



Phase-amplitude coupling in high-gamma frequency range induces LTP-like plasticity in human motor cortex: EEG-TMS evidence

1. Introduction

Phase-amplitude coupling (PAC), a ubiquitous phenomenon in human cortex, couples the amplitude of a fast oscillation, usually in the high-gamma frequency range (defined here as 80–200 Hz) to a specific phase of a slower oscillation. PAC is associated with learning and plasticity [1]. One of the most widely used transcranial magnetic stimulation (TMS) protocols, the theta-burst stimulation (TBS), is inspired by the PAC principle, delivering gamma-frequency bursts at theta frequency [2]. However, conventional TBS is not coupled to ongoing brain oscillations. Recently, it was demonstrated that TMS pulses can be synchronized to brain oscillations by real-time EEG analysis, and that the specific target phase determines the direction and magnitude of plasticity induction [3,4]. In the motor cortex, coupling of high-gamma TMS bursts to the trough of the ongoing sensorimotor μ -rhythm (a state of high corticospinal excitability [3]) mimics PAC in a more physiological way than conventional TBS protocols. Here, we investigated which EEG-synchronized TMS burst frequency is the most effective in inducing motor cortex long-term potentiation (LTP)-like plasticity. We hypothesized this to be the high-gamma frequency range, since high-gamma naturally couples to the trough of the sensorimotor μ -rhythm for modulation of movement in humans [5].

2. Methods

The study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee (064/2021B02). EEG-triggered TMS as described previously [3,4] was used. Left-hemispheric sensorimotor μ -rhythm was extracted using a surface Laplacian montage (EEG sensor C3 referenced to the average of CP1, CP5, FC1 and FC5). For more details on the experimental set-up, data analyses and statistics, please see the Supplementary Material.

Twelve healthy adults completed the study, following a randomized, double-blinded, crossover design (Fig. 1a). The hand representation of left primary motor cortex (M1) was targeted by single-pulse TMS at an intensity of 115% resting motor threshold (RMT). The peak-to-peak amplitude of motor evoked potentials (MEPs) from the first dorsal interosseus muscle of the right hand was measured as readout of corticospinal excitability in blocks of 100 trials each (interstimulus interval of 5 ± 1 s) at two pre- and five post-intervention time points (Fig. 1a). The intervention consisted of 200 quadruplet bursts at 80% RMT, an inter-burst interval of 0.7–1.0 s, and one of 5 conditions: (1) random phase (irrespective of the ongoing μ -rhythm), burst frequency 200 Hz (control

condition); (2) first pulse of the quadruplet on the trough of the ongoing μ -rhythm, 60 Hz (simulating low-gamma); (3) trough, 100 Hz (high-gamma); (4) trough, 200 Hz (high-gamma); trough, 666 Hz (l-wave frequency). Each condition was tested in a separate experimental session at least 72 h apart in randomized order.

3. Results

The effects of CONDITION and TIME on MEP amplitudes of pre- and post-intervention time points were analysed with a linear mixed-effects (LME) model (Fig. 1b–f). The two pre-intervention time points were pooled for analysis. Individual sessions were modelled as random effect to correct for possible between-session variability in MEP amplitude in the pre- and post-intervention period. We observed a significant effect of TIME ($F_{5,41471} = 5.18$, $p < 0.001$) and TIME \times CONDITION interaction ($F_{20,41471} = 13.01$, $p < 0.001$), but not of CONDITION ($F_{4,44} = 2.11$, $p = 0.095$). To test for plasticity induction, MEP amplitudes of each post-intervention time point were compared to the pooled baseline MEP separately in each of the interventions. We found a significant decrease in MEP amplitude at all post-intervention time points of random 200 Hz and only at one time point of trough 60 Hz and trough 666 Hz. In contrast, trough 100 Hz and trough 200 Hz resulted in a significant increase in MEP amplitude at all post-intervention time points (Fig. 1b–f, for more details see Supplementary Material). Moreover, when testing each of the trough interventions against random 200 Hz (control condition) trough 100 Hz was significantly different to random 200 Hz, at 45 and 60 min (Fig. 1d).

Pre-measurement phase-accuracy and mean inter-burst intervals during intervention did not show significant differences across interventions (both $p > 0.05$, for details see Fig. S2 in Supplementary Material), demonstrating that these factors did not account for the observed differences.

4. Discussion

The random 200 Hz condition caused a long-term depression-like decrease in MEP amplitude, most likely explained by the close to 1 Hz frequency burst stimulation in the intervention. In contrast, the trough 100 and 200 Hz condition led to a significant LTP-like increase in MEP amplitude, with the trough 100 Hz condition being different from the control condition. Burst frequencies of 60 and 666 Hz did not show a clear effect. This demonstrates that a range of most potent frequencies for induction of LTP-like plasticity exists in human M1. This range is in the high-gamma spectrum that occurs naturally in cortical PAC in humans [5,6]. At the cellular level

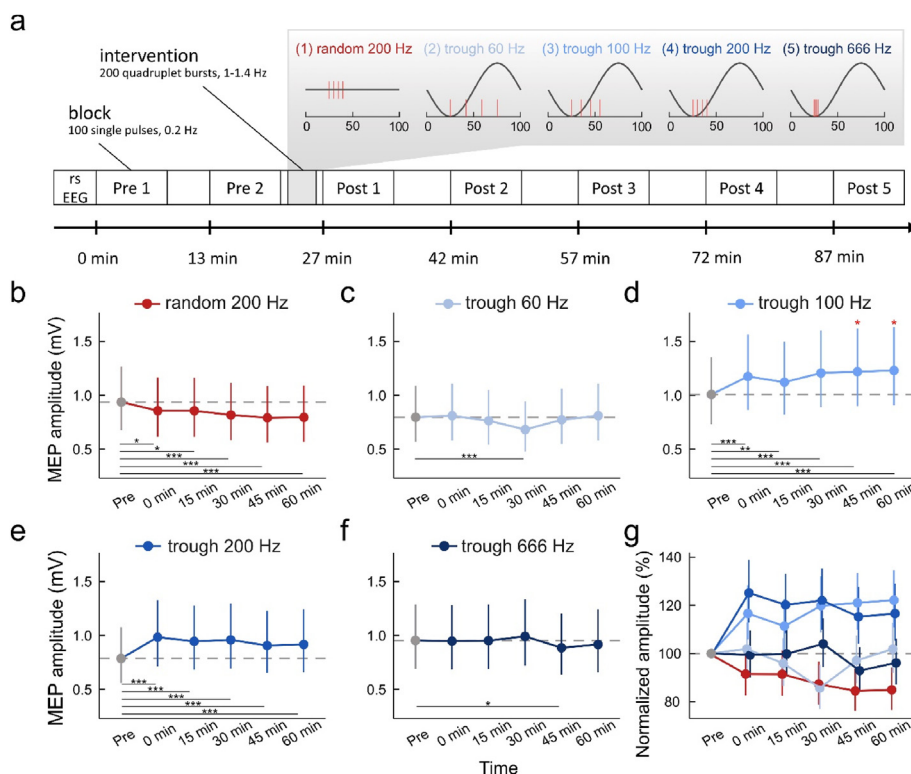


Fig. 1. Experimental design and results. **a** Graphical illustration of the experimental design, grey area illustrates the different conditions of the intervention. Red bins indicate the quadruple burst relative to the μ -rhythm cycle. **b-f** Time course of estimated means (circles) and 95% confidence interval (error bars) of the model across all subjects ($n = 12$) for each condition. Significance: * <0.05 , ** <0.005 , *** <0.0005 . Black asterisks: Single Post time points vs. Pre. Red asterisks: test against the corresponding time point in random 200 Hz. Plotted data were back-transformed to the original MEP scale. **g** Estimates of b-f (same color coding) normalized to the Pre period of the respective condition. Plotted data were back-transformed to the original MEP scale. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the precise nesting of oscillations has been shown to facilitate plasticity inducing states in animal models [7]. PAC is associated with long-term memory formation in rats [8] and improvement of human motor performance [9] and has been proposed as a general mechanism for plasticity induction in the brain [10]. The mimicking of PAC by brain-oscillation synchronized high-gamma TMS bursts might therefore tap into a physiological mechanism for plasticity induction.

Our study has limitations: The variation of burst frequency over a large range resulted in different coverages of one μ -oscillation cycle by one burst ($\sim 4.5\%$ – 50% , cf. Fig. 1a). Further, the first pulse of the bursts was centered on the trough of the μ -rhythm. It is unclear if centering another portion of the bursts on the trough would have resulted in different findings. This could be tested but is beyond the scope of this study.

In summary, imitating PAC for plasticity induction in human cortex by EEG-synchronized high-gamma TMS bursts is an exciting opportunity for individualized brain stimulation, enabling potentially highly effective therapeutic modulation of brain networks in neuropsychiatric disorders.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CZ reports an interest in sync2brain GmbH (Tübingen, Germany), a spin-off start-up company to commercialize real-time EEG analysis technology used in this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2022.11.003>.

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