UNIVERSITÀ DI TRENTO

CIMeC Center for Mind/Brain Sciences

Real-time Brain-State dependent EEG-TMS Stimulation

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Outline

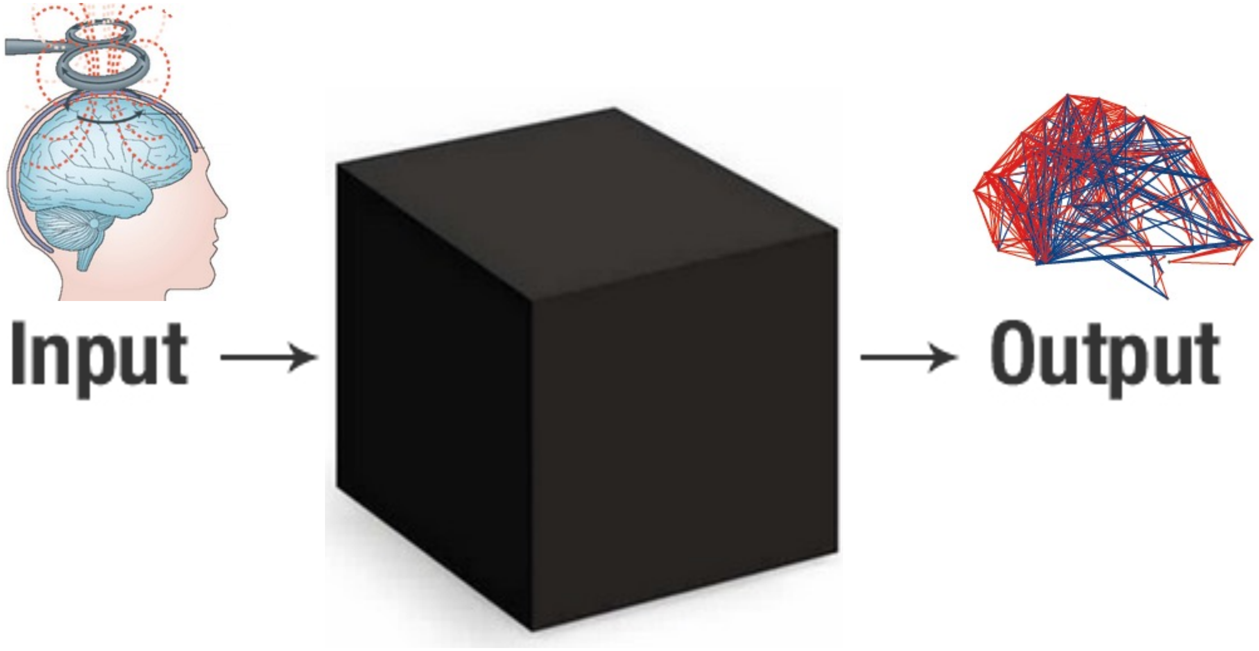
- General concepts of EEG-state triggered-TMS
- Evidences of brain-state dependency of excitability and plasticity in the sensorimotor cortex
- Modulation of brain rhythms and behavior stimulating the dorsolateral prefrontal cortex
- Final considerations on the potential of brain-state dependent stimulation

From TMS-EEG to EEG-TMS

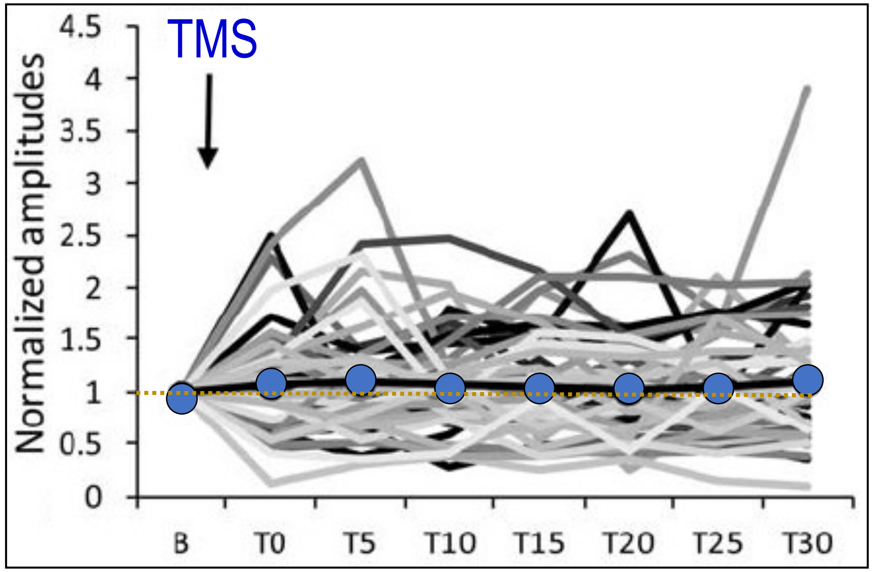
In more than 30 years of modern TMS the brain has been considered as **a black box**

Only responses to TMS have been observed (MEPs, TEPs, Induced Oscillations)

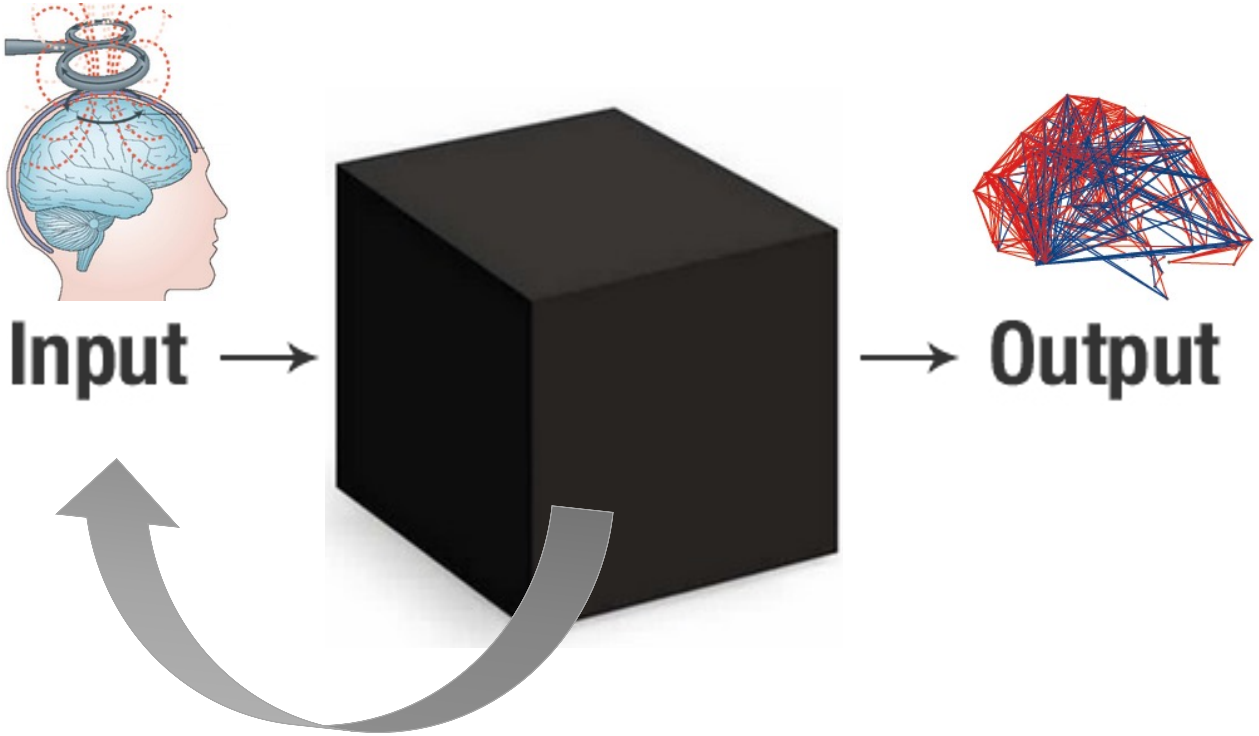
The brain state or activity at the time of the stimulation has never been taken into account!

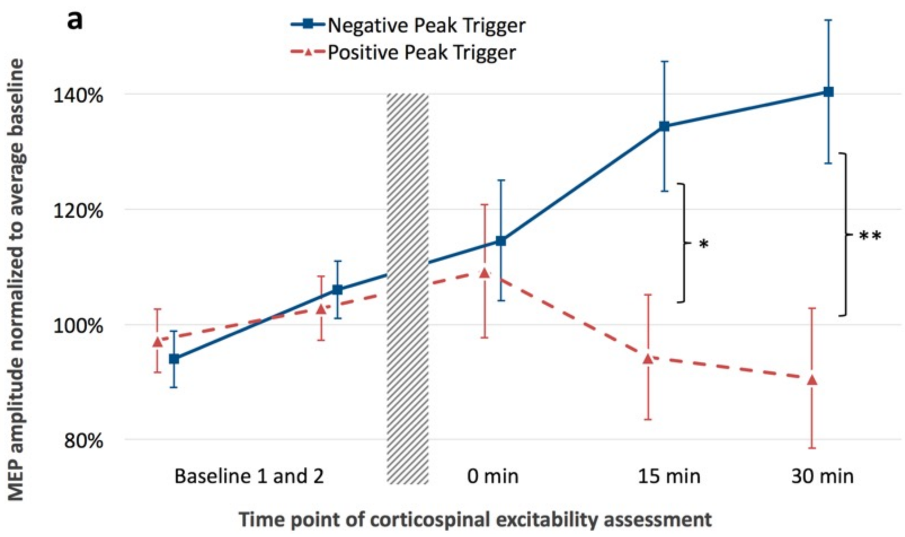


Plasticity induction in healthy subjects



Hamada et al. (2013)





Zrenner et al. (2018)

The EEG-triggered TMS Approach

The efficacy of TMS protocols is proven but:

1. Moderate
2. Effects highly variable (inter- and intra-individuals)

Oscillatory brain activity is not taken into account
but plays a crucial part in neural information processing

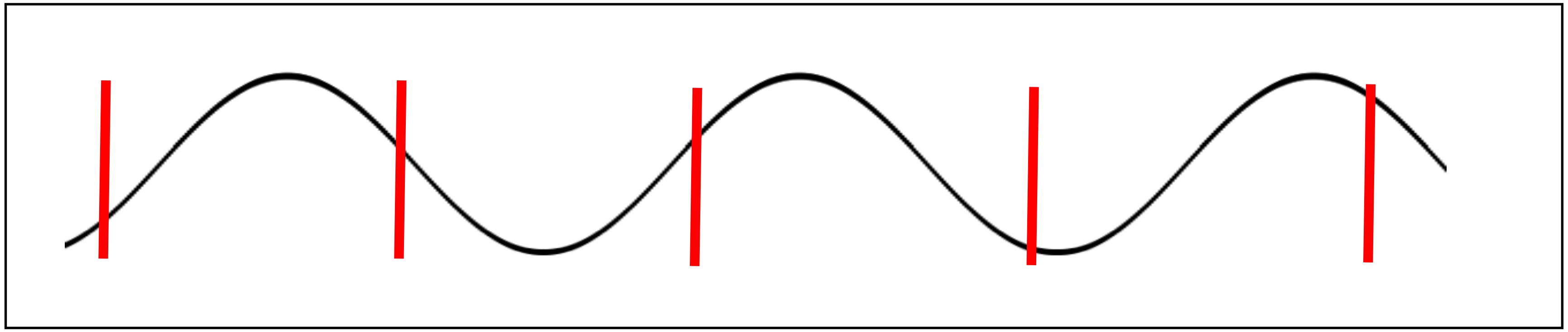
- ➢EEG-triggered TMS enables new stimulation protocols synchronized with oscillating brain states

- ➢This may enable **individualized network modulation** and reorganization in neurological and psychiatric disease

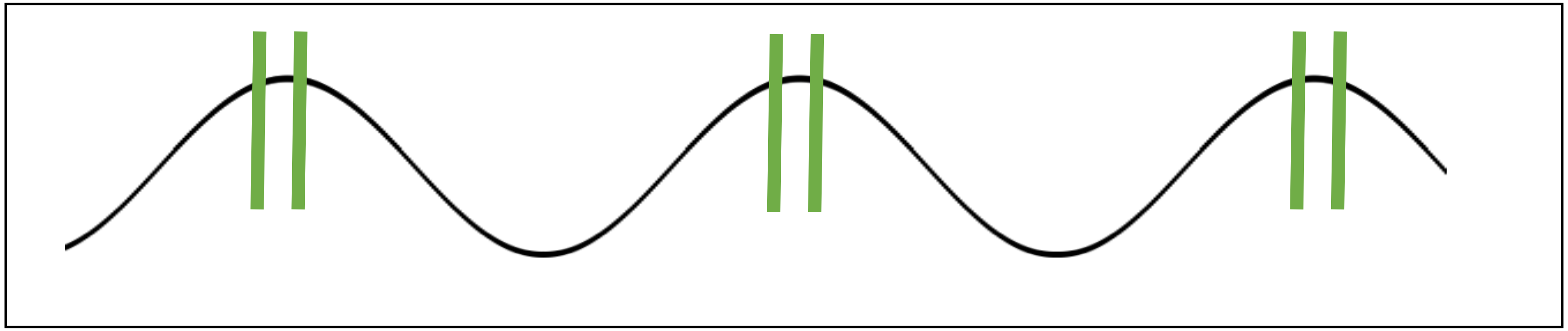
First Priority: Precision in Space and Time

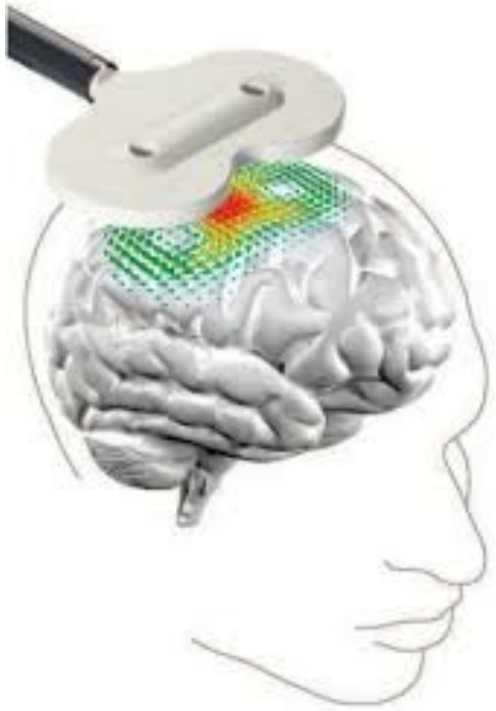
First Priority: Precision in Space and Time

Pre-determined stimulus sequence:



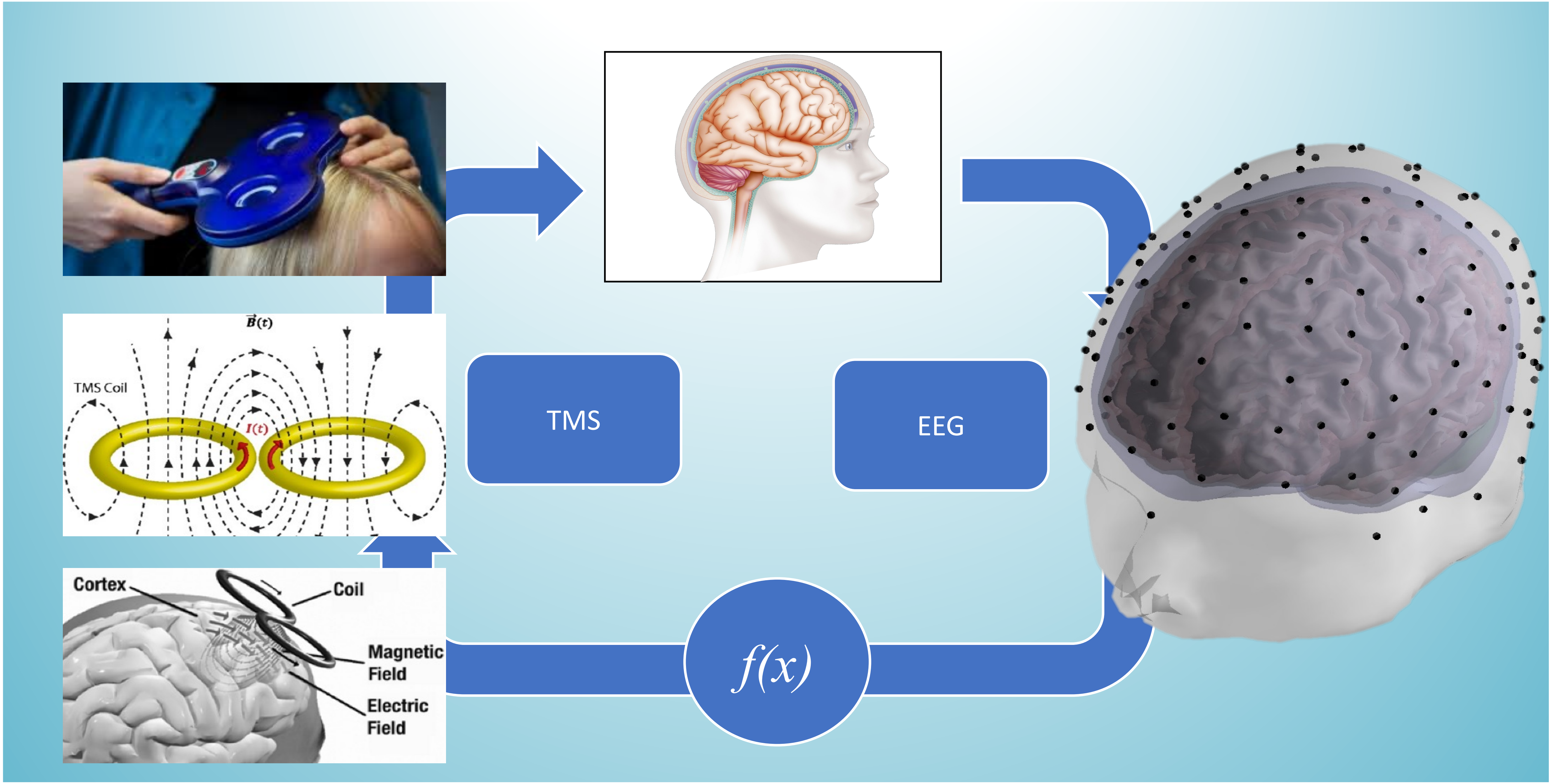
Brain oscillation synchronized „personalised“ stimulation:

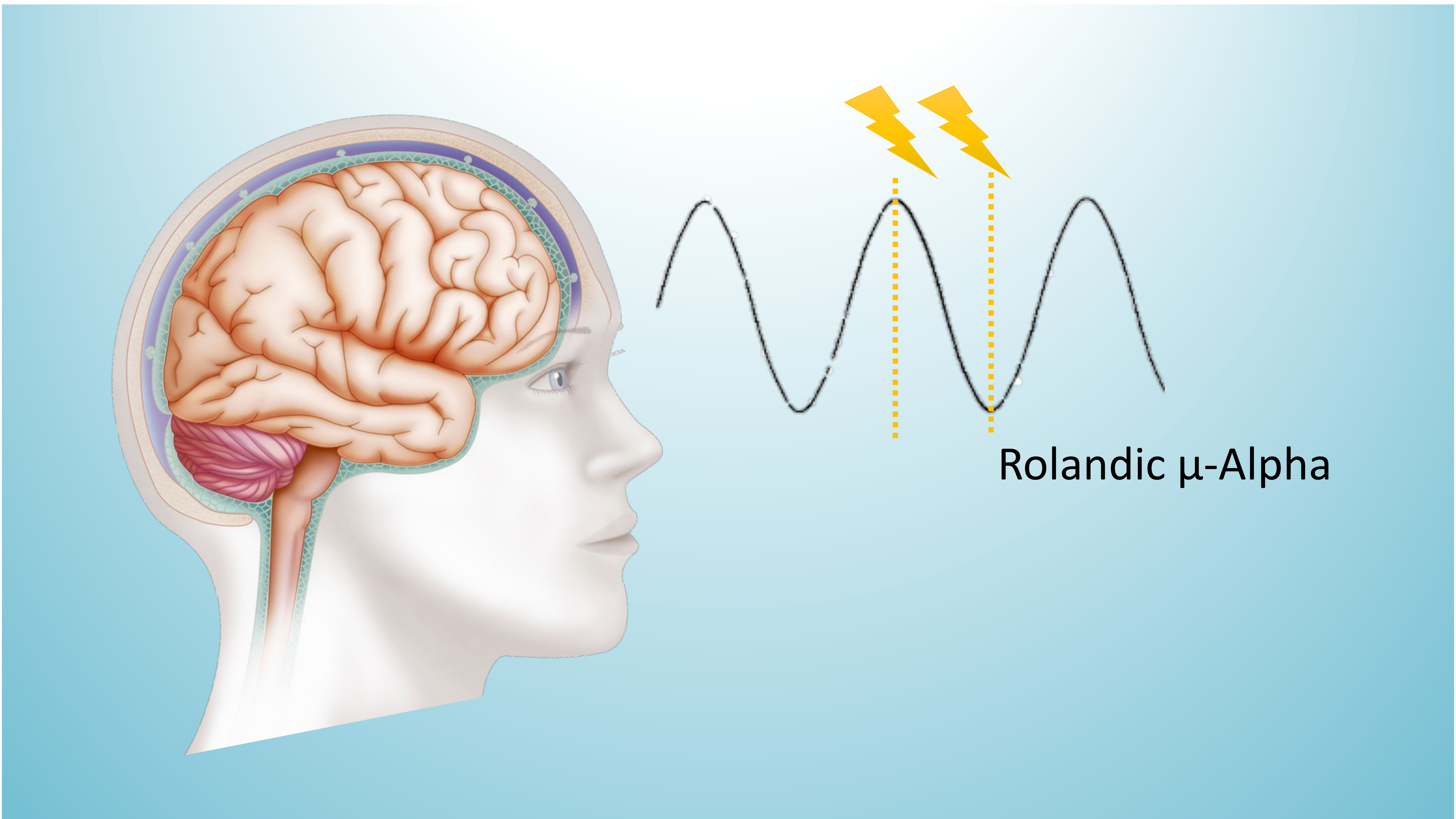




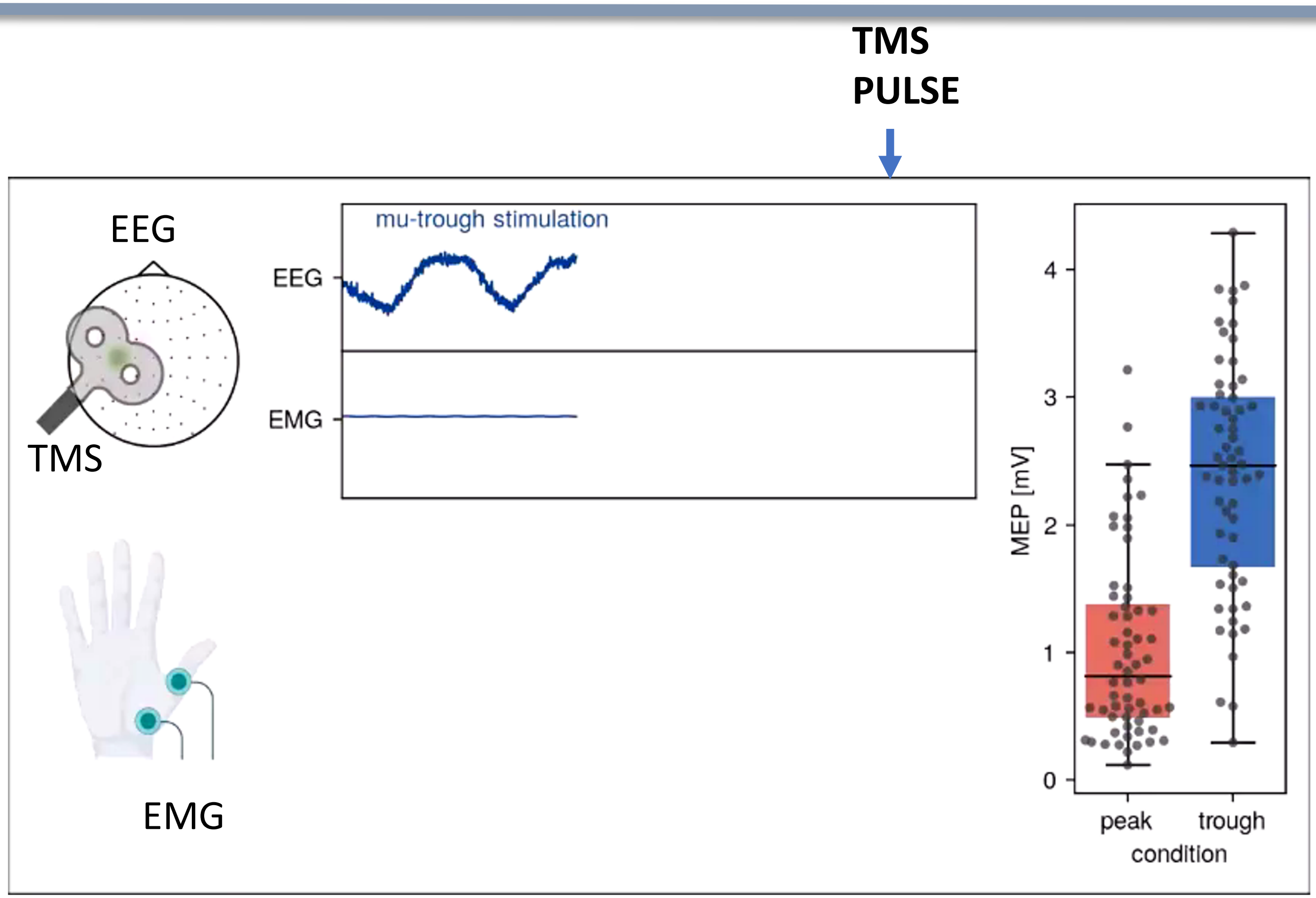
→ **Therapeutic Effectiveness and Reliability?**

A New Chance for Individualized Brain Stimulation and Analysis




Rolandic μ-Alpha

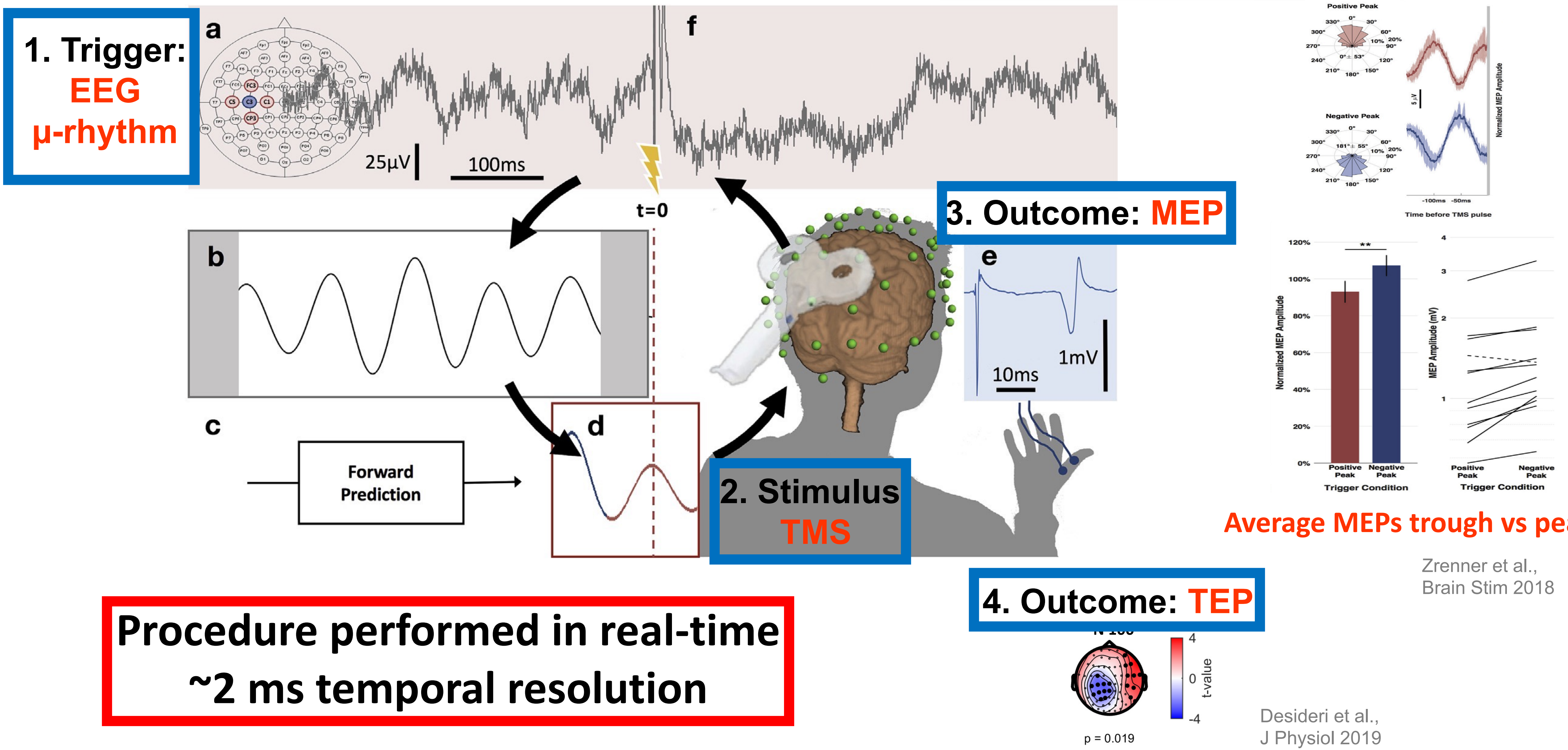
EEG sensorimotor μ-phase matters



Courtesy of Natalie Schaworonkow

Phase of μ-alpha EEG oscillation determines TMS-induced excitability in the motor cortex

Real-time EEG-TMS Stimulation



Average MEPs trough vs peak

Zrenner et al., Brain Stim 2018

Desideri et al., J Physiol 2019

Procedure performed in real-time
~2 ms temporal resolution

Phase of µ-alpha EEG oscillation determines TMS-induced plasticity in the motor cortex

Plasticity experiment

100 single -pulse TMS stimuli
4-6 seconds interstimulus interval
Stimulation intensity calibrated to have on average 1 mV MEP at baseline

Baseline 1 | Baseline 2 | Test time 0 | Test time 15 | Test time 30

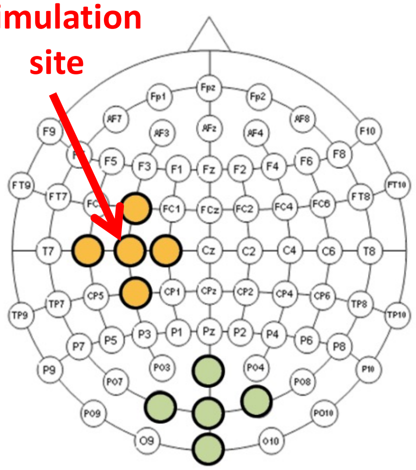
0 | 8 | 15 | 23 | 26 | 34 | 41 | 49 | 56 | 64 | min

Local Hjorth-C3 phase trigger

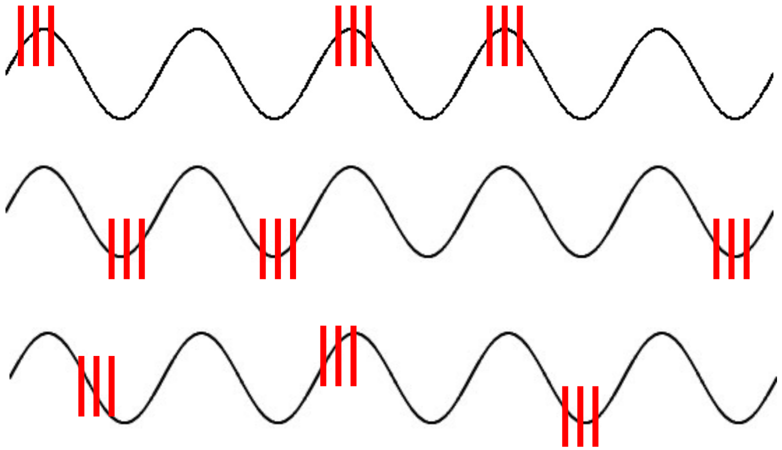
Distal Hjorth-Oz phase trigger

Replay of same pulse sequence

Stimulation site



200 x 100 Hz triplets at 80% RMT

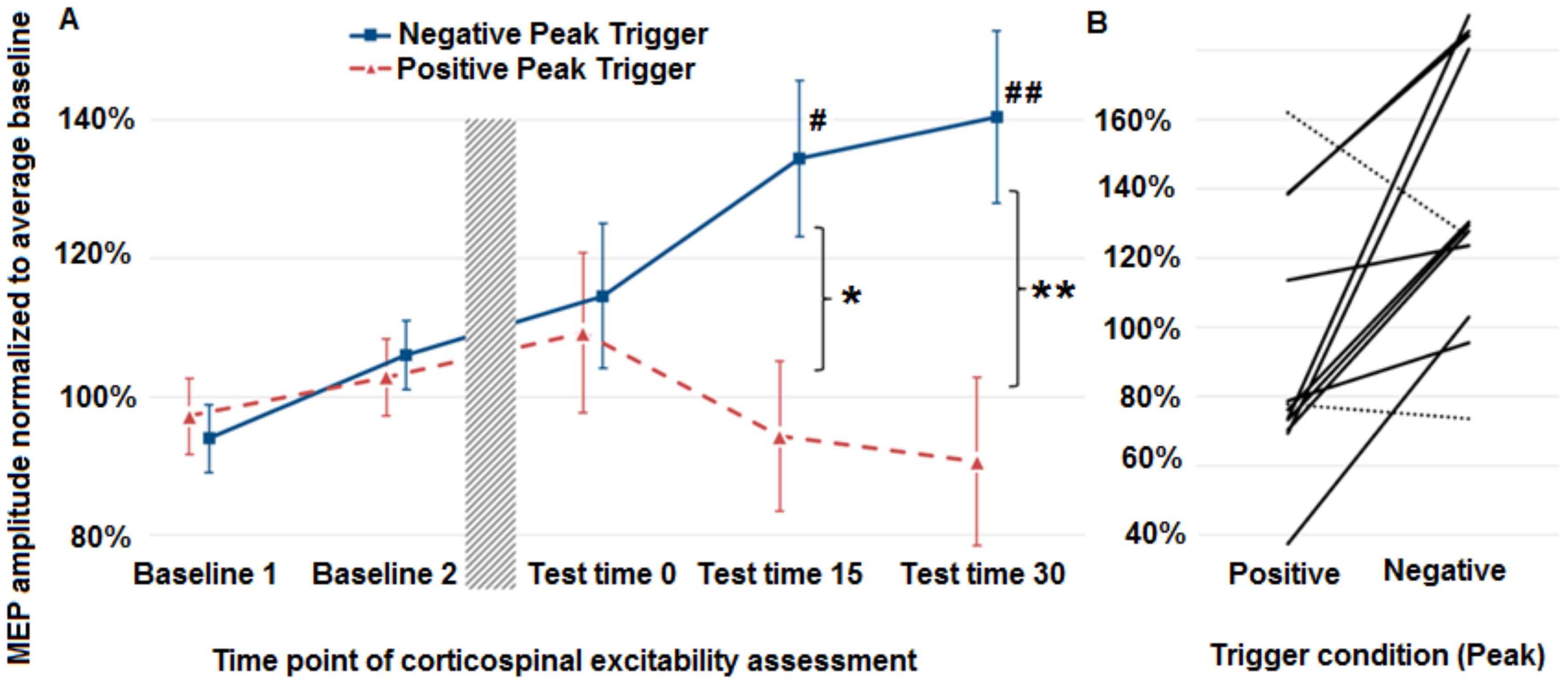


Zrenner et al., Brain Stim 2018

Direction of corticospinal plasticity depends on sensorimotor mu-alpha oscillatory phase

Group

Single Subjects



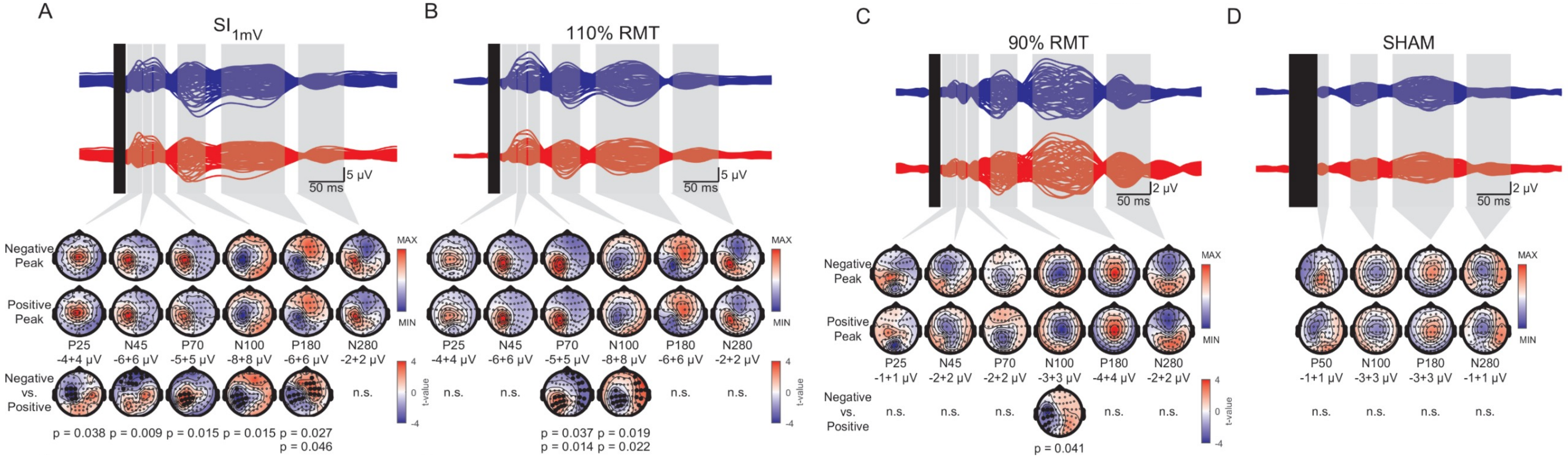
Significant effects of PHASE (rmANOVA $F_{1,11}=7.01$, $p=0.023$) and the interaction of PHASE and TIME ($F_{3,33}=4.78$, $p=0.007$), but not TIME ($F_{3,33}=1.17$, $p=0.34$)

Individual data averaged over the post-rTMS 15- and 30-min time points

Zrenner et al., Brain Stim 2018

What about specific effects of μ-alpha EEG oscillation on TMS evoked potentials (TEPs)?

Phase of sensorimotor µ-alpha modulates cortical responses to TMS on motor cortex

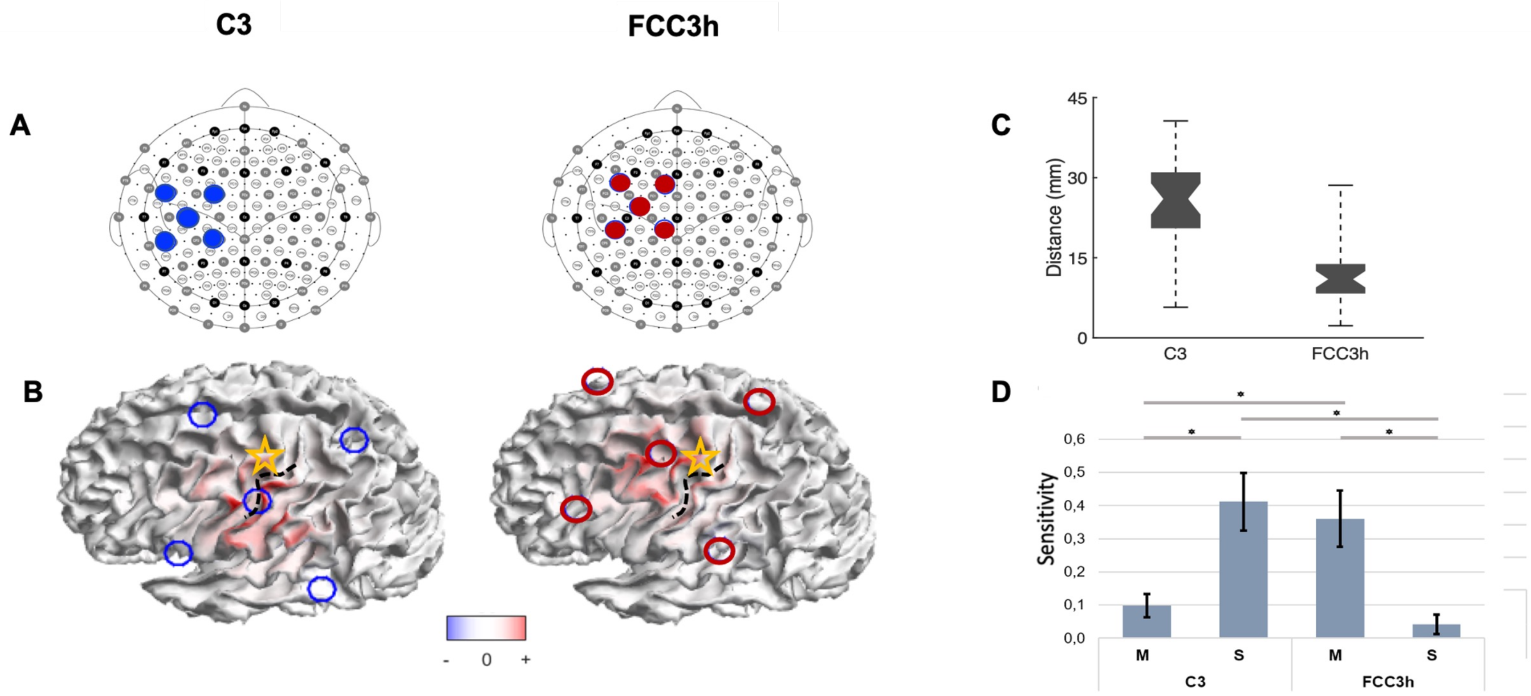


Desideri et al. Journal of Physiology 2019

Brain State: WHERE and WHEN fine-tuning

WHERE - Question: which is the origin of the sensorimotor rhythm relevant for corticospinal excitability/plasticity effects?

μ-phase from somatosensory but not motor cortex correlates with corticospinal excitability in EEG-triggered TMS



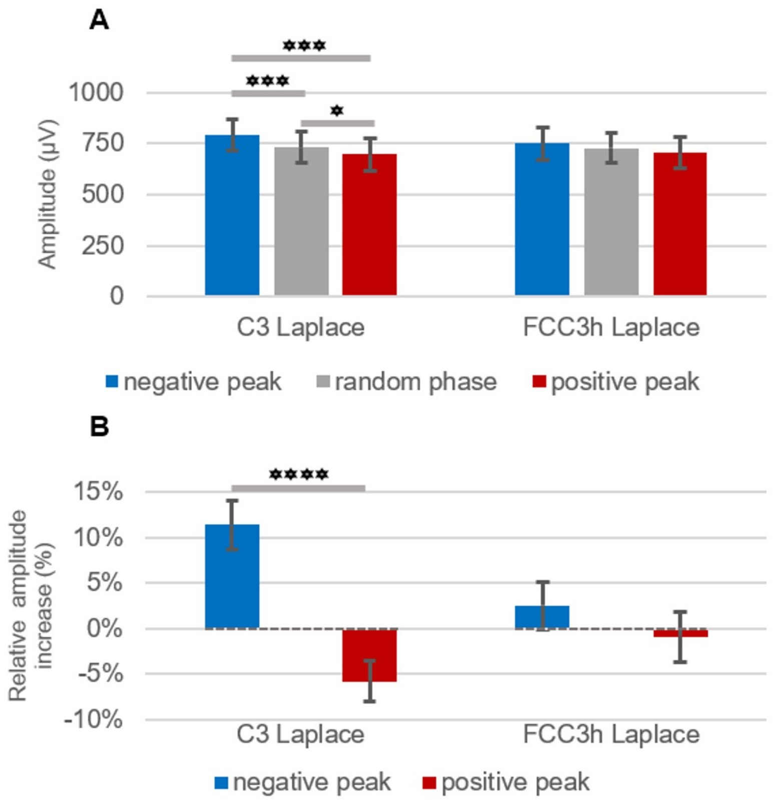
Hypothesis: EEG signal from precentral gyrus (A, B) would correlate more strongly with MEP amplitude (D), given that the corticospinal neurons are located in the anterior wall of the sulcus and the corticospinal tract has input from premotor cortex.

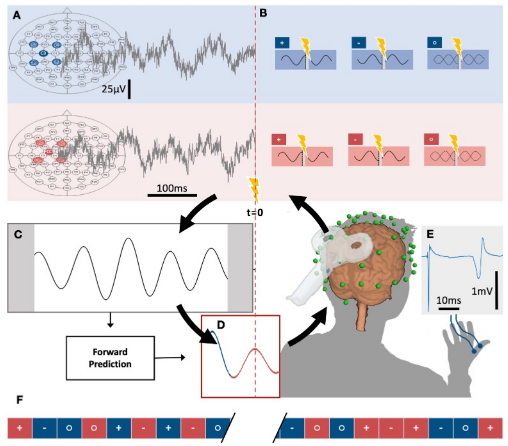
Zrenner , Belardinelli et al. 2022,J Neurosci Methods

Relationship between C3 vs. FCC3h extracted µ-rhythm phase and MEPs

MEP Amplitude

Relative Amplitude Increase





3 different phase conditions of the ongoing µ-rhythm

(**A**) Absolute peak-to-peak MEP amplitudes (in µV), the bottom panel

(**B**) Differences to random phase.

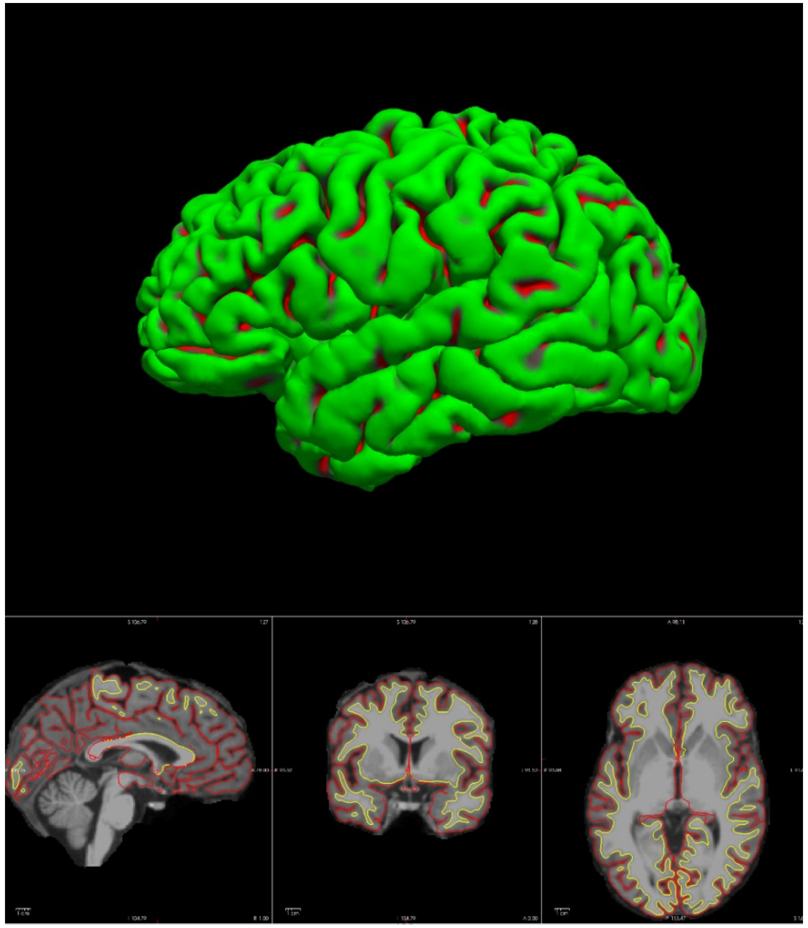
RESULTS

- C3 N vs. P peak µ-peak (postcentral gyrus) correlated with high vs. low MEPs ($p < 0.001$)
- No correlation for µ-rhythm extracted from FCC3 montage (precentral gyrus).
- - -> S1 EEG-signals are better predictors of corticospinal excitability than M1 signals.

Zrenner , Belardinelli et al. 2022,J Neurosci Methods

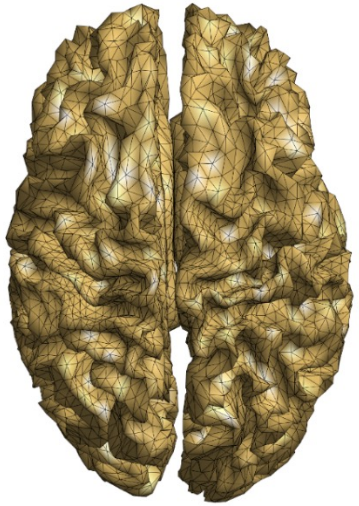
Integration of EEG-TMS results in **one native space** in RT

Cortical source space obtained
by segmentation of individual MRI

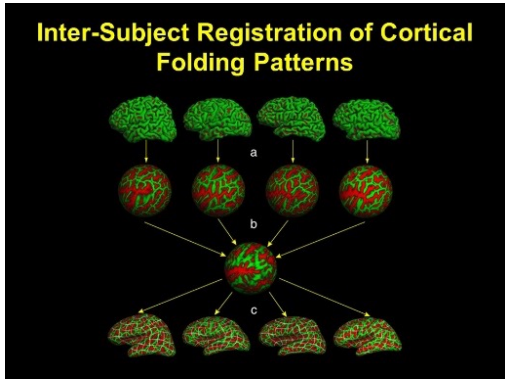


Belardinelli et al., in prep

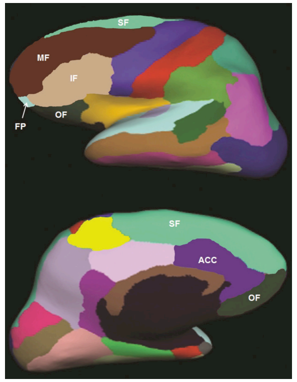
Surface Tessellation
with a Standard Number of Points



164/32/8/4k vertices
per hemisphere
ACPC or sensor coordinates

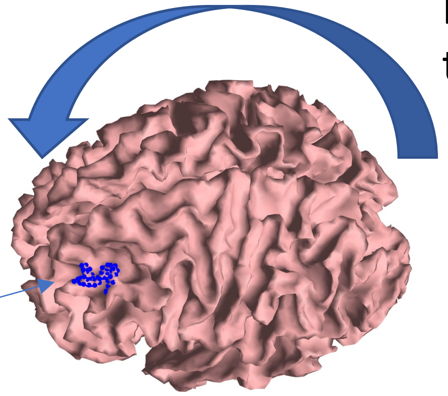


Cortical Parcellation



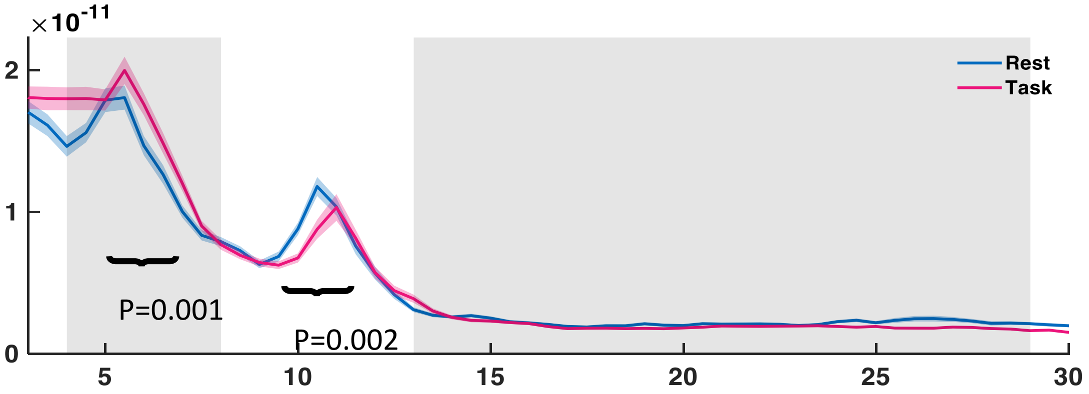
Online and Offline Source Analysis of Brain Oscillations

Frequency Peak decreases along the posterior-anterior axis



A-PRIORI DEFINED SOURCE OF INTEREST

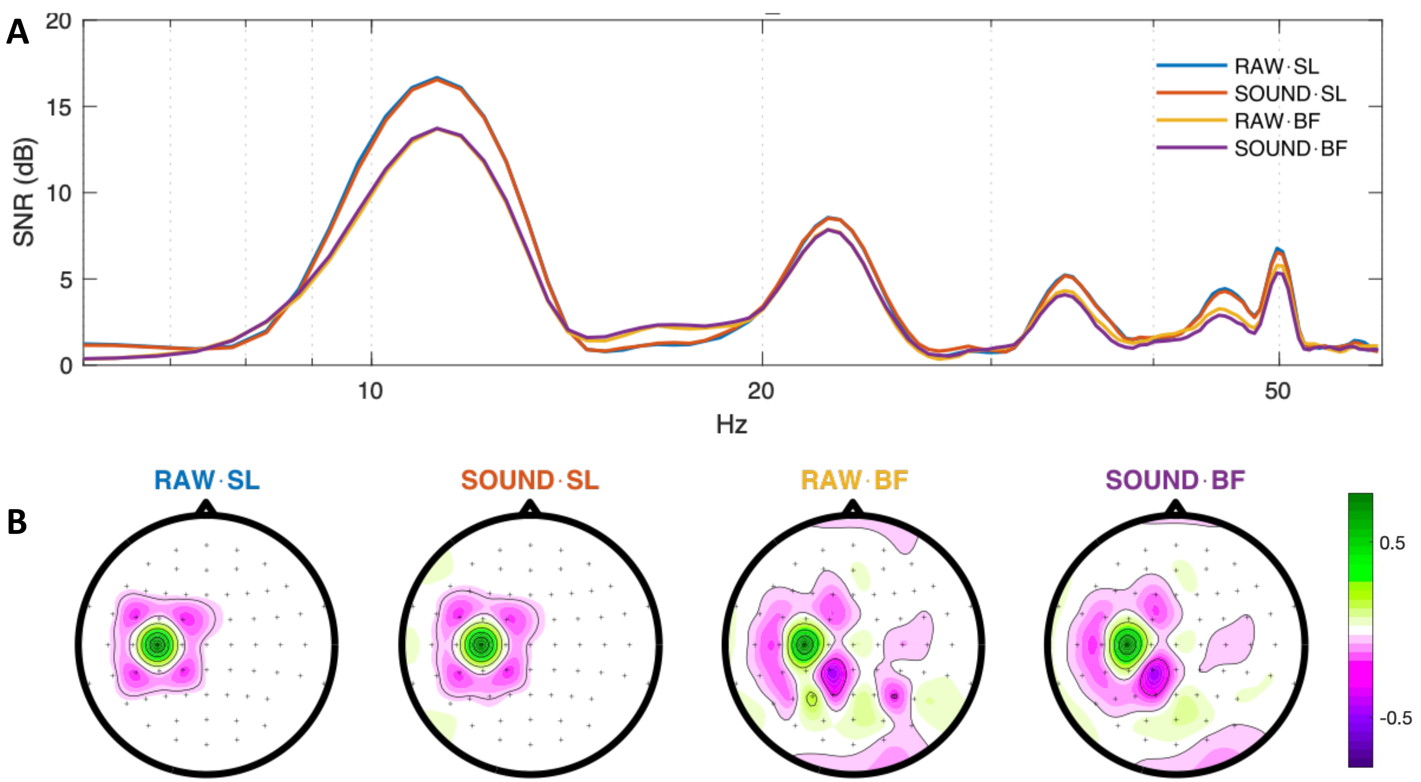
POWER SPECTRUM OF OSCILLATIONS IN THE SOURCE OF INTEREST



Brain-State dependent stimulation: WHEN fine-tuning

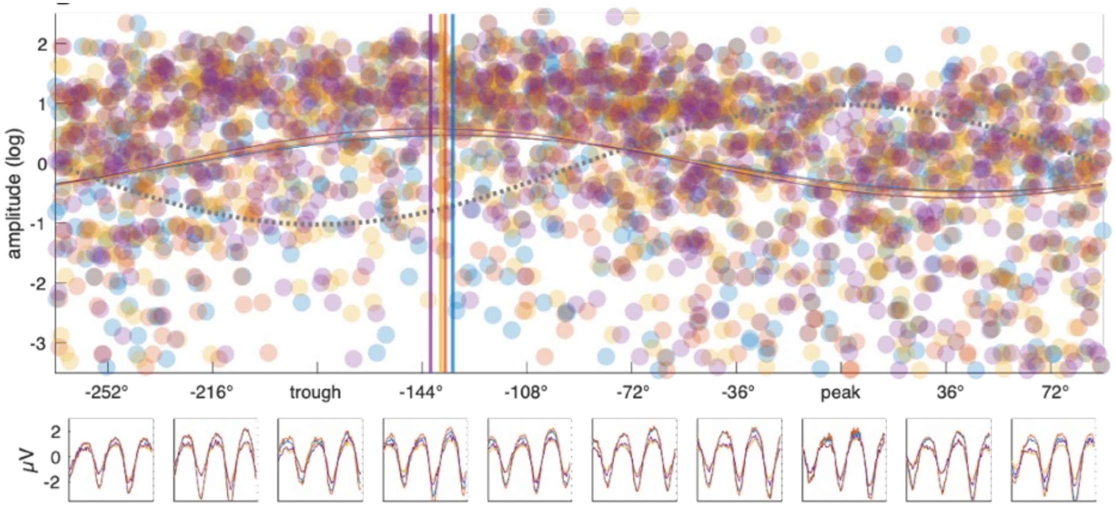
WHEN - Question: which is the origin of the sensorimotor rhythm relevant for corticospinal excitability/plasticity effects?

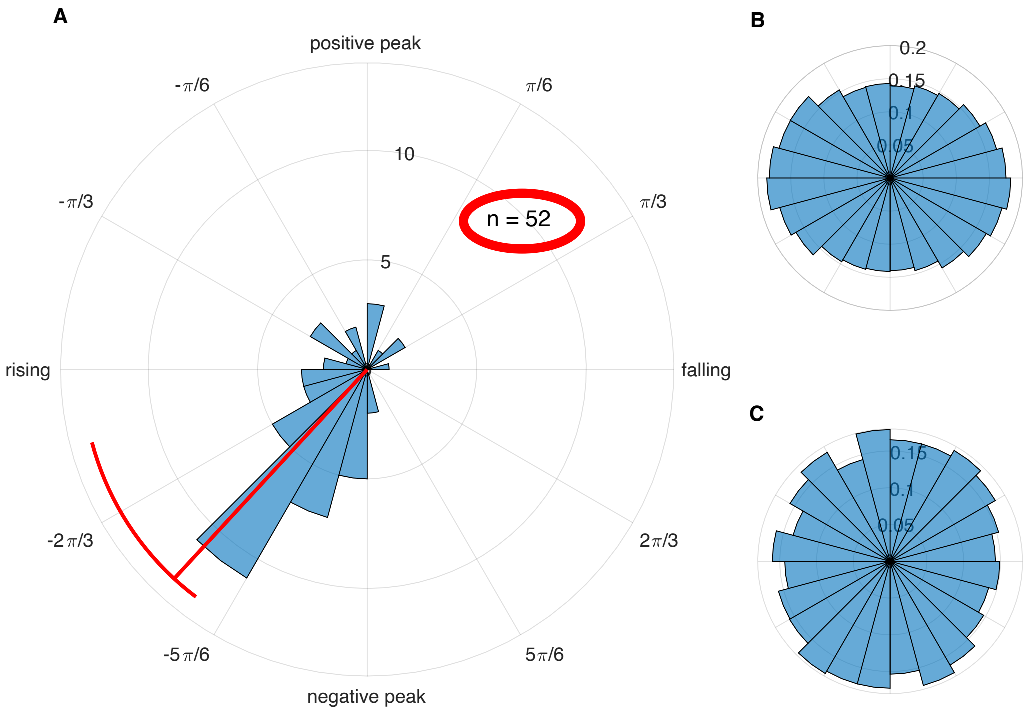
Different filters to obtain the phase-refence signal



Zrenner et al., NeuroImage 2023

Exact mu-alpha phase corresponding to largest MEPs

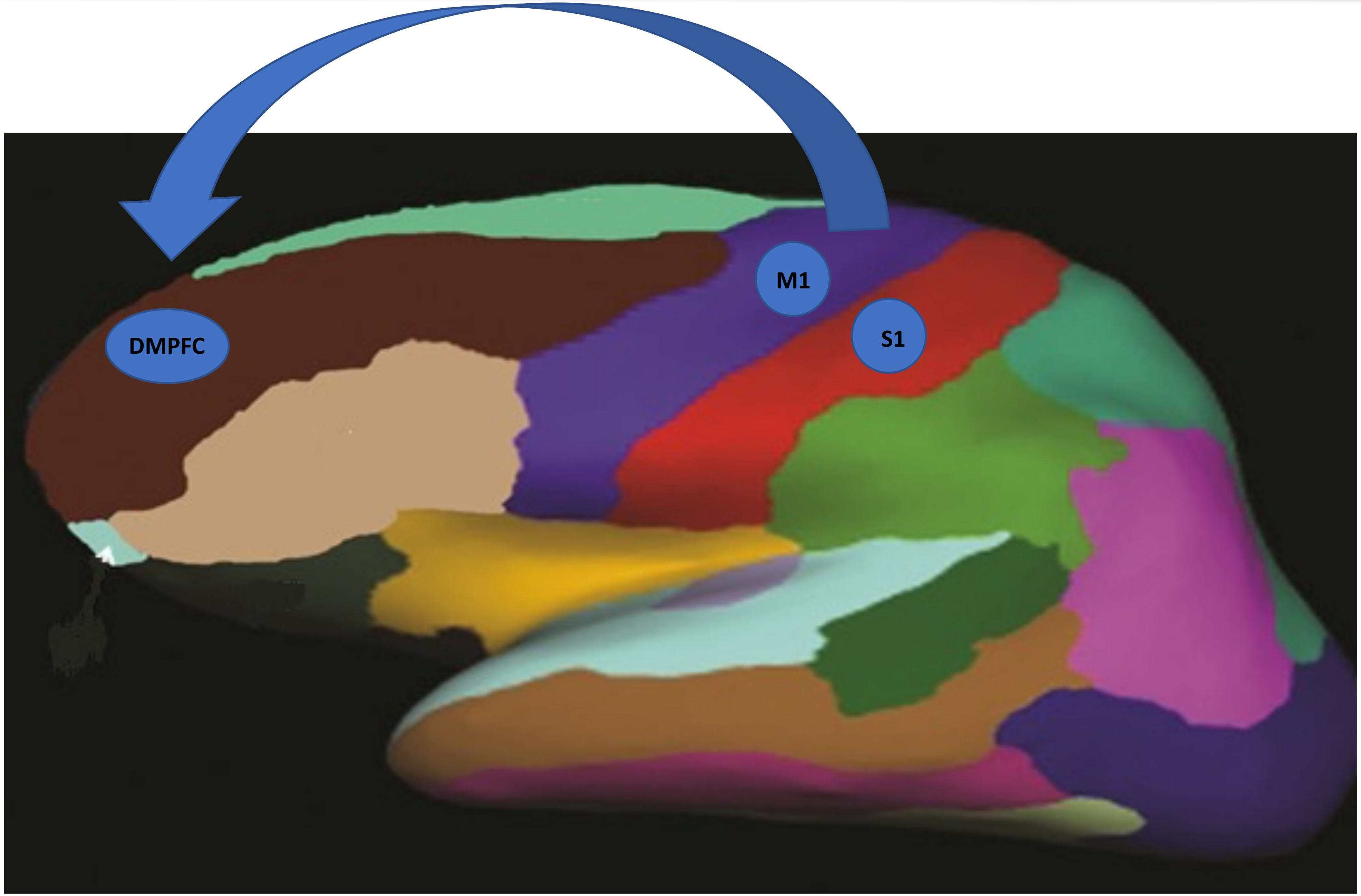




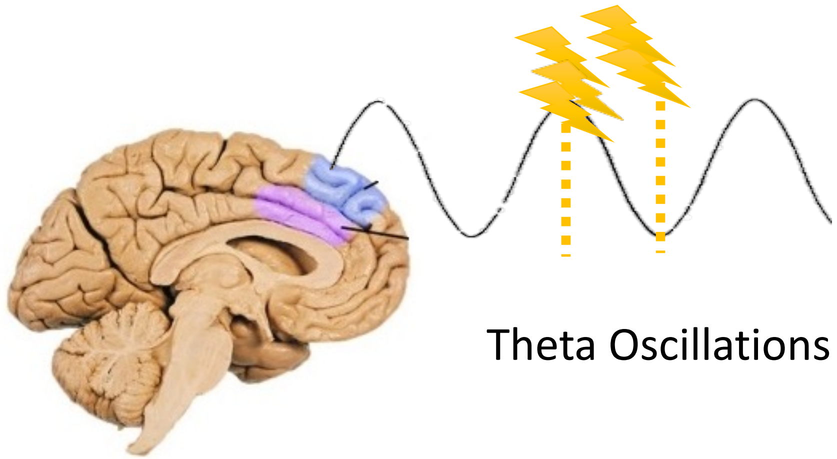
(A) Distribution of phase of maximum corticospinal excitability of sensorimotor
(B) Normalized overall distribution of phase estimates for all 52 participants.
(C) Normalized distribution of phase angle of highest corticospinal excitability for all data with MEP amplitudes randomly shuffled

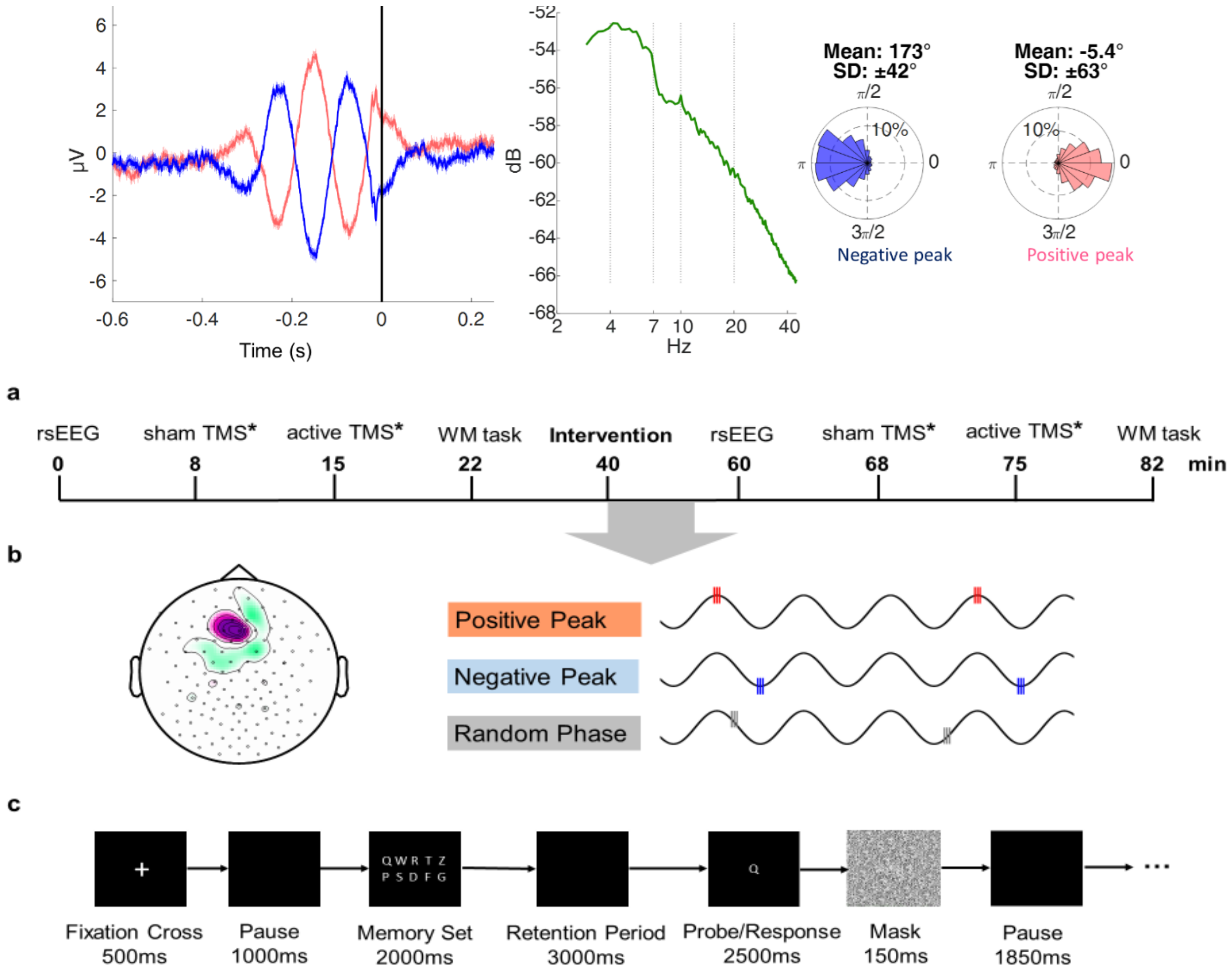
Zrenner et al., NeuroImage 2023

From The sensorimotor system to DMPFC



Can EEG phase-dependent TMS influence Behavior?





Gordon et al., Brain Stim 2022

Effects on single pulse TMS-induced oscillations

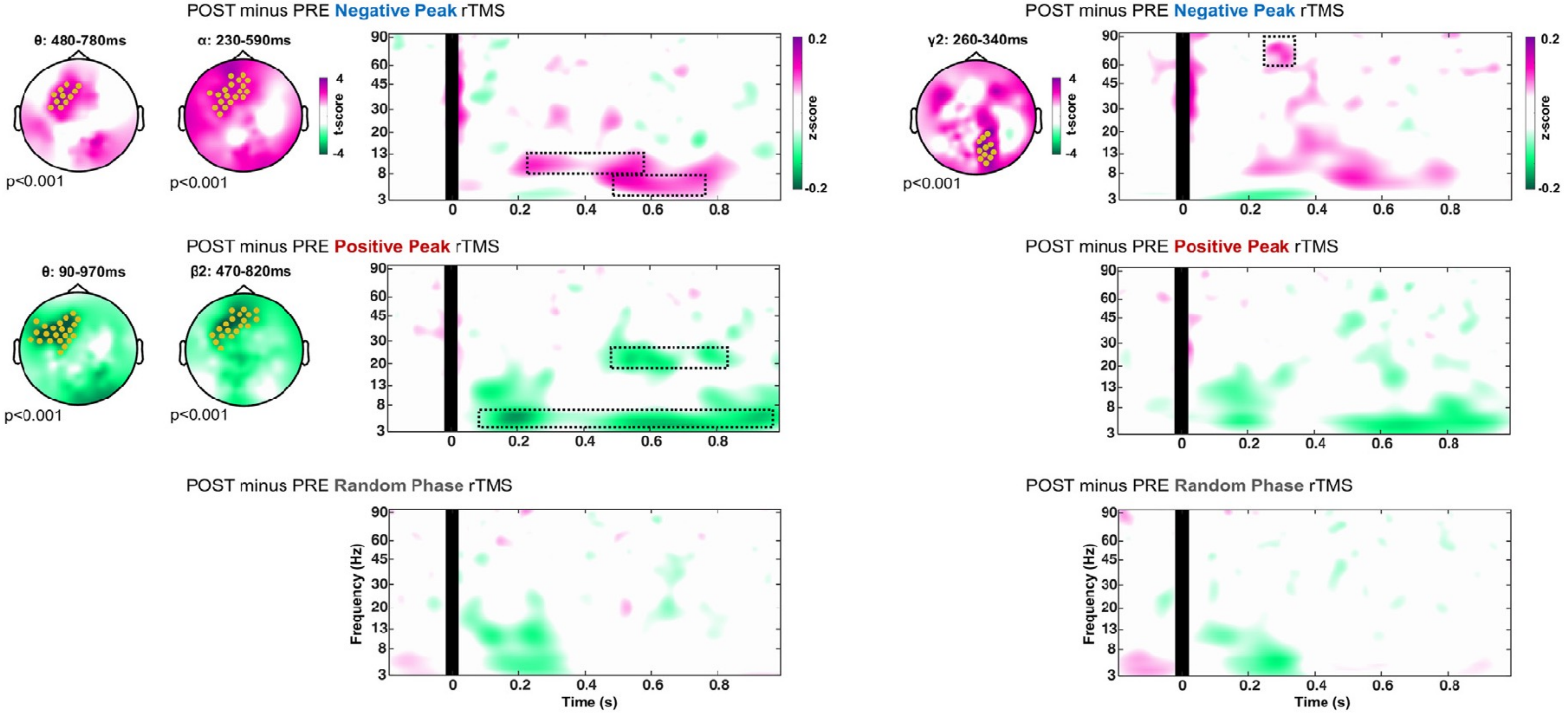
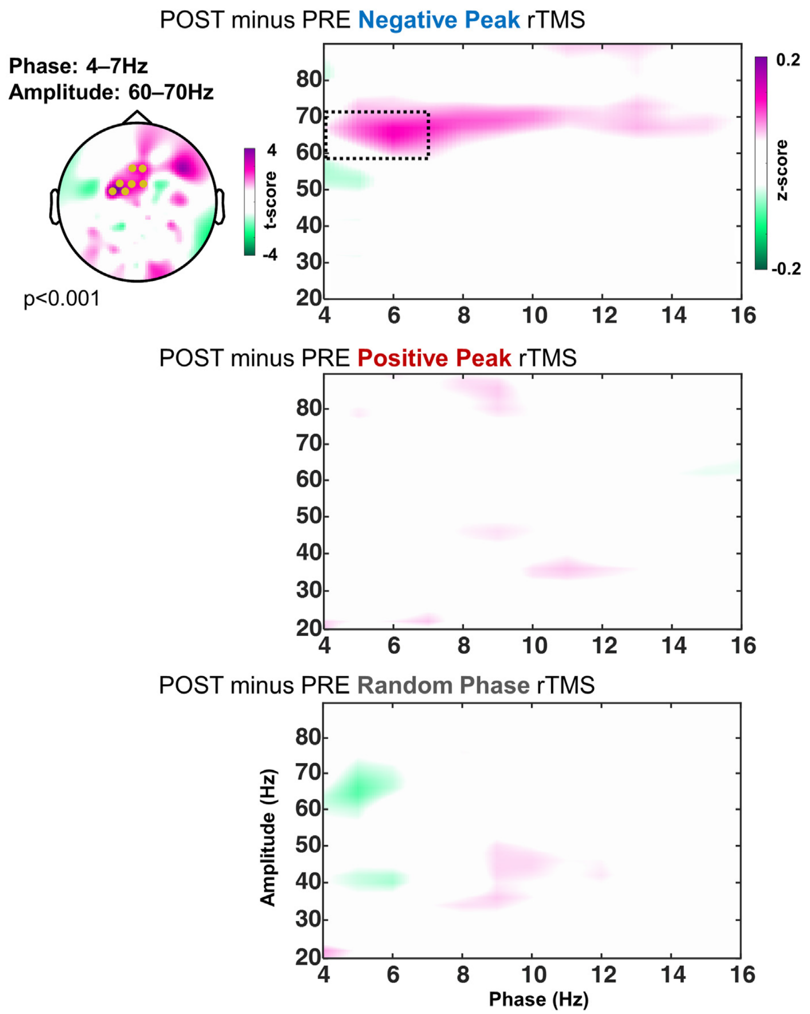


Fig. 4 : Evidence that negative theta-peak rTMS increased single pulse TMS-induced theta power (first row). Conversely rTMS at positive peak decreased the same measure (second row), whereas random phase rTMS did not provide for any significant results in the comparison pre-post rTMS intervention (third row, from Gordon, Belardinelli et al. 2022).

Gordon et al., Brain Stim 2022

Modulation of Phase-Amplitude Coupling



Gordon et al., Brain Stim 2022

Can EEG phase-dependent TMS influence Behavior?

- Three theta-phase specific EEG-rTMS interventions were applied to prefrontal cortex
- Effects were tested by TMS-EEG and working memory performance
- Positive theta-phase rTMS **decreased TMS-induced theta power**
- Negative theta-phase rTMS **increased TMS-induced theta power** and gamma-theta PAC
- **Only Negative theta-phase rTMS improved working memory performance**

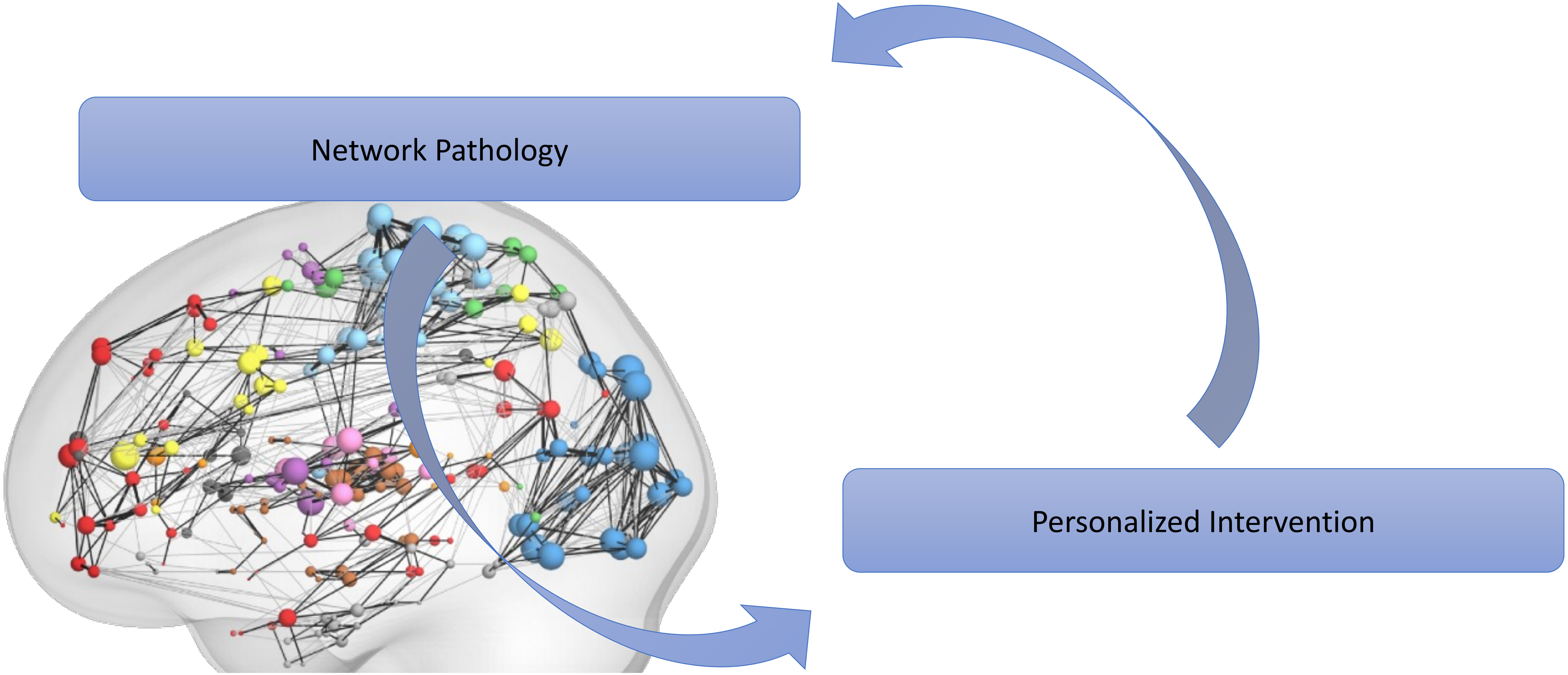
Answer: Yes, it can

Non-invasive state-dependent stimulation in a nutshell

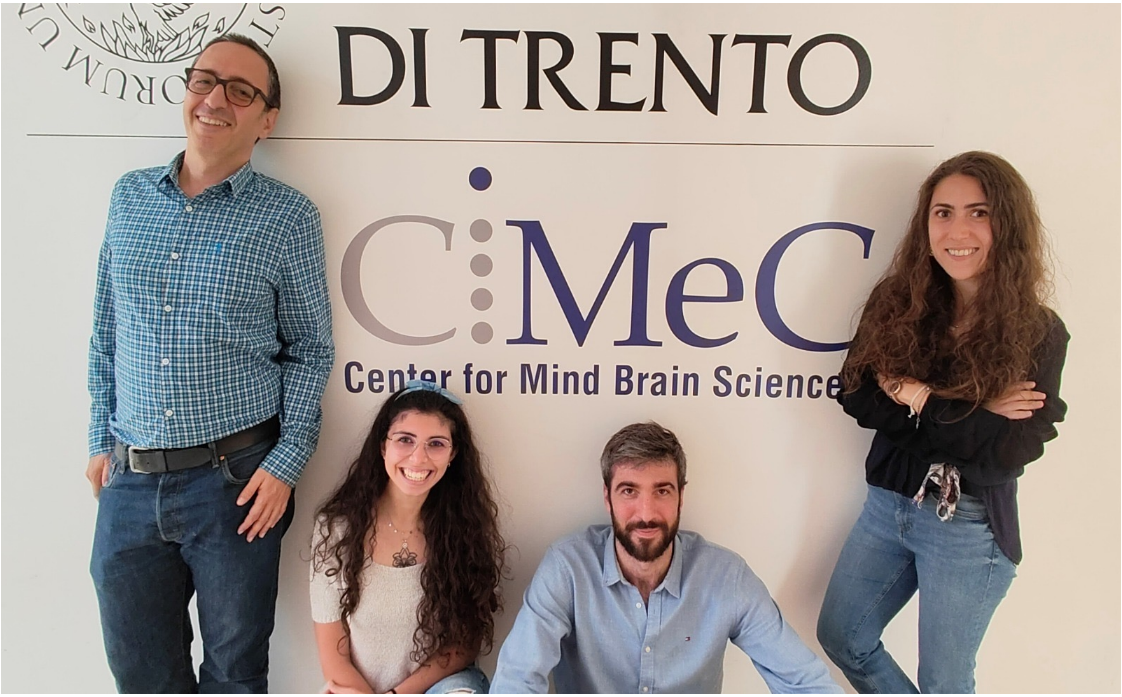
- Instantaneous local phase determines brain excitability and **direction of** plasticity
- Feasibility demonstrated in different cortical areas
- **Negative oscillation peak (and early rising)** appears as a window of marked excitability and prone to LTP
- Spatial (cm) and temporal (ms) accuracies are key
- **Potential massive impact on personalized non-invasive rehabilitation approaches**

Answer: Yes, we can

EEG state-dependent TMS for personalized intervention



Thank you for your attention!



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