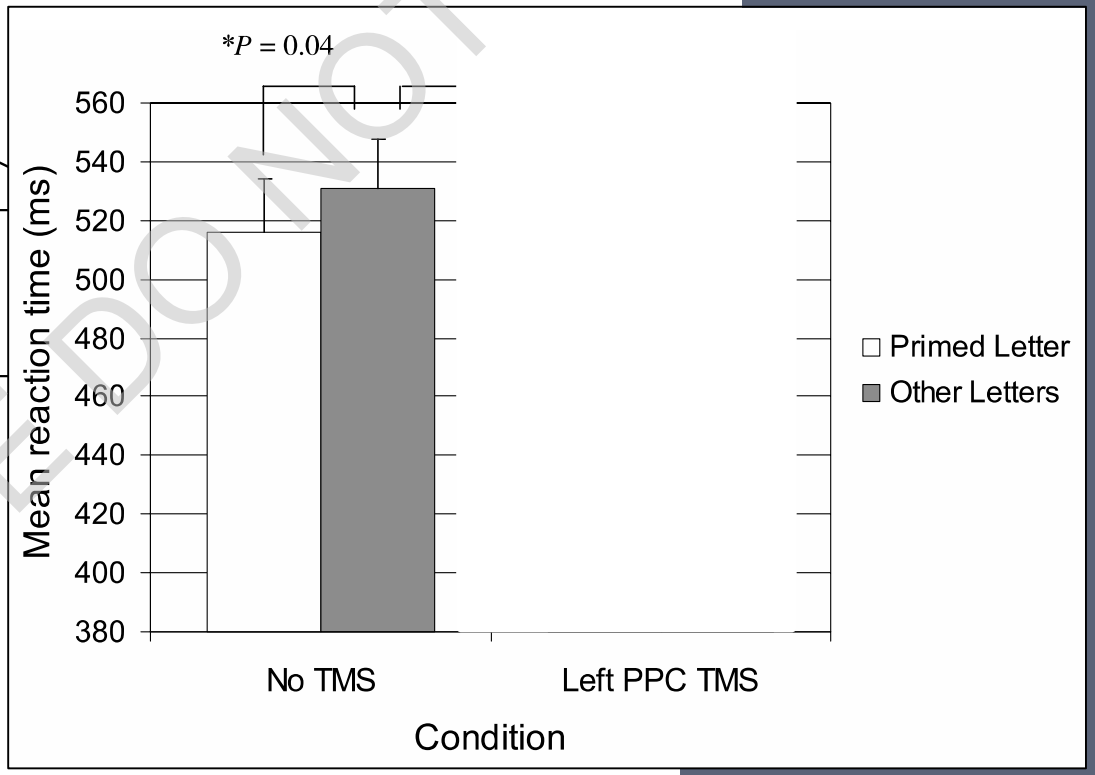
Letter Priming: left PPC





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

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Take Home – Adaptation/Priming

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

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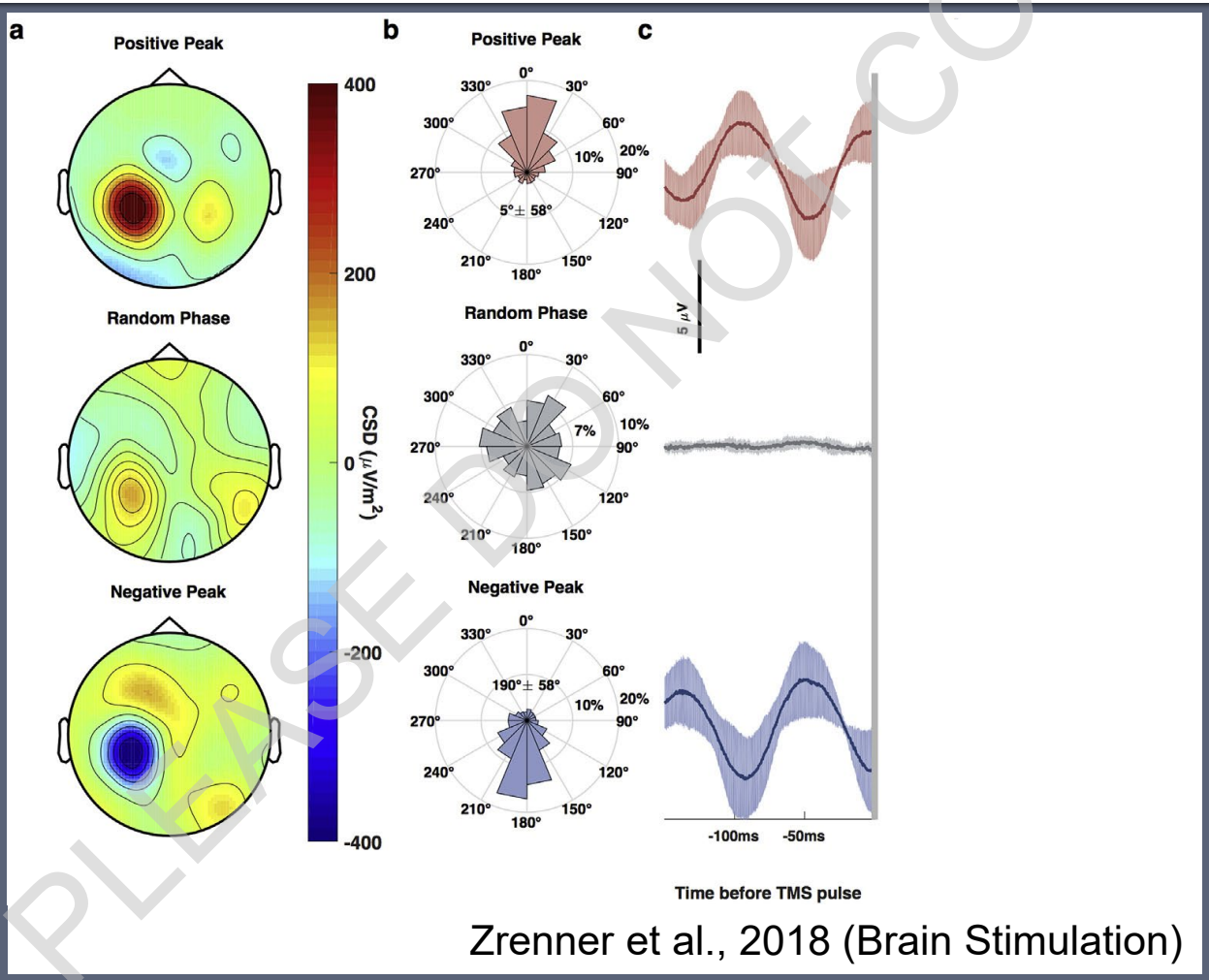
Closed-loop EEG triggered TMS



Zrenner et al., 2018 (Brain Stimulation)

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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

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Convention

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

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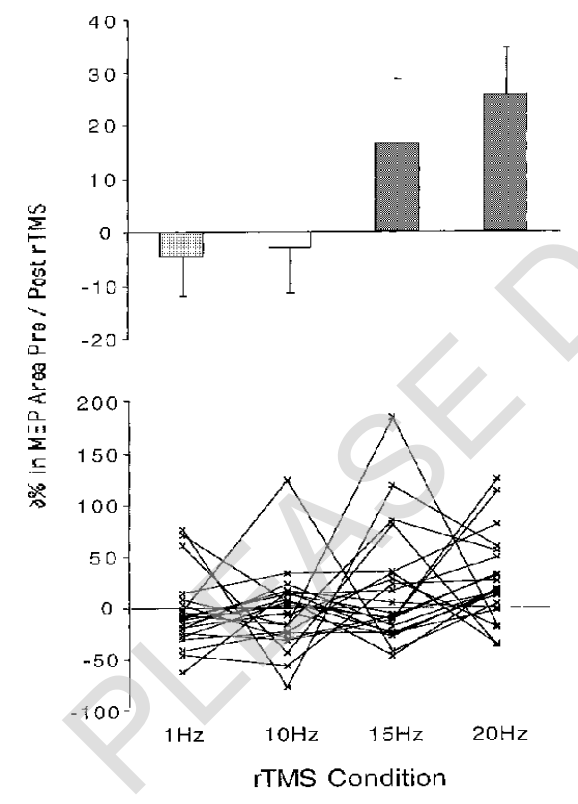
Exp Brain Res (2000) 133:425–430
DOI 10.1007/s002210000432

RESEARCH ARTICLE

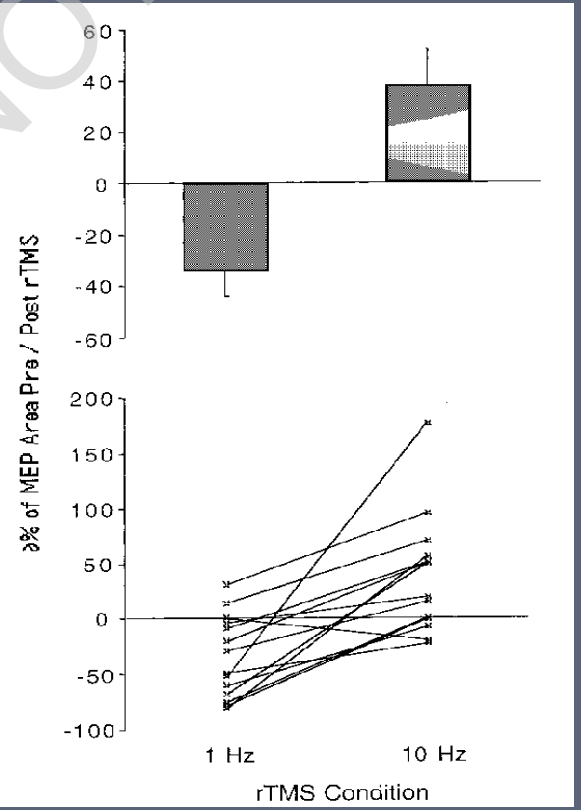
Fumiko Maeda · Julian P. Keenan · Jose M. Tormos
Helge Topka · Alvaro Pascual-Leone

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

240 pulses



1600 pulses



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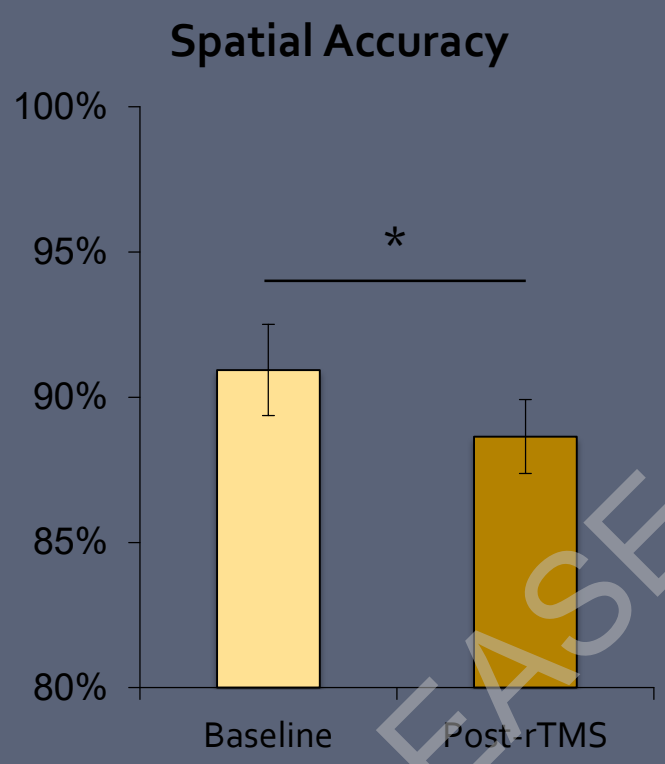
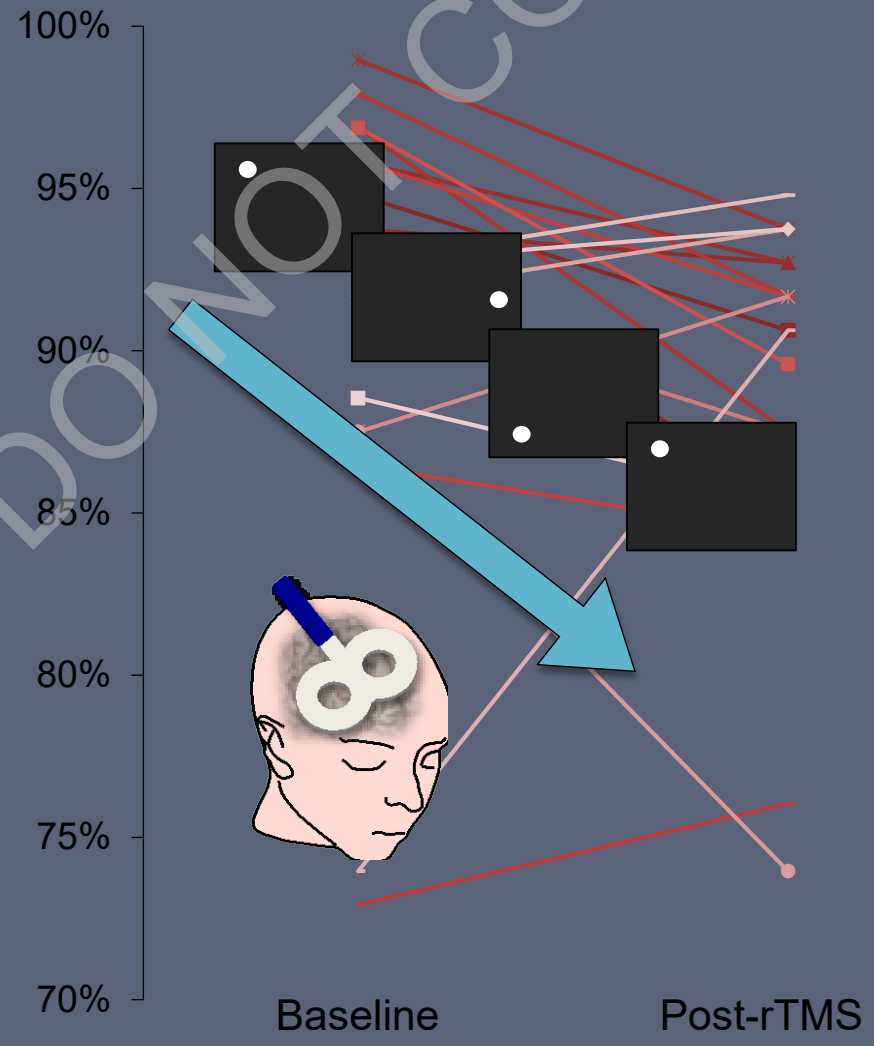
Variability in Cognitive Interventions





Modified from Fried et al., 2014

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Altered response to rTMS in disease

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

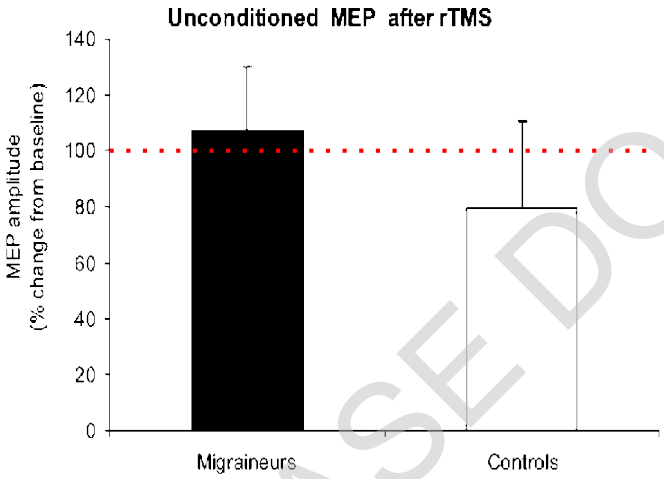

Fig. 1 Mean amplitude (±SD) of MEP to test stimulus alone after 1 Hz rTMS in migraineurs and controls (values are expressed as percentage of baseline MEP).

Brighina et al., 2005 (Experimental Brain Research)

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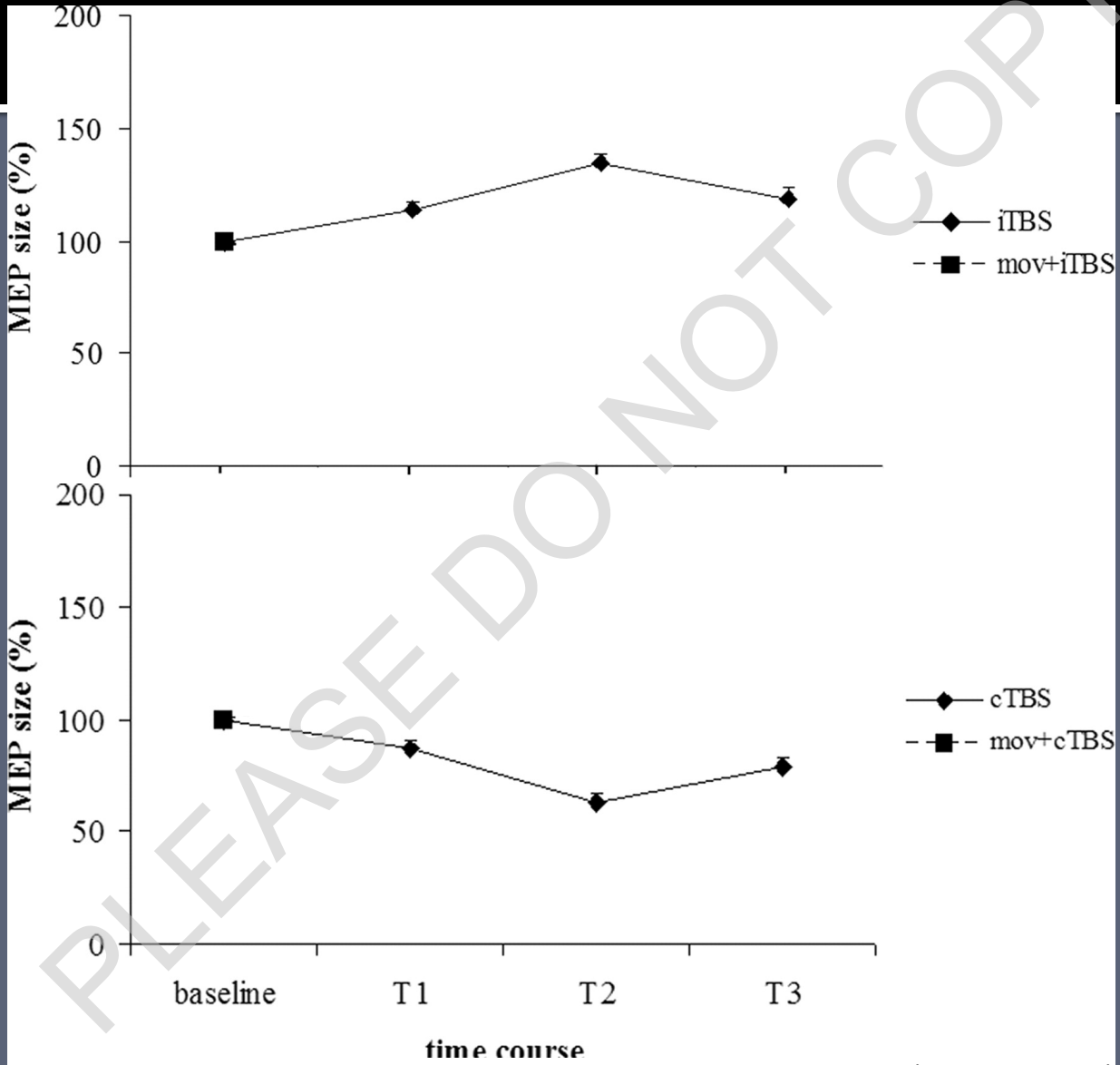
Impact of physiological activity



Iezzi E et al., 2008 (J Neurophysio)

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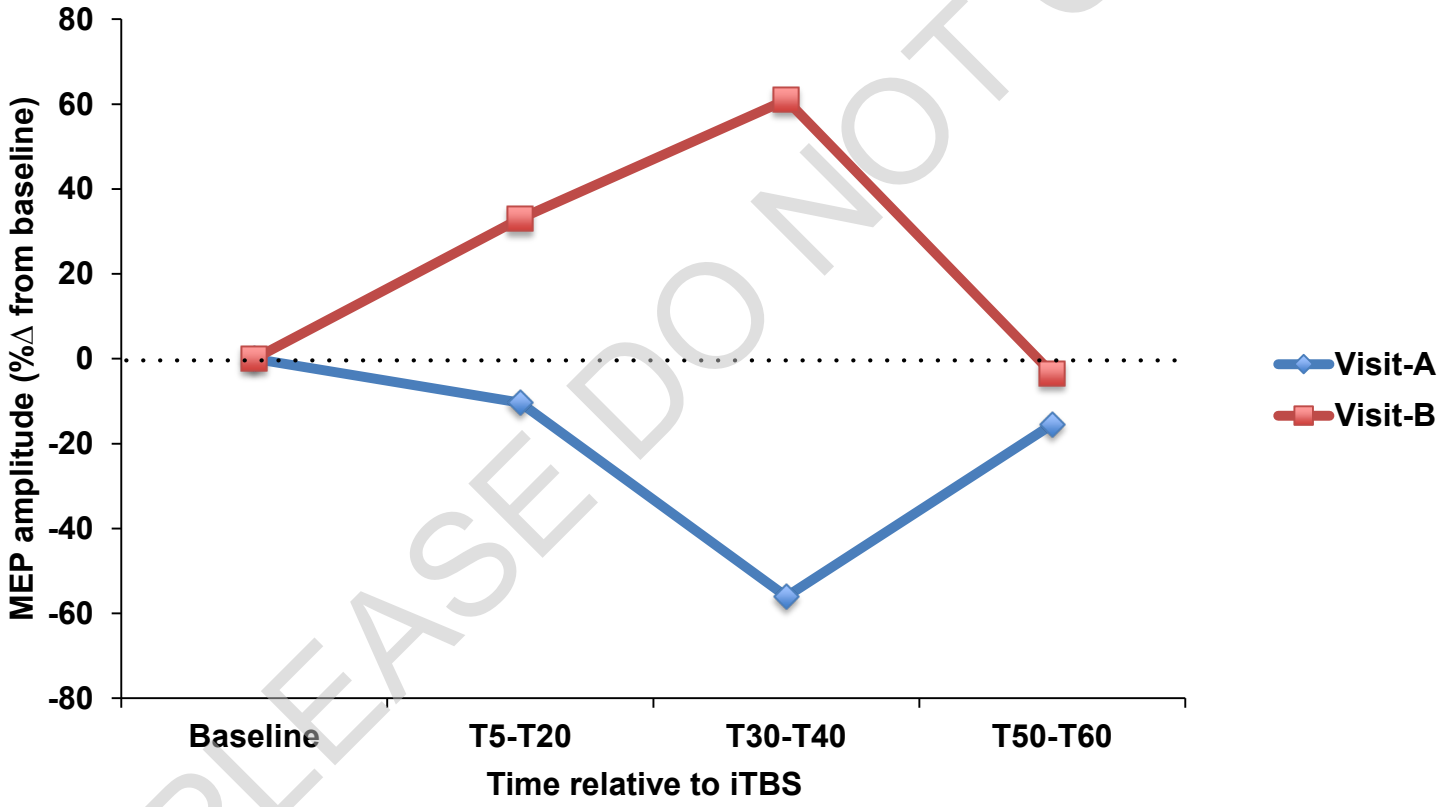
Case example



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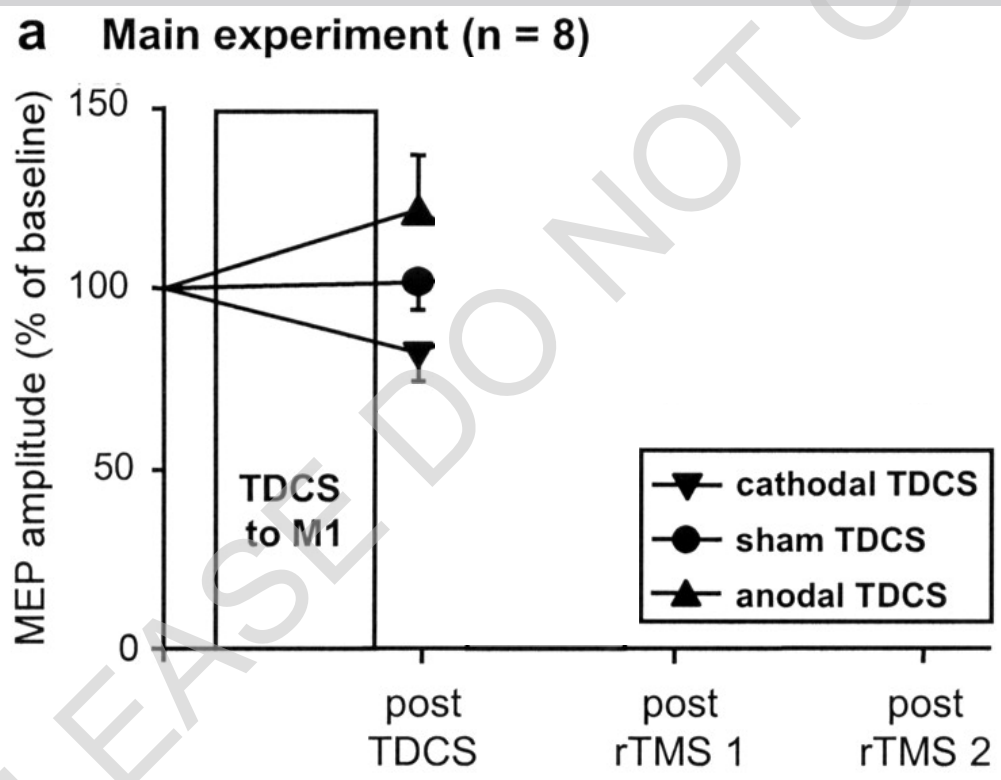
Preconditioning rTMS with tDCS

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



Siebner et al., 2004 (Journal of Neuroscience)

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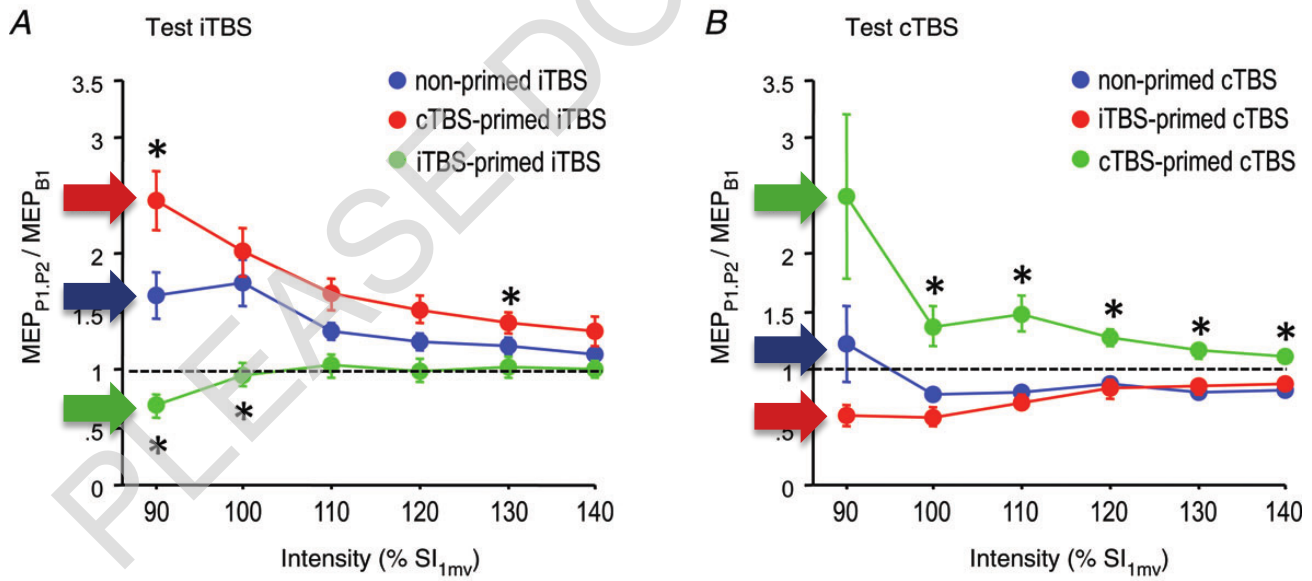
Preconditioning TBS with TBS

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]



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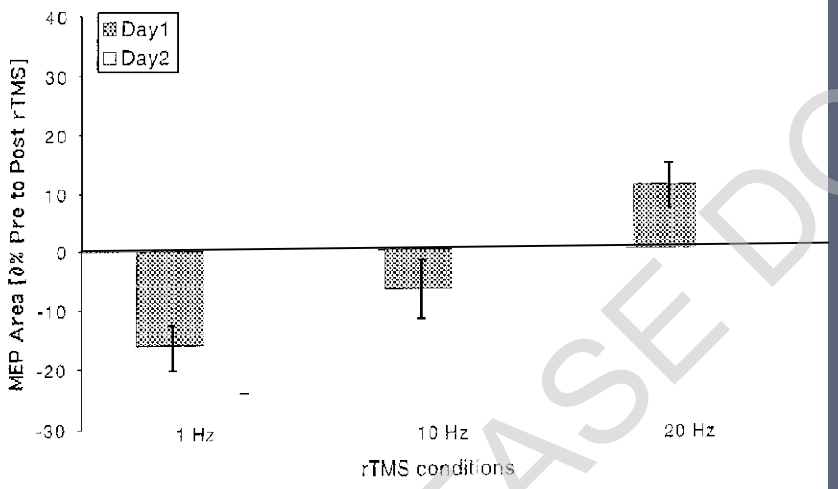
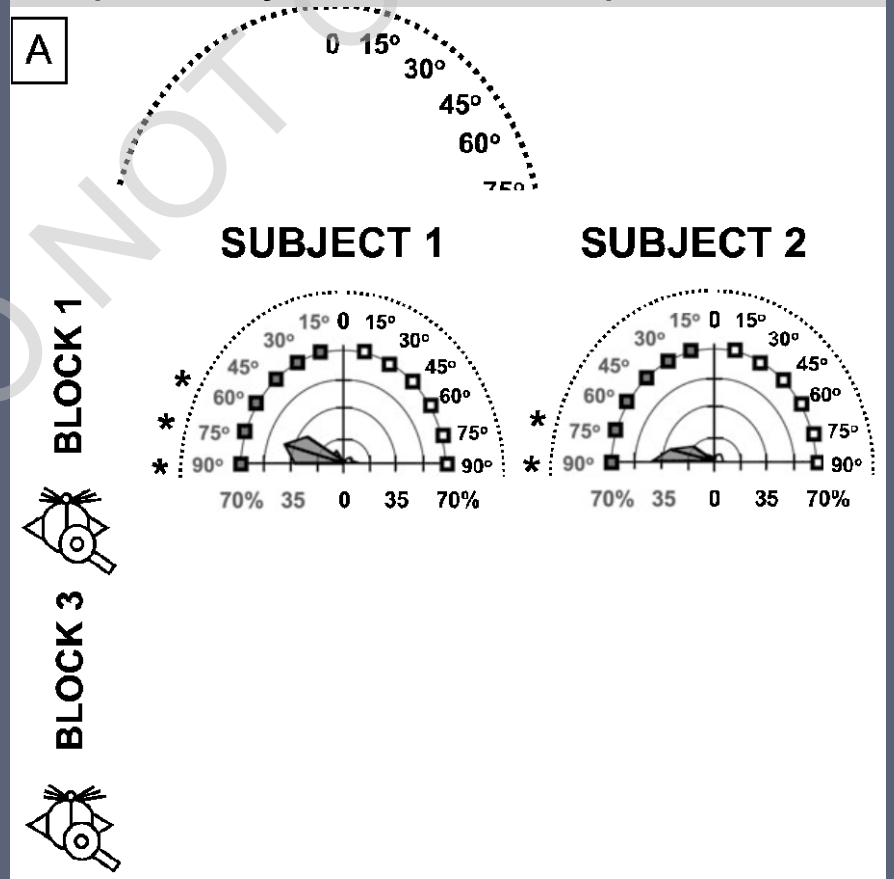
Meta-plasticity: Impact of Cumulative Sessions

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)

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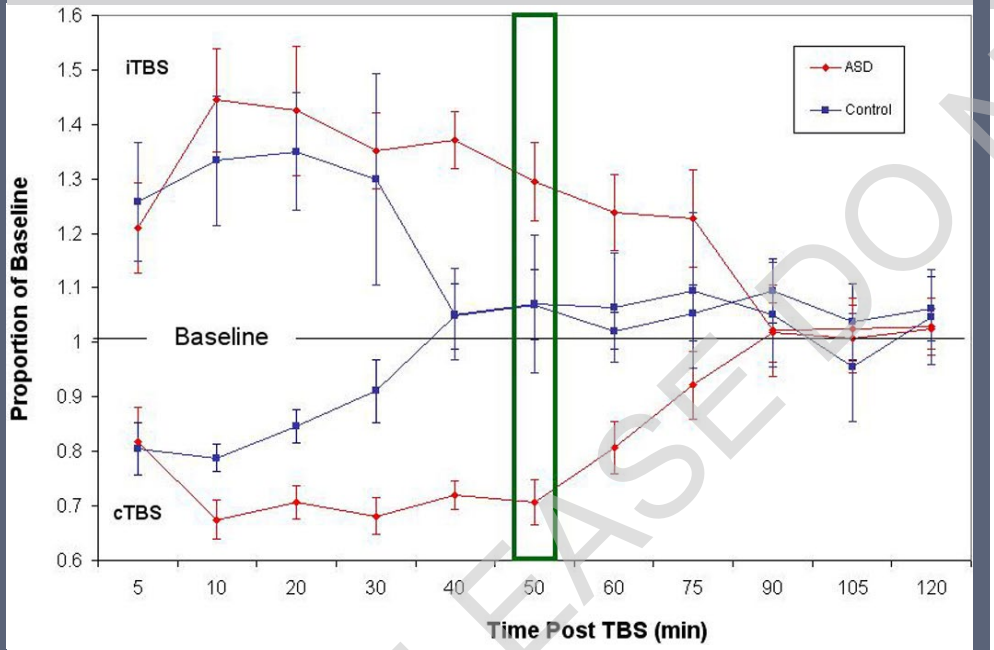
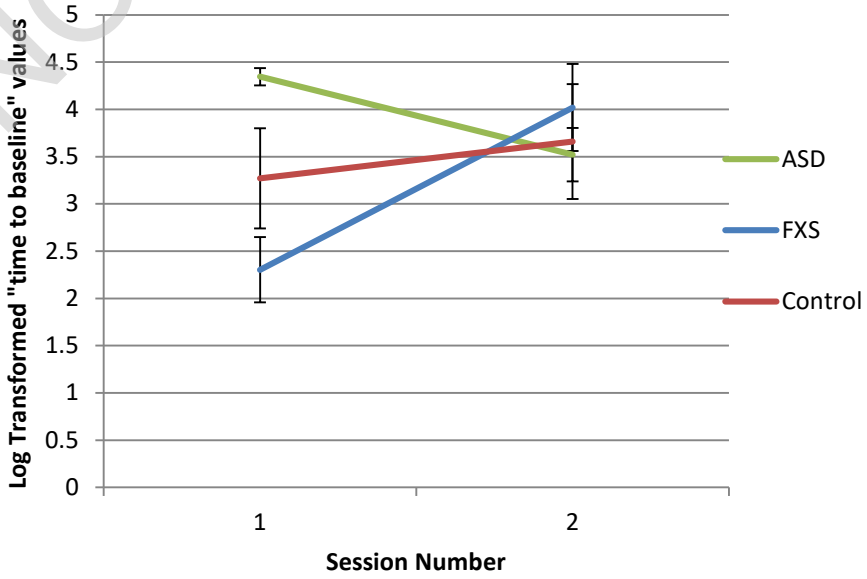
Altered Meta-plasticity in ASD

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)

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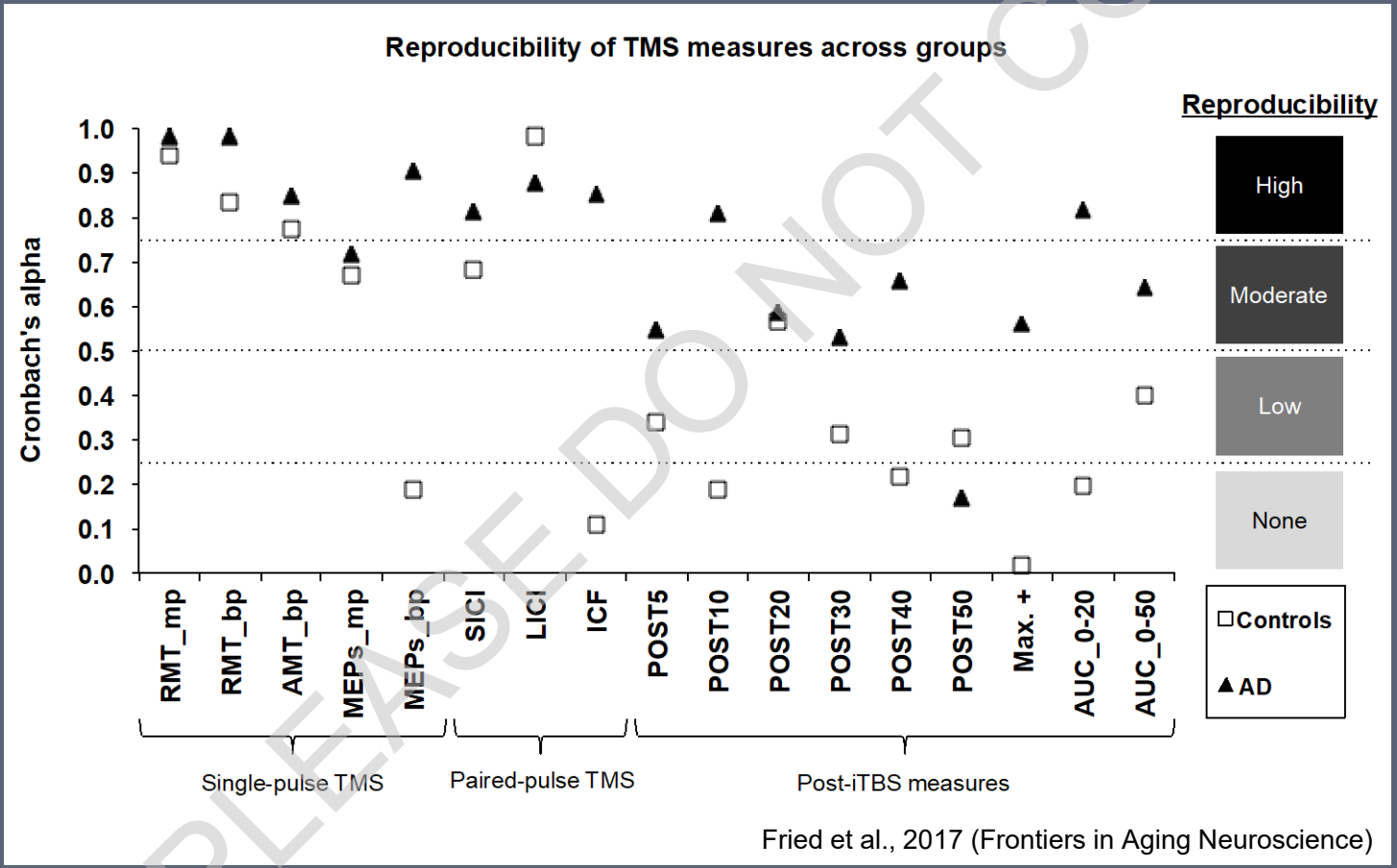
Reproducibility of TMS measures



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

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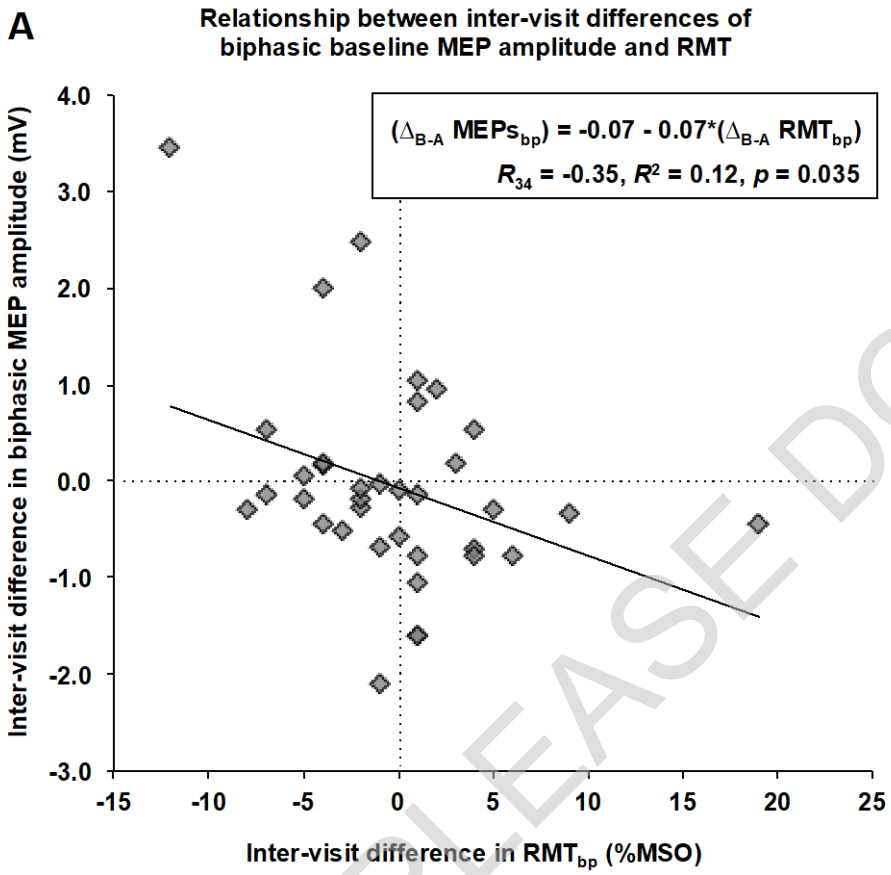
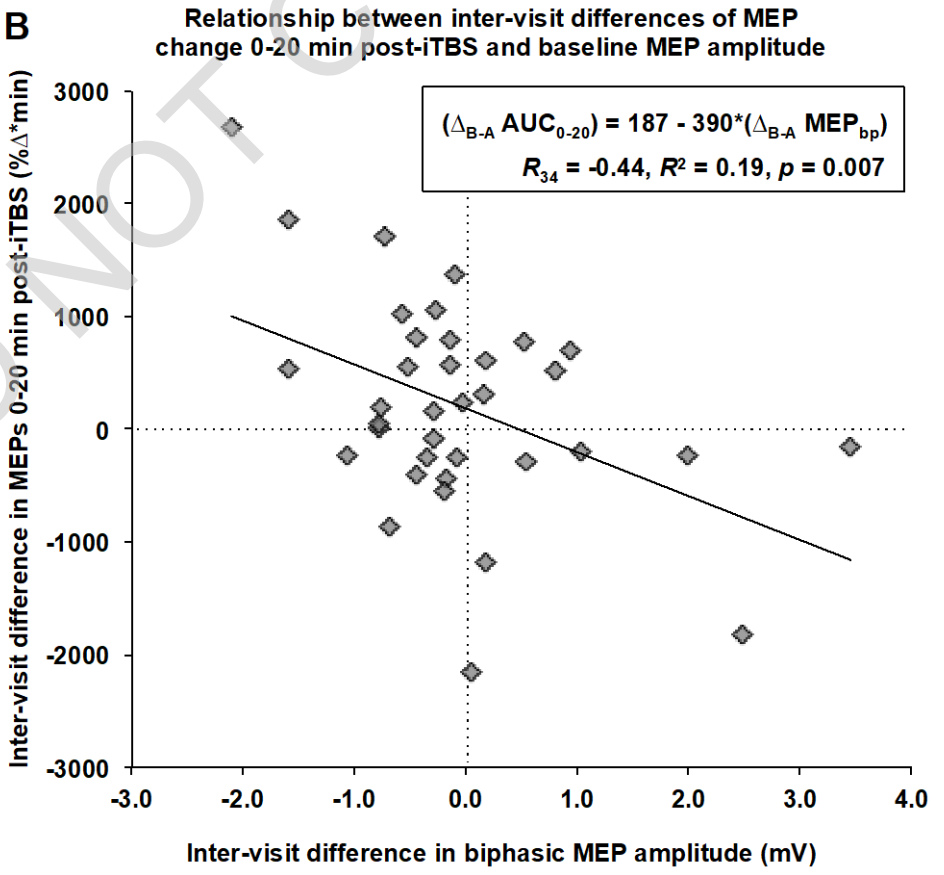
Factors that affect reproducibility





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

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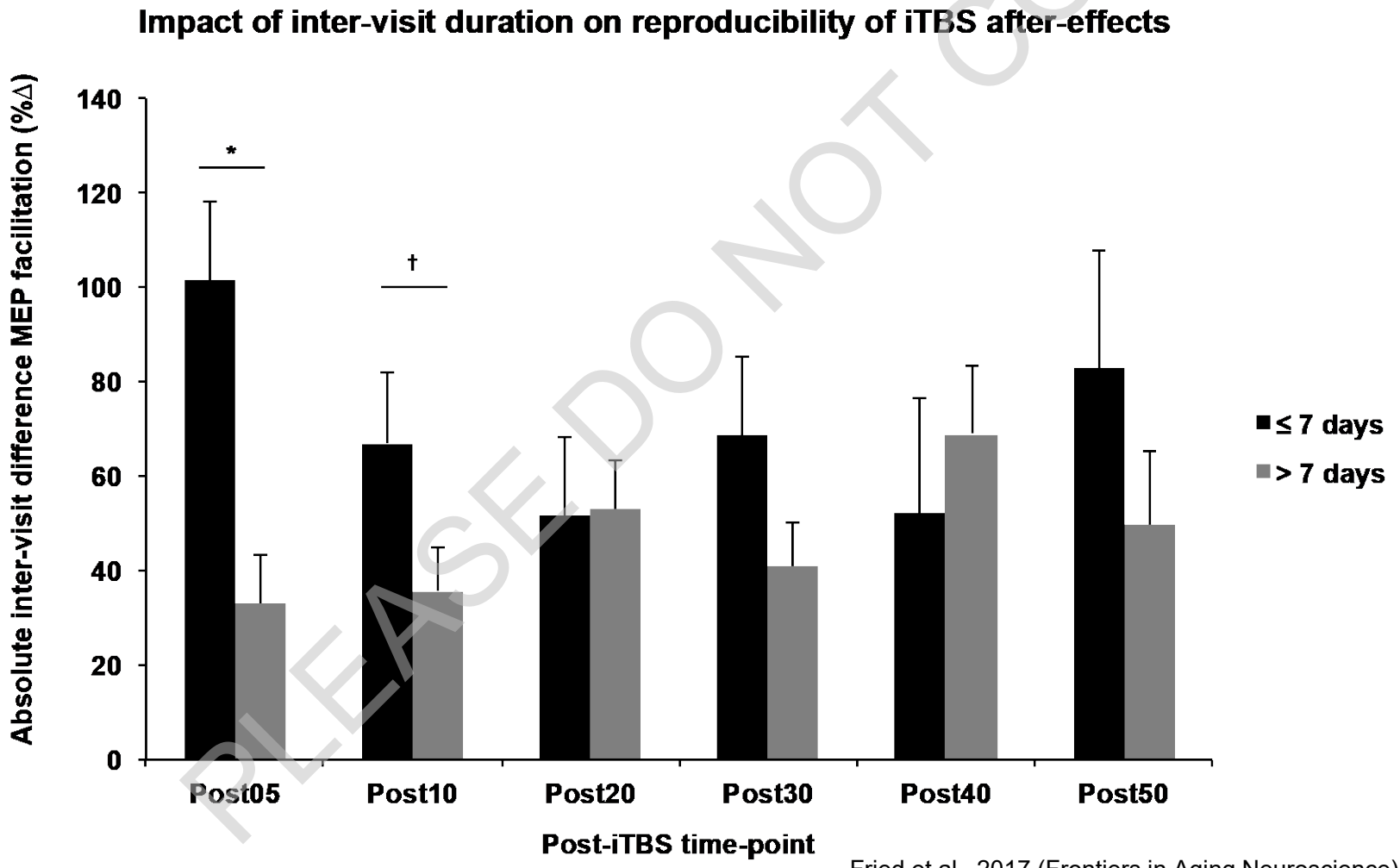
Factors that affect reproducibility



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

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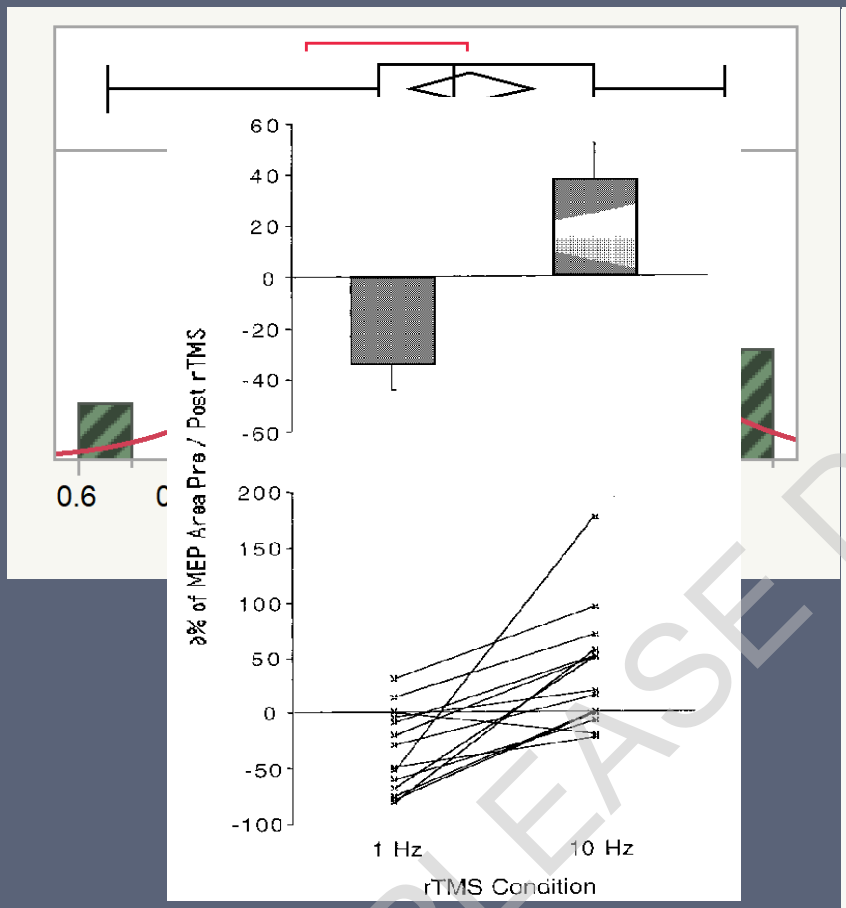
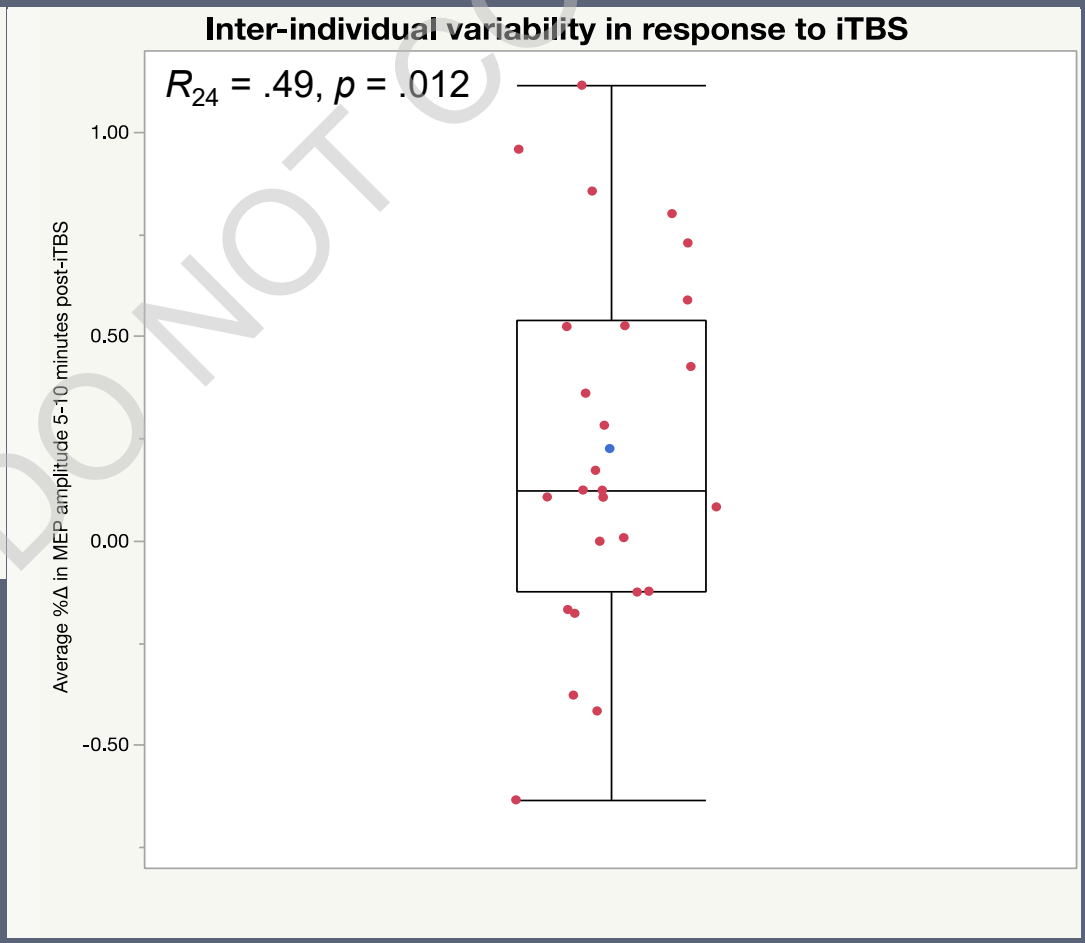
Variability due to study parameters





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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

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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

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Potential Confounds

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Easy to control

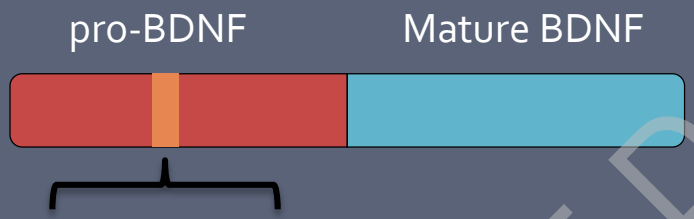
- Caffeine, Rx
- Prior stimulation
- Time of day
- Food intake
- Handedness
- Concomitant activity

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

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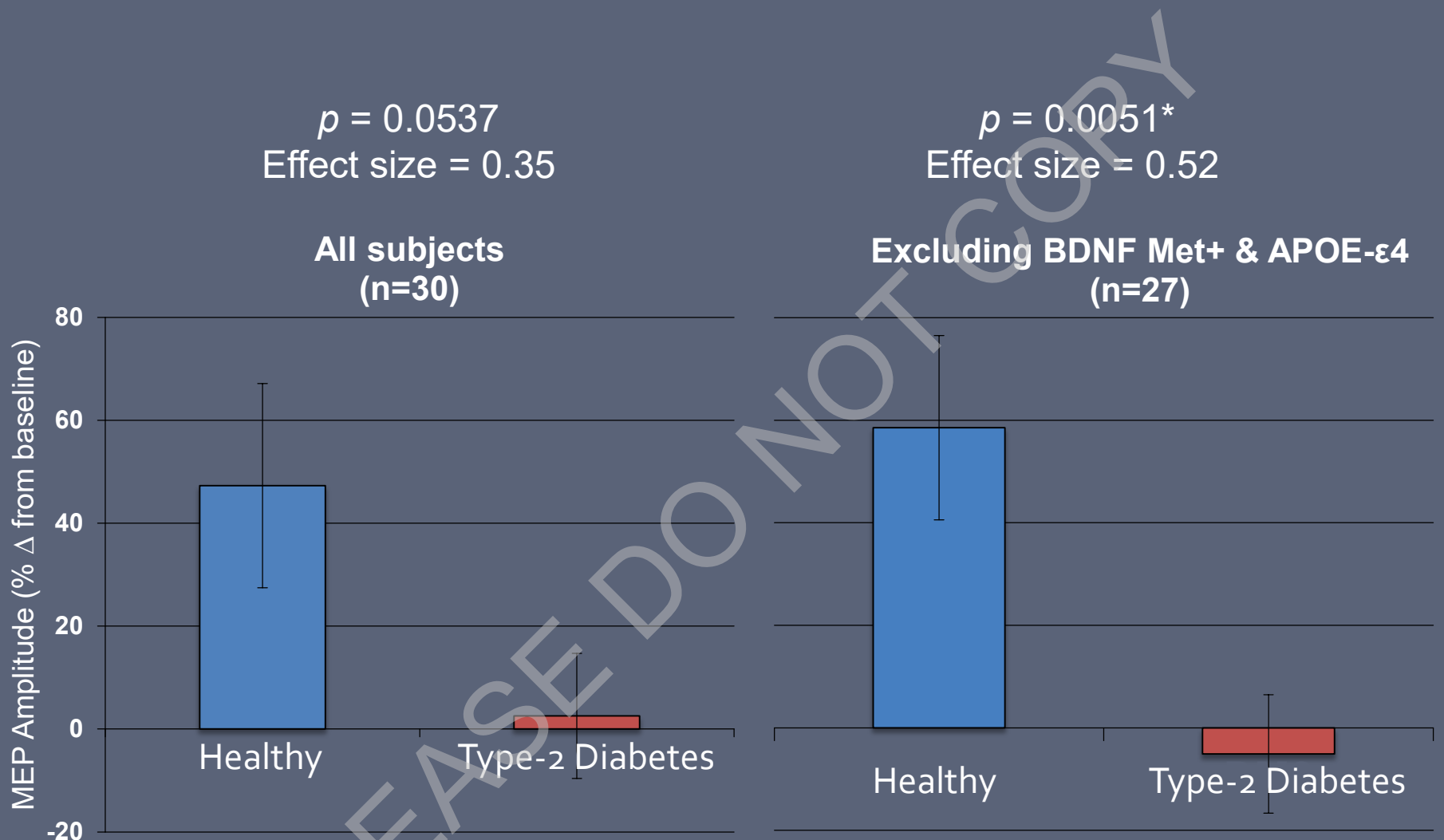

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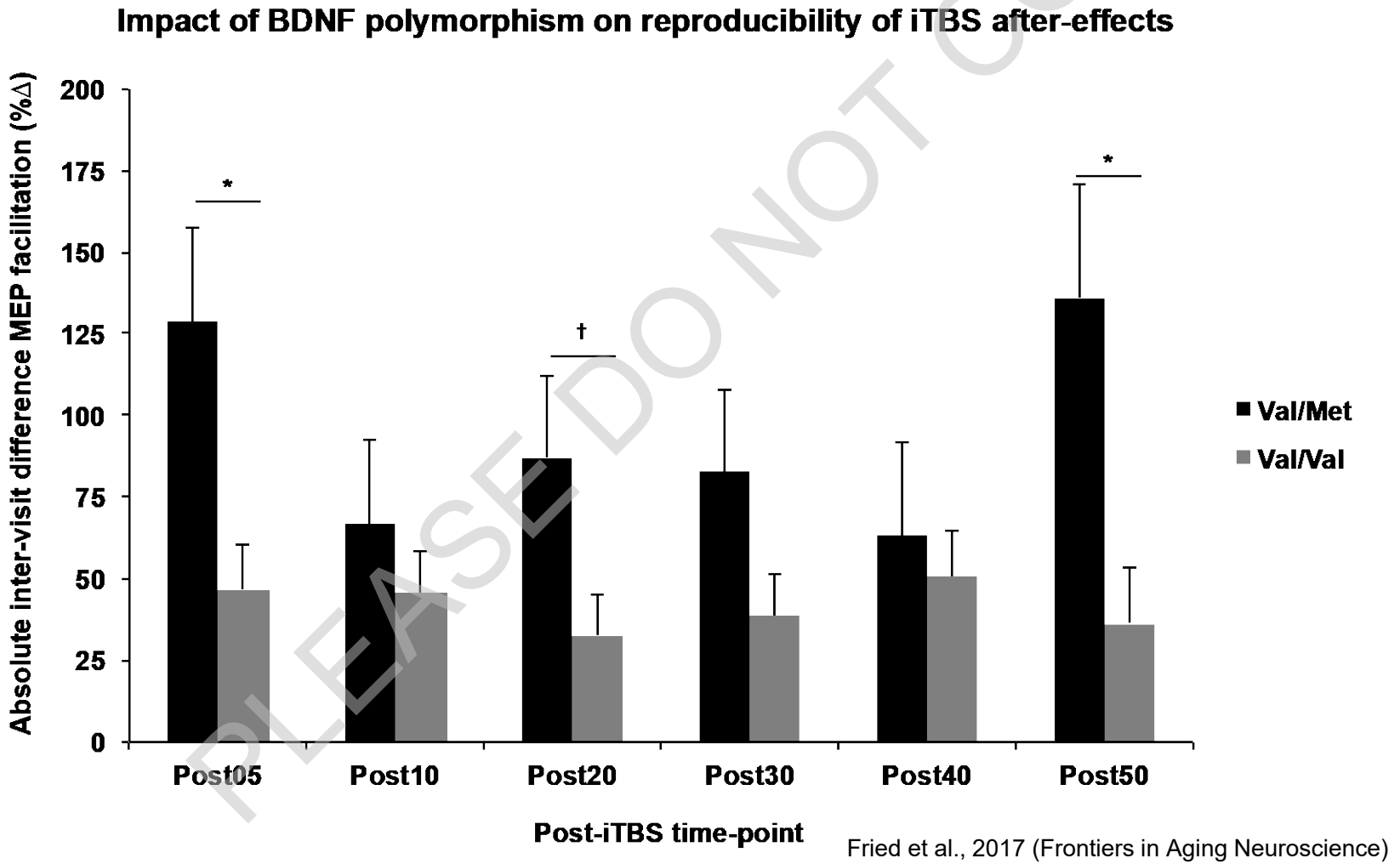
For full study, see Fried et al., 2017 (J Alzheimer's Disease)

Factors that affect reproducibility



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

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What to do? Follow the C's

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

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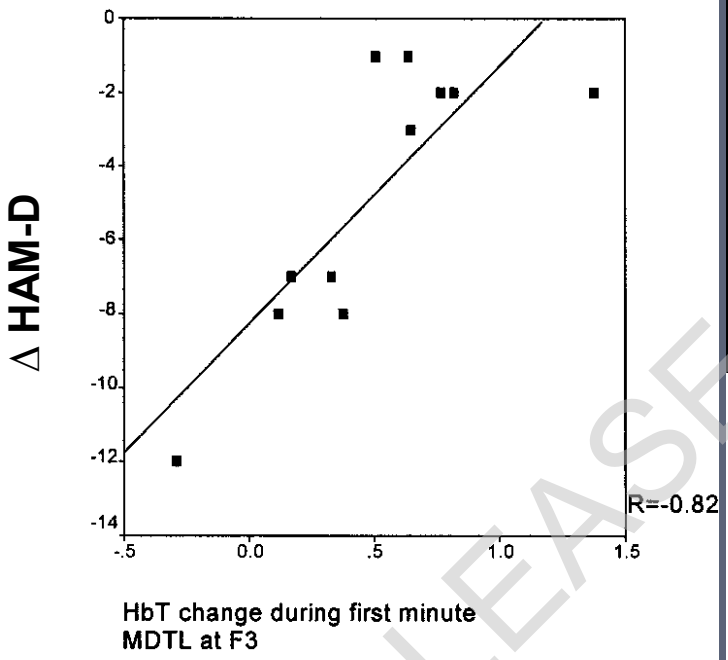
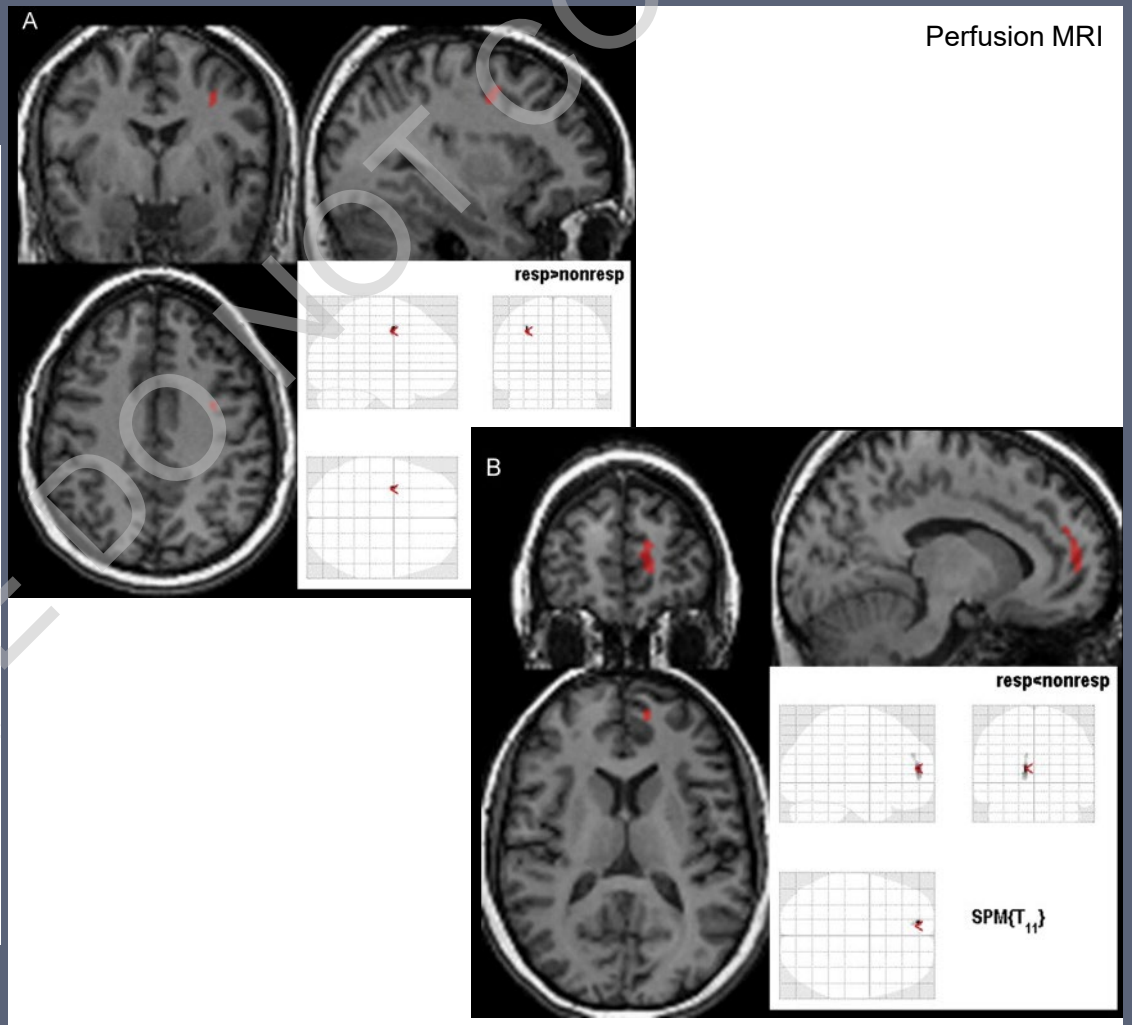
Predicting Therapeutic Outcome: activity in single sites

NIRS



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

Perfusion MRI



Weiduschat and Dubin, 2013 (J Affective Disorders)

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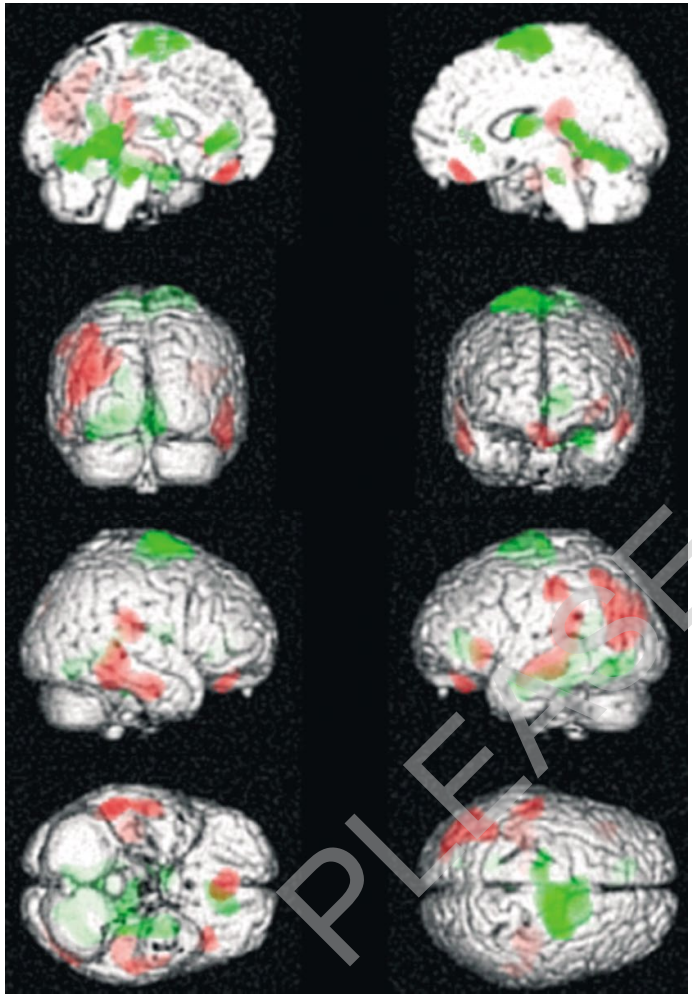
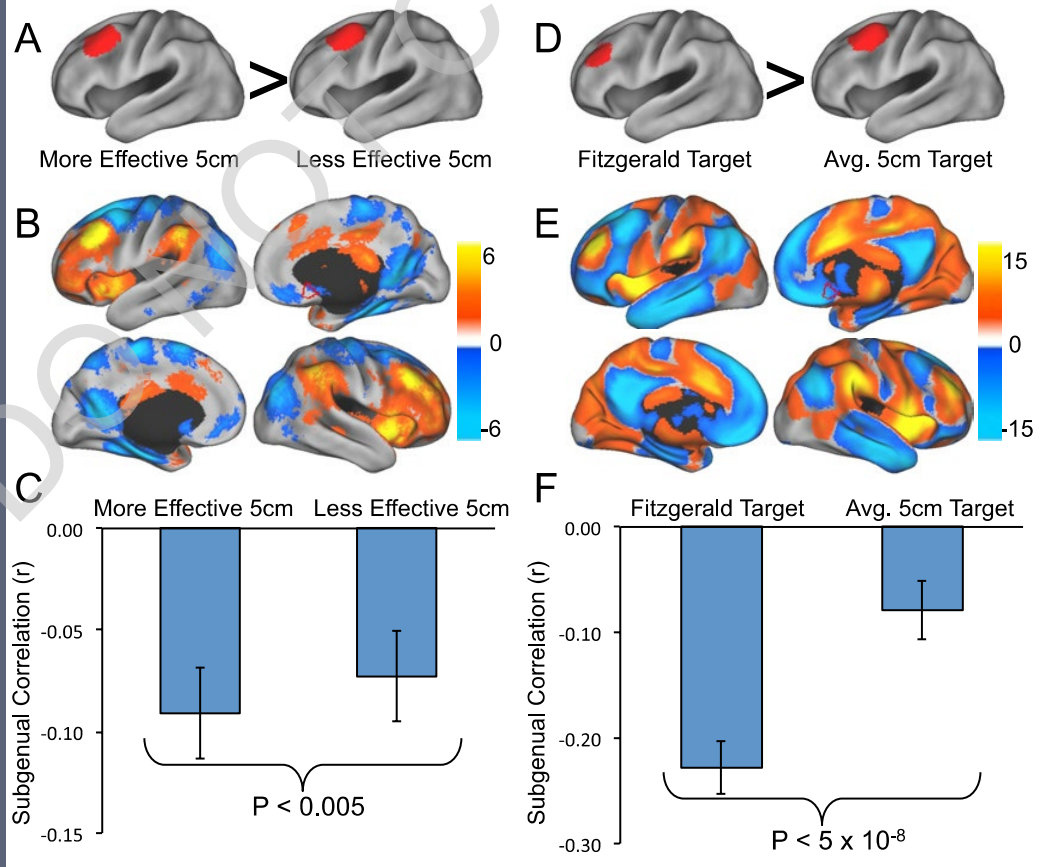
Predicting Therapeutic Outcome: activity across networks

rCBF (SPECT)



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

Resting-state functional connectivity MRI



Fox et al., 2012 (Biological Psychiatry)

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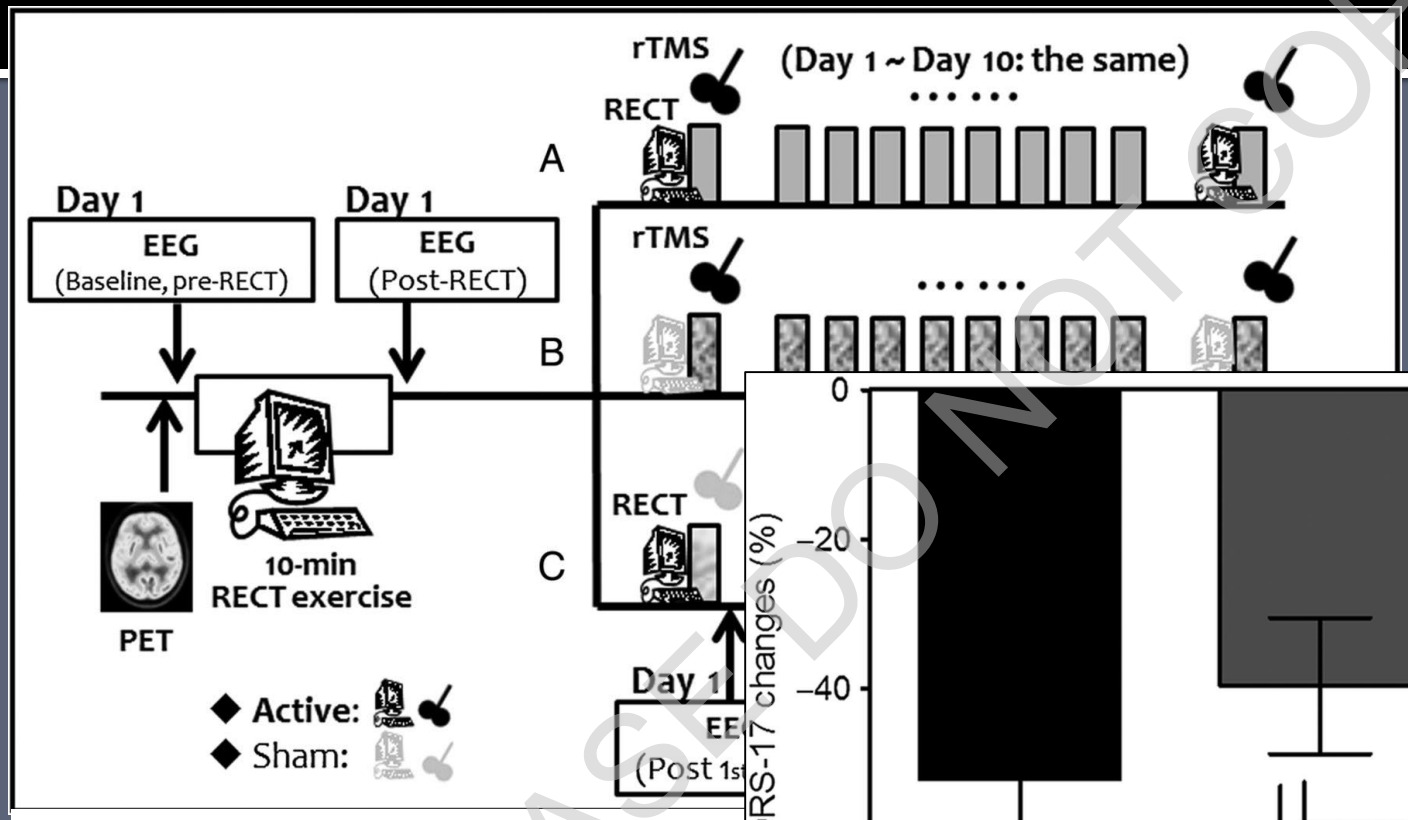
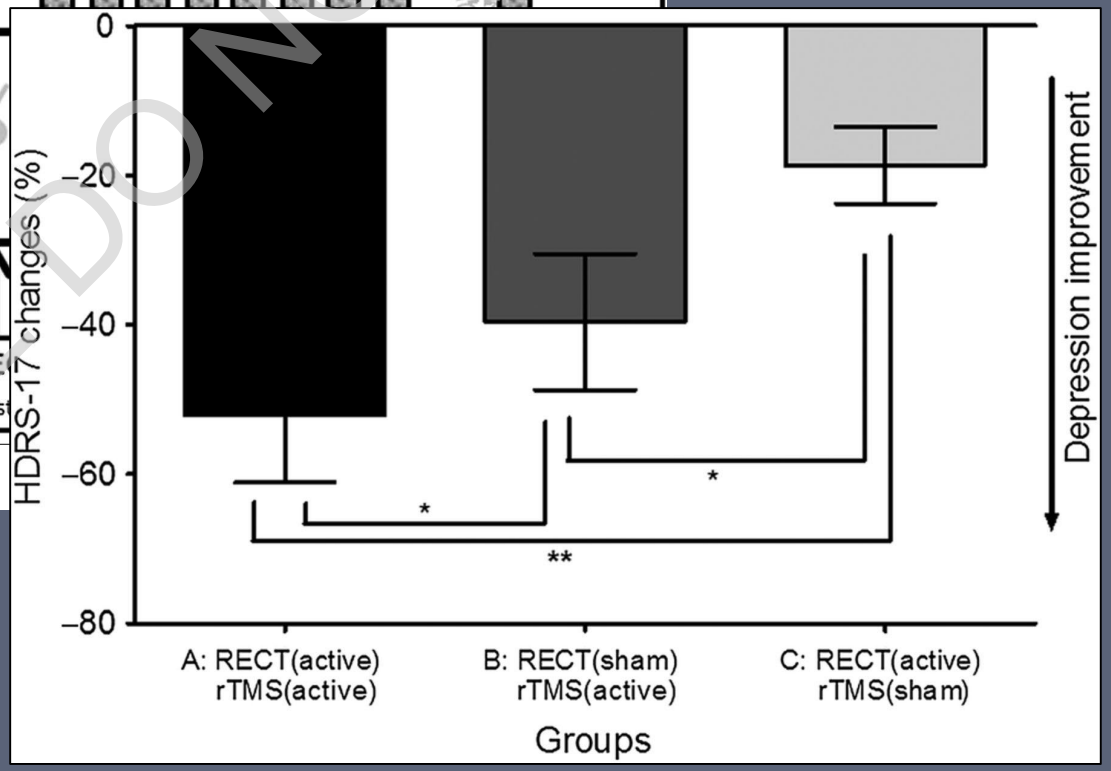
Changing brain state to improve efficacy



Li et al., 2016 (Cerebral Cortex)



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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

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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)

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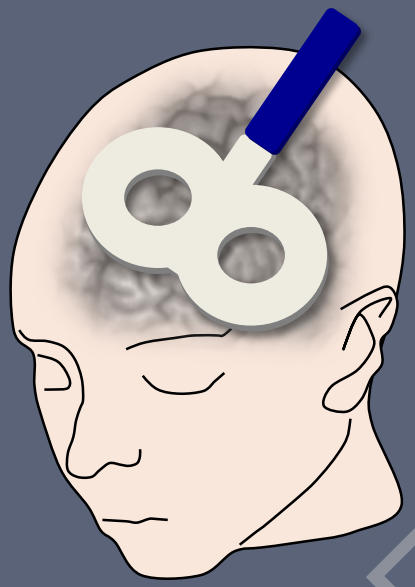
Option 1: Tilt Coil 90°

real



Pros:

Easy, fast, cheap

No switching coils

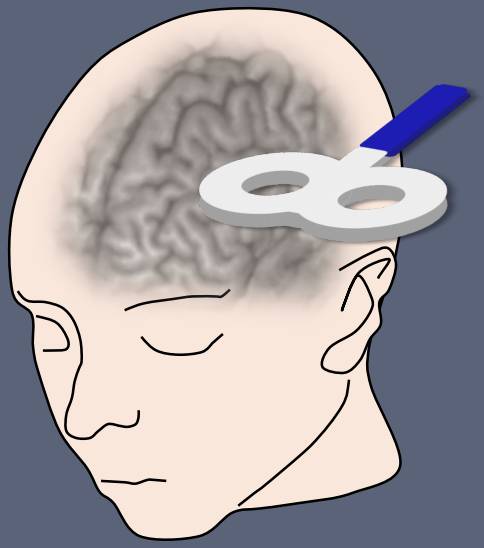
Similar sensations

Cons:

Might induce current

Won't fool non-naïve

sham



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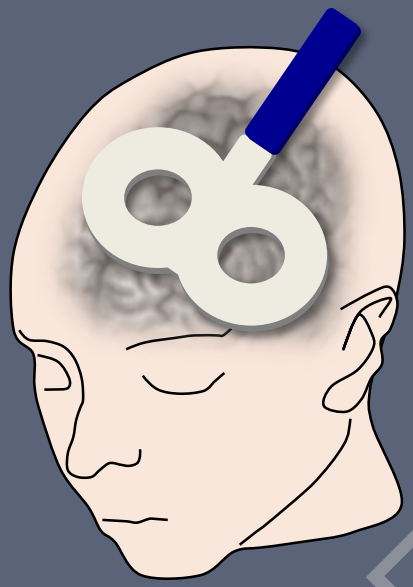
Option 2: Use "sham" Coil

real



Pros:

Similar look and feel

Tech getting better

Cons:

Slow, expensive

Must switch coils

Still doesn't feel the same

sham

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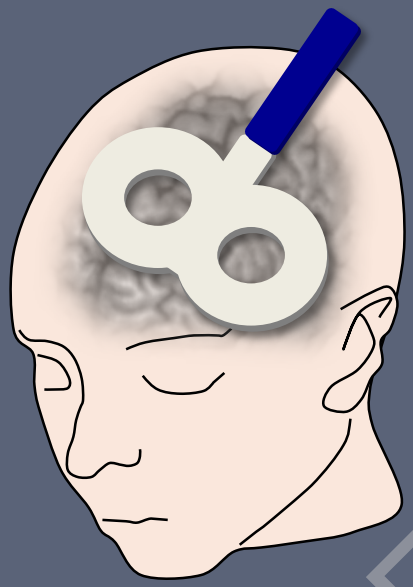
Option 3: Active Control Site

real



Pros:

Easy, fast, cheap

Same sensations

Cons:

Will control site have real effects?

Laterality of sensations

vertex

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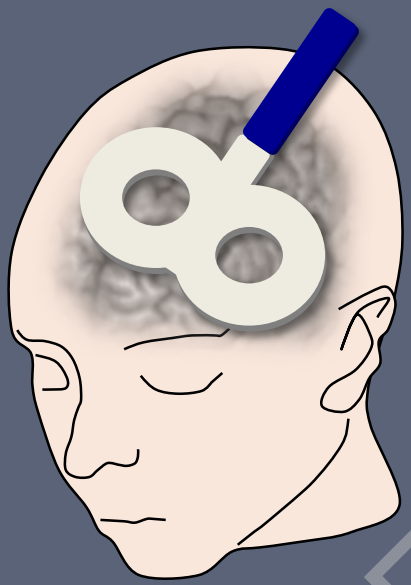
Option 4: Double Dissociation

Left hemisphere



Pros:

Easy, fast, cheap

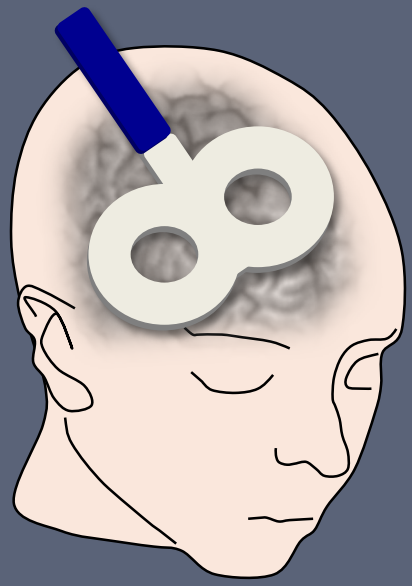
Same sensations

Greater explanatory power

Cons:

More difficult study design

Right hemisphere



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So… Now what?

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