An introduction to transcranial magnetic stimulation (TMS)

Methods in cognitive neuroscience
University of Hamburg, 2012

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There are many ways to stimulate the brain…

indirect stimulation through afferent inputs  
direct stimulation of the cortex
Outline: An introduction to TMS

1) Basics
   → Technical and physiological background
   → Stimulation parameters
   → Methods (site localization, control condition, risks)

2) Applications
   → Clinical diagnostic
   → Experimental: "virtual lesions"
   → Therapy

3) Combination with neuroimaging
   → offline fMRI: TMS after fMRI
   → offline fMRI: rTMS before fMRI
   → online fMRI: concurrent TMS/fMRI
It's all thanks to Mr. Faraday!

Electromagnetic induction

Silvanus P. Thompson trying to electromagnetically stimulating his brain in 1910
Transcranial magnetic stimulation

**Basics**

**Applications**

**TMS-fMRI**

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**Macroscopic response**
- muscle twitch (MEP)
  (visual cortex: phosphene)
- evoked neuronal activity (EEG)
- changes in blood flow/metabolism
  (PET, fMRI, SPECT, NIRS)
- changes in behavior

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**Microscopic response**

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**Intracranial field**
- skull
- precentral gyrus
- pyramidal axons

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**Magnetic field** $B$
**Electric field** $E$

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**Local depolarization**
**Axon membrane**

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**Intracranial field**
- skull
- precentral gyrus
- pyramidal axons
Electric field $\rightarrow$ transmembrane current $\rightarrow$ action potential

Nerve model

- local depolarization
- axon membrane
But the cortex is not a peripheral nerve!

(...and it's not a random structure)
Gyrification matters…

Crown

Wall

Sulcus

Basics

Applications

TMS-fMRI
Distance matters...

Basics
Applications
TMS-fMRI
Geometry of the coil matters…

Basics
Applications
TMS-fMRI
Angle and orientation of the coil matter...

**Angle of coil**

**Coil orientation**

Dubach et al. *Clin Neurophysiol* 2004
"Focal" TMS can induce systems effects

Basics
Applications
TMS-fMRI

orthodromic and antidromic excitation

+ "state"

stimulated cortex
connected cortical area
connected subcortical area
TMS paradigms

TMS protocols

online
  - single pulse
    - MEPs
      - phosphenes
      - chronometry
        - functional relevance
  - paired pulse
    - intracortical: inhibition/facilitation
    - dual-site: interconnected regions
  - repetitive: frequency \( \geq 5\text{Hz} \)
    - larger time window

offline
  - repetitive
    - standard
      - low-frequency \(~1\text{Hz}\)
      - high-frequency \(5-10\text{Hz}\)
    - intermittent (iTBS)
    - continuous (cTBS)
    - thetaburst (TBS)

Sandrini et al. Neurosci Biobehav Rev 2011
Inducing LTP- and LTD-like effects in human motor cortex:

(a) Repetitive TMS (rTMS)
- Low-frequency rTMS (~1 Hz)
- High-frequency rTMS (5 Hz)

(b) Theta-burst stimulation (TBS)
- Continuous TBS (40 s)
- Intermittent TBS every 10 s

Quartarone et al. *Trends Neurosci* 2006
Stimulation intensity

- intensity
  - fixed: % stimulator output
  - % individual threshold
    - phosphene threshold
      - stationary
      - moving
    - motor threshold
      - MEPs
        - rest: > 50µV
        - active: 150-200µV
      - visible movement
        - rest
        - active

Sandrini et al. *Neurosci Biobehav Rev* 2011
Magnitude and direction of TMS effects depend on:

- **internal factors**
- **external factors**

The relationship between these players cannot be predicted by a simple set of rules!
Localization of the TMS target site

- Functional (MEPs, phosphenes)
- "Hunting procedure"
- 10-20 EEG system
- Anatomical landmark (individual MRI)
- Probabilistic (Talairach/MNI coordin.)
- fMRI
- From similar study
- From meta-analysis
- Individual subject
- Group-based

Frameless stereotactic neuronavigation

Basics
Applications
TMS-fMRI

Sandrini et al. *Neurosci Biobehav Rev* 2011
Frameless stereotactic neuronavigation

- localize and track coil placement
Adverse effects and safety precautions

Sensory:

• sensation and loud clicking sound when coil discharges (mechanical deformation)
• sensation due to stimulation of cranial or peripheral nerves

Risks:

• rarely epileptic seizures (particularly with rTMS)
• contraindications: elevated risk for epileptic seizures, pregnancy, electric implants, ferromagnetic intracranial metal particles

→ if proposed safety guidelines with respect to stimulus parameters are followed, risks for seizures are very low (Wassermann *Electroencephalogr Clin Neurophysiol* 1998, Rossi et al. *Clin Neurophysiol* 2009)
What's the appropriate control condition?

• before/after TMS, no TMS

• sham TMS:
  – placebo coil
  – placebo device inducing scalp sensations
  – charging coil tilted 90°, placed upon non-charging coil

• TMS to control region
  – vertex
  – homologous region
  – different regions

• control tasks or conditions within task

→ blinding the investigator and subject is difficult!
Glossary

• **TMS**: transcranial magnetic stimulation
• **rTMS**: repetitive TMS
• **paired-pulse TMS**: a conditioning TMS pulse precedes a test TMS pulse
• **TBS**: theta burst stimulation
• **TDCS**: transcranial direct current stimulation

• **RMT**: resting motor threshold
• **AMT**: active motor threshold

• **FDI**: first interosseus muscle
• **MEP**: motor evoked potential
• **phosphene**: "light flash", perception of light induced by TMS
• **CMCT**: central motor conduction time
• **PMCT**: peripheral motor conduction time
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   → Methods (site localization, control condition, risks)

2) Applications
   → Clinical diagnostic
   → Experimental: "virtual lesions"
   → Therapy

3) Combination with neuroimaging
   → offline: TMS after fMRI
   → offline: rTMS before fMRI
   → online: concurrent TMS/fMRI
Clinical diagnosis and prognosis

- motor threshold
- motor evoked potentials (MEPs)
- central motor conduction time (CMCT)
- cortical silent period
- paired-pulse TMS (intra-cortical inhibition/facilitation, inter-hemispheric interactions)
- visual cortex: phosphenes, masking
- intra-operative monitoring and intensive care
Example: central motor conduction time

**Basics**

- **Applications**
- **TMS-fMRI**

**CMCT**

- anterior spinal horn
- muscle

**PMCT**

- spinal α-motoneuron

**MEP**

**PMCT = (F + M -1) / 2**
## Diagnostic applications of TMS

<table>
<thead>
<tr>
<th>TMS measure</th>
<th>Abnormal findings</th>
<th>Diseases and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMCT&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Long</td>
<td>MS,&lt;sup&gt;23&lt;/sup&gt; ALS, stroke,&lt;sup&gt;23&lt;/sup&gt; secondary parkinsonism,&lt;sup&gt;22&lt;/sup&gt; secondary dystonia,&lt;sup&gt;22&lt;/sup&gt; brain injury, SCI or CS&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>MEP&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Dispersed</td>
<td>MS, stroke&lt;sup&gt;24&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Small or absent</td>
<td>MS, ALS, stroke,&lt;sup&gt;19,21&lt;/sup&gt; brain injury, SCI or CS,&lt;sup&gt;23&lt;/sup&gt; hydrocephalus, Bell’s palsy&lt;sup&gt;25&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>Parkinson’s disease, dystonia&lt;sup&gt;26,27,28&lt;/sup&gt;</td>
</tr>
<tr>
<td>MEP with triple stimulation technique&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Central conduction failure&lt;sup&gt;*&lt;/sup&gt;</td>
<td>MS, ALS (with upper-neuron damage), stroke, secondary parkinsonism, brain injury, SCI or CS, hydrocephalus</td>
</tr>
<tr>
<td>Silent period&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Long</td>
<td>MS, stroke†,&lt;sup&gt;31&lt;/sup&gt; brain injury,&lt;sup&gt;32&lt;/sup&gt; SCI or CS, polyradiculitis, demyelinating polyneuropathy,&lt;sup&gt;33&lt;/sup&gt; epilepsy&lt;sup&gt;24&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Short</td>
<td>ALS, Parkinson’s disease,&lt;sup&gt;22,36&lt;/sup&gt; dystonia,&lt;sup&gt;26,27&lt;/sup&gt; agenesis of corpus callosum</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>SCI or CS&lt;sup&gt;36&lt;/sup&gt;</td>
</tr>
<tr>
<td>Interhemispheric conduction&lt;sup&gt;37,28&lt;/sup&gt;</td>
<td>Long latency&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>MS, stroke, brain injury (with transcallosal lesion), dysgenesis of corpus callosum, hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>Reduced interhemispheric inhibition</td>
<td>MS, ALS&lt;sup&gt;29,40&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Interhemispheric inhibition absent</td>
<td>Stroke (with transcallosal lesion), dysgenesis of the corpus callosum, hydrocephalus</td>
</tr>
<tr>
<td>Motor cortex excitability</td>
<td>High motor threshold&lt;sup&gt;§&lt;/sup&gt;&lt;sup&gt;39,41,42&lt;/sup&gt;</td>
<td>MS, stroke, agenesis of corpus callosum, brain injury, spinal cord injury, CS, ALS,&lt;sup&gt;25&lt;/sup&gt; hydrocephalus,&lt;sup&gt;44&lt;/sup&gt; epilepsy&lt;sup&gt;45&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Low motor threshold§</td>
<td>Early-stage ALS&lt;sup&gt;46,47,48&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Increased intracortical inhibition</td>
<td>Parkinson’s disease,&lt;sup&gt;26,40,50&lt;/sup&gt; SCI or CS, epilepsy</td>
</tr>
<tr>
<td></td>
<td>Decreased intracortical inhibition</td>
<td>Dystonia&lt;sup&gt;29,28&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Enlarged cortical representation</td>
<td>Dystonia&lt;sup&gt;29,28&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CMCT = central motor conduction time; MS = multiple sclerosis; ALS = amyotrophic lateral sclerosis; SCI = spinal cord injury; CS = cervical spondylosis; MEP = motor evoked potential. 
*Central conduction failure indicates smaller size of the test MEP than that of control examined by TST. †Prolonged duration with normal MEP and CMCT may be observed in the motor syndrome with exaggerated inhibition within the motor cortex, resembling motor neglect. ‡The latency for transcallosal inhibition (ipsilateral silent period) following single-pulse TMS (figure 4). §High or low value of the motor threshold indicates that they are higher or lower compared with intact hemisphere or normal individuals.

Kobayashi & Pascual-Leone Lancet 2003
Experimental

• disturb/enhance task performance → causal relevance of brain regions
• localization of involved regions
• cortical mapping
• functional specialization of different brain regions
• functional lateralization of cognitive processes
• interactions between different brain regions involved in a cognitive function
• chronometry
• probe interregional connectivity

…
Example virtual lesion: suppression of visual perception

V1-V5 interactions in motion perception

- Fast back projections from V5 to V1 necessary for motion awareness
- V1 activity gates awareness for motion

Basics
- V5 suprathr.
- V1 suprathr.

Applications
- V5 - V1

TMS-fMRI
- Silvanto et al. Nat Neurosci 2005
- Pascual-Leone & Walsh Science 2001
Role of PMv in tool processing

left ventral premotor cortex (PMv) selective for the category "tools"  Lewis Neuroscientist 2006

→ causal role in semantic tool processing?

Cattaneo et al. Neuroimage 2010
Role of PMv in tool processing

Cattaneo et al. *Neuroimage* 2010
Therapy (repetitive TMS)

- stroke
- epilepsy
- movement disorders
- tinnitus
- pain
- depression
- other psychiatric (schizophrenia, panic disorder, PTSD, obsessive-compulsive disorder)

→ rTMS is unlikely to restore function to specific sets of synaptic connections that are affected by disease or injury because TMS is non-specific in its action on populations of neurons

→ but it can interact with normal processes of brain plasticity that accompany damage or chronic disease

Ridding & Rothwell Nat Rev Neurosci 2007
## Treatment of depression

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Number of studies included</th>
<th>rTMS approach</th>
<th>Outcome measure</th>
<th>Analysis conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Couturier²</td>
<td>6</td>
<td>Randomized sham-controlled trials using LDLPFC rTMS</td>
<td>Change in HAM-D</td>
<td>Suggests rTMS no better than sham</td>
</tr>
<tr>
<td>Martin et al.³</td>
<td>14</td>
<td>Most (13 out of 14 studies) used high frequency LDLPFC and sham control</td>
<td>Change in HAM-D (in all studies) and BDI (7 studies)</td>
<td>Real rTMS significantly greater effect than sham on HAM-D when applied for 2 weeks (but not 1 week) No significant difference for BDI</td>
</tr>
<tr>
<td>Kozel and George⁴</td>
<td>12</td>
<td>Randomized sham-controlled trials involving LDLPFC rTMS</td>
<td>Change in HAM-D</td>
<td>Real rTMS led to small but significantly greater effect than sham</td>
</tr>
<tr>
<td>Burt et al.⁵</td>
<td>16</td>
<td>Randomized controlled (sham or other control) trials predominantly involving LDLPFC/RDLPFC*</td>
<td>Change in HAM-D</td>
<td>Real rTMS significantly better than sham Improvement in HAM-D of ~20% Doubtful clinical significance</td>
</tr>
<tr>
<td>Holtzheimer et al.⁴⁵</td>
<td>12</td>
<td>Most (11/12) used LDLPFC and sham control</td>
<td>Change in HAM-D</td>
<td>Real rTMS significantly better than sham However, clinical significance considered only modest</td>
</tr>
</tbody>
</table>

Ridding & Rothwell Nat Rev Neurosci 2007
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Methods in neuroscience

Interventional protocols vs. Neuroimaging

**Interventional protocols**
- **causal**
  - ECT
  - tDCS
  - cooling
  - offline rTMS
  - online TMS
  - TES
  - DBS

**Neuroimaging**
- **correlational**
  - EEG
  - MEG
  - NIRS
  - fMRI
  - MRS
  - PET
  - SPECT
  - CT
  - sMRI

**Time scales**
- **milliseconds** to **days**

Siebner et al. *Brain Stimul* 2009
Brain imaging vs. brain stimulation

**Functional brain imaging** benefits from brain stimulation
- EEG, MEG, fMRI, PET…
- spatial extent and temporal profile of brain activation during task
- "correlative nature"
→ causal importance of a regional brain activation for behavior?

**Brain stimulation** benefits from functional brain imaging
- TMS (single pulse, repetitive, TBS…), TDCS…
- interventional
- causal inferences of stimulated cortex to a specific brain function
→ interaction of non-physiological mode of brain stimulation with intrinsic neuronal activity in the human brain?
→ mapping the acute and conditioning effects of TMS on brain function
→ optimal site/timing for TMS (in individual subjects or at the group level)
Functional brain imaging with fMRI

- magnetic properties of hemoglobin change in relation of its degree of oxygenation

→ using a strong magnet (1.5-7 Tesla) (MR-Scanner) and radio wave emitter and receiver (coils), this so-called blood-oxygenation-level-dependent (BOLD) contrast can be measured

- BOLD signal is tightly coupled to cerebral blood flow, neuronal activity, and energy use (for review see Logothetis Nature 2008)
TMS-fMRI combination approaches

"Online" approach:
concurrent TMS/fMRI: "perturb-and-measure"

"Offline" approach:
TMS after fMRI: "map-and-perturb"
rTMS before fMRI: "condition-and-map"

no methodological challenges as TMS and fMRI can be separated in time and space

- is the identified region functionally relevant for task?
- functional localization of TMS-target region
TMS after fMRI: Example I

- V1 is activated during Braille reading in blind subjects

  - shown with fMRI
  (Sadato et al. *Neurology Suppl 4* 1995)

  - shown with PET
  (Sadato et al. *Nature* 1996)

- V1 activation functionally relevant for Braille reading? (Cohen et al. *Nature* 1997)
1. Functional localization of hMT/V5 with fMRI

2. fMRI-neuronavigated TMS: critical time window of hMT/V5 contribution to motion perception?

Sack et al. *Neuroimage* 2005
rTMS before fMRI: "condition-and-map"

→ no methodological challenges as TMS and fMRI can be separated in time and space

• reorganization of functional networks

• map short-term plasticity on the systems level
rTMS can induce brain plasticity

- repetitive TMS (rTMS): prolonged trains of stimuli

- conditioning effects beyond the time of stimulation (can last up to 1h, e.g. Siebner et al. *Brain* 2003)

- magnitude and direction of rTMS-induced plasticity depend on:
  - **extrinsic factors** (i.e., the variables of stimulation): intensity, frequency, total number of stimuli
  - **intrinsic factors** (i.e., target region and its functional state)

- conditioning effects not limited to the stimulated cortex but give rise to functional changes in interconnected cortical /subcortical areas

- fMRI can be used to map plasticity within a distributed functional network induced by rTMS

for review see Siebner & Rothwell *Exp Brain Res* 2003
Example:
Reorganization of action selection networks

O'Shea et al. *Neuron* 2007
Reorganization of action selection networks

O’Shea et al. *Neuron* 2007
Reorganization of action selection networks

O’Shea et al. Neuron 2007
Concurrent TMS/fMRI: "perturb-and-measure"

→ methodologically demanding

• map immediate effects of TMS
• map neuronal correlates of a TMS-induced lesion effect
• probe regional response and inter-regional connectivity
Concurrent TMS-fMRI: technical issues

- **Static artifacts**
  - TMS coil: no single ferromagnetic particle, high mechanic stability, fit into MRI head coil
  - TMS stimulator: outside the MR scanner room (long cable to connect TMS coil, up to 8 m) or radiofrequency-shielded
  - image distortions due to presence of TMS coil

- **Dynamic artifacts**
  - radiofrequency (RF) noise by TMS stimulator, antenna-like properties of TMS coil
  - leakage currents
  - TMS pulses distort MRI magnetic field strength

→ temporal gaps between TMS pulses and fMRI image acquisition (interleaved TMS/fMRI)

For review see Siebner et al. *Brain Stimul* 2009

Bestmann et al. *Eur J Neurosci* 2004
Concurrent TMS-fMRI: technical issues

Example of TMS pulse – fMRI image acquisition synchronization

Bestmann et al. Neuropsychol 2006
Example: Context dependent modulation of interhemispheric connectivity

Experimental setup and main effects of grip task

Bestmann et al. *Cereb Cortex* 2007
Summary TMS-fMRI

Offline: TMS after fMRI
- test causal contribution of identified area
- subject-specific functional localization of TMS target area

Offline: rTMS before fMRI
- map changeability of functional systems
- but: direct spreading of TMS effect vs. compensatory activations?

Online: concurrent TMS/fMRI
- map interaction of brain stimulation with intrinsic neuronal activity of the brain
- map neuronal correlates of TMS-induced effects on task behavior
- but: methodologically challenging

➔ pro fMRI: spatial resolution (vs. EEG, PET), mapping on a systems level
➔ con fMRI: temporal resolution (vs. EEG), indirect measure of neuronal activity
TMS and other neuroimaging methods

PET

- similar as with fMRI, here effects of TMS on cerebral blood flow or synaptic activity
- offline (TMS before/after PET), online (concurrent TMS/PET)
- concurrent TMS/PET technically easier to establish than with fMRI
- **but:** spatial resolution lower than with fMRI
- **but:** radiation

EEG/MEG

- map effects of TMS on neuronal activity, direct measure of neuronal activity
- map TMS-induced oscillations
- offline (TMS before/after EEG/MEG), online (concurrent TMS/EEG)
- EEG before TMS: info about optimal TMS pulse timing
- concurrent EEG/TMS: neuronal state-guided TMS
- **but:** low spatial resolution (vs. fMRI, PET), deep brain structures
- **but:** susceptible to TMS-induced artifacts as muscle interference and eye blinks

For review see Siebner et al. *Brain Stimul* 2009
Summary

- TMS is a non-invasive, pain-free method to directly stimulate the cortex
- Inductive (electro-magneto-electric) stimulation of neuronal axons
- "virtual lesions" \(\rightarrow\) test causal contribution of brain area
- Repetitive protocols can induce effects beyond the time of stimulation \(\rightarrow\) probe short term plasticity of functional networks
- Effects depend on internal and external factors
- Only superficial cortical areas can be stimulated \(\rightarrow\) but effects are not restricted to stimulated area (remote effects)
- TMS can profit from neuroimaging
- Neuroimaging can profit from TMS
- Temporal relation between TMS and neuroimaging defines scientific application
Further reading I

Books:


Review articles:

General:

Further reading II

Review articles (continuing):

Combination with neuroimaging:

Clinical focus:
Further reading III

Review articles (continuing):

Physiology:


Safety: