Combined tACS-TMS study:
Effects of phase-dependent and frequency-selective M1 inhibition

Aneta Dvorakova[1,2], Aikaterini Gialopsou[1], Edward de Haan[2], Stephen R. Jackson[1,3]
1 School of Psychology, University of Nottingham, UK, 2 Donders Institute, Netherlands, 3 Institute of Mental Health, University of Nottingham, UK
Aneta.Dvorakova@nottingham.ac.uk

Background

Oscillatory bands in M1 (primary motor cortex)

- Drive inhibition (alpha/beta) and excitation (gamma) (**1**)
- Reflect interaction of **inhibitory interneurons** and **pyramidal cells (2)**

Specific neuronal frequency preference (3,4)

- Pyramidal cells **<30 Hz**
- Inhibitory interneurons **>30 Hz**

tACS (transcranial alternating current stimulation) (**5**)

Can entrain

- Neuronal spike **timing**
- Spiking **phase** of neurons
- Modulate excitation and inhibition

TMS (transcranial magnetic stimulation) measures (**6**)

Single-pulse (SP) TMS
- Corticospinal **excitability** : mediated by **pyramidal cells**

Paired-pulse TMS
- Short Intracortical **Inhibition** (SICI): mediated by **$GABA_A$ergic inhibitory interneurons**)

tACS-TMS studies in M1 show (**1, 2, 7, 8**)

tACS modulation is
- **Frequency-dependent**
- **Phase-dependent**
- Most significant in beta band (~20 Hz)

Aim

Test selective modulation of excitatory-inhibitory balance in M1 across different frequencies

via possibly targeting distinct neuronal populations based on their oscillatory frequency preference and stimulation phase

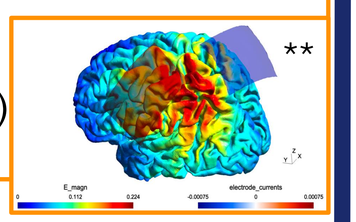
Methods

Design

- **N>24,** healthy adults
- **Within-subject,** 2 sessions, 2 stimulation blocks per session separated by 15-minute break, 3-7 days apart
- **TMS** at **4 non-harmonic frequencies (online),** randomly **across all phases**
- **MEP** from **FDI** muscle **at rest**, EMG

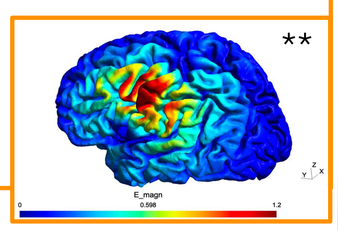
tACS Stimulation Parameters:

- **5x7 cm** sponge electrodes
- Anode: **motor hotspot**; Cathode: **Pz** (10-20 EEG) (**7**, **8**)
- Simulation waveform: **Sinusoidal**
- Duration: **24 minutes**
- Amplitude (peak-to-peak): **1.5 mV** (**5**)
- Frequency: **6, 10, 20, 37 Hz**



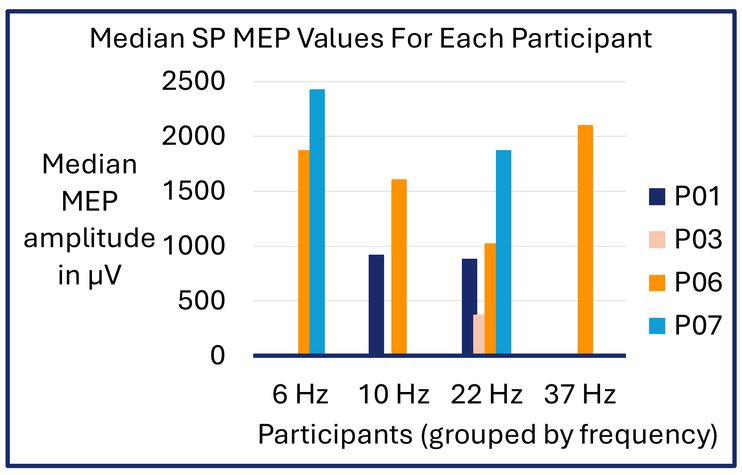
TMS Stimulation Parameters:

- **Monophasic**; 50 mm figure-of-8 coil, **PA** coil orientation
- Brainsight neuronavigation system
- **N ~ 25** pulses per phase (Σ~200) (**9**)
- ITI = **5-7 s (7, 10)**
- **SP**: **120%** of **RMT** (**10**)
- **SICI**: CS = **80% of RMT** (**7**)
  TS = **120% of RMT** (**7, 10**)
  ISI = **3 ms** (**7, 11**)

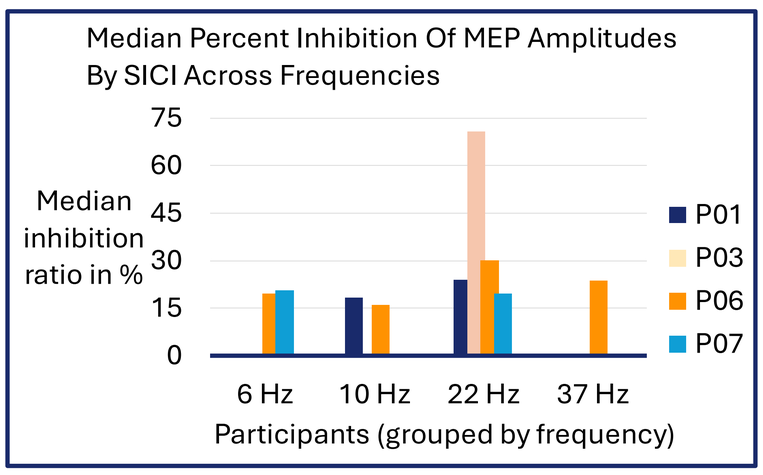


**
Simulated electric field distribution in M1 using subject-specific head model (SimNIBS 4.5.0). Overlay shows field strength for tACS (A) and TMS (B) stimulation in V/m (12).

Preliminary Results



Median of single pulse MEP amplitudes across frequencies
↑ amplitude = ↑ excitation



Bar plot showing the percentage ratio of median SP-SICI MEP amplitudes by frequency.
↑ ratio = ↓ inhibition

- SP responses (mean = 0.514) were significantly higher than SICI (mean = -0.623), Mann-Whitney U test, $p < 0.001$, Cohen's $d = 1.384$
- LME model (ZScore ~ Frequency * Condition + (1|Participant), 1411 observations, 4 participants) showed significant Condition effect ($p < .001$) and Frequency × Condition interaction ($p = .024$); no main Effect of Frequency ($p = .078$). AIC = 3519.5, BIC = 3551.

Processing and Analysis

- **EMG Filtering:** bandpass filter (10-2000 Hz); notch at stimulation frequency
- **Phase identification, MEP Identification, MEP Quantification, SICI Assessment**
- **Statistical analysis (planned):** Linear mixed-effect model with fixed effects: frequency, phase, and their interaction; random effect: participant
- **Controlling for**: Effect of time of stimulation; order of stimulation frequency (possibility of STDP)

Expected Results & Limitations

Modulation of excitatory-inhibitory balance

Effect of Phase

- At all frequencies (**5**)
- 10 Hz: ↑ SP at trough
- 22 Hz: ↑ SP at/before peak

Effect of Frequency (strongest)

22 Hz (Beta):
↑ SICI vs. 6, 10 Hz
↑ SP excitation vs. 6, 10 Hz

37 Hz (Low Gamma):
↑ SICI vs. 6, 10, 22 Hz
↓ SP excitation vs. 6, 10, 22 Hz

Limitations (1, 2, 8)

- Induction of spike timing dependent plasticity
- Large-scale network dynamics vs. local microcircuit modulation
- Inter-individual variability in responsiveness to tACS and TMS

References

1. Rostami, M., Lee, A., Frazer, A. K., Akalu, Y., Siddique, U., Pearce, A. J., Tallent, J., & Kidgell, D. J. (2025). Determining the effects of transcranial alternating current stimulation on corticomotor excitability and motor performance: A sham-controlled comparison of four frequencies. *Neuroscience*, 568, 12–26.
2. Wang, Q., Gong, A., Feng, Z., Bai, Y., & Ziemann, U. (2024). Interactions of transcranial magnetic stimulation with brain oscillations: A narrative review. *Frontiers in Systems Neuroscience*, 18, Article 1489949.
3. Gaugain, G., Al Harrach, M., Yochum, M., Wendling, F., Bikson, M., Modolo, J., & Nikolayev, D. (2025). Frequency-dependent phase entrainment of cortical cell types during tACS: Computational modeling evidence. *Journal of Neural Engineering, 22*(1), 016028.
4. Fellous, J. M., Houweling, A. R., Modi, R. H., Rao, R. P., Tiesinga, P. H., & Sejnowski, T. J. (2001). Frequency dependence of spike timing reliability in cortical pyramidal cells and interneurons. *Journal of Neurophysiology*, 85(4), 1782–1787.
5. Herrmann, C. S., Rach, S., Neuling, T., & Strüber, D. (2013). Transcranial alternating current stimulation: A review of the underlying mechanisms and modulation of cognitive processes. *Frontiers in Human Neuroscience*, 7, 279.
6. Spampinato, D. A., Ibanez, J., Rocchi, L., & Rothwell, J. (2023). Motor potentials evoked by transcranial magnetic stimulation: Interpreting a simple measure of a complex system. *The Journal of Physiology,* 601(13), 2911–2932.
7. Guerra, A., Pogosyan, A., Nowak, M., Tan, H., Ferreri, F., Di Lazzaro, V., & Brown, P. (2016). Phase dependency of the human primary motor cortex and cholinergic inhibition cancelation during beta tACS. *Cerebral Cortex, 26*(10), 3977–3990.
8. Wischnewski M., Schutter DJLG., Nitsche MA. (2019). Effects of beta-tACS on corticospinal excitability: A meta-analysis. *Brain Stimulation*, 12(6):1381-1389.
9. Chang, W. H., Fried, P. J., Saxena, S., Jannati, A., Gomes-Osman, J., Kim, Y.-H., & Pascual-Leone, A. (2016). Optimal number of pulses as outcome measures of neuronavigated transcranial magnetic stimulation. *Clinical Neurophysiology*, 127(8), 2892–2897.
10. de Albuquerque, L. L., Pantovic, M., Wilkins, E. W., Morris, D., Clingo, M., Boss, S., Riley, Z. A., & Poston, B. (2024). Exploring the influence of inter-trial interval on the assessment of short-interval intracortical inhibition. *Bioengineering (Basel),* 11(7), 645.
11. Dyke, K., Kim, S., Jackson, G. M., & Jackson, S. R. (2018). Reliability of single and paired pulse transcranial magnetic stimulation parameters across eight testing sessions. *Brain Stimulation*, 11(6), 1393-1394.
12. Thielscher, A., Antunes, A. and Saturnino, G.B. (2015). Field modeling for transcranial magnetic stimulation: a useful tool to understand the physiological effects of TMS? *IEEE EMBS 2015, Milano, Italy.*