Week 1 TMS: Transcranial Magnetic Stimulation

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- **Learning outcomes**

- What is TMS? An overview on how it works and what it can be used for
- Using TMS for Biological Psychology research
  - The injection of "neural noise" approach using single-pulse TMS (Amassian et al., 1989; Amassian et al., 1993)
  - The "virtual lesion" approach using repetitive TMS
  - The "probing excitability" approach using single-pulse TMS (Eisenegger et al., 2007; Bode et al., 2007)
  - The "probing information transfer" approach using paired-pulse TMS (Fitzgerald et al., 2001)
- Clinical applications

- **History: before & after TMS**

- **Before (neuroimaging techniques)**: studies on patients with **real lesions** have informed on the relationship between cognition & the brain
  a. ***Phineas Gage***: damage to frontal cortex → some cognition lost, personality changes, aggressive behaviour
     - Led to the realisation that via switching off a brain region → something very specific changes
     - Significance: can study which cognitive function is not working
  b. ***Patient H.M.***: severe **antero**grade amnesia after hippocampus, para-hippocampal gyrus & amygdala removal
  c. ***Lesion studies in Broca & Wernicke areas***: link to impairments of **speech production & language comprehension** respectively
  - Issues
    - Circumscribed lesions are **rare**: may not be enough to study all cognitive functions
    - Lesions in single specialised areas are **rare**: often ≥ 1 region is impacted on in brain disorders
    - Brain plasticity & recovery may compensate for lesions → patients become 'special' over time
- **After: development of neuroimaging**
  a. ***Fritsch & Hitzig (1870)***: the first to **electrically stimulate** the cortex of animals
  b. ***D'Arsonval (1896)***: discovered the **magnetic stimulation** of visual cortex can elicit **phosphenes** (the sensation of seeing stars)
  c. ***Magnusson & Stevens (1911)***: developed the first head coil covering the entire head, which resulted in **entire brain stimulation**

- **Definition & mechanisms**

- **Transcranial Magnetic Stimulation/TMS**: **NON-invasive** technique used to create **virtual cortical lesions**; analyses **what function** & **which region** is impaired when the pulses are applied to that particular brain region (usually a few cm of the cortex; **CAN'T** reach deep brain structures)
  - **Lesions**: temporary, reversible & **localised** - for a brief moment the targeted region will not work as well as it normally does
- Use: applied externally by placing a **coil** on the scalp
- Mechanism: the coil produces a rapidly changing magnetic field → induces **electrical currents** in the brain
  - Normally: APs are generated at neuron membrane via depolarisation → spreads to the next neuron's dendrites
  - Currents can **depolarise** the neurons in a small circumscribed (restricted) area of the cortex
  - This causes **random** neuron firing & **increases** the level of **neural noise** → **masks** the correctly firing neurons, leading to the '**virtual-lesion effect**'
- **Current technique**: developed by Barker, Jalinous, & Freestone (1985)
  - To create the current pulse & generate the magnetic field, a capacitor is charged up & then rapidly discharged
  - Advantages: **painless** - due to very localised magnetic field (cf. entire brain) & the specific build-up in the small coil
- **Coils**: vary in **types** & **precision of stimulation generated**
  - **Figure-8 coil**: the most common coil for **rTMS**
    - **Strongest** stimulation in the **centre** & generates magnetic fields which create offset current loops that circulate in opposite directions; strongest effect in centre within radius 3-4mm
    - Results in a **more focal area** of the **cortex** that is stimulated compared to the round coil (has a diffuse area of stimulation)
    - Advantage: gives the researcher has a clear idea of which part of the cortex was affected

- **Charging & discharging process** can be modified to create different sequences of pulses

a. **Repetitive/rTMS**: creates **fast sequences** of multiple pulses; measures **whether & how long (duration)** a function is impaired for
   - 1 single pulse is usually **NOT** enough to create a strong magnetic field for stimulation
   - Rapid **loading times** ~100-200μs & short **durations** <1 ms

b. **Single-pulse TMS**: can inform the **exact timepoint** of functional impairment
   - Exclusive for testing **causal** involvement: if a TMS pulse to a specific region of the cortex disrupts a cognitive function
     - Impossible on other neuroimaging techniques which rely on correlations
   - Method: interferes with the process of interest at the exact time window where the region is required; via **inducing neural noise**
     - These regions **DO NOT stop working** completely, but the neural noise interferes with normal functioning
     - e.g., delayed movements, disrupted visual processing

- **Current studies with TMS**

1. The injection of "**neural noise**" approach: used **single-pulse** TMS to disrupt **cognitive processing**

a. **Amassian et al. (1989)**
   - Method & findings: used 3 alphabetical letters as stimuli under difficult viewing conditions; applied TMS to the primary visual cortex (lower back of the brain; ~2cm above inion); investigated the effects on **visual perception**
     - Varied the **time interval** between visual stimulation & **time of TMS stimulation** → TMS stimulation affected **visual cortex processing** after a critical period of **40-120 ms** after visual stimulation
     - TMS stimulation site was shifted from **L to R** (**horizontal** display) → letter perception in the **contralateral** visual field was impaired
     - TMS stimulation was shifted from **top to bottom** (letters displayed **vertically**) →
       - □ Stimulation above the reference line suppressed letters at the bottom; letters above the centre **could be seen**
       - □ Stimulation below the reference was **NOT possible**: due to the **bone** being in the way

b. **Amassian et al. (1993)**: used **single**-pulse TMS to investigate if a visual mask can **itself be 'masked'**
   - **Masking**: a mask stimulus is immediately shown after stimulus to **suppress perception** of the briefly presented stimulus
   - Mechanism: TMS on the primary **visual** cortex can be used to **disrupt processing** of stimuli
     - Could also potentially disrupt the processing of the mask
     - Thus, this prevents the original visual stimulus from being suppressed → **un**masking
   - Process: present target (3 letters) → mask (3 different letters) → MC stimulus
     - Stimulus onset asynchrony = 100ms
     - Delay for MC suppression of mask = 100ms
   - Findings: NO TMS - at 100 ms **SOA/Stimulus-Onset Asynchrony** (duration between the start of 2 stimuli), detection rate of the original stimulus was 37%; **WITH** TMS - detection rate **increases** to 90%
     - Unmasking: found between **60-140 ms** stimulation after the mask - all the original stimulus target letters were correctly named
   - Conclusion: TMS allows for mapping processes at the neural level, informing us about the **time-course** of processing

2. The "**virtual lesion**" approach: uses **rTMS** to **disrupt/enhance** cognitive processing

- **Steward & Walsh (2006)**: used rTMS to **inhibit** cognitive functions for **longer periods of time**
  - Can then measure **whether & for how long** a particular cognitive task is impaired (cf. single TMS - the exact timepoint)
  - Usually a slowing of function (cf. total loss/disruption)
- There are **strict guidelines** for using rTMS: (not in the 2021 curriculum) must be **< motor threshold**
  - First have to determine how thick the skull is so there is a motor threshold first
  - There are 2 brain regions where TMS effects are immediately visible: the primary visual & motor cortex
  - If you stimulate it multiple times & those that show hand twitching a little, this is a suitable stimulation strength as the stimulation causes neurons in the motor cortex to fire

3. The "**probing excitability**" approach: uses **single**-pulse TMS to test **how responsive/"excitable"** the motor cortex is during a cognitive task
   - Mechanism: if the motor cortex is required for a cognitive task, then it should *already* be activated when TMS is delivered
     - i.e., to measure **how strongly** the motor cortex "reacts" to the pulse (cf. disrupting cognitive functions & measuring the effect of TMS)
   - Method: excitability of M1 is measured by motor evoked potentials/**MEPs** (e- activity of muscles) with

electromyogram/EMG
    - Can then measure MEPs for each stimulation & compare **average** MEPs between experimental conditions

a. **Eisenegger et al., (2007)**: is the **M1** involved in the **mental rotation** of objects?
    - Background: some neuroimaging studies found M1 activation during MR – odd as nothing is 'really' rotated!
    - Method: used MEPs of the right hand & single-pulse TMS; delivered pulses on the left M1
    - Finding: **highest** stimulation of M1/strongest MEPs during **mental rotation** cf. baseline, reading aloud/silently → M1 might be already activated → thus "involved" in this cognitive process
b. **Bode et al., (2007)**: does the involvement of M1 in **mental rotation** depend on **strategy/what we rotate**?
    - Background: some objects can easily be mentally rotated by hand (e.g., tools) while others can't (e.g., buildings)
    - Method: TMS delivered at random times during different tasks to see if MEPs were higher than baseline &/other conditions
    - Findings: MEPs were **equally high** for mental rotation of **all different stimuli** → **strategy** may **NOT** play a role
        - Also slightly ***lower*** MEPs evoked by MR of hands
    - Debate: may be due to spill-over effects - **CANNOT** reveal if M1 was only more excitable because adjacent & interconnected regions (e.g., SMA) were activated

4. The "**probing information transfer**" approach: used **paired-pulse** TMS to test the **built-up** effect of 2 pulses
    - i.e., how strongly the 1st pulse **influences the effect** of the 2nd
    - Method: **paired-pulse** TMS in a brief succession - 1st is usually **sub**-threshold, the 2nd one is **supra**-threshold
    - Mechanism: if there is a modification, then these 2 regions probably communicate → produce an **add-up** effect

- **Fitzgerald et al. (2003)**: schizophrenia ↔ deficits in **motor inhibition**
    - Background: abnormalities in **inhibition of motor cortex activity** in schizophrenia patients - typically ↓ Cortical Silence Period/CSP (period of suppression of tonic motor activity that follows descending excitatory activity)
        - Normal people can **down-regulate** any activity still in the motor cortex
        - Schizophrenics build up this activation that lingers around for longer
    - Method: produced excitatory activity by a 1st TMS stimulus to the L motor cortex; measured the excitability by assessing the effect of a 2nd pulse (via MEPs)
    - Finding: schizophrenia patients with/out medication showed **stronger responses** to the **2nd pulse** → deficits in **motor inhibition**; medication > no medication > control

Clinical applications

- TMS is an approved treatment of **depression**; potentially for other mental disorders
    - Typically as the **last resort** due to mixed evidence for its efficacy, but increasingly accepted owing to + effects on patients
- Method: normally, 1 brain hemisphere is stimulated over the **prefrontal** cortex
- Mechanism: in depression, there is an **imbalance** of prefrontal activity between hemispheres
    - TMS can be used to **increase activity** of the *weaker* hemisphere

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Readings

Eisenegger et al., (2007): The involvement of M1 in mental rotation revealed by TMS

- **Introduction & findings**: used single-pulse TMS of the left hand M1 & motor evoked potentials of the contralateral right abductor pollicis brevis to probe motor cortex excitability during a standard mental rotation task; 2 hypotheses were tested
    a. Is the hand motor cortex activated **more strongly** during mental rotation than during reading aloud/silently?
    - Reading aloud/silently has been shown to **increases** motor cortex excitability substantially in recent studies
    - Issue: incl. no control of **cognitive functions** (e.g., verbal strategies)
    - Method: use reading aloud/silently as controls
    - Finding: activation in M1 in mental rotation tasks → mental rotation & the associated cognitive operations are the processes facilitating motor cortex activation, **NOT** perception of 3D-objects per se; significantly ↑ M1 activation during mental rotation > controls
    b. Is the recruitment of M1 for mental rotation specific for the judgement of **rotated** (but NOT for **nonrotated** Shepard & Metzler figures)?
    - Issue: no **direct indication** of M1's involvement (other factors, e.g., motor preparation & execution)
        - M1 activated during mental rotation mainly when mental rotation is accompanied by **button presses**/explicit answering and not during mental rotation task processing (e.g., Windischberger et al., 2003a, 2003b) [alternative explanation]
    - Method: explicitly avoid motor responses by minimising hand movement → motor prep/exe cannot be the driving forces
    - Finding: strong motor cortex excitability during mental rotation

- **Discussion**
  - M1 involvement can be explained by 3 ways

a. **Direct**: Georgopoulos et al. (1989), BUT lacks evidence for neural operations being implemented in the human motor cortex
b. **Strategy-dependent**: some people may imagine rotating the stimuli using their own hand
c. **Spill-over effect**: **most** likely; spread activations from **adjacent brain regions** during mental rotation; parietal & premotor areas may be the true main brain regions responsible for spatial transformations - M1 only activated due to strong interconnections between primary & premotor

  - Bestmann et al., 2004: found changed haemodynamic responses in areas connected with M1
    - Bestmann, S., Baudewig, J., Siebner, H.C., Rothwell, J.C. & Frahm, J. (2004) fMRI of the immediate impact of TMS on cortical & subcortical motor circuits. Eur. J. Neurosci., 19, 1950–1962.

Bode et al., (2007): Different strategies do not moderate primary motor cortex involvement in mental rotation

- **Abstract**: aims to test the relation between M1 activity & **<u>strategy</u>** (in-/external)
  - **Internal** - imagining rotating with hands & tools ; **external** - rotation driven by external forces; pictures of houses/abstract figures
  - <u>Findings</u>: no interaction between stimulus category & corticospinal excitability; BUT generally > resting baseline although subjects indicated more frequent use of the **external** strategy for all object categories
  - <u>Conclusion</u>: M1 involvement is **NOT** exclusively linked with…**internal** strategy, BUT rather **directly** with the process of mental rotation
    - May support **'spill-over' effect**
- **Results & Discussions**
  - No support for **strategy**: **NO** significant difference between the MEPs obtained during mental rotation of the **different figures**
  - No support for **task difficulty**: **NO** significant correlation between MEPs & **RTs**
    - <u>Rationale</u>: harder tasks = the entire neural circuit operates at a higher activation level
  - Unlikely due to **failure to follow instructions**: all subjects reported having used the general strategy of mental rotation in post-experiment questionnaire

a. Direct involvement

  - Georgopoulos et al., : simply listening to sentences involving hand & foot actions modulated MEP amplitude → neurons in M1 could also play a role in **<u>planning & imagining</u>** of the mental rotation
  - 26, 14-16: MEPs can also be modulated by only **<u>visualising motor actions</u>** without acting them out, and performance in mental rotation of body parts could be disturbed by TMS and intra-cortical stimulation
    - Fadiga L, Buccino G, Craighero L, Fogassi L, Gallese V, Pavesi G: Corticospinal excitability is specifically modulated by motor imagery: a magnetic stimulation study. Neuropsychologia 1999, 37:147-158.
    - Tomasino B, Borroni P, Isaja A, Rumiati AI: The role of the primary motor cortex in mental rotation: a TMS study.
    - Cogn Neuropsychol 2005, 22:348-363. 16. Ganis G, Keenan JP, Kosslyn SM, Pascual-Leone A: Transcranial magnetic stimulation of primary motor cortex affects mental rotation. Cereb Cortex 2000, 10:175-180.

b. Spill-over effect

  - 27, 29: posterior parietal cortex & premotor cortex are activated in mental rotation - involved in spatial transformations & operations
  - May also be due to **task-inducted neural activity**: (premotor cortex activation) which could lead to spill-over effect
    - Lamm C, Windischberger C, Leodolter U, Moser E, Bauer H: Evidence for premotor cortex activity during dynamic visuospatial imagery from single-trial functional magnetic resonance imaging and event-related slow cortical potentials. Neuroimage 2001, 14:268-283.
    - Vingerhoets G, Santens P, Van Laere K, Lahorte P, Dierckx RA, De Reuck J: Regional brain activity during different paradigms of mental rotation in healthy volunteers: a positron emission tomography study. Neuroimage 2001, 13:381-391.
  - 40: only premotor cortex activation during mental rotation using motor imagery
    - De Lange FP, Hagoort P, Toni I: Neural topography and content of movement representations. J Cogn Neurosci 2005, 17:97-112.
  - **Weaker** MEPs in **"hands"** condition: 2 speculations [both require further investigation testing the involvement of premotor cortex/schema]
    i. Premotor cortex activation for hands did not have to be as strong …since subjects indicated that they **did not** make predominant use of a strategy that involved direct motor imagery
    ii. Visualising a rotating body part (e.g. a hand) may lead to **inhibition** of subjects' action schemas → weaker MEPs; warrant future studies