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”

Peter J. Fried, Ph.D.

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Overview

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

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: 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

Baseline | After adaptation to red | After TMS

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

Cattaneo & Silvanto, 2008 (NeuroReport)

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

![Graph showing detection accuracy for different TMS conditions](image)
Letter Priming: left PPC

Cattaneo et al., 2008 (European Journal of Neuroscience)
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
Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability

240 pulses

1600 pulses
Variability in Cognitive Interventions

Spatial Accuracy

Baseline: 95%
Post-rTMS: 90%

Modified from Fried et al., 2014
If you think healthy controls are bad...
Impact of 1Hz rTMS on Motor-Evoked Potential (MEP), Intracortical Facilitation 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 1Hz rTMS on Motor Evoked Potential (MEP) Area

Siebner et al., 1999 (Neuroscience Letters)
Behavioral Preconditioning

Iezzi E et al., 2008 (J Neurophysio)
Case example

![Graph showing MEP amplitude (%Δ) vs. Min post-iTBS](attachment:graph.png)

Visit
- 1
- 2
Preconditioning rTMS with tDCS

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

Main experiment (n = 8)

- TDCS to M1
- real rTMS

- cathodal TDCS
- sham TDCS
- anodal TDCS

Siebner et al., 2004 (Journal of Neuroscience)
Preconditioning TBS with TBS

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
So how much time between sessions?
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

Reproducibility of TMS-based neurophysiological and neuroplasticity measures

Cronbach's alpha

Reproducibility

- Excellent
- Good
- Fair
- Poor

Single-pulse measures
- RMT_mp
- AMT_bp
- MEPs_mp
- MEPs_bp

Paired-pulse measures
- SICI
- LI
- ICF
- POST5
- POST10
- POST20
- POST30
- POST40
- POST50

Post-iTBS measures
- Max. +
- AUC_0-20
- AUC_0-50

Fried et al., 2017 (unpublished – DO NOT SHARE!)
Reproducibility of TMS measures

Reproducibility of TMS-based neurophysiological and neuroplasticity measures

- Cronbach's alpha
- Single-pulse measures
- Paired-pulse measures
- Post-iTBS measures

Fried et al., 2017 (unpublished – DO NOT SHARE!)
Factors that affect reproducibility

Fried et al., 2017 (unpublished – DO NOT SHARE!)
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
  - 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
  - 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

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
$p = 0.0537$
Effect size = 0.35

All subjects

$\frac{\Delta}{\text{from baseline}}$

$\begin{align*}
\text{OHC} & \quad 0 \\
\text{DM2} & \quad 40
\end{align*}$

$\begin{align*}
\text{OHC} & \quad 80 \\
\text{DM2} & \quad 0
\end{align*}$

$\begin{align*}
\text{OHC} & \quad 80 \\
\text{DM2} & \quad 0
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\end{align*}$

$\begin{align*}
\text{OHC} & \quad 80 \\
\text{DM2} & \quad 0
\end{align*}$

$p = 0.0051^*$
Effect size = 0.52

BDNF Val/Met & ApoE ε3/ε4 excluded

All subjects

Effect size = 0.35

BDNF Val/Met & ApoE ε3/ε4 excluded

Effect size = 0.52

Unpublished work – please do not share

For full study, see Fried et al., 2016 (J Alzheimer’s Disease)
Fried et al., 2017 (unpublished – DO NOT SHARE!)

Absolute inter-visit difference in iTBS by BDNF

$p = 0.035$
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

Eberhard-Karls-Universität Tübingen, Clinic of Psychiatry and Psychotherapy, Ostanderstrasse 24, 72076 Tübingen, Germany
Brief report
Prefrontal cortical blood flow predicts response of depression to rTMS

Nora Weiduschat a, Marc J. Dubin b,*

a Department of Radiology, Weill Cornell Medical College, New York, NY, United States
b Department of Psychiatry, Weill Cornell Medical College, 525 East 68th St, Box 140, New York, NY 10065, United States
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 Thal\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., 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
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°

**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

Left hemisphere

Right hemisphere
So... Now what?

What state-dependency?