Journal Club Presentation

Induction of LTD-like corticospinal plasticity by low-frequency rTMS depends on pre-stimulus phase of sensorimotor μ-rhythm

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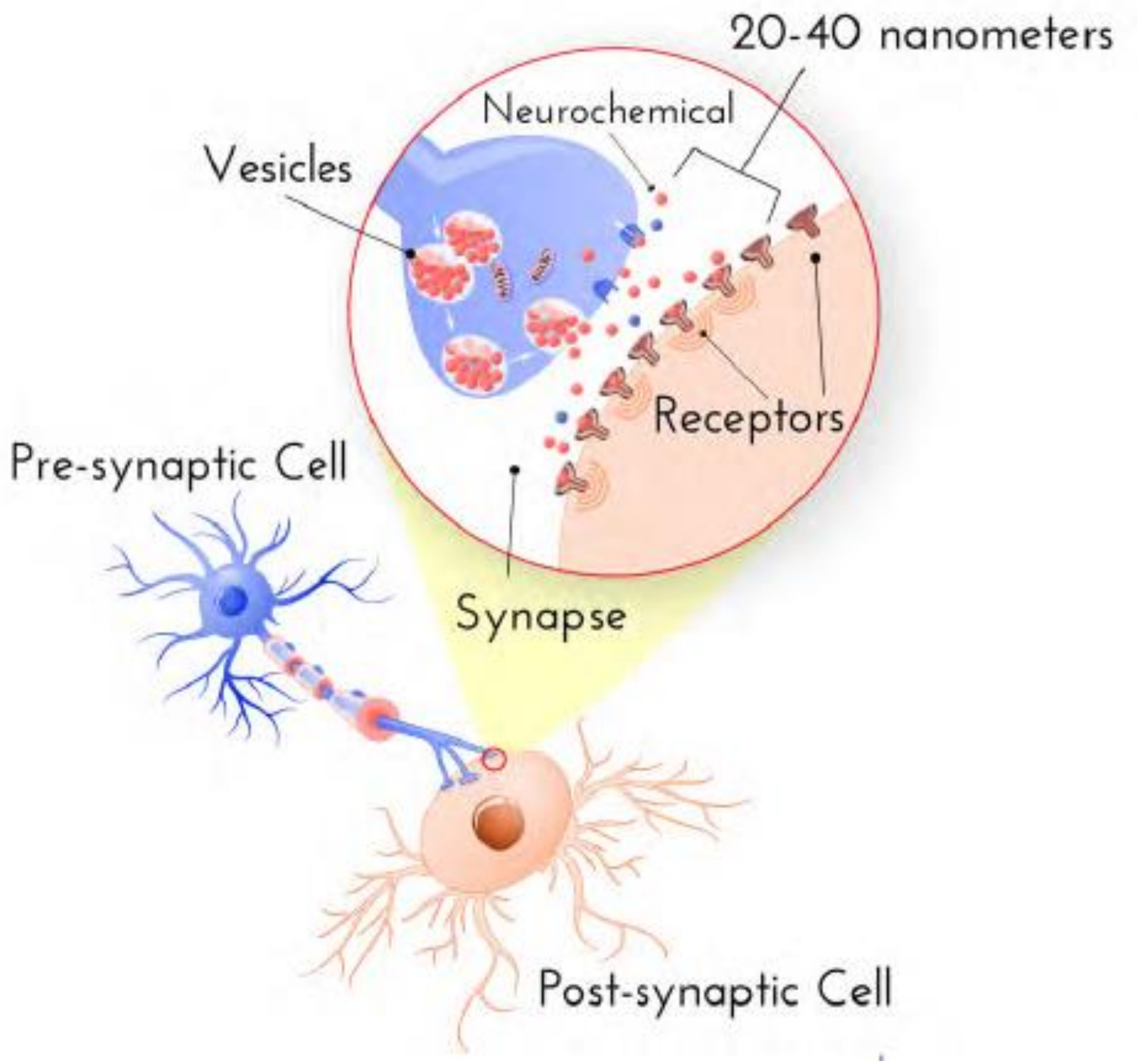


Research Question

Is low frequency rTMS induction of LTD-like corticospinal plasticity in humans enhanced when rTMS is synchronised with the low-excitability state, but decreased or shifted towards LTP-like plasticity when synchronised with the high-excitability state?

LTP: Long Term Potentiation

LTD: Long Term Depression

rTMS: repetitive Transcranial Magnetic Stimulation

Key concepts

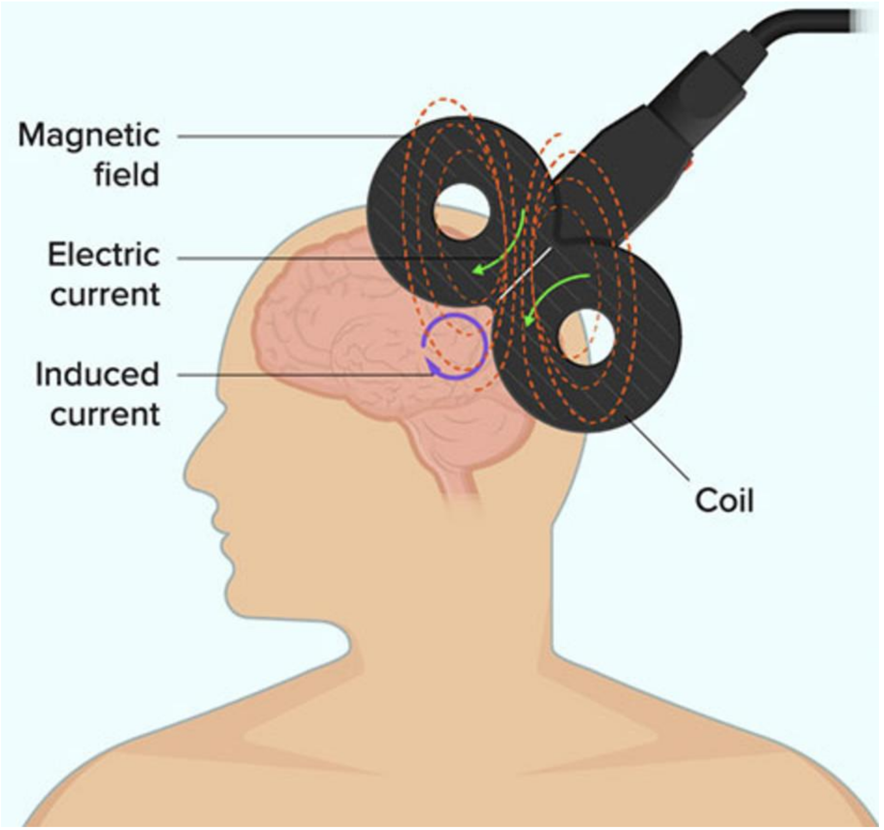
REPETITIVE TRANCRANIAL MAGNETIC STIMULATION

LONG-TERM POTENTIATION AND DEPRESSION PLASTICITY

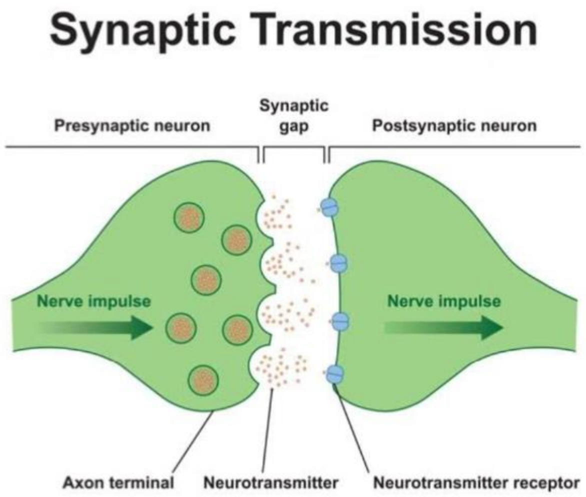
LOW AND HIGH EXCITABILITY OF BRAIN CELLS

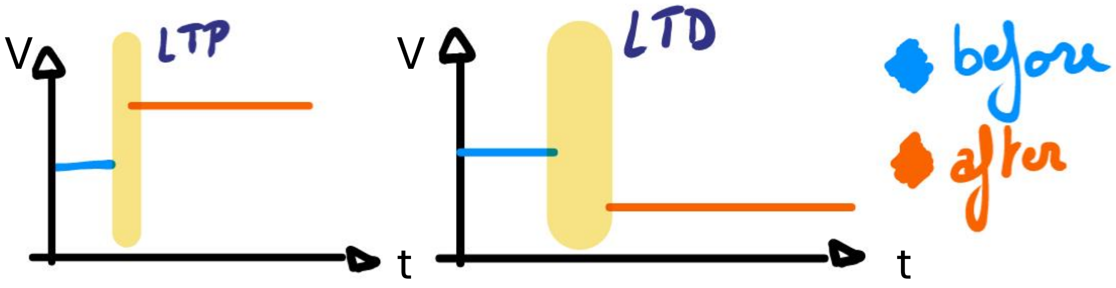
Repetitive Transcranial Magnetic Stimulation

- Series of short pulses
- Stimulates neuron nerves
- Psychiatric and neurological diseases
- Aims to neuron cells in brain circuits involved in disorder
  - Goal: change the dysfunctional brain patterns



Long-term depression and potentiation plasticity



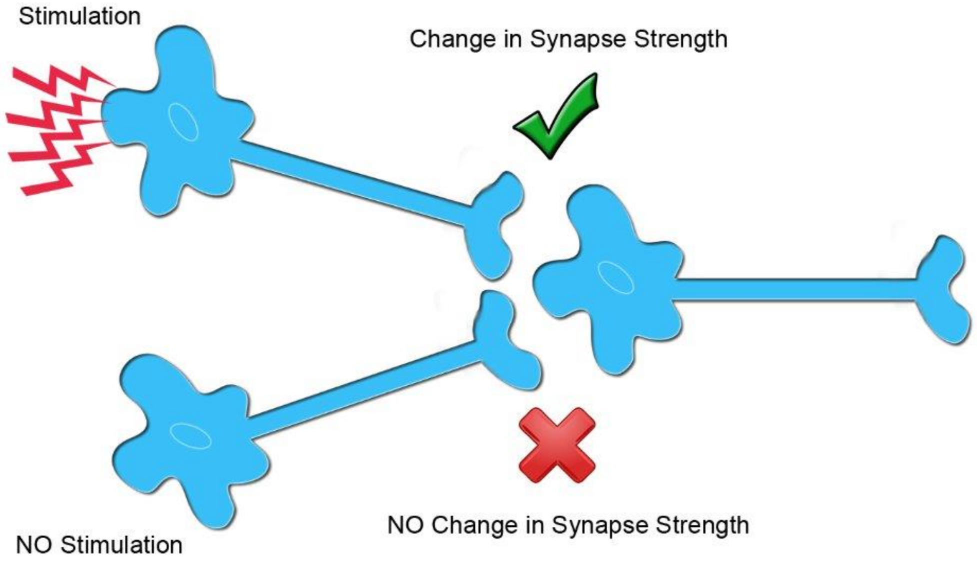


- Long Term Depression is the weakening of synaptic transmission
  - Over time less input from presynaptic cell
  - Post-synaptic cell less sensitive
  - Weakens connection
  - Reduction of efficacy
- Opposite is LTP: enhancement
  - *Long Term Potentiation*
  - As result of repeated low-level activation of the neural pathway responsible for a memory trace

Source: *Andrew Scott, "Storytelling: Andrew Scott," YouTube, Oct. 15, 2023. https://www.youtube.com/watch?v=HTFNQVjKv2I. Accessed: Nov. 25, 2024*

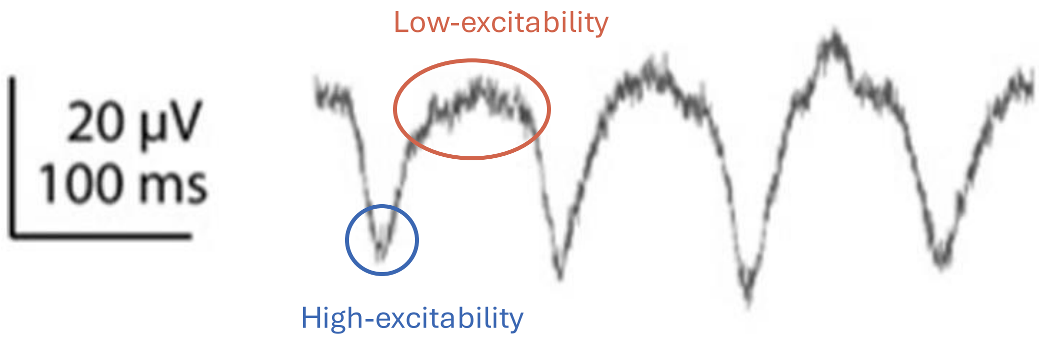
Long-term potentiation and depression plasticity

- LTP: enhancement of synaptic transmission
- LTD: weakening of synaptic transmission
- Induction of plasticity not only dependent on stimulation parameters
  - As stimulus intensity, number of stimuli, coil orientation, pulse wave form
  - Also dependent of excitability state of neurons



Low- and high-excitability of brain cells

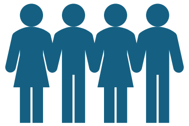
- Triggered by electroencephalogram (EEG)
  - Proved previously linked to positive and negative peaks
  - Sensorimotor of mu-oscilliations
- Decisive role for direction and magnitude of plasticity induction
  - Neuronal excitability is a concept in neuroplasticity
- Changes in excitability or the magnitude of the neuronal response to stimulation, are considered cellular hallmarks



Objectives

- Check if the synchronisation of rTMS with the low- or high-excitability of neurons do influence the LTP and LTD plasticity
- Check if it outlasts the period of stimulation
- Understanding the underlying physiological causes for the observed effects

Rapid summary of the method



12 participants between 19 & 29 years of age

Needed no history of neurological or psychiatric disease or usage of CNS active drugs

In accordance with the Declaration of Helsinki and approved by the local ethics commitee

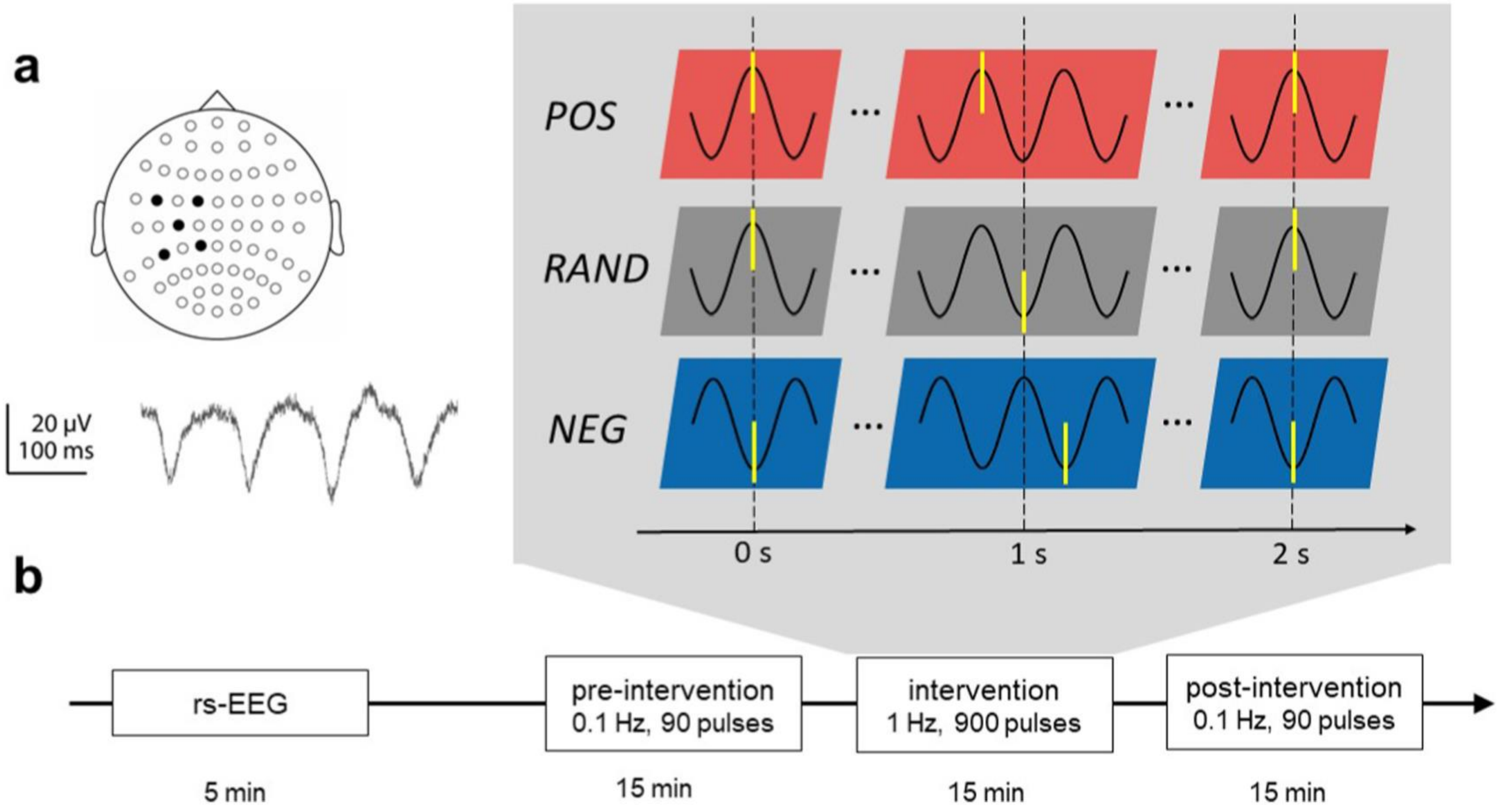
Rapid summary of the method

4 experimental sessions

1 screening to check if participants met all requirements

3 for checking the effect of μ-rhythm phase on MEP-amplitude

Apply 900 TMS pulses at random phase, negative or positive peak

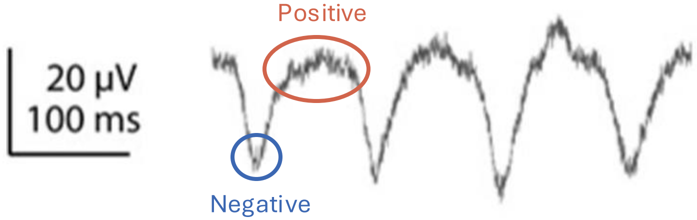


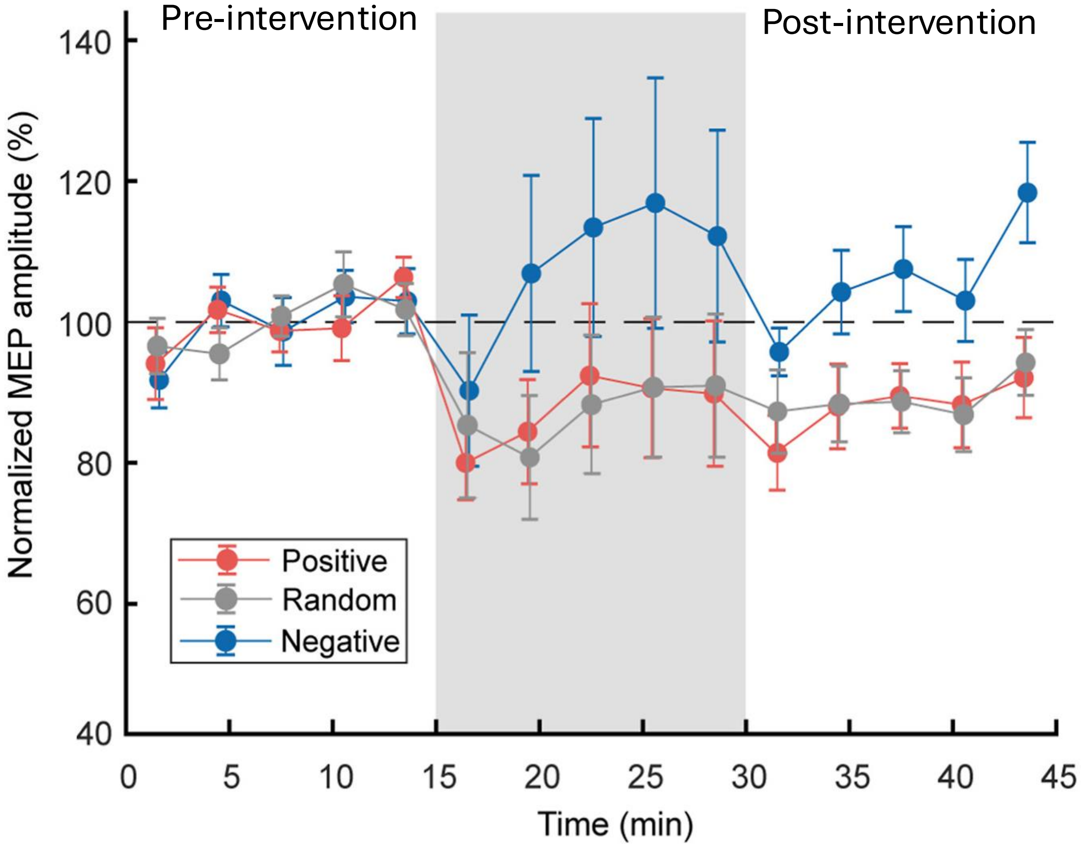
Motor Evoked Potentials (MEPs) are electrical signals generated by stimulating the motor cortex and recording the responses in nerves or muscles. They are used to assess the motor pathways from the brain to the muscles, with their effectiveness being affected by anesthetics and neuromuscular blockers.

Novelty

Induction of LTD-like corticospinal plasticity in human motor cortex depends not only on parameters of the stimulation protocol, but also **on the state of corticospinal excitability**, as indexed by the phase of the ongoing μ-oscillation.

Motor Evoked Potentials (MEPs) are larger if the TMS pulse is applied at the time of the negative peak of the sensorimotor μ-oscillation compared to the positive peak.





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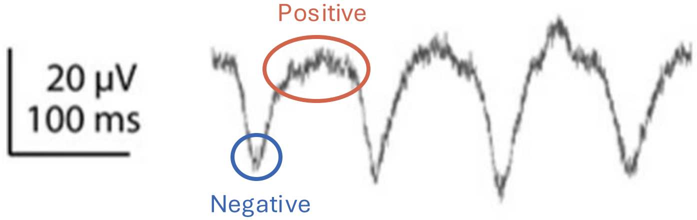

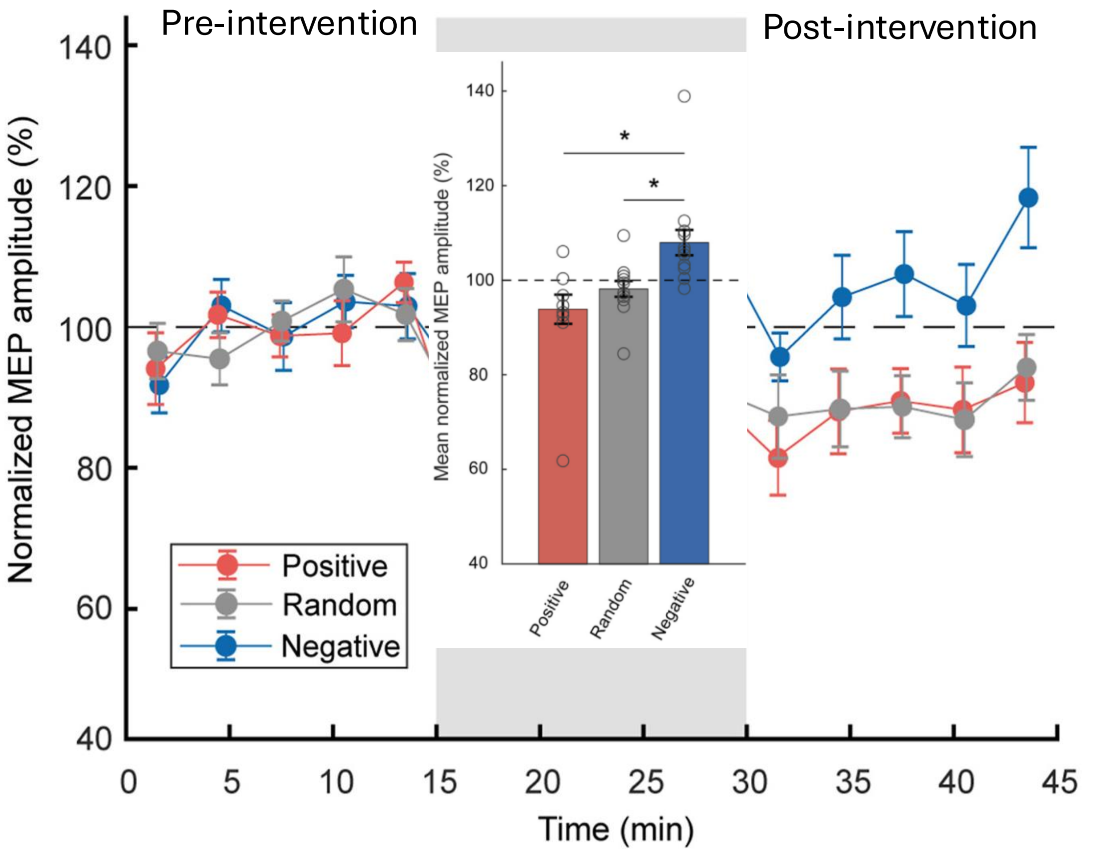

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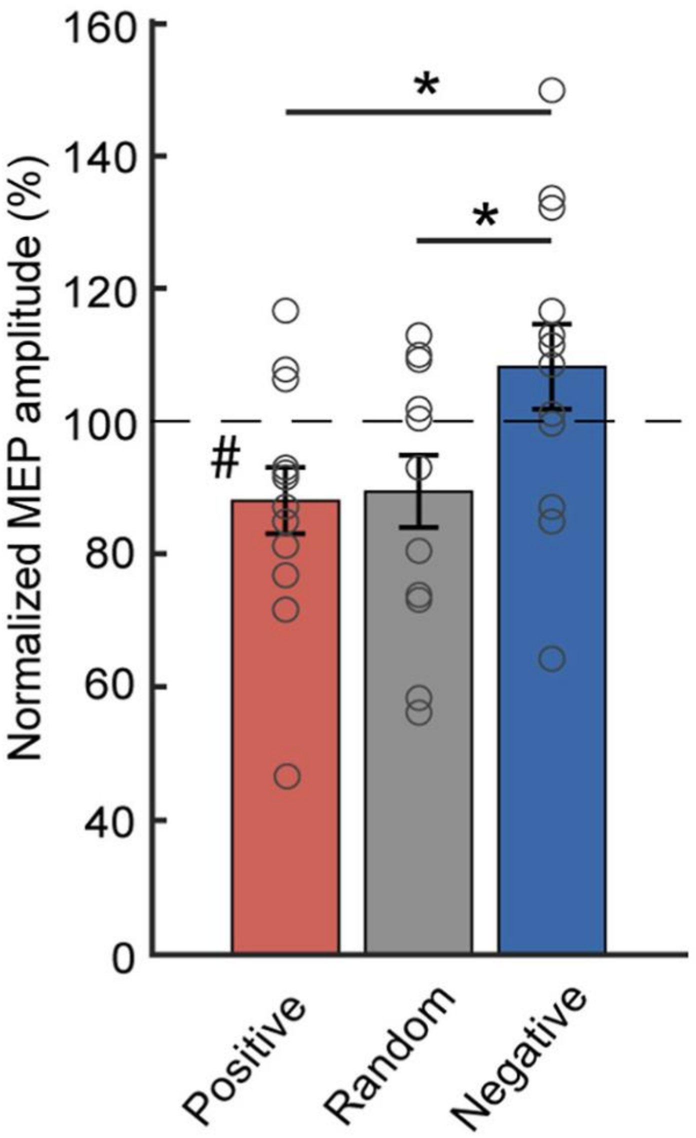
Motor Evoked Potentials (MEPs) are larger if the TMS pulse is applied at the time of the negative peak of the sensorimotor μ-oscillation compared to the positive peak.

Significant decrease of MEP amplitude post-intervention vs. pre-intervention only for the positive peak condition



Limitations

- Magnitude of 1Hz differential rTMS-induced LTD-like effect depends on stimulation intensity
  - Higher intensities lead to more pronounced effects
  - Observed differential effect of phase of mu-oscillation was thus likely underestimated
- Duration of the observed effect is unclear since recording lasted only 15 min post-intervention
- Small sample size (n=12)
- Requirement of good SNR (Signal to Noise Ratio)

Challenges in the process ⚠

- Large inter-/intra-subject variability
- On average, nil effect of rTMS plasticity protocols
- Aftereffects of low-frequency rTMS stimulation influenced by many factors:
  - Stimulus intensity, number of stimuli, coil orientation and pulse wave form
  - Current state of the brain (mu-wave)
- The negative peak lasts a short time in comparaison to the positive peak due to the asymmetric shape of the μ-rhythm
  - Random phase condition has increased probability triggering TMS pulses at the low-excitability

Open questions ?

- How to improve the random aspect of the random phase condition?
  - ➢Impose weights to equilibrate odds of being in the positive or negative state
- Why is the negative peak of the μ-rythm a more excitable state of the M1 output neurons?
  - ➢Study radially oriented pyramidal cells
- How is it possible to amplify the effects outlasting the stimulation time of rTMS while keeping safety at a maximum?
  - ➢Pair rTMS with other stimulation techniques (e.g., tDCS) to boost effects.
- Is there a way to detect the μ-rythm in smaller regions with non-invasive techniques?
  - ➢Invesigate other non invasive techniques

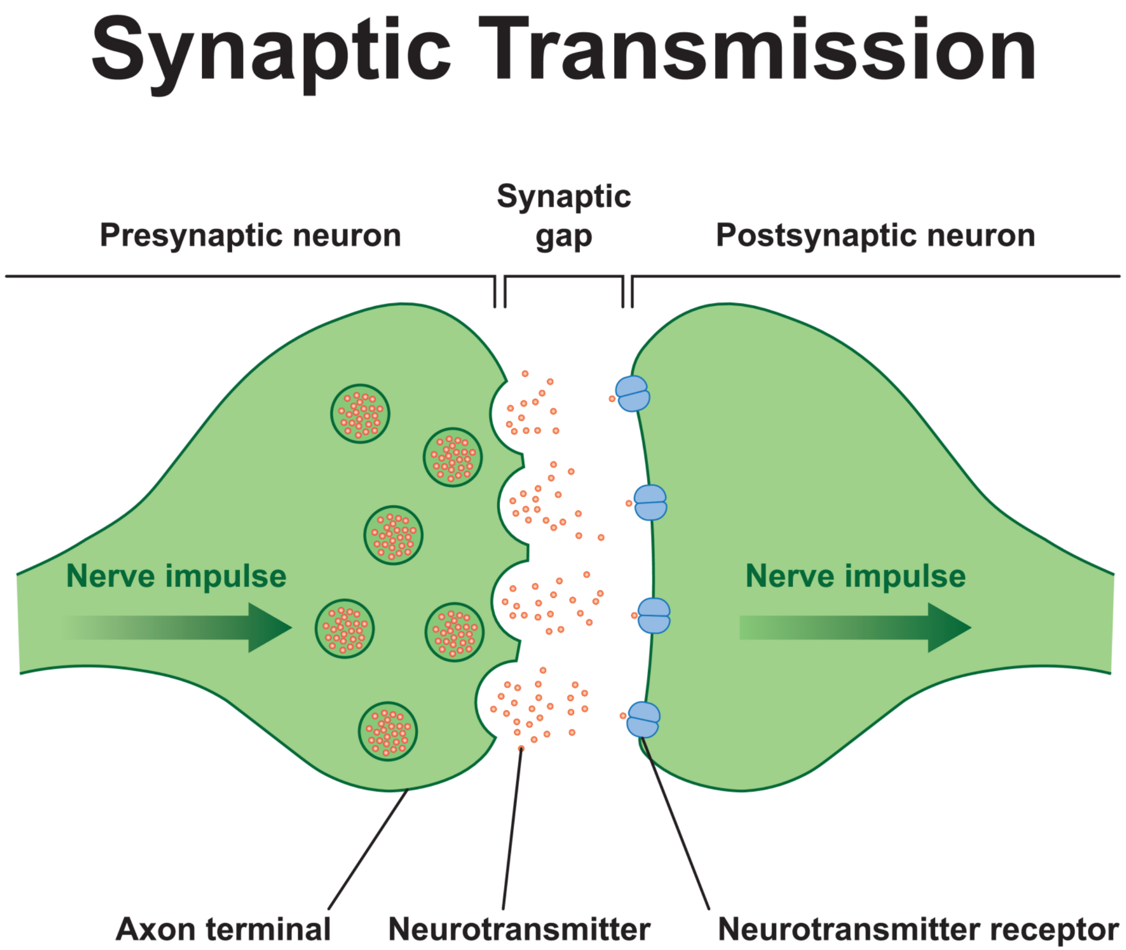
Potential applications

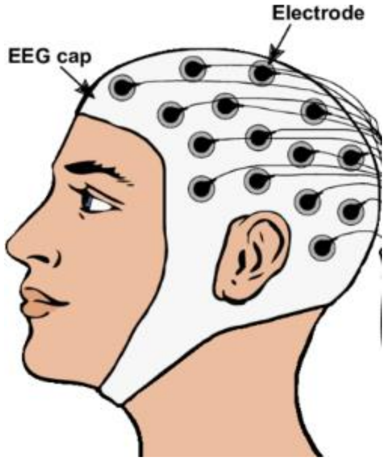
The novel real-time EEG-TMS technology may be used to develop brain-state-dependent personalized stimulation protocols for plasticity induction that are characterised by reduced inter-subject variability and larger effect size, features that likely will turn out beneficial for rTMS treatment of brain disorders.

Ressources

- [1] https://www.mayoclinic.org/tests-procedures/transcranial-magnetic-stimulation/about/pac-20384625
- [2] https://www.camh.ca/en/health-info/mental-illness-and-addiction-index/repetitive-transcranial-magnetic-stimulation
- [3] https://www.sciencedirect.com/science/article/pii/S0006322323017456
- [4] https://pmc.ncbi.nlm.nih.gov/articles/PMC3118435/

Extra slides

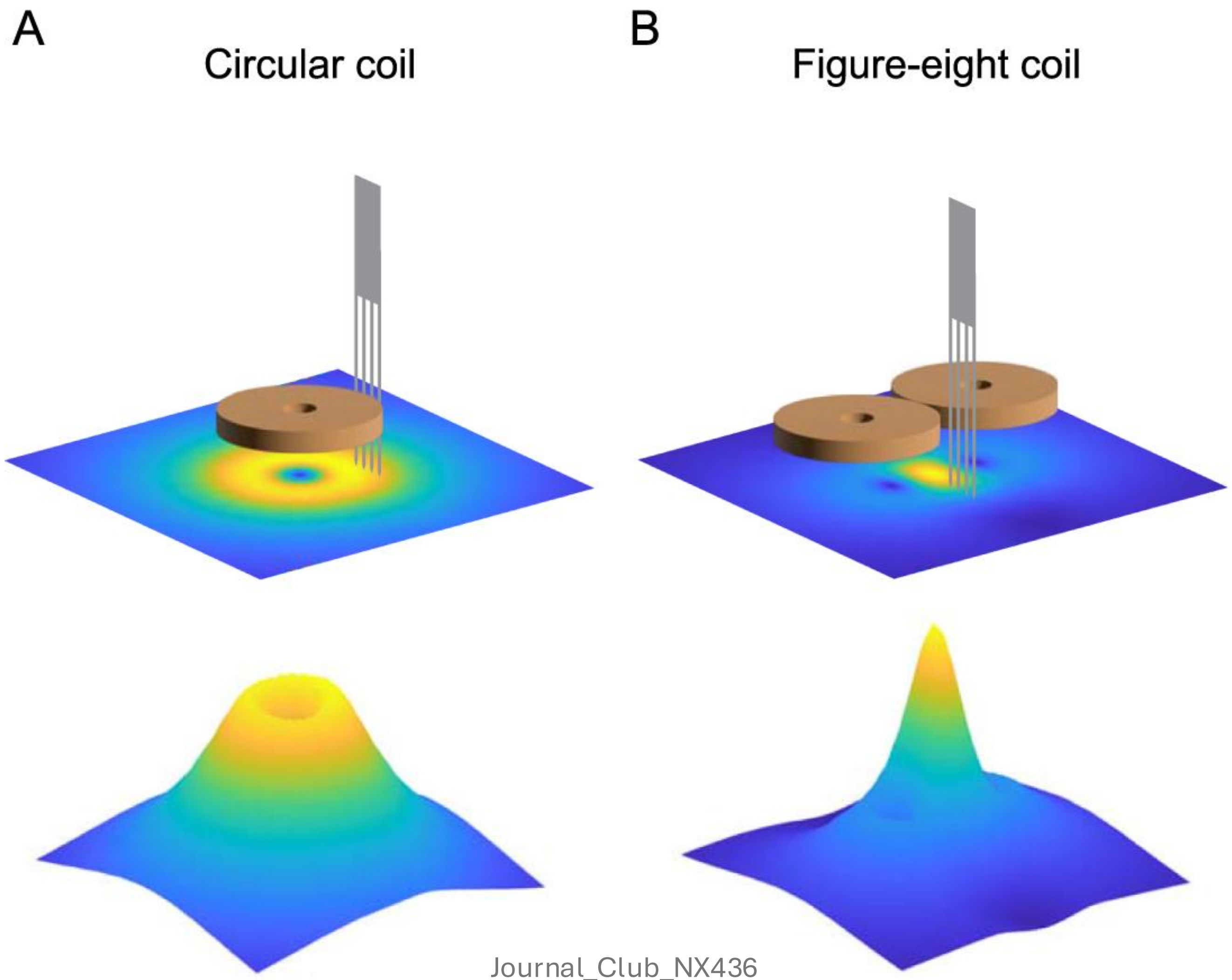




What is EEG (Electroencephalogaphy)

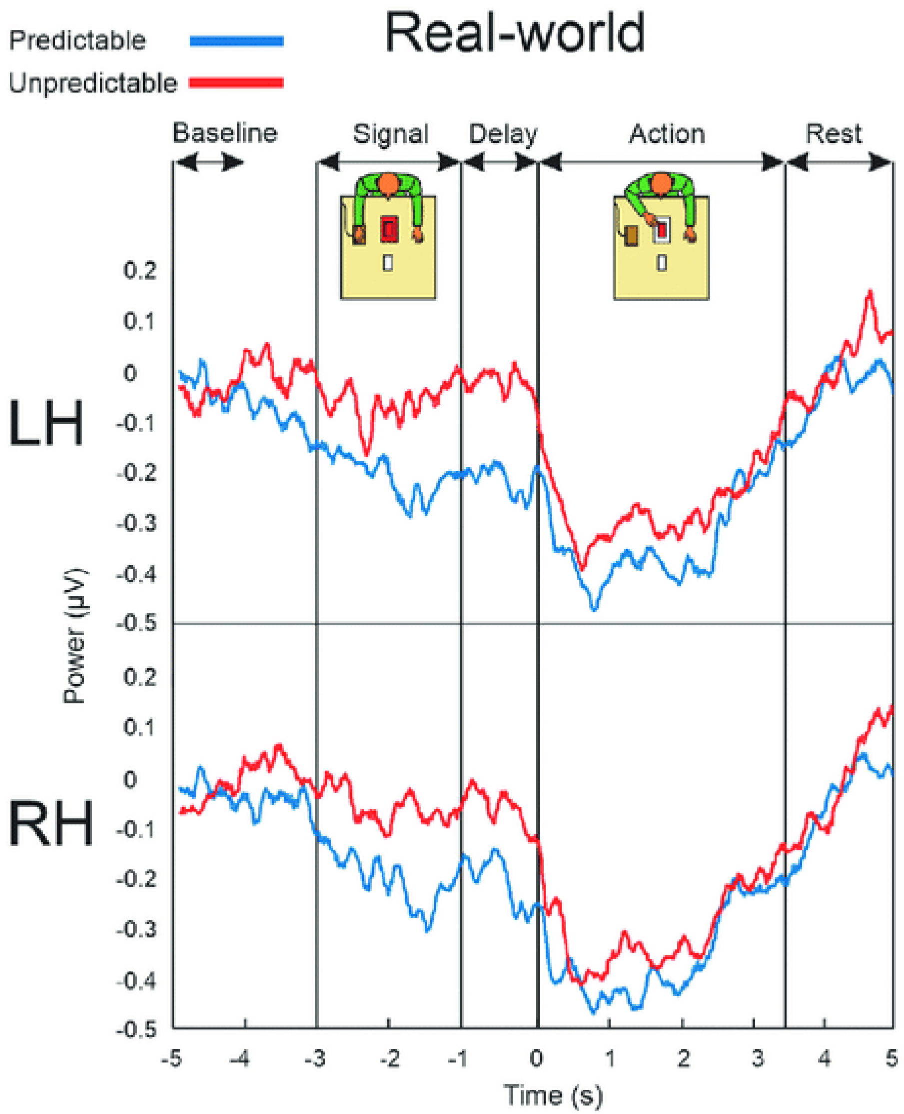
- Used measure electrical activity of the brain
  - o Detects activity of large groups of neurons active same time
- Primarily measures postsynaptic potentials (not action)
- Measure brain activity during an event (order milisecond)
- LIMITATIONS
  - o Poor spatial precision
  - o Limited ability accurately record from structures deeper than

Figure of 8 coil advantage



Sensorimotor μ-rhythm

- synchronized patterns of electrical activity found in the motor cortex involving large numbers of neurons, probably of the pyramidal type
- most prominent when the body is physically at rest
- μ-rhythms are supressed when performing motor actions
- μ-wave between 8 and 13 [Hz]
- Some BCIs use event-related desynchronization (ERD) of the μ-wave in order to control the computer



μ-rhythm averaged over the 9-electrode cluster of the left hemisphere (LH), for the predictable and unpredictable actions

[5] https://doi.org/10.1080/17470919.2022.2083229

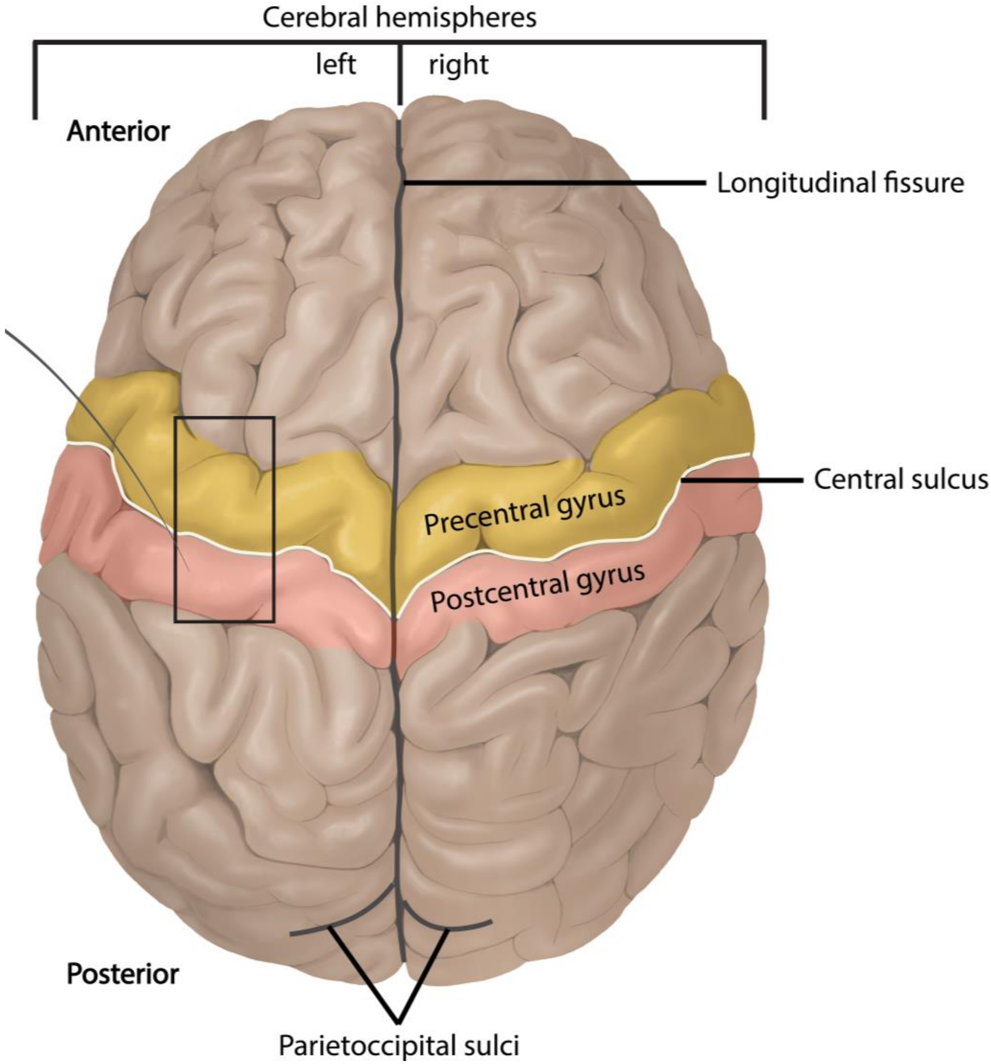
Declaration of Helsinki

"The Declaration of Helsinki (DoH, Finnish: Helsingin julistus) is a set of ethical principles regarding human experimentation developed originally in 1964 for the medical community by the World Medical Association (WMA).[1] It is widely regarded as the cornerstone document on human research ethics."

Citation from:
https://en.wikipedia.org/wiki/Declaration_of_Helsinki#:~:text=The%20Declaration%20of%20Helsinki%20(DoH,document%20on%20human%20research%20ethics.

More information about EEG-TMS Setup

- EEG recorded from 64-channel TMS-compatible sintered ring
  - Electrodes prepared mild skin abrasion utilizing abrasive gel
- EMG recorded simultaniously with 24-bit biosignal amplifier sample rate 5kHz
- TMS figure-of-eight coil connected to magnetic stimulator
  - Biphasic single cosine cycle pulses with period of 160 µs
  - Major second component of induced electric field oriented from lateral posterior to medial-anterior (orthogonal to the central sulcus)
- Stimulation intensity (0 to 5V) determined by RMT and MEP (Motor Evoked Potential)
  - RMT defined lowest intensity that elicited MEPs with peak-to-peak amplitude (>= 50 µV)



https://med.libretexts.org/Bookshelves/Anatomy_and_Physiology/Human_Anatomy_%28Lange_et_al.%29/11%3A_Central_Nervous_System/11.03%3A_Brain_-_Cerebrum

Why is the negative peak of the μ-rhythm a more excitable state of M1 output neurons?

This higher excitability might be induced by pulsatile excitatory inputs, received by these neurons at the instant of the negative EEG peak, rendering their postsynaptic potential towards stronger depolarization. Indeed, EPSPs at the apical dendrites (superficial layers) of radially oriented pyramidal cells underlying the EEG montage are considered to be a major contributor to the negative deflection of the overlying surface EEG.

Yet, the precise mechanisms of these relationships remain elusive at the moment and need to be addressed in further research work.

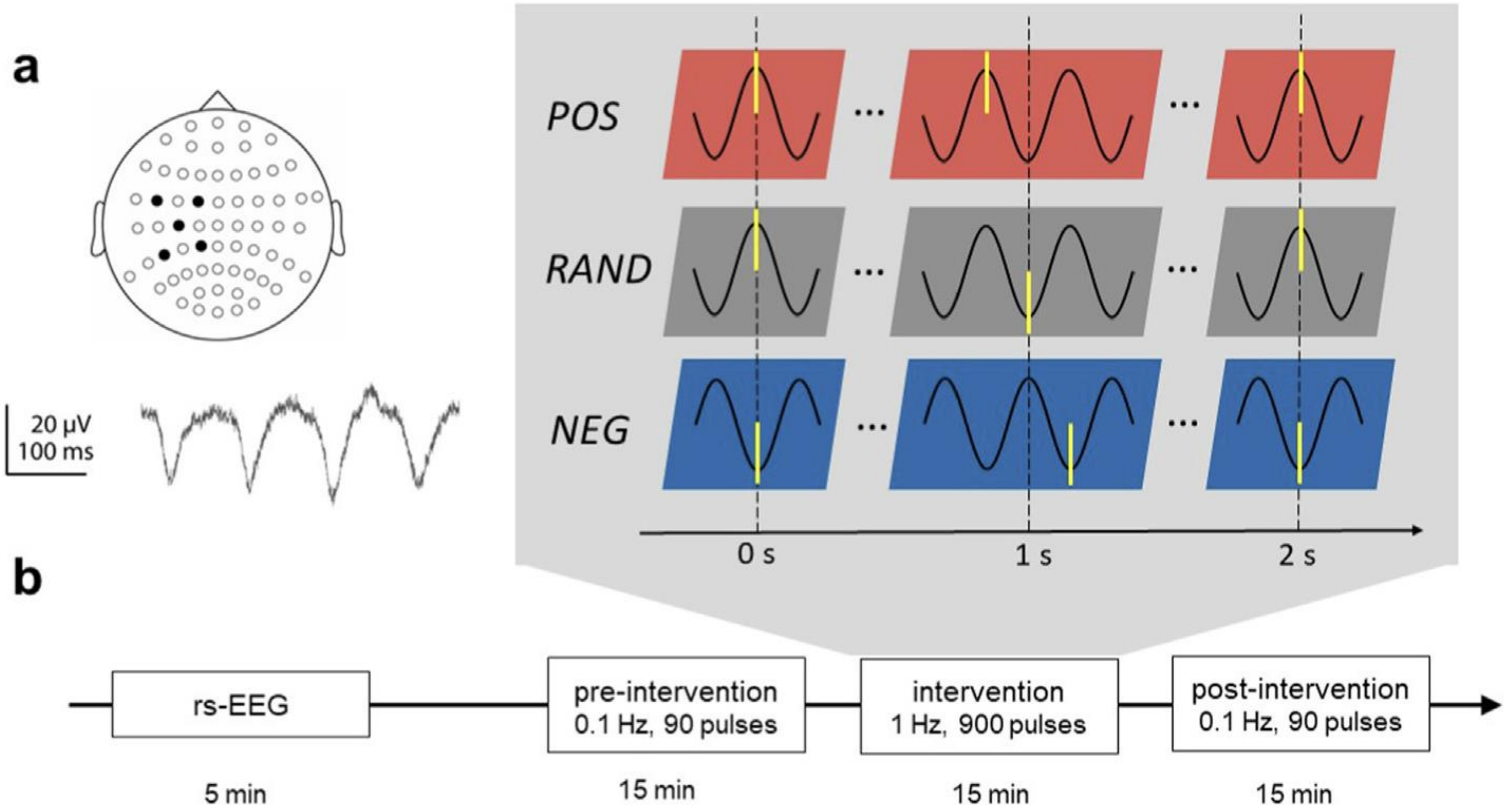


Fig. 1. Experimental design. a µ-rhythm was derived using a 5-channel (black dots) Laplace transform centered on EEG sensor C3 (top), an example raw data trace is shown at the bottom. **b** Plasticity sessions started with a 5 min resting-state EEG (rs-EEG) to test the accuracy of our phase triggering algorithm. Thereafter, each plasticity session contained a block of 90 single TMS pulses at a rate of 0.1 Hz before and after the rTMS intervention block, with TMS pulses applied irrespective of the EEG signal ("open loop"). For the intervention block, a double-blind, randomized crossover design was applied, so that each participant received 900 pulses of ~1 Hz rTMS in the positive peak condition (POS), 1 Hz rTMS in the random phase (RAND, irrespective of µ-rhythm) or ~1 Hz rTMS in the negative peak condition (NEG). Time points of stimulation are indicated schematically by yellow bars. TMS was applied to the hand representation of left primary motor cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

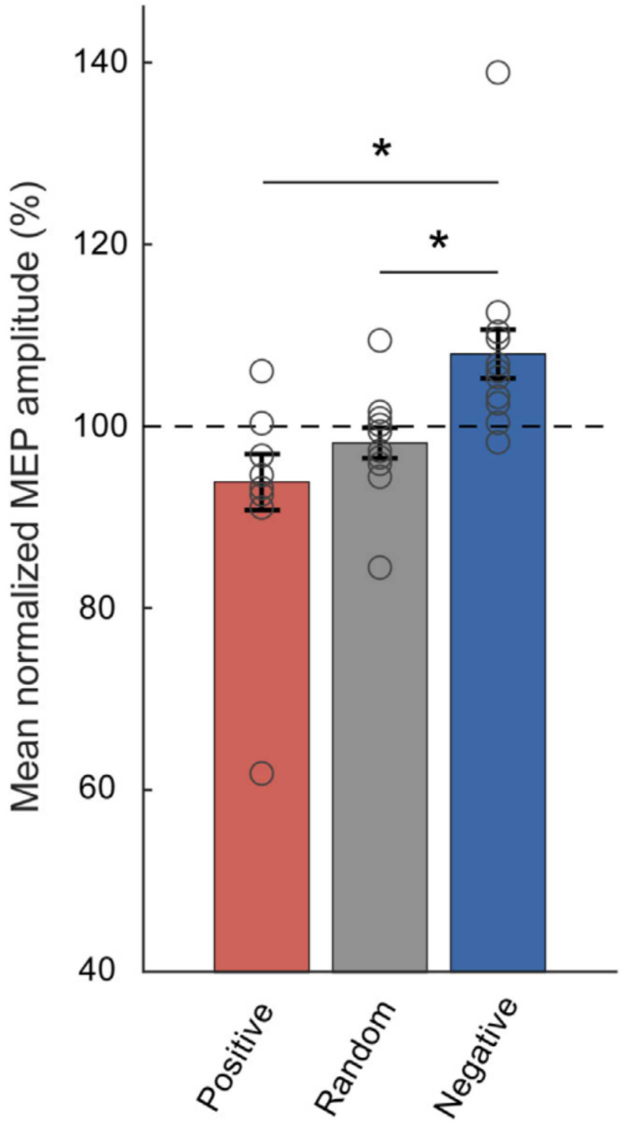


Fig. 2. Excitability data. Bars represent mean ± 1 SEM ($n = 12$) of the MEP amplitude in the positive peak (red), at random phase (grey), and negative peak (blue) phase conditions of the ongoing μ-rhythm, normalized to the mean of all three conditions. Individual data are shown by circles. $*p < 0.05$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

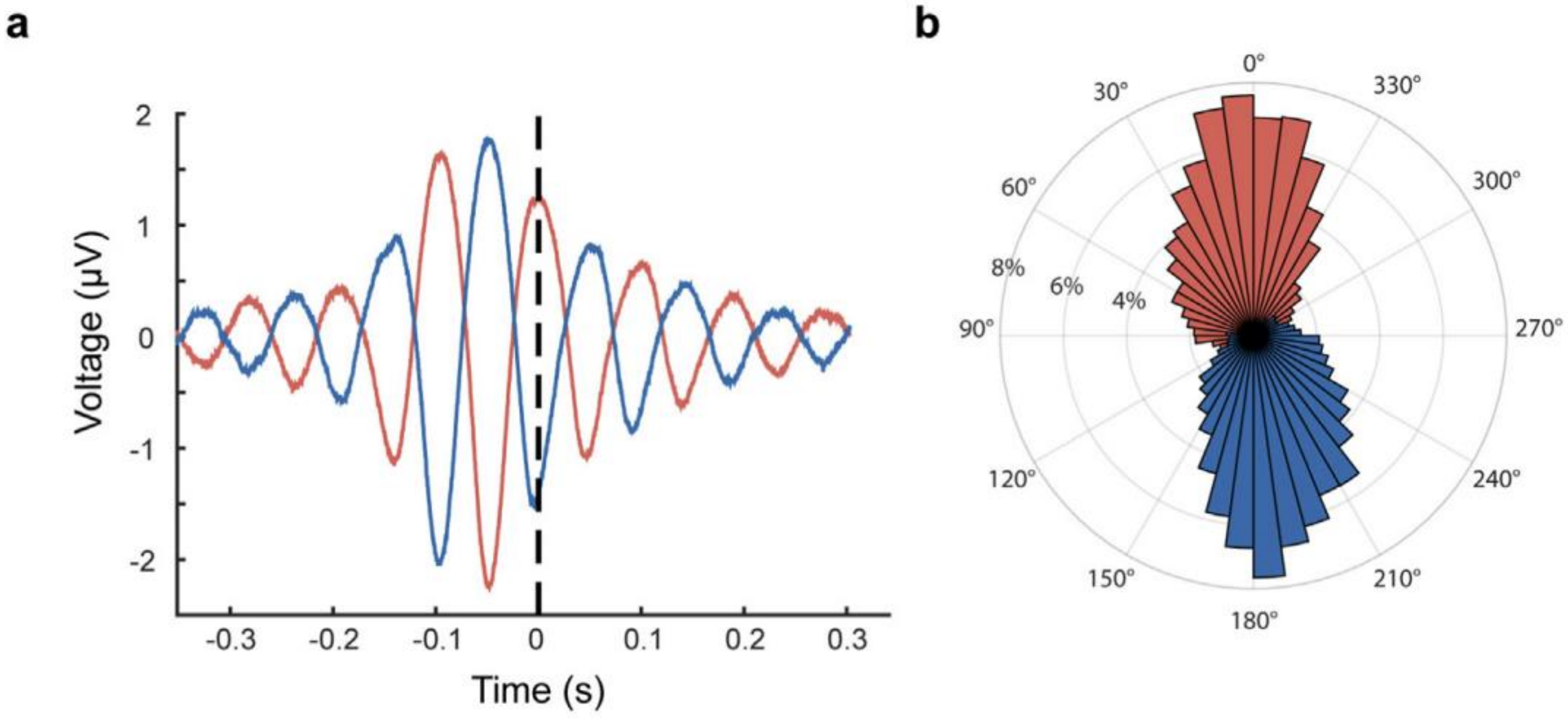


Fig. 3. Phase accuracy tested in the triggered but non-stimulated rs-EEG. a Mean C3-centered Laplace-transformed EEG signal for negative peak (blue) and positive peak (red) across all real-time triggered but non-stimulated trials of all subjects (n = 12). Dashed vertical line represents time point of the trigger. **b** Binned distribution (7.5° per bin, 2% frequency steps) of actual phase angle at the time of trigger of non-stimulated trials as determined by Hilbert transformation of the band-pass filtered segment of data before and after each marker. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

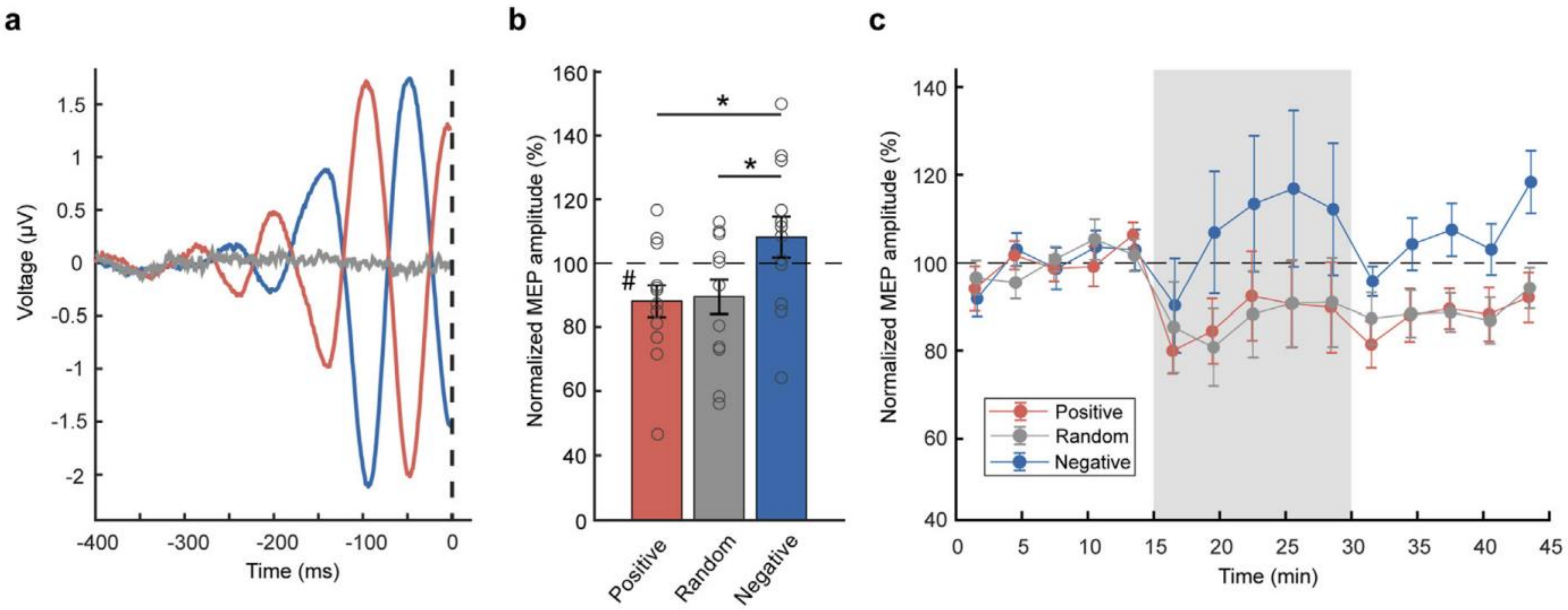


Fig. 4. Plasticity experiment data. a Mean pre-stimulus C3-Hjorth EEG signal for all stimuli in the rTMS intervention period for positive peak (red), random phase (grey) and negative peak condition (blue), approximately 900 trials per condition and subject, across all 12 participants. The dashed vertical line represents the time of the TMS pulse. **b** Mean ± 1 SEM ($n = 12$) post-intervention MEP amplitude normalized to mean pre-intervention MEP amplitude in the three phase conditions. Circles indicate individual data. *$p = 0.02$ (two-sided two-tailed t-tests), #$p < 0.05$ (one-sided two-tailed *t*-test, indicating difference from 100%). **c** Mean MEP amplitude for each Phase condition, binned in 3 min segments. RTMS intervention period is indicated by the grey area. Data is normalized to the mean pre-intervention MEP amplitude of each participant and Phase condition (100%, black dashed line). Error bars indicate ±1 SEM. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)