State-Dependent Effects of Transcranial Magnetic Stimulation

“The cause of, and solution to, some of TMS’s variability
And a way to potentially increase its selectivity”

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Overview

- What is ‘state-dependency’?
- Single Pulse TMS (specificity)
- Repetitive TMS (meta-plasticity)
- Implications for study design
The basal or ongoing state of the brain influences the outcome of stimulation.

What is ‘State-dependency’?
Paired-Pulse TMS

Test pulse (alone)  Conditioning Pulse + Test Pulse

Intracortical Inhibition (ISI = 1-6ms)

Intracortical Facilitation (ISI = 8-30ms)

0.5mV

25 ms

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: Prolonged prior exposure to stimulus reduces neural activity and response to subsequent presentation

Priming: Transient prior exposure to stimulus increases neural activity and response to subsequent presentation
Color Adaptation: area V1

Modified from: Silvanto et al., 2008 (Trends in Cognitive Sciences)
Motion Adaptation: area V5/MT

Each trial lasted approximately 2 s and each block approximately 64 s.

Cattaneo & Silvanto, 2008 (NeuroReport)
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”
Overview

- What is ‘state-dependency’?
- Single Pulse TMS (specificity)
- Repetitive TMS (meta-plasticity)
  - Inter-individual variability
  - Altered impact in disorders
  - Preconditioning, accumulation
- Implications for study design
Convention
Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability
Variability in Cognitive Interventions

Spatial Accuracy

Baseline vs. Post-rTMS

Modified from Fried et al., 2014
Variability due to disease

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

![Graph showing MEP amplitude](image)

**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)
Case example
Preconditioning rTMS with tDCS

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

Main experiment (n = 8)

MEP amplitude (% of baseline)

post TDCS

post rTMS 1

post rTMS 2

TDCS to M1

real rTMS

Siebner et al., 2004 (Journal of Neuroscience)
Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex

Takenobu Murakami¹, Florian Müller-Dahlhaus¹, Ming-Kuei Lu¹,² and Ulf Ziemann¹,³
Meta-plasticity: Impact of Cumulative Sessions

Impact of rTMS on Motor-Evoked Potentials

Maeda et al., 2000 (Clinical Neurophysiology)

Valero-Cabré et al., 2008 (European Journal of Neuroscience)
Altered Meta-plasticity in ASD

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

Cumulative Impact of Back-to-Back TBS

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

Oberman et al., 2016 (J Child Adolescent Psychopharm)
Reproducibility of TMS measures

Reproducibility of TMS-based neurophysiological and neuroplasticity measures

Cronbach's alpha

Reproducibility

Excellent

Good

Fair

Poor

Single-pulse measures  Paired-pulse measures  Post-iTBS measures

Fried et al., 2016 (unpublished – DO NOT SHARE)
Reproducibility of TMS measures

Fried et al., 2016 (unpublished – DO NOT SHARE!)

Reproducibility of TMS-based neurophysiological and neuroplasticity measures

Cronbach's alpha

Single-pulse measures
- RMT_mp
- AMT_bp
- MEPs Mp
- SCL
- ICF
- POST10
- POST20
- POST30
- POST40
- POST50
- Max. + AUC_0-20
- AUC_0-50

Paired-pulse measures
- MEPs_bp
- LI

Post-iTBS measures

Reproducibility
- Excellent
- Good
- Fair
- Poor

Please do not copy.
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 cancel out
  - Daily sessions → build up facilitation
Overview

- What is ‘state-dependency’?
- Single Pulse TMS (specificity)
- Repetitive TMS (meta-plasticity)
- Implications for study design
  - Follow the three C’s
  - Predicting Therapeutic Outcome
  - 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
Brain-derived neurotrophic factor (BDNF)

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

pro-BDNF | Mature BDNF
--- | ---
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
All subjects

$\rho = 0.0537$
Effect size = 0.35

BDNF Val/Met & ApoE ε3/ε4 excluded

$\rho = 0.0051^*$
Effect size = 0.52

Unpublished work – please do not share

For full study, see Fried et al., 2016 (J Alzheimer’s Disease)
Absolute inter-visit difference in iTBS by BDNF

$p = 0.035$

Fried et al., 2016 (unpublished – DO NOT SHARE!)
What to do? Follow the C’s

- Collect / Correlate
- Control / Counter-balance
- Co-opt / Capitalize
Left prefrontal activation predicts therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) in major depression

Gerhard Wilhelm Eschweiler*, Christine Wegerer, Wilfried Schlotter, Christoph Spandl, Andreas Stevens, Mathias Bartels, Gerhard Buchkremer

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Brief report

Prefrontal cortical blood flow predicts response of depression to rTMS

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![Brain images](image-url)
Correlation of cerebral blood flow and treatment effects of repetitive transcranial magnetic stimulation in depressed patients

Felix M. Mottaghy\textsuperscript{a,b}, Christian E. Keller\textsuperscript{a}, Massimo Gangitano\textsuperscript{a}, Jennifer Ly\textsuperscript{a}, Mark Thall\textsuperscript{a}, J. Anthony Parker\textsuperscript{c}, Alvaro Pascual-Leone\textsuperscript{a,*}

Fig. 1. The correlation maxima are superimposed on a standard rendered brain. Green shows the negative correlations between rCBF and $\delta$-HDRS; red indicates region that are positively correlated ($P < 0.05; k = 20$).
Efficacy of Transcranial Magnetic Stimulation Targets for Depression Is Related to Intrinsic Functional Connectivity with the Subgenual Cingulate

Michael D. Fox, Randy L. Buckner, Matthew P. White, Michael D. Greicius, and Alvaro Pascual-Leone
Rostral aCC & frontal theta-power

Li et al., 2014 (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 \( \text{(Broadbent et al. 2011, World J Bio Psychiatry)} \)

- Patients correctly guessed Tx condition above chance \( \text{(Berlim et al. 2013, Int J Neuropsychopharm)} \)
Option 1: Tilt Coil 90°

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

**Pros:**
- Easy, fast, cheap
- Same sensations
- Greater explanatory power

**Cons:**
- More difficult study design
So... Now what?

What state-dependency?