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Cumulative effects of single TMS pulses during beta-tACS are stimulation intensity-dependent

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ABSTRACT

Background: Single transcranial magnetic stimulation (TMS) pulses activate different components of the motor cortex neural circuitry in a stimulation intensity-dependent way and may lead to a cumulative increase of corticospinal excitability (CSE) during the same stimulation session. Furthermore, transcranial alternating current stimulation (tACS) has been shown to increase in a frequency-specific way the level of CSE probed by single-pulse TMS. The interaction of these two phenomena, i.e. cumulative increases and baseline shifts of CSE, and the involved neural circuitry has not been studied yet.
Objective: The aim of this study was to investigate stimulation intensity-specific online effects of simultaneous TMS and tACS on CSE.
Methods: Single-pulse TMS was applied concurrent to 20 Hz tACS over the left primary motor cortex of thirteen healthy subjects to probe CSE indexed by motor evoked potentials (MEPs) recorded from the contralateral extensor carpi radialis muscle of the right hand during rest. Six different TMS intensities (90%, 100%, 110%, 120%, 130%, and 140% of resting motor threshold, RMT) were studied in a randomized blocked design. In each block, 40 pulses were applied with an inter-stimulus interval of 5 s and a jitter of ±0.5 s, i.e. at a stimulation frequency of 0.2–0.25 Hz.
Results: Beta-tACS has a general facilitatory effect on CSE across the tested TMS intensities. The results of the block wise regression of the MEP amplitudes show a more specific effect. Combining tACS and TMS leads to a cumulative increase in CSE for the stimulation intensity of 120% RMT only ($p = 0.0004$).
Conclusion: CSE increases due to beta-tACS and cumulative TMS pulses may be mediated by different neuronal mechanisms.

Introduction

Transcranial magnetic stimulation (TMS) has been established as a powerful mapping tool to probe corticospinal excitability (CSE) for clinical and research applications in humans [1]. TMS over the primary motor cortex (M1) evokes multiple descending volleys, generated by direct (D-wave) and indirect (I-waves) activation of the corticospinal pathway [2]. The stimulation intensity determines the recruitment of neuronal structures [3]: TMS intensities below 110% resting motor threshold (RMT) induce MEPs via the recruitment of early I-waves [4], while later I-waves gradually mediate the propagation of the motor signals with increasing stimulation amplitude [2,5]. These later waves are thought to be generated by a cortico-cortical circuitry projecting to the corticospinal neurons [6]. When further increasing the stimulation intensity, the axons of the corticospinal neurons are directly activated (D-wave; Lazzaro et al., 1998). MEP changes during an intervention may thus inform about the involved neural circuitry, when induced by specific TMS intensities only.

Furthermore, MEP amplitudes show a considerable intra- and inter-individual variability despite unchanged stimulation parameters; a phenomenon that is most likely related to the fluctuating responsiveness of the neuronal structures to TMS pulses [7,8]. Particularly, sensorimotor oscillations determine the brain's responsiveness to such an input and reflect the current excitatory state [9] with high and low activity suggesting an inhibitory and excitatory brain state, respectively, caused by thalamo-cortical and cortico-cortical interdependences [10,11]. These oscillatory variations of the intrinsic brain state have, therefore, been targeted by different endogenous and exogenous interventions; novel

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closed-loop technology modulated the oscillatory brain state during TMS by either volitional self-regulation [12,13], peripheral proprioceptive [14,15] or functional electrical stimulation [16,17], or by transcranial alternating current stimulation (tACS [18,19]).

More specifically, robust increases of CSE occurred, when TMS pulses were applied during motor imagery-related beta-band desynchronization, while the identical stimulation pattern, when applied independent of the brain state, resulted in a decrease of corticospinal excitability [13]. Moreover, beta-tACS, when applied concurrent to single-pulse TMS, increased CSE in a frequency-specific way during rest [19], but not during motor-imagery [18]. These findings revealed, thus, brain state-dependent systematic baseline shifts of the CSE.

On the other side, recent evidence suggests that single TMS pulses may by themselves induce changes in neuronal excitability - at both random and fixed inter-stimulus intervals (ISI) - which ultimately resulted in a cumulative CSE increase in the course of stimulation [20]. The interaction of these two phenomena, i.e. baseline shifts and cumulative increases of CSE, and the involved neural circuitry has not been studied yet.

Here, we applied beta-tACS concurrent to single TMS pulses in the resting state, an approach that has been shown to increase CSE [19]. The application of TMS was, however, modified in the present study, i.e. with an increased number of pulses and decreased ISI, to match the protocol that has been shown to induce cumulative CSE increases [20]. The TMS intensity was, furthermore, modulated in a randomized blocked design to target different components of the corticospinal pathway.

Recent studies have explored the influence of endogenous [21–23] or exogenously modulated [24–28] cortical rhythms on the MEP. We stimulated, therefore, at four different phases (i.e., at 0°, 80°, 180°, and 270°) of the beta-tACS cycle; the stimulation pulses were evenly distributed along the cycle to reduce any influence of the oscillatory phase on the cumulative CSE change.

We expected in the current study CSE increases for the simultaneous applications of beta-tACS and single-pulse TMS for supra-threshold intensities on the basis of previous findings [19]. Due to the previously described impact of beta-tACS on corticospinal coherence and behavioral measures [29,30] we expected a more general impact of tACS on other components of the motor pathway, i.e. probed by different TMS intensities, as well. We, furthermore, hypothesized that the robust cumulative increase of CSE during single-pulse TMS at 120% RMT [20] would not be compromised by the simultaneous tACS, and tested whether this effect would be observable with different stimulation intensities as well.

Material and methods

Subjects

Thirteen, right-handed healthy subjects (7 females, age: 25 (20–28) years) took part in this study after providing written informed consent. None of the subjects had any history of neurological diseases or medication. The study protocol was approved by the local ethical committee of the medical faculty of the University of Tuebingen and was carried out in accordance with the principles of the Declaration of Helsinki. The combined TMS/tACS set-up and analysis has been described in detail previously [24] and is cited here where applicable.

Preparation

Bipolar electromyography (EMG) recording of the extensor carpi radialis (ECR) muscle of the right hand was performed in belly-tendon montage with a sampling rate of 5 kHz (BrainAmp ExG, Brain Products, Munich, Germany). The TMS hotspot for the recorded muscle was determined as the cortical location in the left hemisphere robustly eliciting MEPs with the lowest stimulation intensity. The hotspot search procedure started at a location on the scalp overlaying the left parietal bone and corresponding to the C3 electroencephalogram (EEG) sensor (according to the international 10/20 system) with a coil orientation perpendicular to the scalp and in the posterior-anterior direction. The initial TMS amplitude was set at 40% of the maximum stimulator output; the stimulation was manually triggered while the coil was gradually moved around the initial position [31]. If the search did not elicit any detectable MEP, the intensity was increased in 5% steps and the search was repeated. Once the location that robustly elicited the highest MEPs was detected, the stimulator intensity was reduced by using a staircase approach to diminish the current spread of the stimulation, hence restricting the hotspot area eliciting MEPs. The overall procedure resulted in a minimum of 40 manually triggered TMS pulses [32]. TMS was delivered by an integrated neuro-navigated system (Nexstim, Helsinki, Finland) with a figure-8-shaped coil that induced a posterior-anterior current flow in the first phase of a biphasic waveform [33]. Once the hotspot had been determined, a rubber ring electrode (internal diameter 2.5 cm, external diameter 5 cm) was positioned over the hotspot and a second rectangular electrode (5×6cm) was positioned over Pz. Both electrodes were attached to a DC/AC stimulator (NeuroConn, Ilmenau, Germany) and electrolyte gel was used to keep the impedance below 10 KΩ. The electrodes were kept in place by a tight EEG cap that covered the scalp. In addition, a fraction of the tACS signal current was routed via current division (1 MΩ versus 1 kΩ) and subsequently recorded using a bipolar amplifier with 5 KHz sampling rate. Since the amplifier's input resistance was 10 GΩ, the current lost to recording was negligible. Furthermore, we added two passive Ag/Ag-Cl-electrodes next to the hotspot position, i.e. directly under the TMS-coil, to detect any artifacts. Having positioned the stimulation electrodes, we used the neuro-navigated TMS system to keep coil position and orientation constant over the determined hotspot during the subsequent measurement and intervention. We assessed the resting motor threshold (RMT) of the ECR using a staircase procedure to detect the TMS intensity inducing motor-evoked potentials (MEPs) above 50 mV in 50% of the pulses. We calculated six stimulation intensities (SI) at 90%, 100% 110% 120% 130% and 140% relative to the RMT for each subject and acquired a baseline measurement with 10 stimuli at each SI (TMS-only condition) [24].

Technical procedure

The intervention was performed in six runs (or blocks), in each of which TMS was applied at a different SI (tACS-TMS condition). The order of the SI of each run was randomized across subjects. Each run lasted for 200 s, with a 1-min break between runs. During each run, tACS (20 Hz, 1 mA, 1 s ramp-up, 1 s ramp-down) was delivered to the subject, limiting the total stimulation duration of the study to 20 min [17]. The experimental design and temporal structure of the study are specified in Fig. 1. In earlier research, we observed that 20 Hz tACS are liable to induce phosphene sensations [34]. However, none of the subjects in this study reported neurosensory effects. The TMS was triggered to hit the tACS waveform with an equal distribution of stimulation pulses within one run, i.e. although the stimuli were applied in random order their distribution over the tACS waveform was even. The specific methodology has been describe earlier by our group [24] and is cited here: At the beginning of each run, we used a series of TMS test pulses to synchronize tACS phase and TMS stimulation timing. To achieve the necessary precision, we synchronized the two stimulators using a closed-loop automatic calibration lasting for approximately 1 s at

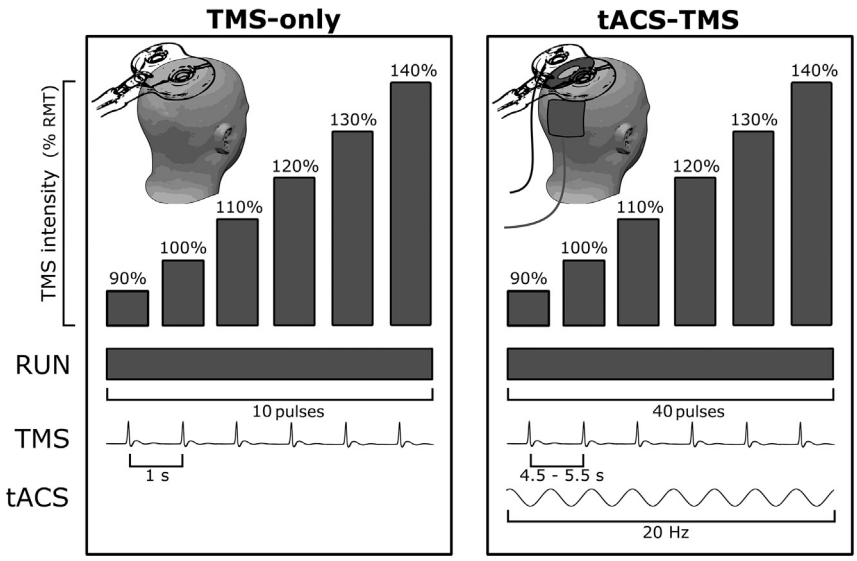

Fig. 1. Shows the experimental procedure and setup. The study was divided in a TMS-only stimulation and the tACS-TMS intervention. Six different intensities were tested; one for each separate run. The temporal characteristics of each run are shown in the lower part of the figure.

the beginning of each run. For this calculation, a random TMS pulse was briefly triggered at the onset of the tACS while the phase that was hit by this first TMS test pulse was analyzed. TMS pulses were triggered at the run-specific intensity every 5 s (±500 ms predefined jitter) while targeting one of four specific tACS phases: peak, falling flank, trough, and rising flank (i.e. 0°, 90°, 180° and 270°) in random order. Each of these four phases was targeted at random 10 times during each run, resulting in a total of 40 stimulation pulses per run/block, i.e. SI [24].

Preprocessing and analysis

The analysis was performed using custom made MATLAB scripts. The recorded EMG data was divided in epochs, with a time range of ±500 ms centered on the TMS artifact. The data was visually inspected, and trials contaminated by artifacts, and thus preventing the detection of MEPs, were removed. The peak-to-peak amplitude of the MEPs was measured as the range of the EMG trace from 10 to 50 ms following the TMS pulse. Within each subject, MEP amplitudes were normalized relative to the MEP amplitude at the 95th percentile of all measured MEPs.

To see how TMS intensity modulates the baseline shift of tACS-TMS we performed a series of paired T-tests on the sizes of MEPs elicited with and without tACS, for each of the tested intensities separately. To balance the two measurements, we selected the first 10 pulses of the tACS-TMS stimulation and compared with the 10 pulses of the TMS-only condition. We then tested how the cumulative increase in CSE by single-pulse TMS was modulated by the concurrent tACS stimulation and by varying TMS intensity. To this end, we performed a linear regression test on the size of the MEPs within each stimulation block corresponding to specific TMS intensities.

Furthermore, we performed an analysis of variance to explore the influence of TMS intensity (6 levels from 90 to 130%), number of pulses (as linear factor), tACS condition (tACS-TMS versus TMS-only) and subject (as random factor), and their interaction. We hypothesized to find a TMS intensity-specific effect on the MEP slope across pulses, but no TMS intensity-specific effect on the mean MEP increase between tACS conditions. As an intensity-specific slope during tACS-TMS has the risk of being aliased as an intensity-specific mean increase between tACS-conditions, we included two interaction terms to separate these effects. The first was 2-way between tACS condition x intensity, the second was 3-way between tACS condition x intensity x number of pulses. Significance of the first interaction term would evidence an intensity-specific effect of tACS on the average MEP amplitude, and significance of the second interaction an intensity-specific effect on MEP slope across pulses, depending on whether tACS was applied or not.

In all tests, significance was set at $p = 0.05$, and adjusted for multiple comparisons (for 6 intensities: $p = 0.0083$).

Results

Beta-tACS had a general facilitatory effect on CSE across the tested TMS intensities (Fig. 2, upper row). The *t*-test revealed significance for the stimulation intensities at 100%, 110%, 120%, and 140% RMT (see Table 1). The 90% condition showed a similar effect, but did not reach significance after multiple comparison correction ($p = 0.0084$). The 130% condition showed an increase in CSE during tACS-TMS, but was characterized by a large variability in the no-tACS condition, which affected the significance of the results.

The results of the regression (see Table 2) showed a more specific effect (Fig. 2, lower row). Combining tACS and TMS led to a cumulative increase in CSE for the stimulation intensity of 120% RMT ($p = 0.0004$). The slope was significant for this condition only with no evidence for such an effect for other TMS intensities.

These findings were confirmed by the analysis of variance (see Table 3). We found no significant 2-way-interaction between tACS condition and intensity, suggesting that the average MEP increase due to tACS was independent of the TMS intensity. We found a significant 3-way-interaction between tACS condition, TMS intensity and number of pulses. Together with the previous findings (Fig. 2), this suggests that the MEP slope depended on the TMS intensity.

Discussion

This study contributes two novel findings: (i) Beta-tACS over the primary motor cortex increased corticospinal excitability over a broad range of stimulation intensities of concurrently applied single TMS pulses. (ii). The cumulative increase of CSE in the course of one block of TMS pulses was present during simultaneous beta-tACS and occurred for the stimulation intensity of 120% RMT.

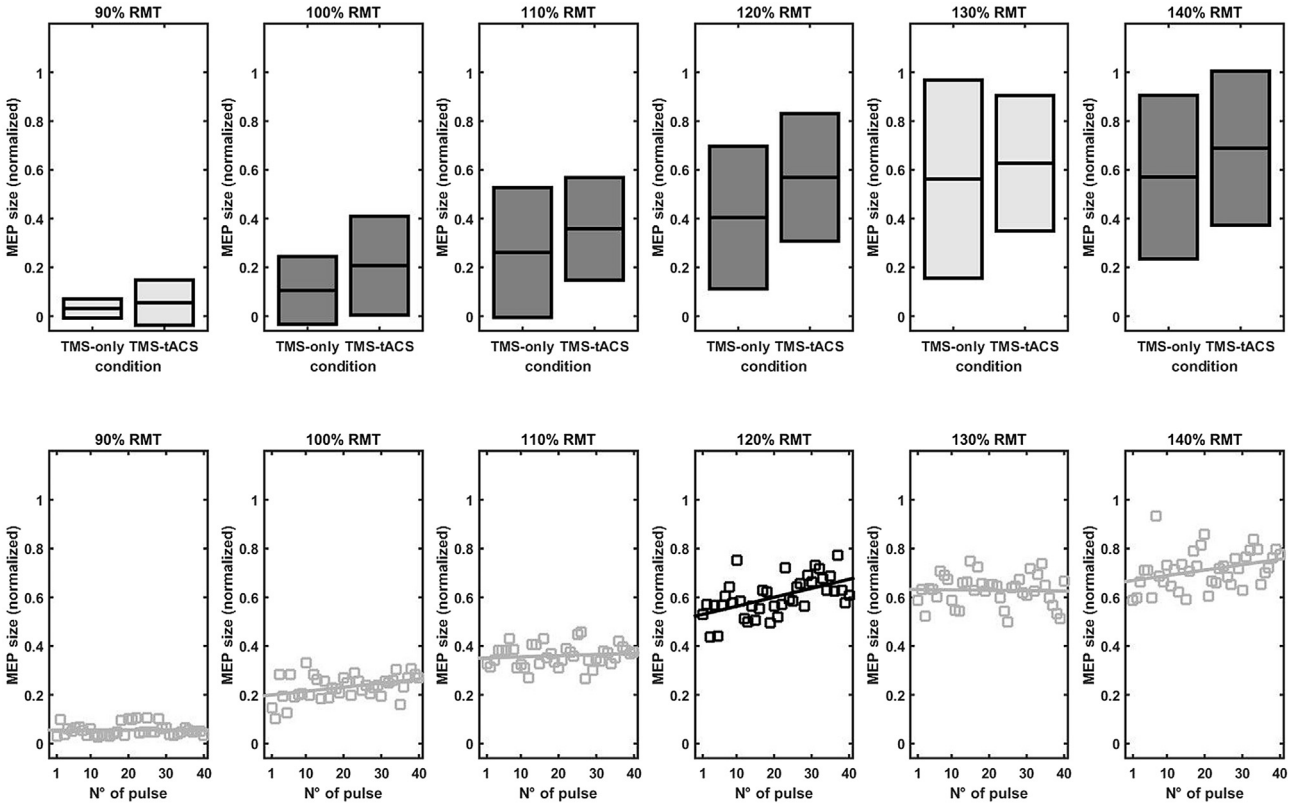

Fig. 2. Shows the results of the within intensity t-tests and regressions. The upper row shows the mean and standard deviation of the normalized MEPs elicited before and during tACS stimulation. Dark boxes indicate a significant *t*-test between the two groups. The lower row shows the within block linear regression of normalized MEPs during tACS-TMS stimulation. Each subplot shows the regression line and the averaged MEP values across subjects for each TMS pulse. The dark plot at 120% RMT condition indicates a significant regression ($p = 0.0004$). For all other intensities, the regression test did not reach significance.

By showing that beta-tACS during rest increased CSE, we confirmed previous work that combined single-pulse TMS and tACS [18,19]. We extended these findings by demonstrating that the CSE increase was present for a broad range of TMS stimulation intensities. Higher and lower TMS intensities have been suggested to recruit D-waves in layer 5 and interneuronal populations in layer 1 to 3 [35], respectively. It is, furthermore, known that cortical beta-oscillations are driven by simultaneous dendritic input at multiple layers [36], and that tACS may entrain cortical neuronal networks [37]. We, therefore, interpret the general increase of CSE following 20-Hz tACS as a modulation of different input components of the upper motor neuron circuitry. The cumulative CSE increase, on the other side, was found to be TMS intensity-specific. It has been argued that the increase of CSE in the course of one block of TMS pulses would reflect a summation of neuronal depolarization akin to charge accumulation in the stimulated neuronal tissue, thereby, priming

Table 1
Shows the results of the *t*-test between the TMS-only and tACS-TMS conditions.

	90% RMT	100% RMT	110% RMT	120% RMT	130% RMT	140% RMT
P-val	0.0084	0.0000	0.0029	0.0000	0.1291	0.0012
T-val	- 2.6777	- 4.6045	- 3.0394	- 4.5896	- 1.5276	- 3.3047
DoF	129	129	129	129	129	129
Std	0.1015	0.2512	0.3638	0.4089	0.4838	0.4083
Mean TMS-only	0.0318	0.1056	0.2612	0.4043	0.5621	0.5703
Mean tACS-TMS	0.0556	0.2070	0.3581	0.5689	0.6270	0.6886

Table 2
Shows the results of the regression test during tACS-TMS stimulation.

	90% RMT	100% RMT	110% RMT	120% RMT	130% RMT	140% RMT
P-val	0.9357	0.0246	0.5578	0.0004	0.8828	0.0408
Slope	0.0000	0.0017	0.0005	0.0037	−0.0002	0.0022
Intercept	0.0552	0.1977	0.3510	0.5264	0.6322	0.6669
DoF	38	38	38	38	38	38
F-Stats	0.0065	5.0810	0.3440	12.8750	0.0218	4.2055

Table 3
Shows the results of the analysis of variance.

Source	MSS	d.f.	F-value	P-value
Intensity	17.82	5	307.9	$<10^{-277}$
Subject	0.811	12	14.01	$<10^{-28}$
tACS-Condition	7.485	1	34.74	$<10^{-4}$
Intensity × tACS-Condition	0.042	5	0.718	0.610
Intensity × Pulse Number × tACS-Condition	0.163	5	2.819	0.015
Error	0.058	3871		

MSS: mean square of sums, d.f. degrees of freedom, values were gaussian-rounded.

background activity towards an increase in excitability [20,38]. The present study contributes to the discrimination of neuronal structures involved in these processes. Previously, it was not possible to discriminate, whether the cumulative CSE increase was mediated through spinal circuitry changes controlled via cortico-spinal connections or via interneuronal cortical networks [20]. The results of this study suggest the latter in line with previous findings that propose CSE to be determined by cortico-cortical networks via oscillatory synchronization in selected frequency bands [39].

Future research needs to explore whether the tACS-TMS induced CSE increase would result in more lasting plastic effects than TMS only. Furthermore, the present study balanced the applied TMS pulses across the tACS cycle to avoid phase-dependent effects. Future studies would need to explore, whether the tACS-TMS effects are phase-dependent as well [24,25,28]. The involved interneuronal circuitry could, moreover, be probed with different stimulation protocols [25]. Recently, Romei and colleagues [40] demonstrated that TMS entrainment effects were maximal at the individual beta-frequency; this suggests to apply tACS at individualized beta-frequency in future work.

In summary, our findings indicate that beta-tACS induces a general increase of CSE, suggesting the recruitment of global interneuronal input to the upper motor neuron. The specific interaction between stimulation intensity and cumulative CSE increase during TMS suggests, however, the involvement of a more specific neuronal network in this phenomenon.

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