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.
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

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
Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability
Variability in Cognitive Interventions

Spatial Accuracy

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).

**Fig. 2** Mean amplitude (±SE) of conditioned MEP at 2 and 10 ms ISI before and after rTMS in migraineurs and controls (values are expressed as percentage of changes from test stimulus alone).

Brighina et al., 2005 (Experimental Brain Research)
Writer’s Cramp (focal dystonia)

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)
Preconditioning rTMS with tDCS

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

Main experiment (n = 8)

MEP amplitude (% of baseline)

 TDCS to M1
 real rTMS

cathodal TDCS
 sham TDCS
 anodal TDCS

post TDCS
post rTMS 1
post rTMS 2

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

Takenobu Murakami, Florian Müller-Dahlhaus, Ming-Kuei Lu, and Ulf Ziemann
• So how much time between sessions?
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-Cabrè 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., (unpublished – 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 cancel out
  - Daily sessions → build up facilitation
Overview

- What is ‘state-dependency’?
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- 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

![Diagram showing pro-BDNF and 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
$p = 0.0537$
Effect size = 0.35

All subjects

$BDNF\ Val/Met & ApoE\ \varepsilon 3/\varepsilon 4$ excluded

$p = 0.0051^*$
Effect size = 0.52

Unpublished work – please do not share
Follow the Three (6) 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

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