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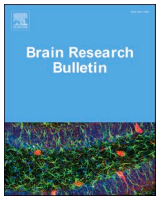

Research report

# Influences of current direction on 1 Hz motor cortex rTMS

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ABSTRACT

*Objective:* Neuromodulatory changes induced by repetitive transcranial magnetic stimulation (rTMS) are highly variable and lack replicability. Amongst many influencing factors, the current direction of the stimulation is known to affect rTMS aftereffects. In this study, we investigated the influence of current direction on cortical and peripheral markers of motor cortex plasticity as induced by 1 Hz rTMS as well as the correlation of cortical and peripheral markers. Additionally, we investigated possible confounding variables.
*Methods:* Twenty-five healthy subjects received 2000 pulses of 1 Hz rTMS at 110 % resting motor threshold intensity over the left motor hotspot inducing anterior-posterior – posterior-anterior (AP-PA) and posterior-anterior – anterior-posterior (PA-AP) current directions in the brain. Motor evoked potentials (MEPs) and transcranial evoked potentials (TEPs) before and after rTMS were assessed with single pulses. Coil placement was ensured by a neuronavigated robot-assisted setup.
*Results:* In sum, 1 Hz rTMS resulted in higher amplitudes of MEPs and TEP components N15, N45 and P60 and a reduced amplitude of N100, whereby the induced PA-AP current direction in the brain elicited higher effects. MEP and TEP N15 latency were prolonged and N100 shortened after rTMS. PA-AP current direction elicited stronger changes in latency for MEPs and N15. N45 and MEP correlated in the PA-AP pre rTMS condition with negligible effect size.
*Conclusions:* Our findings of facilitatory pre-to-post rTMS changes are in contrast to preliminary assumptions that 1 Hz rTMS acts inhibitory. However, since high variability and low reliability of rTMS aftereffects are prominent in the current literature, these results shed light that potential influencing factors need to be better reported, controlled and investigated. We suggest to further investigate effects of stimulation intensity and tiredness of subjects on rTMS. We were able to replicate current direction effects which strengthens the hypothesis of activation of different sets of neurons.

## 1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation (NIBS) method to assess cortical excitability (Barker et al., 1985; Hallett, 2000), which is commonly used in research and clinical diagnostics (Hallett, 2000; Di Lazzaro et al., 2004). By delivering a short current pulse through a coil placed over the scalp, TMS produces a rapidly changing magnetic field, which induces an electrical field in the underlying tissue that can lead to depolarization and action potential propagation in the cortical neurons (Di Lazzaro et al., 2018). Through suprathreshold TMS pulses applied over the motor cortex, so-called motor evoked potentials (MEPs) can be derived via electromyography (EMG) from the respective contralateral muscle in the periphery. These are typically used as a marker for cortico - spinal excitability (Pascual-Leone et al., 1998; Di Lazzaro and Rothwell, 2014).

Cortical excitability can be directly measured via transcranial evoked potentials (TEPs), which represent cortical responses to TMS pulses and are derived from electroencephalography (EEG; Bergmann et al., 2016). When TMS is applied over the motor cortex, the evoked brain activity is represented by a waveform of positive and negative peaks at consecutive latencies which are referred to as the N15, P30, N45, P60 and N100 TEPs (Bonato et al., 2006; Tremblay et al., 2019; Ahn and Fröhlich, 2021).

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During this propagation of neuronal signal, TEPs differ spatially, i.e. in topography, and are affected by confounding signal, indicating that different cortical areas and networks are involved in the signal propagation of all peaks (Momi et al., 2021; Zazio et al., 2021, 2022; Farzan and Bortoletto, 2022). The combined peak-to-peak amplitude of N15 and P30 has been found to correlate with MEP amplitude and thus might reflect the underlying motor cortical excitation (Mäki and Ilmoniemi, 2010; Gedankien et al., 2017). The components N45 and P60 are associated with reafferent motor signals during stimulation of the motor cortex (Mäki and Ilmoniemi, 2010; Petrichella et al., 2017; Ahn and Fröhlich, 2021). N100 is argued to represent inhibitory processes (Rogasch et al., 2013) and motor activity (Roos et al., 2021). Later TEPs like the P180 and N280 were not associated with motor activity (Casula et al., 2014) and showed confounded signal, mainly auditory (Ahn and Fröhlich, 2021), which is why we did not include them in our analyses. Additionally, the M1-P15, a positive TEP peak over contralateral fronto-central electrodes of the stimulated motor cortex was found to reflect cortico-cortical inhibition (Bortoletto et al., 2021; Zazio et al., 2022; Guidali et al., 2023). In contrast to MEPs, TEPs can be elicited by subthreshold stimulation and thus can provide a more sensitive and immediate measure of cortical responses to TMS (Komssi et al., 2004). However, TEPs are also sensitive to confounding activity, such as somatosensory and auditory stimulation (Conde et al., 2019), which further complicates causal interpretation.

In order to alter cortical excitability, TMS pulses are applied in a rhythmic manner at certain frequencies which is termed repetitive transcranial magnetic stimulation (rTMS) and is a frequently used neuromodulation technique with effects outlasting stimulation offset (Ridding and Rothwell, 2007). Hence, rTMS is capable to induce neuroplasticity and is thus utilized in a wide range of basic science experiments (Fitzgerald, 2002; Todd et al., 2010; Patel et al., 2020) as well as in clinical settings as a therapeutic option for various neuro-psychiatric diseases (Mishra et al., 2011; Lefaucheur et al., 2014).

The underlying mechanisms of inducing neuroplasticity via rTMS have not been fully understood yet. It is suspected that depending on the frequency of rTMS, mechanisms of long-term depression (LTD) or long-term potentiation (LTP) of synaptic strength are accountable (Hallett, 2000; Fitzgerald et al., 2006). Commonly low frequency rTMS is assumed to inhibit cortical excitability, whereas high frequency stimulation acts excitatory (Fitzgerald et al., 2006; Thut and Pascual-Leone, 2010). We refer to this assumption as the lofi-hife heuristic: low frequency inhibitory – high frequency excitatory (Prei et al., 2023). These rTMS effects or pre-to-post changes can be observed for cortico-spinal excitability in the healthy population in increased MEP amplitudes after excitatory high frequency protocols and lower MEP amplitudes after inhibitory low frequency protocols (Pascual-Leone et al., 1994; Wassermann et al., 1996; Tang et al., 2019). However, these findings are not always reproducible (Prei et al., 2023) and show only low to moderate reliability (Kanig et al., 2023). Due to the high variability of findings, it is advisable to treat the effects of rTMS with caution and to set up experiments as objectively as possible and to systematically investigate possible influencing factors.

Only few studies investigated neuromodulatory effects on TEPs in healthy subjects. Casula et al. (2014) found increased P60 and N100 amplitudes after 1 Hz rTMS over the left motor cortex. Zhou et al. (2022) reproduced this effect partially by evoking an increased N100 and reduced P60. After 0.6 Hz rTMS, an immediate numeric reduction and subsequent significant increase to baseline levels of N45 was found by van der Werf and Paus (2006). During application of 20 Hz rTMS over the left primary motor cortex, increased cortical responses in early TEPs (P5, N8) over electrode C3 were found along with shorter latencies, whereas no differences in P30 and N45 occurred (Veniero et al., 2010).

In sum, rTMS effects are highly variable as can be seen in heterogeneous findings (Thut and Pascual-Leone, 2010; Kanig et al., 2023; Schoisswohl et al., 2024). Contributing factors to this variability are choices in experimental design (Iezzi et al., 2008; Fleming et al., 2012; Pellegrini et al., 2020), physiological (Todd et al., 2010; Di Lazzaro et al., 2015) and also technical parameters (Sommer et al., 2002; Tings et al., 2005; Lang et al., 2006). Stimulation parameters like induced current direction in the brain are known to influence cortical and cortico-spinal excitability measures: in single pulse TMS, different resting motor thresholds (Kammer et al., 2001; Davila-Pérez et al., 2018), MEP latency and reliability of MEP amplitude (Davila-Pérez et al., 2018) were found for varying current directions. Casula et al. (2018) reported greater positive TEP peaks for monophasic posterior-anterior (PA) current direction and greater negative TEP peaks for both monophasic anterior-posterior (AP) or biphasic anterior-posterior – posterior-anterior (AP-PA) current direction, while TMS stimulus intensities were overall higher for the AP current direction. Also, topographies of components until 80 ms differed between current direction (Casula et al., 2018). It is discussed that different current directions activate different sets of neurons in the pre- and post-central gyrus (Li et al., 2017; Di Lazzaro et al., 2018). In response to rTMS, MEPs showed higher excitatory pre-to-post changes after 5 Hz rTMS for induced posterior-anterior - anterior-posterior (PA-AP) current direction in the brain than AP-PA pulses (Sommer et al., 2013a). The same pattern of MEP excitation (averaged normalized MEP modulation amplitudes) was found to correlate stronger with peak values of AP depolarizing pulses than PA depolarizing pulses (Halawa et al., 2021). Yet, stronger inhibition after 1 Hz rTMS was found for monophasic PA in contrast to AP induced current in the brain (Goetz et al., 2016). Hereby, it is to be noted that for biphasic pulses the second phase is more effective (depolarizing) than the first, corresponding to the direction of the monophasic pulse phase (Salvador et al., 2011).

In the present study, we investigated the pre-to-post changes of 2000 pulses of 1 Hz rTMS for default and reversed current direction of a MagVenture MagPro X100 pulse source in several neurophysiological metrics - MEPs and TEPs. We examined the differences between both current directions in rTMS changes as well as the underlying correlations of cortico - spinal (MEPs) with cortical measures (TEPs) to possibly deduce a cortical marker to equally assess the excitability and plasticity effects induced by TMS and rTMS, which then may be used as more proximal categorization variable of rTMS effects. Since findings on TMS and rTMS show only low to moderate reliability (Kanig et al., 2023; Osnabruegge et al., 2023; Prei et al., 2023) we intended to increase cortical inhibition effects of 1 Hz rTMS by increasing the intensity to suprathreshold level (Fitzgerald, 2002; Lang et al., 2006). Additionally, we used a state of the art robot-guided neuronavigated TMS setting (Goetz et al., 2019; Rossi et al., 2021) in combination with a within-subject experimental design.

## 2. Methods

The present experiment was conducted in compliance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the local ethics committee of the University of Regensburg (ethical approval number: 21–2662–1–101). All participants gave written informed consent before study begin.

### 2.1. Participants and exclusion criteria

Our sample included 25 healthy subjects (15 female) aged between 19 and 42 years ($M = 25$, $SD = 4$). All participants were German-speaking, right-handed ($M = 87.96$, $SD = 13.67$; Oldfield, 1971) had a mean intelligence quotient of $110.12 \pm 11.56$, assessed with the German version of the multiple-choice vocabulary intelligence test (MWTB-Q; Lehrl, 2018) and had no neurological, psychiatric or other severe somatic condition, which was examined by a trained clinical professional. Depression, assessed with the Major Depression Inventory (Bech et al., 2001), was not present ($M = 4.28$, $SD = 2.72$, Maximum = 10) in any subject. Other exclusion criteria were a high stimulation intensity, that would have exceeded our safety requirements (> 80 % maximum

stimulator output, which produces local sensations that are hard to tolerate), intake of psychoactive substances or medication as well as contraindications with respect to TMS and magnetic resonance imaging (MRI). The latter include ferromagnetic implants and a history of severe brain injuries or epileptic seizures. All participants received monetary compensation.

In two of the 25 subjects, EMG data was very noisy (mean MEP-to-baseline-ratio = 0.8 and 0.9) and thus, no MEPs could be identified for the condition before rTMS with reversed current direction in one subject and in the condition after rTMS with default current direction in another subject. Therefore, for MEP analyzes and the correlations, but not TEP analyzes, these two subjects for the respective condition were removed.

### 2.2. Procedure

The experiment consisted of two experimental sessions and a pre-session. In the pre-session, inclusion- and exclusion criteria were checked, informed consent was given, questionnaires were filled out and a T1-weighted MRI scan (MPRAGE 160 slices, 256 × 256, voxel size = 0.977 × 0.977 × 1 $mm^3$, flip angle 9°, TR/TE/TI = 1910/3.67/1040 ms) was made for the purpose of neuronavigation (3 Tesla; Siemens, Munich, Germany). In an experimental session, all TMS and rTMS stimulations were conducted with one current direction (default or reverse), whereby the starting direction was randomized a priori via number generation. 14 subjects started with default and 11 subjects started with reversed current direction, whereby all participants were blinded to the current direction used throughout the experiment. The experimental sessions started with rating visual analogue scales (VAS) from 1 (minimum) to 10 (maximum) on subjective attention, excitement, and tiredness levels, which was repeated after the session to track changes. Subjects were instructed to remove all electronic devices from their body and clothing, to sit as still as possible, keep their hands relaxed and their eyes on a fixation cross during all measurement procedures. EEG and EMG of the first dorsal interosseous (FDI), abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscle were attached and recorded throughout the TMS and rTMS measurements. The motor hotspot for optimal representation of the FDI muscle with default current direction was identified with a grid-based semi-automated method using cobot-assisted neuronavigated TMS setup; for a detailed description see Agboada et al. (2023). Hereby, high and stable MEPs in the FDI were aimed at whilst having relatively less activity in the APB and ADM as well as relatively lowest stimulation intensity. The individual motor hotspot elicited with default current direction was used throughout the whole experiment to ensure that the coil position and thus qualitative course of the induced electric field is comparable between current directions. Additionally, the resting motor threshold defined as 50 % of TMS stimuli resulting in a MEP in the FDI over 50 μV was determined (Rossini et al., 2015). 1 Hz rTMS intervention was made over subjects' individual motor hotspot at 110 % resting motor threshold (RMT) with 2000 pulses for each current direction. These suprathreshold and prolonged stimulation parameters were chosen to enhance the achievable rTMS effect (Maeda et al., 2000; Fitzgerald, 2002; Peinemann et al., 2004; Lang et al., 2006). Before and after rTMS, 100 single TMS pulses were applied at the individual motor hotspot at 110 % RMT as well, with an inter-stimulus interval (ISI) of 10 s and jitter of 2 s. All TMS pulses were masked throughout the entire experiment by a masking noise composed of 70 % white noise combined with 30 % TMS click noise created with the TMS Adaptable Auditory Control (TAAC) toolbox (Russo et al., 2022) in Matlab (Matlab R2018b; Mathworks, USA), and loudness adapted to individual perception level (max. 85 dB SPL) and delivered through ER-3C 10 Ω Insert Earphones (Etymotic Research Inc., USA) together with an iPod Touch 7th Generation (Apple Inc., Cupertino, California, USA). After the stimulation session, VAS scales were rated again and post questionnaires on perceptions for example of the TMS coil click sound were filled out. The second session was held at least one week after the first session and at the same time of day. It was scheduled the same way as the first session, but the current direction was set to the other condition for all magnetic stimulations. An overview of the experimental procedure is depicted in Fig. 1.

### 2.3. Transcranial magnetic stimulation (TMS)

For all magnetic stimulations, a MagPro X100 stimulator with MagOption and a figure-of-eight Cool-B65 A/P coil (MagVenture A/S, Farum, Denmark) were used. All pulses had a biphasic shape and a pulse width of approximately 280 μs as declared by the manufacturer (MagVenture A/S, Farum, Denmark). The biphasic waveform was chosen to ensure identical stimulation conditions during rTMS with single pulses before and after (Peinemann et al., 2004). The coil position was held stable throughout the experiment at the hotspot with a 45° angle to the midline via neuronavigation software (Localite GmbH, Bonn, Germany) in combination with a collaborative robotic coil holder (cobot; Axilum Robotics, Schiltigheim, France). With this setup, we were able to ensure a continuous placement and alignment onto the participants' hotspot at an accuracy of 2 mm within and across sessions even when small head movements occurred. The two current directions in this experiment refer to the *default* setting of the MagPro X100 stimulator with an induced current flow of AP-PA in the brain (default current direction) and to the *reversed* setting, which induced a current flow of PA-AP in the brain (reversed current direction). This parameter can be simply changed in the stimulation parameter settings of the TMS device.

### 2.4. Electromyography (EMG)

EMG data of the FDI, ADM and APB of the right hand were recorded with Ag/AgCl surface electrodes in bipolar belly-tendon montage (ground: processus styloideus ulnaris) in combination with ActiCHamp with BIP2AUX adapters (Brain Products GmbH, Germany). For MEP analyzes, we only analyzed FDI data. Raw EMG signal from the Brain Vision Recorder (Brain Products GmbH, Germany) was read into and preprocessed with Matlab (R2021b; Mathworks, USA). EMG data was filtered with 4th order two-way butterworth filter for high-pass 10 Hz and low-pass 500 Hz. MEPs were identified in the time window between 10 and 50 ms after the TMS pulse. In order to only analyze valid MEPs, attributable to the brain response to a TMS pulse, for each trial in which the corresponding EEG data was artefact-free, the MEP peak-to-peak amplitude and latency were computed. MEP latency was defined as onset of the first detected peak and extracted at the point where 10 % of the maximal amplitude was reached based on the definition by İşcan et al. (2018). In EMG data where the MEP-to-baseline-ratio was below 1.6, the MEP did not exceed 50 μV or there was muscle activity with ± 100 μV in the 100 ms before the TMS pulse, we did not include these trials in the analyzes. The data was structured corresponding to the TEPs, so that MEP amplitude and latency was extracted per subject and trial for the 100 TMS trials *pre* and *post* rTMS. The *pre-to-post changes* were computed as *post* minus *pre* rTMS condition per current direction, subject and trial for MEP amplitudes and latencies.

### 2.5. Electroencephalography (EEG)

EEG data was recorded with the software Brain Vision Recorder version 1.24.0101 (Brain Products GmbH, Germany) together with an ActiCHamp amplifier (Brain Products GmbH, Germany) and a TMS-compatible electrode cap with 64 passive electrodes (Easycap GmbH, Germany) placed according to the 10–20 location system (Klem et al., 1999). EEG signal was recorded at a sampling rate of 5 kHz and online referenced to FCz (GND: AFz). Impedances were kept below 10 kΩ. Raw EEG signal was read into Matlab (Matlab R2021b; Mathworks, USA) and pre-processed with the EEGLAB toolbox (Delorme and Makeig, 2004) together with the TMS-EEG Signal Analyzer extension (TESA; Rogasch et al., 2017). The preprocessing procedure followed the suggested TESA

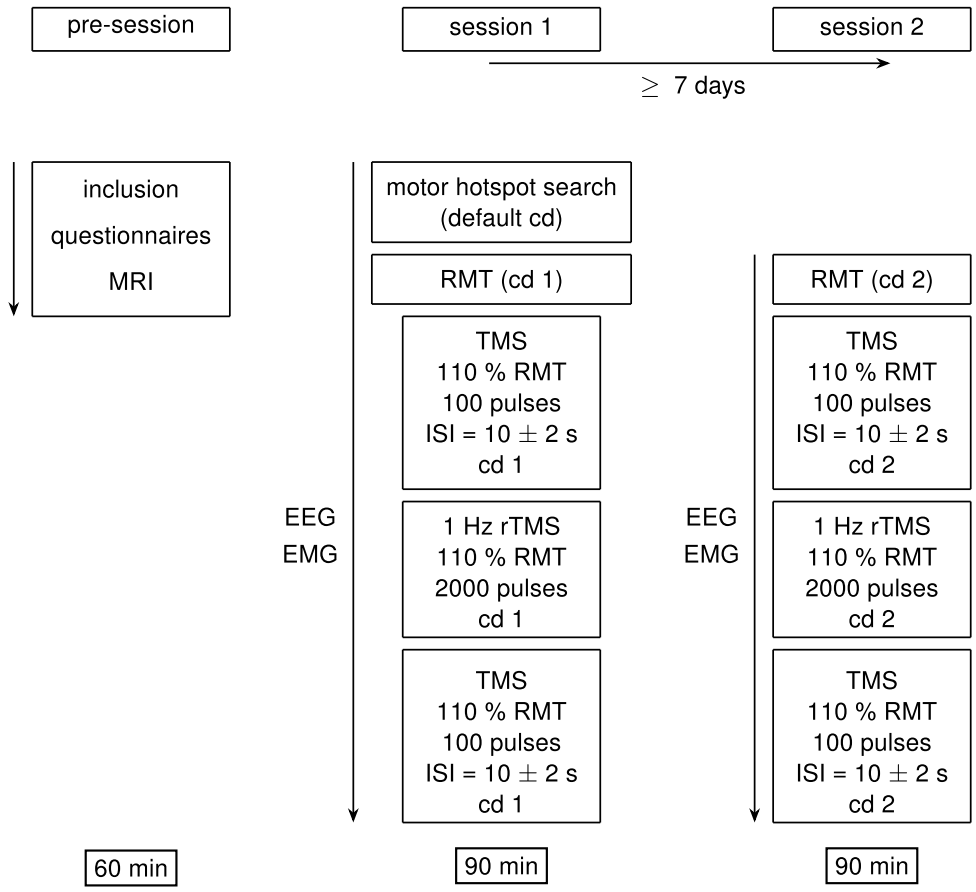


**Fig. 1.** Experimental procedure. After a pre-session, the first experimental session started with motor hotspot search and RMT determination. 100 TMS pulses, 2000 rTMS pulses in 1 Hz frequency and again 100 TMS pulses were administered with the first current direction. Concurrently, EEG and EMG were recorded. The second session was scheduled at least 7 days after and its procedure was the same as the first, but all stimulations were applied with the second current direction. Starting current direction was randomized a priori. MRI = Magnetic Resonance Imaging. Cd = Current Direction. EEG = Electroencephalography. EMG = Electromyography. ISI = Inter Stimulus Interval. RMT = Resting Motor Threshold.

example pipeline. To identify the TMS artefact, we used the C3 electrode. Afterwards, the data was epoched from 300 ms before to 500 ms after the TMS pulse. Channels that had a kurtosis of $z > 5$ were automatically rejected, resulting in a maximum of 7 rejected channels per subject and condition (10 % of the data). After subtracting the average activity of the overall epoch from every single timepoint within the epoch (demeaning), we removed the TMS artefact in each epoch by replacing the data from 13 ms before until 8 ms after the TMS pulse with zero amplitudes and subsequently interpolated these timepoints via cubic interpolation (Thut et al., 2011). Hereafter, the data was downsampled to 1 kHz. After visual removal of trials with artefacts such as brief muscular activity or eye blinks with a temporal relation to the TMS pulse (mean of 20 % of the trials), further eye blinks as well as non-neuronal activity that was not identified as electrode noise of muscular activity were identified and removed using fast ICA (toolbox http://research.ics.aalto.fi/ica/fastica/). Hereby, a maximum of 20 % of components were rejected. For reduction of electrode noise and muscle artefacts, we used source-based artefact-rejection algorithms: the source-estimate-utilizing noise-discarding algorithm (SOUND; Mutanen et al., 2018; Mutanen et al., 2022) and signal-space-projection-source-informed reconstruction (SSP-SIR; Mutanen et al., 2016; Biabani et al., 2019; Mutanen et al., 2022). Default settings were used in the former and for the latter we rejected a maximum of 5 components. The data was filtered using 4th order, two-way Butterworth bandpass (1–100 Hz) and bandstop (48–52 Hz) filters. Lastly, bad channels were interpolated via spherical spline interpolation (Perrin et al., 1989) and data were re-referenced to average. For quality check of the signal, we summarized butterfly plots per condition in Fig. 2.

We extracted TEP amplitudes and latencies per subject and trial for single pulse TMS measurements. Hereby, we wanted to account for the differences of current direction in the topography of TEPs (Casula et al., 2018) whilst comparing the same features within one current direction from pre to post rTMS. Thus, we inspected the same time intervals and EEG electrodes for pre and post rTMS measurements per TEP component and current direction. To achieve this, we extracted the mean TEP latencies ± 5 ms (± 10 ms for N100) from the Cz channel for the *pre* condition only per current direction and identified the topography clusters of 6 neighboring electrodes with maximal (positive TEPs) and minimal (negative TEPs) activation within these mean latency time intervals. Fig. 3 features the mean time courses over electrode Cz that were used for latency extraction. Fig. 4 depicts TEP topographies and summarizes the mean latencies and electrode clusters for each TEP component per current direction. Subsequently, for each subject, trial and condition, we extracted the individual TEP latency at the individual TEP peak within the mean of the identified cluster channels and the TEP amplitude as mean over the cluster channels and individual latencies ± 5 ms or ± 10 ms for N100. To compute the *pre-to-post change* data we subtracted the *pre* rTMS condition from the *post* rTMS condition per current direction, subject and trial for TEP amplitudes and latencies.

### 2.5.1. Statistical analyzes

MEP and TEP data as well as demographic data were analyzed in R (R Core Team, Austria, Version 4.3) with the packages BSDA (Arnholt and

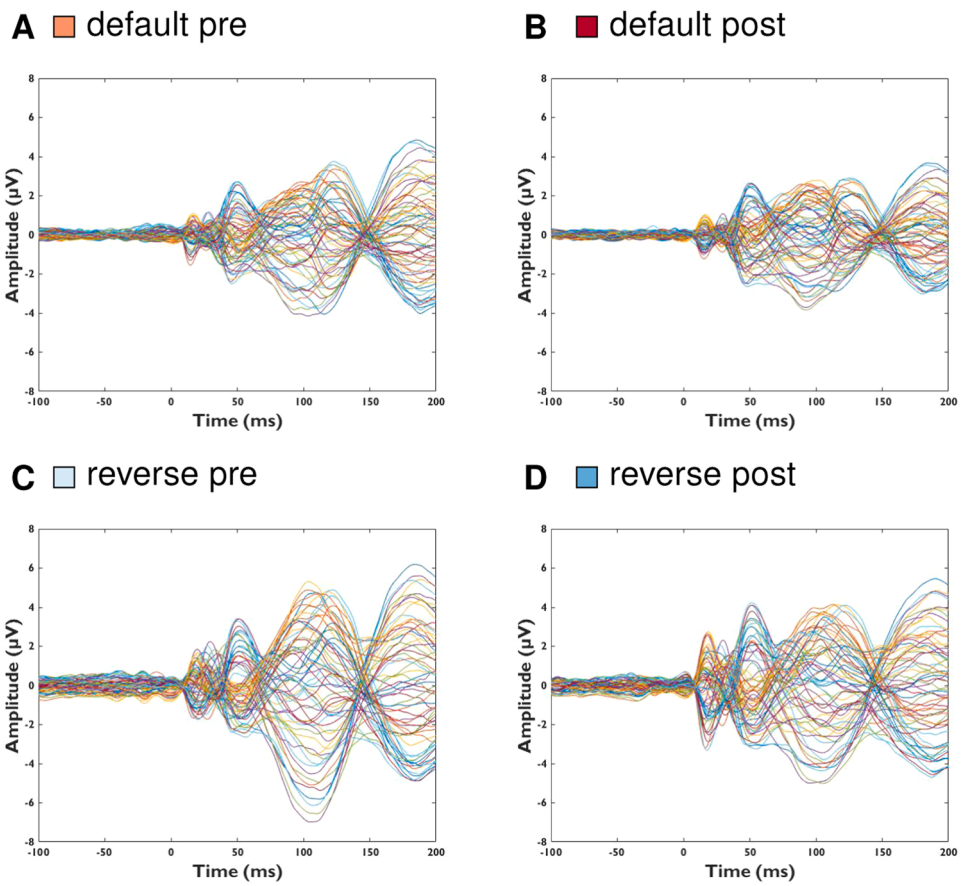


**Fig. 2.** Mean butterfly plots per condition. Fig. 2A depicts the butterfly plot of all EEG channels as mean time course over all 100 trials and 25 subjects for the condition pre rTMS with default current direction. Fig. 2B represents the butterfly plot of all EEG channels for the condition post rTMS with default current direction. Fig. 2C illustrates the butterfly plot of all EEG channels as mean time course for the condition pre rTMS with reversed current direction and Fig. 2D shows the butterfly plot of all EEG channels for the condition post rTMS with reversed current direction. All plots share the x-axis from 100 ms before the pulse until 200 ms after the pulse and the y-axis from −8 to 8 μV for comparability.

Evans, 2023), stats, lmerTest (Kuznetsova et al., 2017) and emmeans (Russell V. Lenth, 2023). Plots were constructed using ggplot2 (Gómez-Rubio, 2017). MEP and TEP amplitude and latency were analyzed with linear mixed effect models. Hereby, we compared models with the predictors *time* (pre vs post 1 Hz rTMS), *current direction* (default vs reverse) and their interaction against the intercept model without predictors in a stepwise selection approach, using AIC, BIC and a Likelihood Ratio test as criteria (Hastie, 2017). Only when all three parameters were lower (AIC, BIC) and significant (Likelihood Ratio test) in the more complex model, it was considered as better model than the one with one predictor less or the intercept model. The variance explained by the resulting models was calculated using marginal and conditional $R^2$ (Nakagawa et al., 2017). The factor subject was implemented as random effect in all models, so that the full model was as follows: *data* ~ *time* + *current direction* + *time*current direction* + *(1|subject)*. To investigate the differences between default and reverse current direction in changes from pre to post 1 Hz rTMS, we computed the *pre-to-post change* condition per current direction by subtracting the *pre* from the *post* condition per subject and trial for all TEP and MEP components (amplitude and latency). To analyze the *pre-to-post change* data of TEPs and MEPs, we tested the full model (*data* ~ *current direction* + *(1|subject)*) against the intercept model without predictors, congruently. We tested the fixed effects of each final model via expected mean square approach. With post-hoc Tukey t-tests and Tukey adjusted p-values, we only investigated the contrasts between *pre* and *post* conditions per current direction (*time* | *current direction*). For the *pre--to-post change* data, we analyzed the difference between current directions using the same statistical tests. For all analyzes, the level of significance was set at $\alpha = .05$.

Additionally, with paired t-tests (t), Wilcoxon signed-rank tests (V) or sign tests (S) in case of violation of prerequisites, we analyzed potential current-direction-specific differences in RMT, TMS masking loudness and the perceived loudness of the TMS click during stimulation. We investigated changes from pre to post rTMS as well as differences in current direction for attention, excitement and tiredness via Friedman tests (*time* * *current direction*) and post-hoc paired t-tests or sign tests.

With the repeated measures correlation coefficient (Bakdash and Marusich, 2017, 2019), we additionally correlated MEP latencies with TEP latencies as well as MEP amplitudes with TEP amplitudes for all *pre* , *post* and *pre-to-post change* data. We wanted to look at all the data to map any relationship between MEPs and TEPs, even if they are not equally transformed by rTMS. Thus, we corrected α for all possible combinations that we investigated (5 *TEP components [N15, P30, N45, P60, N100]* x 3 *conditions [pre, post, change]* x 2 *current directions [default, reverse]* x 2 *derivations [amplitude, latency]* = 60). We used the R package rmcorr, that includes subject as random factor in the correlations.

## 3. Results

RMT for default current direction ($M = 50.76$, $SD = 9.207$) was significantly lower than for the reverse current direction ($M = 61.16$, $SD = 9.114$; $t_{(24)} = -8.291$, $p < .001$). Yet, the loudness of the masking noise did not differ between current directions ($S = 9$, $p = .424$, $n = 25$),

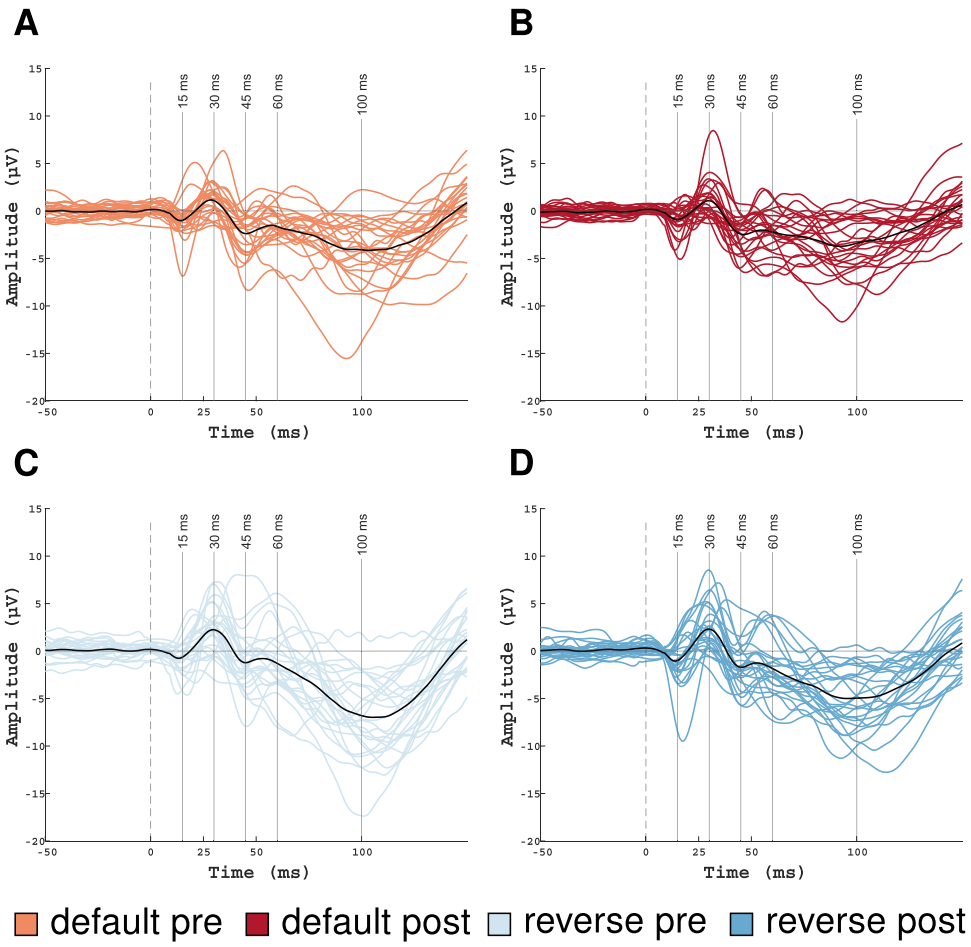


**Fig. 3.** Mean TEP time courses over Cz electrode per subject and overall. Fig. 3A depicts the mean TEP time course for the condition pre rTMS with default current direction (orange). Fig. 3B shows the mean TEP time course for the condition post rTMS with default current direction (red). Fig. 3C illustrates the mean TEP time course for the condition pre rTMS with reversed current direction (light blue) and Fig. 3D represents the mean TEP time course for the condition post rTMS with reversed current direction (blue). Colored lines depict the mean TEP time courses over 100 trials of one subject per condition and the black line represents the mean TEP time course over all subjects for the respective condition.

referring to about 75 dB SPL ($M_{default}$ = 10.52, $SD_{default}$ = 2.084, $M_{reverse}$ = 11.28, $SD_{reverse}$ = 1.621). Neither did the participants' perception of loudness change ($V$ = 65, $p$ = .897, n = 25; $M_{default}$ = 3, $SD_{default}$ = 1.601, $M_{reverse}$ = 3.22, $SD_{reverse}$ = 1.948). In analysis of the VAS scales, time had a significant effect on tiredness ($F_{(1,72)}$ = 6.141, $p$ < .05, $\eta_p^2$ = .079), whereby tiredness levels were higher after rTMS than before ($M_{pre}$ = 4.52, $SD_{pre}$ = 2.16, $M_{post}$ = 5.42, $SD_{post}$ = 2.34, $t_{(49)}$ = -2.534, $p$ < .05). Also on excitement levels, time had a significant effect ($F_{(1,72)}$ = 11.233, $p$ < .01, $\eta_p^2$ = .135), whereby excitement was lower after rTMS than before ($M_{pre}$ = 2.22, $SD_{pre}$ = 1.36, $M_{post}$ = 1.71, $SD_{post}$ = 0.81, $S$ = 21, $p$ < .01, n = 25). Concerning attention, the main effect of time was also present in the Friedman test ($F_{(1,72)}$ = 3.98, $p$ < .05, $\eta_p^2$ = .052). But the post-hoc sign test did not reveal significant differences between pre and post rTMS ($M_{pre}$ = 6.79, $SD_{pre}$ = 1.74, $M_{post}$ = 6.25, $SD_{post}$ = 1.78, $S$ = 27, $p$ = .088, n = 25). No main effect of current direction or any interaction effect for tiredness, excitement or attention reached significance.

### 3.1. MEPs

For MEP peak-to-peak amplitude, the fixed effects of *time*, *current direction* and interaction of *time*current direction* were significant via expected mean square approach. Post-hoc Tukey t-tests showed that MEP amplitude was significantly higher after rTMS than before in both default ($t_{(6619)}$ = -2.118, $p$ = .034) and reversed current direction ($t_{(6617)}$ = -8.828, $p$ < .001). In analysis of the pre-to-post changes, *current direction* was a significant fixed effect. The pre-to-post change from lower to higher amplitude was larger for the reversed current direction than for default ($t_{(2382)}$ = -6.354, $p$ < .001).

For MEP latency data, the fixed effects of *time*, *current direction* and interaction of *time*current direction* were significant. Latency was prolonged after 1 Hz rTMS with both default ($t_{(6613)}$ = -8.629, $p$ < .001) and reversed current direction ($t_{(6612)}$ = -4.77, $p$ < .001). *Current direction* was a significant fixed effect for pre-to-post changes in MEP latency. The pre-to-post change from shorter to longer latency was higher for the reversed current direction than for default ($t_{(2375)}$ = -4.332, $p$ < .001). Descriptive MEP mean and standard deviation values are depicted in Fig. 5 along with the respective significant difference results from the linear mixed effect model analyses. The linear mixed effect models that were identified to have the best fit along with statistics on significant fixed effects as well as marginal and conditional $R^2$ are listed in the Supplementary Table 1. Supplementary Table 2 summarizes all post-hoc Tukey t-tests and contains estimated mean values. Supplementary Figure 1 depicts the mean MEP time courses and those for each subject per condition.

### 3.2. TEPs

For N15 amplitude data the fixed effects of *time, current direction*, and *time*current direction* were significant. Post-hoc Tukey t-tests revealed

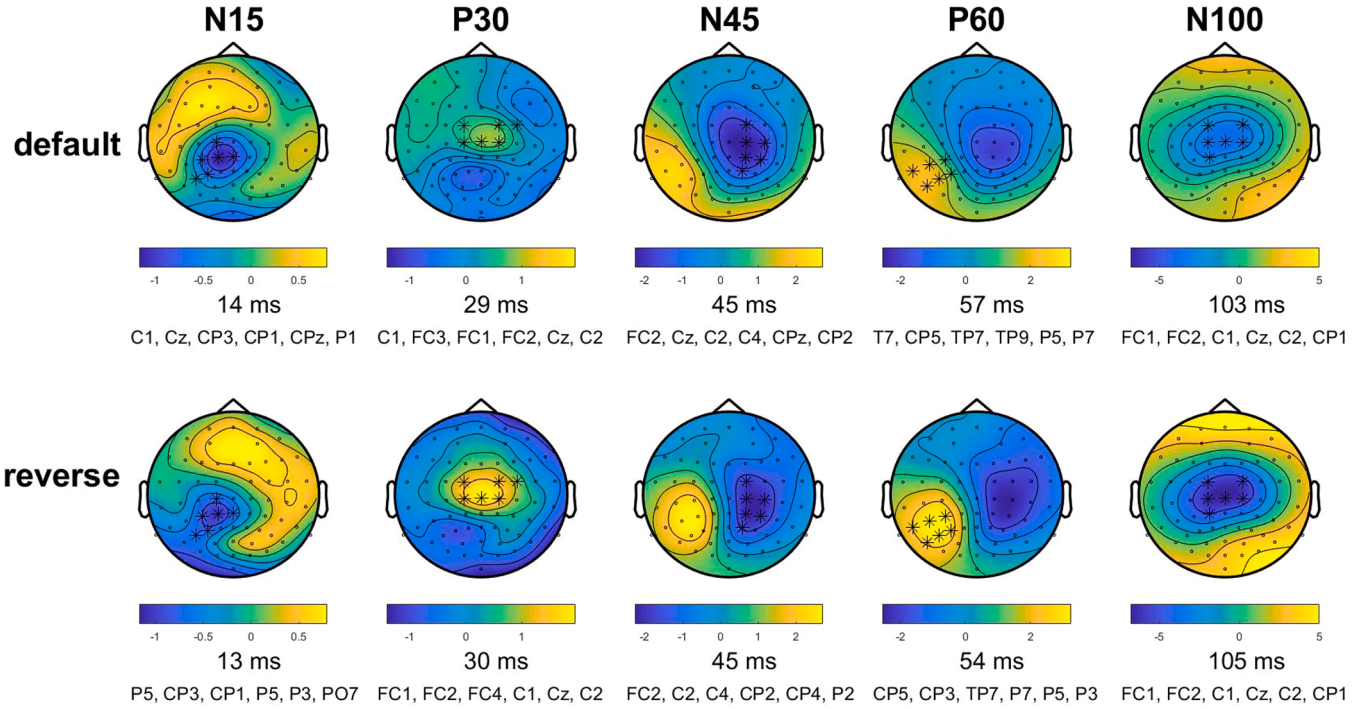


**Fig. 4.** Topographies of TEP components. Each column represents one TEP component and rows refer to the current direction. Mean topographies for the conditions before rTMS (*pre* ) are depicted. The six electrodes with the minimal or maximal activation are highlighted as asterisks and written as names below the respective topography plots. Below each TEP component topography and for both current directions the mean latencies identified over Cz are noted.

no difference between pre and post rTMS for the default current direction ($t_{(8954)}$ = -1.403, $p$ = .161), but with reversed current direction, the N15 amplitude was larger, i.e. more negative after rTMS than before ($t_{(8955)}$ = 12.436, $p$ < .001). The model for pre-to-post N15 amplitude changes had a significant fixed effect of *current direction*. Pre-to-post N15 amplitude changes were significantly larger for the reversed than the default current direction ($t_{(4039)}$ = 9.479, $p$ < .001), revealed by the post-hoc Tukey *t*-test. Hereby, the descriptive direction of the effect was different for default (reduction of amplitude) than reversed current direction (enhancement of amplitude).

For N15 latency data significant fixed effects were *time, current direction*, and *time*current direction.* N15 latency was not different from pre to post rTMS with the default direction ($t_{(8954)}$ = -1.403, $p$ = .161), but was significantly prolonged after rTMS than before with the reversed current direction ($t_{(8955)}$ = 12.436, $p$ < .001). The significant fixed effect for the data of pre-to-post changes in N15 latency was *current direction*. Post-hoc t-tests revealed that the pre-to-post changes were significantly larger for the reversed than the default current direction, meaning that latency was significantly more prolonged after 1 Hz rTMS than before for reversed current direction than N15 latency was shortened after 1 Hz rTMS than before for the default current direction.

Concerning P30 amplitude and latency data the fixed effect of *current direction* was significant in the respective optimal model. For both amplitude and latency of P30 pre-to-post change data there was no significant fixed effect. Thus, no post-hoc t-tests were conducted for P30 amplitude and latency nor the respective pre-to-post change data.

The fixed effects of *time, current direction*, and *time*current direction* were significant for N45 amplitude data. Post-hoc Tukey t-tests revealed no difference from pre to post rTMS in the default condition ($t_{(8954)}$ = 0.53, $p$ = .597), but significantly larger, i.e. more negative N45 amplitude after rTMS than before in the reversed current direction ($t_{(8955)}$ = 5.459, $p$ < .001). Also, for the pre-to-post N45 amplitude change data, a significant fixed effect of *current direction* was present. The pre-to-post N45 amplitude changes, i.e. more negative N45 amplitude after rTMS than before, were larger for reversed than default current direction ($t_{(4049)}$ = 3.58, $p$ < .001).

No significant fixed effect was identified in the models for N45 latency data and pre-to-post change data of N45 latency. Thus, no post-hoc t-tests were computed for N45 latency and the respective pre-to-post change data.

Significant fixed effects for the P60 amplitude data were *time, current direction*, and *time*current direction*. Post-hoc Tukey t-tests revealed no difference from pre to post rTMS for default current direction ($t_{(8954)}$ = -0.214, $p$ = .831), but for reversed current direction a larger P60 amplitude was shown after rTMS than before ($t_{(8954)}$ = -6.622, $p$ < .001). For the P60 amplitude pre-to-post change data the fixed effect of *current direction* was significant. Hereby, the pre-to-post enhancement in P60 amplitude was significantly larger in the reverse than in the default current direction ($t_{(4042)}$ = -4.772, $p$ < .001).

Concerning P60 latency, the fixed effect of *current direction* was significant and no significant fixed effect was identified for the P60 data of pre-to-post changes in latency. Since no significant fixed effects of *time* and *current direction* were present in the models for P60 latency and P60 latency pre-to-post change, respectively, no post-hoc t-tests were conducted.

All fixed effects (*time, current direction*, and *time*current direction*) were significant for the N100 amplitude data. Post-hoc Tukey t-tests revealed a significantly smaller N100 amplitude, i.e. less negative after than before rTMS in both default ($t_{(8954)}$ = -5.767, $p$ < .001) and reversed current direction condition ($t_{(8954)}$ = -14.461, $p$ < .001). For the pre-to-post change data of N100 amplitude, the optimal model showed a significant fixed effect of *current direction*. Post-hoc Tukey t-tests revealed that the reduction of N100 amplitude, i.e. becoming less negative from pre to post rTMS, was significantly larger in the reversed than default current direction ($t_{(4040)}$ = -5.754, $p$ < .001).

The fixed effects of *time* and *current direction* were significant for N100 latency data. N100 latency was shortened after rTMS than before in both default ($t_{(8955)}$ = 6.485, $p$ < .001) and reversed current direction ($t_{(8955)}$ = 6.485, $p$ < .001). For the N100 latency pre-to-post change data there was no significant fixed effect and thus, no further tests were

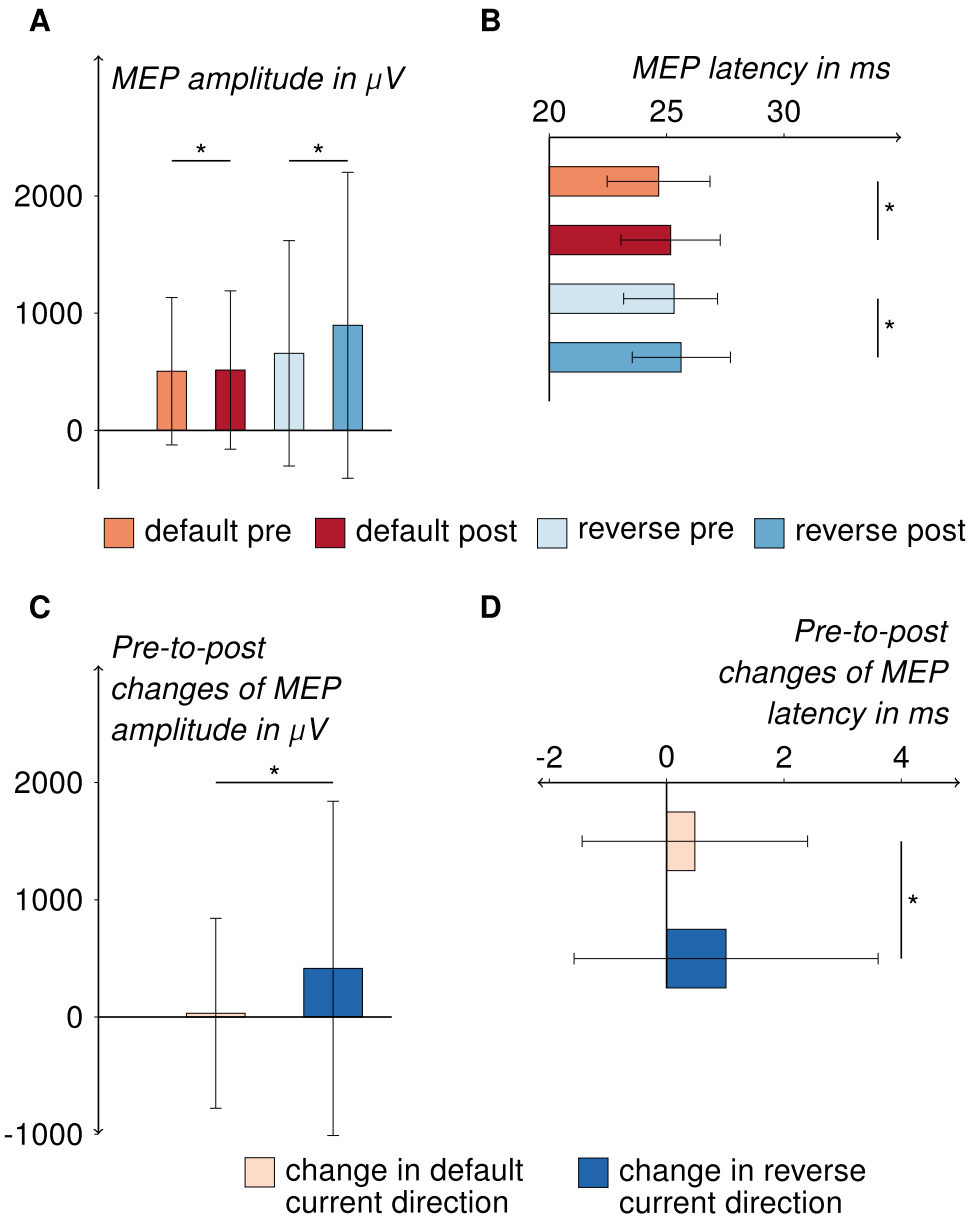


**Fig. 5.** MEP amplitude and latency and their respective pre-to-post rTMS changes. Fig. 5A depicts the mean MEP amplitude per condition (orange = pre rTMS with default current direction, red = post rTMS default, light blue = pre rTMS with reversed current direction, blue = post rTMS reverse). Fig. 5B shows the mean MEP latency per condition with congruent colors. Fig. 5C depicts the MEP amplitude change from pre to post 1 Hz rTMS for default (light orange) and reversed current direction (dark blue) and Fig. 5D represents the MEP latency pre-to-post change per current direction with congruent colors. Error bars represent the standard deviations. Asterisks indicate significant differences ($p < .05$) between conditions, as resulted from the linear mixed effect model Tukey post-hoc tests.

carried out.

For detailed inspection, descriptive mean TEP amplitudes and their standard deviations are depicted in Fig. 6 along with significance indications resulted from the linear mixed effect model analyses. Fig. 7 features TEP latency mean and standard deviation values with the significance indications from the model fitting analyses. Linear mixed effect models that were identified by the model fitting procedure to have the best fit on TEP data as well as statistics on significant fixed effects and marginal and conditional $R^2$ are listed in the Supplementary Table 1. As summary, post-hoc Tukey t-tests and estimated mean values are shown in Supplementary Table 2.

### 3.3. Correlation of MEPs with TEPs

We observed a significant but negligible correlation of peripheral and central electrophysiological measures for the amplitudes of the N45 with MEPs pre rTMS for the reversed current direction ($r = 0.088$, $p < 0.001$). All other correlations did not reach significance.

## 4. Discussion

In 25 healthy subjects we investigated the pre-to-post changes of interventional 1 Hz rTMS over the motor cortex on cortico – spinal and cortical excitability via MEPs and TEPs. 100 single TMS pulses were applied prior and after 2000 pulses of 1 Hz rTMS on two days separated by at least one week. For all magnetic stimulations per day, we used one of two different current directions that refer to the default and reversed setting in the MagVenture MagPro X100 stimulator (MagVenture A/S, Farum, Denmark), inducing AP-PA (default) and PA-AP (reverse) currents in the brain, respectively. Linear mixed effect models were used to analyze differences between pre and post rTMS for each current direction as well as differences in current direction of the pre-to-post 1 Hz

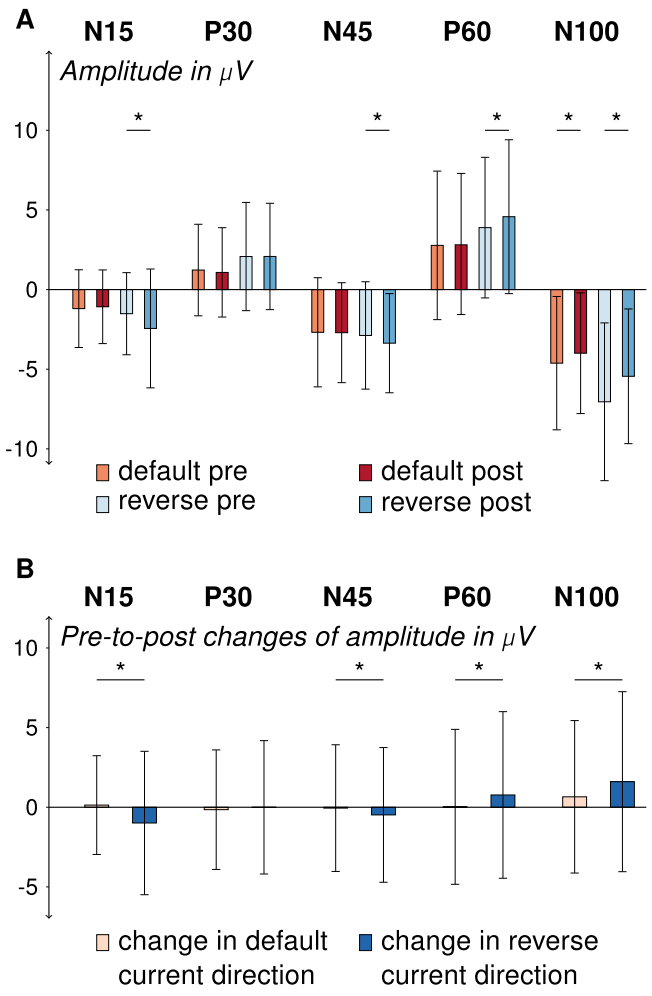


**Fig. 6.** TEP amplitudes per condition and pre-to-post rTMS changes per current direction. Fig. 6A depicts the mean amplitude per condition (orange = pre rTMS with default current direction, red = post rTMS default, light blue = pre rTMS with reversed current direction, blue = post rTMS reverse), which are faceted per TEP component. Fig. 6B shows the TEP amplitude changes from pre to post 1 Hz rTMS per current direction, whereby default is depicted in light orange and reversed current direction in dark blue. Error bars represent the standard deviations. Asterisks indicate significant differences ($p < .05$) between conditions, as resulted from the linear mixed effect model Tukey post-hoc tests.

rTMS changes. We additionally investigated correlations of MEPs with TEPs and differences between current direction conditions in the RMT, masking noise loudness and TMS coil click perception as well as VAS data.

Pre-to-post 1 Hz rTMS changes in amplitude and latency were prominent in both MEPs and TEPs, however the amplitude of the P30 did not show any influence by rTMS in general or current direction. Also, TEP latencies only revealed pre-to-post differences in the N15 and N100 component. In the derivations, when significance level was reached, these pre-to-post changes were larger when elicited with the reversed than the default current direction, although for N15 amplitude and latency the descriptive direction of change was not equal between current directions.

MEP amplitudes increased from before to after 1 Hz rTMS in both current directions, but the reversed current direction showed a larger increase in the pre-to-post changes than the default current direction. This finding indicates that in our experimental setup, 1 Hz rTMS did not act inhibitory as assumed by the lofi-hife heuristic and other previous research (Pascual-Leone et al., 1994; Wassermann et al., 1996; Tang et al., 2019; Schoisswohl et al., 2024), but rather had a facilitatory effect on cortico-spinal excitability. Since not all factors that contribute to rTMS effects have been identified, one can only speculate about reasons for the derivations of our results from the heuristic. These could be either due to experimental decisions, technical stimulation or intrapersonal parameters. Firstly, in our experiment the stimulation intensity was suprathreshold (110 % RMT) in contrast to other experiments using subthreshold intensity (van der Werf and Paus, 2006; Goetz et al., 2016; Zhou et al., 2022) and the number of applied pulses was higher in our procedure than in others (van der Werf and Paus, 2006; Goetz et al., 2016; Zhou et al., 2022). Yet, literature suggests that higher intensities and longer stimulation duration enhance neuromodulatory effects (Maeda et al., 2000; Fitzgerald, 2002; Lang et al., 2006), thus we would not have expected a contrary result to the expected direction but rather an enhanced one. Metaplasticity effects for example of the effect of higher stimulation intensity may have contributed to our findings. Previous research hereto has found individual intensity dependence of inhibitory or excitatory effects of cTBS (Sasaki et al., 2018). Thus, further investigation of intensity dependence of 1 Hz rTMS is needed, since it likely affected both the individual reactions as well as the comparability of rTMS effects between studies. The rationale that higher intensities evoke higher effects seems to be dependent on the stimulation parameters. Secondly, we used biphasic pulses for all magnetic stimulations, but monophasic pulses were found to be more effective in modulating cortico - spinal excitability than biphasic pulses (Sommer et al., 2002; Arai et al., 2005; Tings et al., 2005; Goetz et al., 2016). Yet, also for biphasic stimulations, inhibitory 1 Hz rTMS effects were found (Wassermann et al., 1996; Taylor and Loo, 2007). Pulse width was found to also influence 1 Hz rTMS effects with longer pulses (120 μs) resulting in excitation and shorter pulses (40 μs, 80 μs) resulting in inhibition (Halawa et al., 2019), which might explain our excitation effect with a pulse width of 280 μs. Yet, since pulse widths are not typically reported in the experimental procedures and little is known about the influence of all phase components, we cannot directly compare our results to previous research. Thirdly, it is known that subject-specific parameters influence cortical and cortico - spinal excitability and neuromodulatory responses (Guerra et al., 2020). Factors such as age (Bashir et al., 2014), handedness (Triggs et al., 1994), genetics (Di Lazzaro et al., 2015) and intrinsic state (Stefan et al., 2004) are found to contribute to TMS response differences between and within participants. The influence of sex on TMS and subsequent excitability measures appears to be negligible (Livingston et al., 2010; Cueva et al., 2016). Although we know that also attention (Conte et al., 2008) influences the efficacy of NIBS induced excitability, in our experiment we tried to eliminate this factor by instructing the participants to look at the fixation cross while keeping the stimulated hand at rest and assessing attention along with tiredness and excitement in the VAS scales. Hereby, the Friedman tests showed no differences in attention from pre to post rTMS, but increased tiredness and reduced excitement levels after rTMS than before, indicating that the subjects were getting familiar with the procedure, but also showed fatigue. This might have influenced the facilitation of cortico - spinal excitability as well, since increases in MEP amplitude were found for small reductions in alertness levels, i.e. wake to drowsy before sleep (Noreika et al., 2020). During sleep, on the other hand, a reduction of MEP amplitude has been demonstrated in the literature (Avesani et al., 2008). In summary, due to the complexity of parameters that influence neuromodulatory effects, it is likely that a combination of the discussed parameters is responsible for the high variability of experimental findings and thus the non-conformity of our results to the lofi-hife heuristic.

Concerning the differences of MEP amplitudes between current directions, the found excitatory 1 Hz rTMS effect was even more pronounced for the reversed than for the default current direction, which corresponds to findings of 5 Hz rTMS (Sommer et al., 2013a). For 1 Hz rTMS the opposite effect was found; monophasic PA, corresponding to the dominant phase of the MagVenture default current direction elicited stronger inhibitory effects than monophasic AP (corresponding to reverse) current direction (Goetz et al., 2016). Our findings mainly align

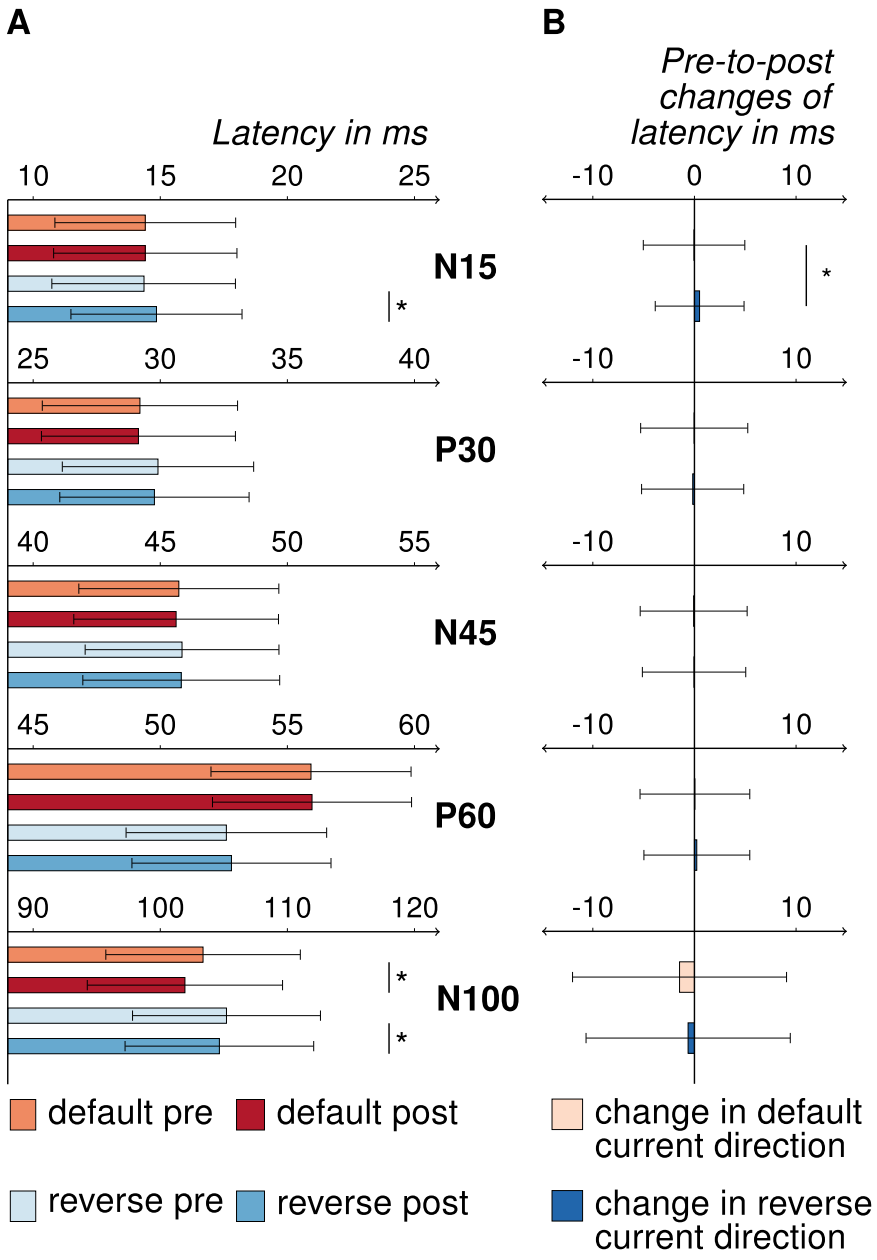


**Fig. 7.** TEP latencies per condition and pre-to-post rTMS changes per current direction. Fig. 7A shows the mean TEP latency per condition (orange = pre rTMS with default current direction, red = post rTMS default, light blue = pre rTMS with reversed current direction, blue = post rTMS reverse) and faceted per TEP component. Fig. 7B depicts the TEP latency change from pre to post 1 Hz rTMS per current direction. Hereby, the default current direction change is depicted in light orange and the change for reversed current direction in dark blue. Error bars represent the standard deviations. Asterisks indicate significant differences ($p < .05$) between conditions, as resulted from the linear mixed effect model Tukey post-hoc tests.

with the previous literature, indicating that the induced PA-AP (reversed) current direction acts more effectively than the induced AP-PA (default) current direction onto neuromodulatory mechanisms in the brain (Sommer et al., 2013a; Halawa et al., 2021). Yet, results for the inhibitory 1 Hz rTMS protocol seem to be directed oppositely (Goetz et al., 2016). Although the RMT and thus stimulation intensity between current directions differed significantly, we are confident to have induced comparable physiological responses over the exact same cortical position since the stimulation intensity is matched to the individual RMT per condition. Differences in current direction should therefore only occur based on the underlying cortical structures and their interaction with the magnetic field. Since for the reversed current direction the stimulation intensity was significantly higher, it is possible that with the elicited higher field strength also more neurons might be recruited for the reversed current direction.

MEP latency was significantly prolonged after rTMS than before for both current directions. The literature mainly reports no differences in MEP latencies after rTMS in both inhibitory and facilitatory rTMS protocols (Lorenzano et al., 2002; Arai et al., 2005; Gilio et al., 2009; Sommer et al., 2013b). Yet, during one facilitatory 5 Hz rTMS protocol, in which MEP amplitudes were increased, MEP latencies were found to be shortened (Tings et al., 2005). The reasons why in our experiment MEP latencies were prolonged after 1 Hz rTMS could be diverse. Some findings indicate that stimulation at a suboptimal hotspot prolongs MEP latency due to an increase of indirect transsynaptic propagation (Fuhr et al., 1991). Since our experimental setting included automatized placement of the coil with a cobot-assisted neuronavigation system, we can rule out large spatial deviations from the initial hotspot. Another

explanation might be the increased tiredness of our participants after the rTMS application than before. It was found that sleepiness and sleep prolonged MEP latency compared to wakefulness (Avesani et al., 2008).

Also for MEP latency the reversed current direction showed a larger pre-to-post change than the default current direction. This finding is in line with results that showed that MEP latencies were shorter for monophasic PA, corresponding to the dominant phase of the default current direction, than monophasic AP pulses, corresponding to the dominant phase of the reversed current direction (Tings et al., 2005; Hamada et al., 2013; Davila-Pérez et al., 2018; D'Amico et al., 2020; Guidali et al., 2023), as well as biphasic AP-PA TMS single pulses (Davila-Pérez et al., 2018). Different latencies for current directions indicate an activation of different neural elements, such as later I-waves (Di Lazzaro et al., 2001) and sets of neurons (Li et al., 2017; Di Lazzaro et al., 2018).

TEP amplitudes that showed a significant pre-to-post change were mainly enhanced after inhibitory 1 Hz rTMS. Hence, N15 and N45 amplitude were more negative after 1 Hz rTMS than before and P60 was more positive after rTMS than before. N100 amplitude was the only component to be reduced after 1 Hz rTMS in both current directions, i.e. having a less negative amplitude after rTMS than before. Although this pattern shares one similarity to the study that found increased P60 (Casula et al., 2014) after 1 Hz rTMS, the differences in outcomes predominate: increased N100 (Casula et al., 2014; Zhou et al., 2022) and reduced P60 (Zhou et al., 2022) show opposite findings to ours. In the literature on 1 Hz rTMS and TEPs, rTMS inhibited MEP amplitude (Casula et al., 2014) or showed no influence (van der Werf and Paus, 2006; Casula et al., 2014; Zhou et al., 2022). Thus, it seems as if our results did not reproduce the inhibitory effects of 1 Hz rTMS of other experiments. Yet, when comparing our data to facilitatory protocols, contrary to null results of the N45 amplitude from the 20 Hz rTMS experiment by Veniero et al. (2010), our data showed an enhancement of the N45 amplitude elicited with reversed current direction, which corresponds to the current direction elicited by the Magstim Super Rapid stimulator (Orth and Rothwell, 2004) used in the experiment by Veniero et al. (2010). Since N100 is suspected to represent inhibitory processes (Premoli et al., 2014; Casula et al., 2024), a reduction of N100 after rTMS as in our findings could be interpreted as reduction of inhibition or enhancement of facilitation. As N45 is influenced by the inhibitory neurotransmitter GABA(A) (Premoli et al., 2014) and P60 by the excitatory neurotransmitter glutamate (Belardinelli et al., 2021) and both amplitudes were larger after rTMS than before, we cannot say with certainty that in our experiment only cortical excitability was increased. Maybe increased cortical and cortico – spinal excitability was just the dominant finding.

Within all significant pre-to-post rTMS changes for the respective TEP components, the reversed current direction elicited a stronger effect than the default current direction, concordant to our MEP amplitude results. Although, it is to be noted that for the N15 component, only the pre-to-post changes in amplitude and latency for the reversed current direction were significant and that the pre-to-post change elicited with the default current direction descriptively went in the opposite direction. Contrary to our results, in previous literature, biphasic current directions corresponding to the MagVenture default current direction (inducing a current direction of AP-PA in the brain) elicited larger negative TEP amplitudes, corresponding to N45 and N100, than the reversed current direction (PA-AP; Casula et al., 2018). Yet, when comparing the results for monophasic pulses that correspond to the second phase of biphasic pulses, to our findings, the monophasic AP current direction congruent to reverse (PA-AP) elicited more negative TEP amplitudes than the PA current direction congruent to default (AP-PA) (Casula et al., 2018). For positive TEP components comparable to P30 and P60, Casula et al. (2018) found larger amplitudes for default than reversed current direction. For the M1-P15, the AP current direction also elicited higher amplitudes than the PA current direction (Guidali et al., 2023). Our data proposes an overall enhancement of the induced rTMS neuromodulatory changes in TEP amplitude by the reversed current direction in comparison to default. This phenomenon might be affected by the overall stronger induced electrical field for stimulations with reversed current direction due to higher stimulation intensities. In an experiment with prefrontal intermittent theta-burst stimulation by Krile et al. (2023), with 120 % RMT the N120 was more negative than elicited with 110 % RMT. Yet, higher dosage does not always result in stronger effects, since with increased number of pulses in 1 Hz rTMS, no linear change of amplitude was found for MEPs and most TEP components (Schoisswohl et al., 2024). Thus, a dose-response relationship of intensity and duration of rTMS should be further investigated. It might be that other parameters such as attention also influence TEP components for example N100 amplitude (Kaarre et al., 2018). Although in our experiment, the interaction effect of time and current direction did not reach significance, the interaction of attention, current direction and neuromodulatory responses should be thoroughly investigated in future research.

We found significantly prolonged TEP latencies after rTMS than before for N15 in the reversed current direction and significantly shortened latencies after rTMS than before for N100 in both current directions. No such findings were reported in previous literature. Since MEP latency was also prolonged after 1 Hz rTMS in our experiment, this prolongation of N15 might be due to the current direction effect and difference of acquired sets of neurons (Li et al., 2017; Di Lazzaro et al., 2018). And thus, tiredness may not only influence MEP latency but also TEP latency. Contrary to our findings, Roos et al. (2021) found a relationship with higher MEPs and prolonged N100, but no effect of 1 Hz rTMS was investigated. A shortened latency after rTMS than before of TEP component N100 as in our experiment could reflect a trajectory effect of the rTMS procedure on neuronal projections and consecutive heightened plasticity, but further investigation is needed to replicate results and identify reasons for this latency difference.

The pre-to-post change of TEP latency was only different between current directions in the N15 component, revealing that the N15 latency elicited by reversed current direction was more prolonged after 1 Hz rTMS than before than the N15 latency elicited by default current direction which was shorter after 1 Hz rTMS than before. Our finding for the N15 latency current direction difference, likewise to the MEP latency results, resembles the findings from M1-P15 (Guidali et al., 2023) and could be caused by the different sets of neurons that are recruited with different current directions (Li et al., 2017; Di Lazzaro et al., 2018). Another reason might also be the different stimulation intensity and thus induced electric field as well as muscle recruitment which might affect signal recovery. Since no other pre-to-post change of TEP component latency was influenced by current direction, maybe this activation of different sets of neurons only manifests in early TEP components and for later TEPs the accumulative neuronal propagation overshadows this difference.

Although both EEG and EMG derivations are used to examine excitability in TMS and plasticity in rTMS, we only found a significant correlation of the MEP and N45 amplitude elicited with reversed current direction before rTMS. Yet, this correlation remained negligible ($r = 0.088$). Thus, we cannot infer to an equally suitable cortical marker of TMS and rTMS effects, compared to the cortico-spinal derivation, i.e. MEP, yet. Previous literature also indicated that the N45 component is associated with motor activity (Ahn and Fröhlich, 2021), especially elicited with suprathreshold intensity rather than subthreshold intensity (van der Werf and Paus, 2006). Yet, correlations were also found between MEP and other TEP amplitudes like N15-P30 or P60 (Mäki and Ilmoniemi, 2010; Gedankien et al., 2017; Bigoni et al., 2024) and other experiments found no correlation of MEPs and TEPs (Bonato et al., 2006; Casula et al., 2014). The finding of low correlation in our experiment along with heterogeneous findings may refer to mediation effects of subject internal processes, such as brain state (Bigoni et al., 2024), alertness or tiredness (Noreika et al., 2020).

With regard to our hypotheses, we did not find inhibitory effects of

1 Hz rTMS. Since comparisons with previous literature are limited due to differences in setup, dependent variables and analyses, we can only draw partial conclusions about the effects of 1 Hz rTMS on TEPs. Our results show cortico-spinal pre-to-post rTMS changes in the excitatory direction, i.e. higher amplitudes after 1 Hz rTMS, that resemble findings from experiments investigating high frequency rTMS (Fitzgerald et al., 2006; Thut and Pascual-Leone, 2010). For TEP components N45 and P60 previous literature shows a diffuse picture. However, N100 usually increased after 1 Hz rTMS (Casula et al., 2014; Zhou et al., 2022) but decreased in our findings. The differences in current direction are mainly concordant with previous study findings, indicating that the current direction that corresponds to the reversed one in our experiment achieved larger effects than the current direction corresponding to default (Sommer et al., 2013a; Goetz et al., 2016; Halawa et al., 2021). Yet, hereby a different stimulator was used (cTMS) with rectangular pulses (Goetz et al., 2016; Halawa et al., 2021) or no manufacturer was reported (Sommer et al., 2013a). Although different sets or neurons are activated by different current directions (Li et al., 2017; Di Lazzaro et al., 2018), the induced rTMS effect was mainly similarly directed. Since for the treatment of neuro-psychiatric diseases like tinnitus, the current direction seems to determine the success of the treatment (Schoisswohl et al., 2023), it might be worth to further investigate the reasons for larger rTMS effects.

## 5. Limitations

Limitations to our findings are mainly due to restrictions on comparability of the current direction conditions. To ensure that differences in topography and TEPs do not occur because of different hotspots and thus recruited cortical regions, but because of differences in current direction within the same brain region, we decided to determinate the individual motor hotspot only with default current direction. But to enhance comparability between the current direction conditions, we assessed the RMT at the hotspot with each current direction separately. Since the RMT for default was significantly less than for reversed current direction, we have different physical but probably physiological equal stimulation intensities for the current directions, which may cause a systematic error in our data. Additionally, findings across the current literature are difficult to compare due to differences in the experimental setup and stimulation parameters. Investigation of other current directions (for example lateral to medial) can additionally give insight into direction specific reactions to rTMS procedures. Whereas induced current directions can be directly or indirectly derived from the methods, other parameters such as stimulation intensity and channels as well as pipelines used for TEP and MEP preprocessing and extraction are very variable (Rogasch et al., 2022). Also, different pulse sources are not directly comparable in pulse width, induced electrical field strength and derived parameters (van Doren et al., 2015; Osnabruegge et al., 2024). In our experiment, since we investigated both TEPs and MEPs simultaneously, we decided for suprathreshold TMS stimulation for all measurements, whereas other experiments stimulated with subthreshold rTMS (van der Werf and Paus, 2006; Casula et al., 2014; Goetz et al., 2016; Zhou et al., 2022). Thus, our EEG data might be biased by additional somatosensory input (Paus et al., 2001). Further investigations of TEPs should also consider analyzing N15 and P15 simultaneously and compare the respective data to differentiate between effects on different brain regions.

## 6. Conclusion

In summary, we elicited excitatory effects with suprathreshold 1 Hz rTMS applied with 2000 biphasic pulses at a pulse width of 280 μs over M1 that were more pronounced in the reversed current direction than in the default direction. The findings on pre-to-post rTMS changes are mainly contrary to the current literature. Yet, findings on the difference between current directions were mainly according to the literature. Despite having chosen stimulation parameters based on experiments that showed enhancement of inhibitory effects, like suprathreshold intensity (Fitzgerald, 2002; Lang et al., 2006) and longer duration (Maeda et al., 2000), no reproduction of 1 Hz rTMS effects was possible. Thus, we call upon a more detailed inspection of confounding variables in TMS and rTMS research: Firstly, although confounding factors like subject-related variability, differences in experimental setup and stimulation parameters are known to influence both TMS and rTMS measures (Guerra et al., 2020), their individual extent and interaction with other parameters needs to be disentangled. For example, differences in stimulation of the cortex and assessment of MEPs and TEPs during versus before and after rTMS could bias the derived excitability, like inhibition during and excitation after stimulation dependent on monophasic or biphasic stimulation (Halawa et al., 2019). Secondly, exact replication of previous findings should be encouraged for future experiments, with a detailed description of experimental setup, stimulation and preprocessing of data, since many findings were found to not be transferable to other laboratories and setups (Héroux et al., 2015; Gutiérrez-Muto et al., 2023). Thirdly, both the induced excitability and plasticity effects of TMS and rTMS along with the corresponding influences of the confounding factors should further be investigated on their reliability. Currently, low to moderate reliability of rTMS effects (Prei et al., 2023) as well as individual differences of rTMS responses (Schoisswohl et al., 2024) are predominant in the literature. Above all, care must be taken when using rTMS in therapy or other clinical use on the basis of the lofi-hife heuristic assumptions. Our findings suggest that expected inhibitory changes from pre to post 1 Hz rTMS application remain absent or invert to contrary effects, which in the worst case could deteriorate the patients' symptoms. Thus, personalized application could increase the therapeutic effect (Schoisswohl et al., 2021). Additionally, since the set current direction of pulse sources often differs (van Doren et al., 2015), in order to achieve better responses, researchers or clinical personnel may consider adjusting the current direction settings.

## Author contributions

CK, MO, MS and SS contributed to study conceptualization and methodology. CK and MO did the data acquisition. WM, MS and SS performed supervision. CK conducted data curation, formal analysis, visualization and drafted the manuscript. All authors reviewed and edited the manuscript.

## CRediT authorship contribution statement

**Florian Schwitzgebel:** Writing – review & editing. **Mirja Osnabruegge:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Carolina Kanig:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Stefan Schoisswohl:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Martin Schecklmann:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Wolfgang Mack:** Writing – review & editing, Supervision, Funding acquisition.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.brainresbull.2025.111484.

## Data availability

Data will be made available on request.

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