State-Dependent Effects of Transcranial Magnetic Stimulation

“The cause of—and solution to—some of TMS’s variability”

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Overview

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

The basal or ongoing state of the brain influences the outcome of stimulation.
Paired-Pulse TMS

<table>
<thead>
<tr>
<th>Test pulse (alone)</th>
<th>Conditioning Pulse + Test Pulse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intracortical Inhibition (ISI = 1-6ms)</td>
</tr>
<tr>
<td></td>
<td>Intracortical Facilitation (ISI = 8-30ms)</td>
</tr>
</tbody>
</table>

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

Relative neural activity

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)
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”
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
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
Altered response to rTMS in disease

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 physiological activity

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

![Graph showing MEP amplitude (%Δ from baseline) over time relative to iTBS for Visit-A and Visit-B.]
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

tDCS

post

post

post

TDCS

rTMS 1

rTMS 2

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
Meta-plasticity: Impact of Cumulative Sessions

Impact of rTMS on Motor-Evoked Potentials

Impact of daily 1Hz rTMS on visuo-spatial detection

Maeda et al., 2000 (Clinical Neurophysiology)

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., 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

Impact of inter-visit duration on reproducibility of iTBS after-effects

Fried et al., 2017 (Frontiers in Aging Neuroscience)
Variability due to study parameters

Unpublished data – 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

Pro-BDNF to 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
(n=30)

$\text{OHC DM2}$

$p = 0.0051^*$
Effect size = 0.52

BDNF Val/Met & APOE4 excluded
(n=27)

Healthy Type-2 Diabetes

For full study, see Fried et al., 2016 (J Alzheimer's Disease)
Factors that affect reproducibility

Impact of BDNF polymorphism on reproducibility of iTBS after-effects

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

\[
\text{HbT change during first minute} \\
\text{MDTL at F3}
\]

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

\[
\Delta \text{HAM-D}
\]

\[
R = -0.82
\]

Weiduschat and Dubin, 2013 (J Affective Disorders)
Predicting Therapeutic Outcome: activity across networks

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

rCBF (SPECT)

Resting-state functional connectivity MRI

A
More Effective 5cm
Less Effective 5cm

D
Fitzgerald Target
Avg. 5cm Target

B

C
More Effective 5cm
Less Effective 5cm

E

F
Fitzgerald Target
Avg. 5cm Target

Subgenual Correlation (r)

P < 0.005

P < 5 x 10^-8

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°

**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?