Week 1: Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS)

- a "non-invasive" technique to create virtual cortical "lesions" (part of brain doesn't work, e.g. stroke, accident)
- E.g. (patient w/ real lesion) Phineas Gage, a railroad construction worker, with a serious injury by an iron rod piercing his head and frontal cortex → severe changes in his personality, impulse control
- Temporary and reversible, localised lesions (at a far smaller scale) could allow for better understanding the function of specific brain regions

Why not always use patients?

E.g. H.M. Removing most parts of his hippocampus, parahippocampal gyrus and amygdala (in response to his epilepsy) → led to severe anterograde amnesia

(Similarly, lesions in Broca and Wernicke areas → impairments of speech production and language comprehension, respectively)

- Because might not be enough patients with circumscribed lesions to study all cognitive functions. Lesions in single, specialised areas are rare.
- Recovery and brain plasticity might compensate for lesions over time - patients might become quite 'special'

Using TMS:

- TMS can be applied externally, using a coil placed on the scalp that produces a rapidly changing magnetic field to induce electrical currents in the brain. These currents depolarise neurons in a small, circumscribed area of cortex
- TMS-induced current causes neurons to fire randomly, increasing the level of neural noise (due to current), thereby masking the neurons that are firing correctly
- Fritsch & Hitzig (1870) were the first to electrically stimulate the cortex of animals
- D'Arsonval (1896) discovered that the magnetic stimulation of the visual cortex can elicit "phosphenes" (seeing light without light actually entering eye)
- Magnusson & Stevens (1911) developed the first "head coil" covering the entire head
- Barker, Jalinous & Freestone (1985) developed the current TMS technique, which was not painful. In order to create the current pulse (which generates the magnetic field) a capacitor is charged and then suddenly discharged.
- Can create a fast sequence of pulses ("repetitive", or rTMS)
- To create a magnetic field strong enough for stimulation, very fast loading times (~100-200 μs) and short durations (<1 ms) are required.
- The most common coil is the 'figure-eight' coil.
  It generates magnetic fields in the opposite direction, thereby generating offset current loops that circulate in opposite directions, allowing for a more focal area of the stimulation (compared to round coils).

Different ways TMS can be used in research : Injection of "neural noise" approach

Using single-pulse TMS to specific cortical region disrupts cognitive processing → finds out causal relationship, rather than correlation (which other neuroimaging techniques rely on)

- Interfere w the process of interest at the exact time window in which region is required, inducing "neural noise". Regions don't stop working completely, but "neural noise" interferes with normal functioning/performance.
- *Study:* researchers used 3 alphabetical letters as stimuli presented under difficult viewing conditions using illuminated frames/background
  Magnetic stimulation was applied ~ 2 cm above the inion (bone at base of skull) over visual cortex. Effects on letter perception were investigated when varying the interval between visual stimuli and time point of TMS stimulation.
  At 80-100ms, stimulation affected letter detection performance so visual processing occurs 80-100ms after visual stimuli shown

  When shifting the stimulation site from left to right, perception of letters in the contra-lateral visual field was predominantly impaired.
  (e.g. shifting stimulation left = right letter perception impaired)

  When moving the TMS stimulation up and down at midline, and letter were displayed vertically, stimulation above the reference line suppressed bottom letters.
  (e.g. shifting stimulation up = bottom letter perception impaired)
  Stimulating below the centre was impossible (below inion is end of brain)

Study: Researchers investigated whether a 'visual mask' can itself be 'masked'using single-pulse stimulation, thereby 'unmasking' the stimulus (As TMS can be used to disrupt processing of stimuli, it could potentially also disrupt processing of the mask, thereby preventing the suppression of the stimulus)
Without mask: 100% detection rate
With TMS, at 100ms: 37% detection rate
With TMS following the mask: 90% detection rate (increase)
Unmasking was found between 60 and 140 ms stimulation after the mask. This technique can inform us about time-course of processing.

The "virtual lesion" approach: Using repetitive rTMS to interrupt or enhance cognitive processing

- It is also possible to inhibit cognitive functions for a longer period of time by applying repetitive TMS (rTMS = fast sequence of pulses)
- It can then be measured whether (and for how long) a specific cognitive task is impaired (usually slowing instead of total loss of function)

The "probing excitability" approach using single-pulse TMS

- Test how responsive (or "excitable") the motor cortex is during a cognitive task
- If the motor cortex is required for a cognitive task, then it should already be activated when single-pulse TMS is delivered
- Instead of aiming at disrupting cognitive functions (and measuring the effect of TMS on performance), the measure of interest is how strongly the motor cortex "reacts" to the pulse itself
- Excitability of the primary motor cortex can be measured by recording "motor evoked potentials" (MEPs, which are measured amplitudes) using the electromyogram (EMG), which is electrical activity of muscles
- One can then measure MEPs for each stimulation & compare average MEPs between experimental conditions

Study: Is the primary cortex (M1) involved in the mental rotation of objects?

- Some neuroimaging studies found activation of M1 (primary motor cortex) during mental rotation (nothing is 'really' rotated)
- Stimulation of M1 during mental rotation elicited stronger MEPs as compared to baseline, reading aloud and reading silently
- Evidence that M1 is more excitable during mental rotation → might be already activated, and hence, involved in the cognitive process

Study: Does the involvement of M1 in mental rotation depend on strategy?

- It's been suggested that some objects can easily be imagined (e.g. rotation using hand) while others can't (e.g., building)
- However, MEPs were equally high for mental rotation of all different stimuli, so probably strategy does not play a role (MEP equal for rotation of objects you normally touch vs those you don't)
- What the studies cannot say is whether M1 was only more excitable because adjacent and interconnected regions (e.g. SMA) were activated ('spillover' effect)

Probing information transfer using the "paired-pulse approach"

- Uses two pulses, delivered in brief succession – one is usually sub-threshold while the second one is supra-threshold (Sub-threshold: e.g. stimulating but have no effect, hand doesn't twitch)
  (Supra-threshold: e.g. hand does twitch)
- The question is how strongly the first pulse influences the effect of the second

Study: In Schizophrenia, abnormalities in inhibition in the motor cortex have been suggested (takes longer to get rid of activation). In particular, there is evidence that the cortical silence period (CSP) – a period of suppression of tonic motor activity that follows descending excitatory activity – is reduced.

- The researchers produced the excitatory activity by a first TMS stimulus to the left motor cortex, and measured the excitability by assessing the effect of a second pulse (via MEPs)
- Results show that, compared to controls, parents with and without medication showed stronger responses to the second pulse (twitch more and higher MEPs)
- This points to general deficits in motor inhibition.

Clinical applications of TMS

- ✓ TMS as a treatment option for depression
- ✓ Usually, one hemisphere is stimulated over prefrontal cortex with the idea that depression is linked to in imbalance of prefrontal activity between hemispheres
- ✓ Typically a treatment of a last resort when all other treatments have failed
- ✓ Mixed evidence of effectiveness but increasingly accepted as an option
- ✓ Debated as potential treatment of mental disorders

Week 2: Statistics

Statistical hypothesis testing:

We need to know how likely it is that we get results by chance or that the result actually represents a real difference by comparing results to a probability distribution representing chance.

This means while for every outcome there is a possibility that this was only due to chance (we will never know for sure!) some outcomes are *highly unlikely.*

- We want to find out how *unlikely* our empirical result was under the chance distribution (null hypothesis; H_0)
- If "very unlikely" we decide to reject the H_0 (i.e. the assumption that it was all due to chance), and start believing that we have found something *real)*
- *But* there is always the probability that we are wrong (depending on where we set the cut-off, i.e. alpha level)

T-distribution:

- Can't use a z-distribution because we would need to know the population standard deviation – which we don't know (we're trying to find out about population).
- The t-statistic takes into account both the expected mean and a measure of the *standard error of the mean* based on the *sample.* T-distribution approximates the population distribution (more people, the more accurate).

Unlike z-distribution, t-distribution changes depending on our sample size / degrees of freedom (df). Distribution looks broader for lower df, and more like a normal distribution for larger df.

So, our cut-off will vary with our df.

Single sample, between-groups, and repeated measures experimental designs

Single-sample design: We have one group with values coming from different people. This is compared to a single value.

Advantages:

- Can be used to compare group data to known values

Disadvantages:

- We may not always know population values
- We may want to compare two groups, or to investigate the change of behaviour over time

Between-groups / Independent measures design: We have two groups, and the values come from *different* people (i.e. each person provides one measure in one group only).

Advantages:

- The measurements are independent
- We don't have to worry about learning effects due to repeated exposure (don't have to worry about them knowing they are the control group, e.g. could use deception)

Disadvantages:

- People in the different groups might be quite different in various ways: Personality, motivation, level of schooling etc. We need *large sample sizes* to average out these effects, or we need to *counterbalance* all factors that we know might influence the results
- We cannot study behaviour over time

Within-group / Repeated measures design: There is a single group which provides data for both conditions, i.e. the values from each condition come from the *same people.*

Advantages:

- We don't have to think about differences in baseline factors such as personality, motivation, schooling etc. because this will always affect both conditions equally.
- We can study changes in behaviour over time
- We can usually test less people

Disadvantages:

- Measurements are *not* independent → we need to calculate the variance differently
- People know the treatment after the first condition and can't be naïve in the second round. This might not work for every experiment

- We need to carefully counterbalance the conditions to avoid unwanted order effects (e.g. one half of group does one treatment while other half does other, then swap)

Comparing means

One sample t-tests

E.g. For defining the motor threshold using TMS, researchers often use the following rule: The motor threshold is the stimulation strength that is needed to evoke a detectable MEP in 50% of all trials (in this example, 10 out of 20 trials). Hence, this is the chance level when no task is performed. We now stimulate four people 20 times each during a mental imagery task, and on average this results in M = 16 trials in which an MEP was registered. Did this task excite the motor cortex significantly more than chance?
Hypotheses:

H_0 = Sample is drawn from a population $\mu=10$

H_1 = Sample is drawn from a population $\mu>10$

Remember: We will assume that H_0 is true until we are sufficiently convinced that our result is "very unlikely" under this hypothesis.

We have not yet covered how to *quantify* the effect. The *t*-value itself does **NOT** tell us how strong the effect really is! For this, you will have to calculate the *effect size*. We will introduce the effect size at the end of this lecture.

Week 3: Electroencephalography (EEG)

- EEG is a method of detecting neural activity by placing electrodes on the scalp. These electrodes pick up small fluctuations of electrical signals, originating from activity of (mostly cortical) neurons.
- Raw signals recorded are very noisy and might not look like much, but are systematically related to cognitive processes. So, we can use these signals to learn something about cognition when people perform tasks
- EEG recorded at the scalp is non-invasive. But, it is also possible to record intra-cranial EEG by measuring activity directly at the exposed cortex.
- cheap and (relatively) easy to conduct. Measure electrical activity against a reference (e.g. the bone behind the two ears, which are so thick we can't pick up neural activity)
- Discovered by Hans Berger, who also described the *alpha* rhythm - when people closed their eyes, the electrical signal was not constant, but it varied with a characteristic (high) frequency of 8-13 Hz
  Initially, he used two electrodes placed under the scalp, one attached to the front of the head and one to the rear, and recorded the potential (i.e. voltage) difference between them. Initially, electrodes were silver wires placed under the scalp. Later, electrodes were placed on the scalp

Use of EEG

- Advantages: Temporal resolution is great → measure signals across small units of time (e.g. milliseconds)
- Disadvantages: Spatial resolution isn't good → hard to reconstruct source of electrical signal
- What is better depends on what you want to know (e.g. fMRI use is better to know signals from specific brain region)

Amplify signals, and while recording EEG, can make participant do something
Deduce what happens when they do something (e.g. mental rotation, decision-making)

Neurophysiology of EEG

- EEG activity doesn't reflect action potentials but originates mostly from post-synaptic potentials – voltages that arise when neurotransmitters bind to receptors on the membrane of the post-synaptic cell
- This causes ion channels to open or close, leading to graded changes in the potential across the membrane
- Signals from single cells are not strong enough to be recorded outside of the head, but if many neurons spatially align, then their summed potentials add up and create the signals we can record
- This pooled activity from groups of similarly oriented neurons mostly comes from large cortical pyramid cells
  The functional unit is >10,000 simultaneously activated neurons.
  - The orientation of the neurons determines the sign of the recorded potentials
  - Some orientations lead to signals which cannot be recorded

Looks like a dipole with a many neurons

Limitations

- EEG is biased to signals generated in layers of cerebral cortex on the gyri (ridges) directly bordering the skull
- Signals in the sulci are harder to detect than from gyri, and may also be masked by the signals from the gyri
- The meninges, cerebrospinal fluid (CSF) and skull "smear" the EEG signal, making it difficult to localise the source
- This is known as the *inverse problem:* If the sources are known, the resulting scalp configuration of signals can be reconstructed; however, the reverse isn't true – one given scalp configuration of signals can have multiple dipole solutions (we don't really know where one signal comes from)

Analysing EEG data

- EEG signals measured from the scalp in relation to a *reference electrode* which should be a neutral point (e.g., tip of the nose, mastoids), but some people reference to the average of all scalp electrodes.
- EEG signals have a typical amplitude of 10µV to 100µV – tiny signals! So they need to be amplified, typically by a factor of 1,000 to 100,000
- The signal is then (typically) digitalized. Typical sample frequency is 256-1024Hz, but can be >4000Hz
- Signal is band-pass filtered to remove the low (<0.5-1Hz) and high frequencies (typically >35-70Hz) because they cannot reflect brain activity.
- EEG signals are the sum of signals originating from many different neural units!
- When looking at *frequency information*, (e.g. sleep research), raw signals might show systematic variations and more of a specific frequency.
  When studying cognitive processes, raw data has to be "cleaned" before it can be interpreted (many steps!)