Transcranial Magnetic Stimulation

Session 4 – Virtual Lesion Approach I

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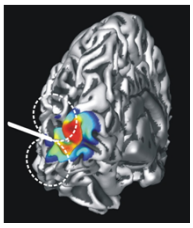


Today's Schedule

Virtual Lesion Approach : Study Design

- Rationale
- Measurements
- Temporal modes
- Spatial modes
- Coil placement
- Stimulation intensity
- Control conditions

Virtual Lesion Approach: Overview

Virtual lesion (*Walsh & Rushworth, 1999*):
Mimic a brain lesion temporarily in a circumscribed area without cortical re-organization.

Use TMS pulses to interfere temporarily with the neural processing in the stimulated area while the subject is performing a behavioral task.

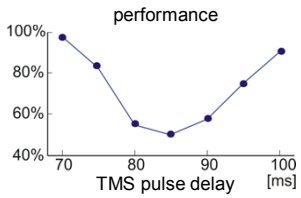
Effects of TMS on reaction times or error rate indicate that the stimulated area is crucially involved in the task.

With the virtual lesion approach, TMS is a tool for neuroscience which allows to disentangle the necessity of brain regions for a specific task compared to the mere involvement of it (causality vs. correlation). Furthermore, this methodology can be used to measure the chronometry of neural information processing.

Measurements

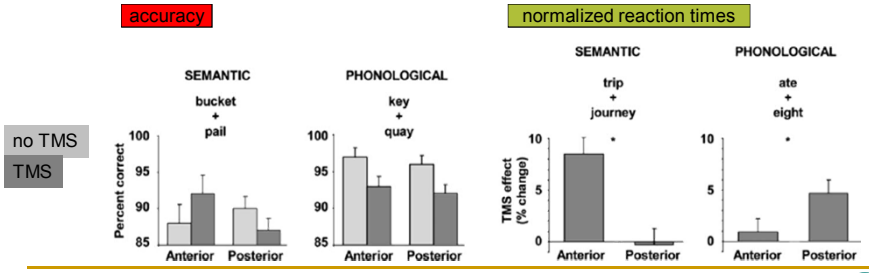
Error rates

- Mainly used in early areas, e.g. visual suppression



Reaction times

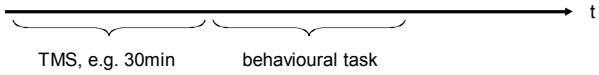
- Mainly used in higher areas
- Error rates are often not sensitive enough, e.g. *Gough et al, 2005*:
  semantic and phonological processing in the LIFC, stimulation at 2 brain sites



Temporal Modes

Repetitive TMS

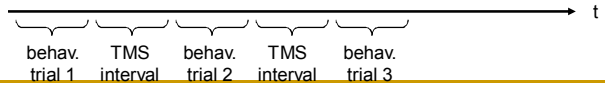
- Deliver TMS stimulation for several minutes (e.g. up to 30min) (see also rTMS in M1)
  - low frequency (1-3 Hz) ➔ decrease in cortical activity (lasts 3-30 minutes)
  - sometimes: high frequency (> 5Hz) ➔ increase in cortical activity



- Pre-post design (blocked)
  with all pitfalls of a pre-post design (time-, learning-, attention effects, fatigue, etc.)
- Sham/verum-post design (blocked)

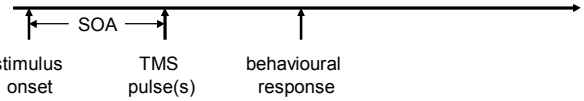
„Interleaved" TMS (*Campana et al, 2002*)

- Investigate consolidation of events, priming, or short-term memory

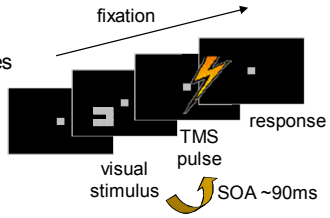


Temporal Modes

Online methods



- Single pulse
  - Delivers precise chronometry of brain processes
  - Works well in early brain areas
    e.g. visual suppression (*Amassian et al, 1989*)



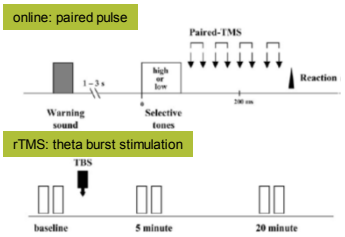
- Burst / train
  - Typical interstimulus interval (ISI): 50-100ms
  - Often needed in higher brain areas
    e.g. disturbance of language (e.g. *Gough et al, 2005*: 3 stimuli / trial)
  - Good technique to start with a new paradigm

Temporal Modes – Comparison (*Mochizuki et al, 2005*)

direct comparison of two protocols: role of dorsal premotor area in reaction task

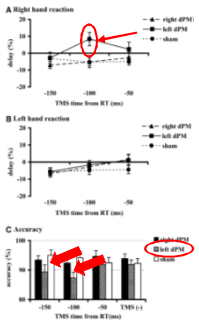
task: contract left or right hand as fast as possible dependent on pitch of a tone

online: paired pulse



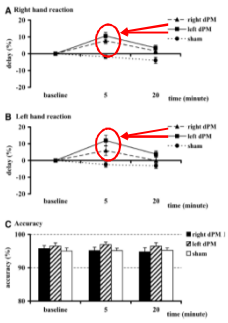
rTMS: theta burst stimulation

online: paired pulse



TMS over left dPM:
↗ RT of right hand
↗ error rate

rTMS: theta burst stimulation



TMS over either dPM:
↗ RT of both hands
no effect on error rate

Temporal Modes – Comparison

Conclusion from *Mochizuki et al, 2005*:

Online methods

➔ When is the function of a cortical area essential for a behavioural task?

Repetitive TMS

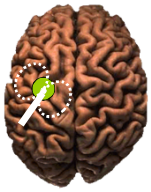
- Widespread changes in activity
- More complex effects on behaviour

➔ Hypothesis: give insight into changes that might occur after brain injury

Repetitive TMS	**Online methods**
+ no direct interference from TMS pulse (startle, coil click, muscle twitch)	+ high temporal resolution
- no temporal resolution	- possible interference from TMS side effects (startle, coil click, muscle twitch)

Spatial Modes

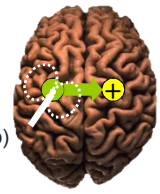
Disrupt function at site of stimulation



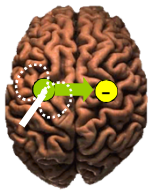
Induce noise in a secondary site by

disinhibiting the site (a)

disrupting pre-processes to this site (b)

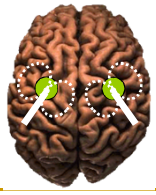


a: inhibitory connection



b: downstream area

Investigate timing of interaction between two areas



Spatial Modes – Some Remarks

Most commonly it is assumed that the function at site of stimulation is disrupted.
This approach needs a hypothesis based on anatomy.

Think of possible effects from secondary sites when observing „strange“ effects.

Interleaved TMS/fMRI as tool to disentangle TMS effect on different brain sites.

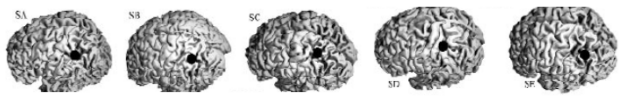
Beware of rash conclusions when observing improvement of function!
Alternative explanations can be

- Motor facilitation
- Intersensory facilitation (coil click, somatosensory stimulation)

Coil Placement

Relative to "hand knob" or inion

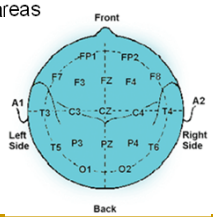
- e.g. *Desmurget et al, 1999:* 4.5cm caudal and 0.5cm medial from „hand knob" (determined with TMS) to reach the posterior parietal cortex (PPC)



- e.g. *Amassian et al, 1989:* round coil placed at the midline with lower edge approximately 2cm above the inion to reach early visual areas

International 10-20 EEG system

- F3 and F4 ➔ dorsolateral prefrontal cortex
- P3 and P4 ➔ around the intraparietal sulcus
- Interindividual precision about 2cm (*Herwig et al, 2003*)



Coil Placement

TMS localizer

- Using a „hunting procedure" (*Ashbridge et al, 1997*), like „hotspot" search in M1
- Use same task as in the experiment (e.g. visual suppression)
- Use a special „localizer task"
  - e.g. a visual search paradigm to identify the right PPC for a spatial neglect study (*Bjoertomt et al, 2002*)
  - e.g. moving phosphenes to identify hMT/V5+

Pitfalls of a special „localizer task"

- Localizer task might work not in all subjects (e.g. moving phosphenes can be elicited only in a small number of participants (*Pascual-Leone & Walsh, 2001*))
- Location criterion might not be specific for the intended region (e.g. moving phosphenes can also result from stimulation at other cortical sites (*Fernandez et al, 2002*)

Coil Placement

trackable spheres on coil and subject

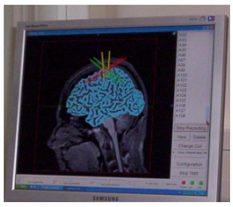
IR tracking cameras

Neuronavigation

- „Gold standard“
- Precision 2-3mm
- Anatomical MR scan: individual anatomy
- Initial referencing procedure is crucial for precision

Possibilities to determine stimulation site

- Individual anatomical landmarks
- fMRI localizer: individual functional anatomy
- TMS localizer



neuronavigation software, e.g. BrainView

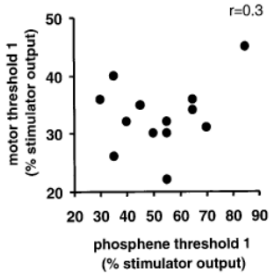
Stimulation Intensity

Problem: Magnetic field strength depends on stimulator + coil combination.
➔ no standard measurement available

intensity often used for visual areas: x% of individual‘s phosphene threshold
intensity most often used for higher areas: x% of individual‘s rMT

BUT: within subject‘s the excitability of brain areas is quite variable: no correlation between motor and phosphene threshold (*Stewart et al, 2001*)

The same intensity may as well be used for all subjects.



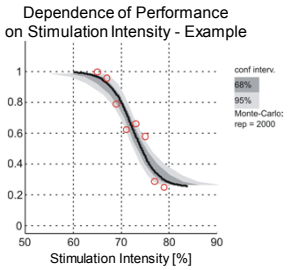
Stimulation Intensity

Alternative ways to determine the stimulation intensity

Rationale:
The higher the intensity the bigger the effect
BUT also possible side effects and the discomfort for the subject.

Mapping of performance to stimulation intensity

- high efford, paradigm has to be known well
- advantage: intensity can be adjusted well to fit a desired performance level



Use highest possible intensity without side effects

- avoid M1 stimulation if task is motor related

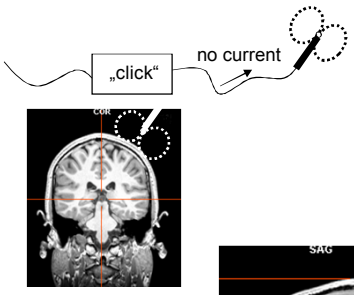
Control Conditions

Control for „general“ or unwanted TMS effects!

Sham stimulation

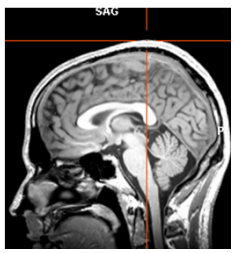
- sham coil: only „click“, no current
- normal coil perpendicular to skull
- drawback: no peripheral stimulation

!!! use of control sites (see below) is sometimes also called „sham stimulation“ !!!



Vertex stimulation

- vertex: most superior point of the skull (CZ)
- some peripheral stimulation with small brain stimulation
- drawback: less uncomfortable / disturbing



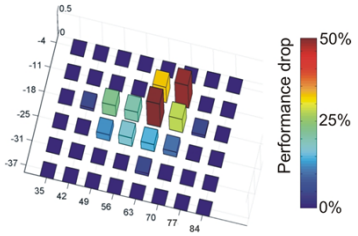
Control Conditions

Stimulation of contralateral hemisphere

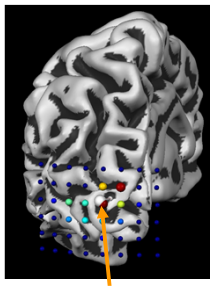
- feasibility depends on the kind of task (lateralization)
  e.g. usable for early visual areas, or language studies
- controls for TMS discomfort

Stimulation of adjacent sites / grid / mapping

- gain spatial resolution



example: visual suppression mapping

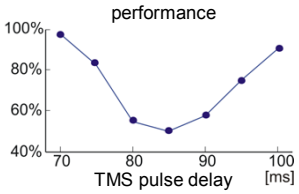


center of mass (CoM)

Control Conditions

Timing

- also stimulate at earlier or later timepoints
- unrecognizable for the subject
  (if the timepoints are not too distant!)
- needs precise timing but also delivers chronometry



Control task

- both tasks have to be matched in difficulty
- e.g. *Ellison et al, 2007*: visual search conjunction paradigms - colour/orientation vs. motion/orientation
- e.g. *Gough et al, 2005*: semantic vs. phonological task

- in combination with stimulation at two different sites allows for double dissociation of the task specific processes and the tested brain sites

brain sites used by *Gough et al, 2005*