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LTD-like plasticity of the human primary motor cortex can be reversed by γ-tACS

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ABSTRACT

Background: Cortical oscillatory activities play a role in regulating several brain functions in humans. However, whether motor resonant oscillations (i.e. β and γ) modulate long-term depression (LTD)-like plasticity of the primary motor cortex (M1) is still unclear.
Objective: To address this issue, we combined transcranial alternating current stimulation (tACS), a technique able to entrain cortical oscillations, with continuous theta burst stimulation (cTBS), a transcranial magnetic stimulation (TMS) protocol commonly used to induce LTD-like plasticity in M1.
Methods: Motor evoked potentials (MEPs) elicited by single-pulse TMS, short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were evaluated before and 5, 15 and 30 min after cTBS alone or cTBS delivered during β-tACS (cTBS-β) or γ-tACS (cTBS-γ). Moreover, we tested the effects of β-tACS (alone) on short-latency afferent inhibition (SAI) and γ-tACS on SICI in order to verify whether tACS-related interneuronal modulation contributes to the effects of tACS-cTBS co-stimulation.
Results: cTBS-γ turned the expected after-effects of cTBS from inhibition to facilitation. By contrast, responses to cTBS-β were similar to those induced by cTBS alone. β- and γ-tACS did not change MEPs evoked by single-pulse TMS. β-tACS reduced SAI and γ-tACS reduced SICI. However, the degree of γ-tACS-induced modulation of SICI did not correlate with the effects of cTBS-γ.
Conclusion: γ-tACS reverses cTBS-induced plasticity of the human M1. γ-oscillations may therefore regulate LTD-like plasticity mechanisms.

Introduction

Cortical oscillatory activities are known to be associated with several brain functions, including motor tasks, perception and cognition [1–5]. Also, in animals there is evidence that brain oscillations interact with cortical plasticity mechanisms. Indeed, some studies have shown that brain rhythms are affected by experimentally-induced changes in synaptic plasticity [6,7] and others have demonstrated that cortical oscillations can modify responses to plasticity-inducing protocols [8–10]. In humans, synaptic plasticity can be non-invasively tested by applying specific transcranial magnetic stimulation (TMS) paradigms that elicit long-term potentiation (LTP) and depression (LTD)-like changes in motor cortex excitability. Despite the advances made in recent decades on the understanding of the physiological mechanisms underlying synaptic plasticity [11–13], whether and how brain oscillations modulate LTP/LTD-like phenomena is still a missing knowledge in humans.

A possible approach to address this issue is the recording of electroencephalographic (EEG) or magnetoencephalographic signals during and after TMS [5,14]. By using this method various changes in brain rhythms have been demonstrated after the induction of synaptic plasticity, the most reliable being the modulation of theta power in the stimulated cortical area [14–17]. Another experimental approach to investigate the link between brain

Abbreviations: primary motor cortex, (M1); resting motor threshold, (RMT); active motor threshold, (AMT); transcranial alternating current stimulation, (tACS); transcranial magnetic stimulation, (TMS); short-interval intracortical inhibition, (SICI); short-latency afferent inhibition, (SAI); intracortical facilitation, (ICF); continuous theta-burst stimulation, (cTBS); gamma, (γ); beta, (β).

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oscillations and plasticity is combining TMS protocols eliciting LTP/LTD-like phenomena with transcranial alternating current stimulation (tACS). Indeed, tACS is a novel technique that entrains brain oscillations by inducing coherent changes in the firing of neurons [18–20], particularly when the stimulation frequency is close to the natural rhythm of the targeted area (i.e. resonance principle) [21–23]. We recently demonstrated that tACS delivered at the gamma (γ) frequency boosts and prolong the LTP-like plasticity of the primary motor cortex (M1) induced by intermittent theta burst stimulation (iTBS) with mechanisms of rhythm-dependent metaplasticity [24]. However, electrophysiological studies have demonstrated that intracortical circuits are differentially involved in LTP- and LTD-like plasticity of M1 [12,25,26], and no study has yet investigated the effects of tACS, delivered at the main motor resonant rhythms (i.e. beta -β- and γ), on LTD-like plasticity. A better understanding of the physiological mechanisms influencing LTD-like plasticity would allow the design of novel neuromodulating protocols possibly contributing to a better control of responses to non-invasive brain stimulation [27,28].

In this study, we applied β- or γ-tACS over M1 concomitantly with continuous TBS (cTBS), a TMS protocol commonly used to induce LTD-like plasticity [12,29]. We examined the effects of the combined tACS-cTBS stimulation on motor evoked potentials (MEPs) elicited by single-pulse TMS and on short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF), as assessed by paired-pulse TMS. Previous studies have shown that β-tACS reduces cholinergic intracortical inhibition, as tested by short-latency afferent inhibition (SAI) [23], and that γ-tACS modifies GABA-A-ergic activity, as tested by SICI [24,30], two interneuronal circuits involved in M1 plasticity mechanisms [12,27,31]. Thus, we tested the effects of β-tACS (delivered alone) on SAI and γ-tACS on SICI, so as to assess any correlations between tACS-induced modulation of interneurons and tACS-related changes of cTBS-induced plasticity.

Material and methods

Participants

Eighteen healthy subjects (12 males; mean age ± SD: 26.1 ± 1.9) were enrolled in the study. None of the subjects had any neurological and/or psychiatric disorders, and none was taking drugs known to influence brain excitability. No participant had any contraindications to TMS or tACS, as indicated in the current international safety guidelines [32,33]. The study was conducted in accordance with the Declaration of Helsinki.

TMS protocols

Single- and paired-pulse TMS were performed by using MAGSTIM 200 and a standard figure-of-eight 70 mm coil delivering monophasic pulses (Magstim Company Limited). The 'hotspot' (i.e. optimal scalp position to elicit MEPs) of the right first dorsal interosseous (FDI) muscle was identified with the handle of the TMS coil pointing posteriorly and laterally to the midsagittal line. This procedure was repeated twice: first, in order to center the stimulating electrode of tACS over M1; second, after the electrodes had been positioned on the participant's head, when the site was marked over the sponge in order to ensure reliable coil repositioning during the experiment. Resting motor threshold (rMT) and active motor threshold (AMT) were then determined according to the international guidelines [34]. MT_{1mV} was considered as the minimum intensity required to produce MEPs of ≈1 mV in size. MEPs were recorded at rest through a pair of surface electrodes in a belly/tendon montage. Electromyographic (EMG) signals were amplified (Digitimer D360 amplifier; Digitimer Ltd), digitized at 5 kHz (CED 1401; Cambridge Electronic Design) and stored on a computer for off-line analysis (Signal software).

SICI and ICF

SICI and ICF were tested according to standardized protocols [35–37]. Paired pulses were delivered at an inter-stimulus interval (ISI) of 2 and 4 ms for SICI ($SICI_{2ms}$ and $SICI_{4ms}$) and 10 ms for ICF. The following intensities were used: the conditioning stimulus (CS) was set at 80% of the AMT while the test stimulus (TS) was set at MT_{1mV}. We decided to test SICI at these specific ISIs and intensities to avoid any contamination by short-interval intracortical facilitation [36,38].

SAI

SAI was studied by using the standard technique [39]. Median nerve stimulation was performed at the wrist by means of a 0.1-ms electrical rectangular pulse (Digitimer DS7A) using a bipolar electrode and an intensity that induced a painless thumb twitch. The intensity of the TMS was set at MT_{1mV}. Two ISIs (interval between the median nerve and the cortical stimulation) were tested, i.e. 22 ms and 24 ms ($SAI_{22\,ms}$ and $SAI_{24\,ms}$).

cTBS

cTBS was delivered by using a high-frequency biphasic magnetic stimulator (Magstim SuperRapid). The stimulating protocol consisted of 200 bursts of three pulses at 50 Hz, repeated every 200 ms and delivered in a continuous train lasting 40 s (600 pulses in total). AMT was measured again by means of the biphasic stimulator and cTBS was tested by using the stimulation intensity corresponding to 80% of AMT [12,29].

tACS

tACS was performed by using conductive rubber electrodes (5 × 5 cm of size) enclosed in sponges soaked in saline solution through a BrainSTIM (EMS, Italy). The stimulating electrodes were centered over M1 and Pz, as described in previous studies [23,24,40–42]. Impedance was kept at <10 kΩ, as measured by the stimulation device. As described in our previous works [24,41,42], 20 Hz and 70 Hz were used for the β- and γ-tACS frequencies, respectively. Sinewave stimulation was delivered with no direct current offset and a peak-to-peak amplitude of 1 mA with 3-s ramping-up and ramping-down periods. Fig. 1 shows the corresponding estimated current density distribution. If this intensity induced unpleasant visual or skin sensations, the stimulation amplitude was gradually lowered until the discomfort disappeared. As a result, participants did not perceive any sensation during β or γ tACS and they were, therefore, unable to distinguish among the different stimulation conditions. The stimulation intensity eventually used for β-tACS was 0.78 ± 0.23 mA (mean ± SD), whereas that used for γ-tACS did not need to be reduced in any subject (Table 1).

Experimental paradigms

Each of the 18 participants underwent three experiments.

Experiment 1 (Fig. 2, *upper part)* was designed to evaluate the effects of cTBS-tACS co-stimulation on corticospinal excitability. It consisted of three separate and randomized sessions, performed at least 7 days apart: i) cTBS alone (cTBS); ii) cTBS during γ-tACS (cTBS-γ); iii) cTBS during β-tACS (cTBS-β). Fourty-eight TMS stimuli (16 single-pulses, 16 $SICI_{2ms}$ and 16 ICF) were randomly delivered at rest before (T0) and 5 min (T1), 15 min (T2) and 30 min (T3) after cTBS over M1. In the cTBS-γ and cTBS-β sessions, tACS was activated only 7 s before the TMS protocol started and was switched off as

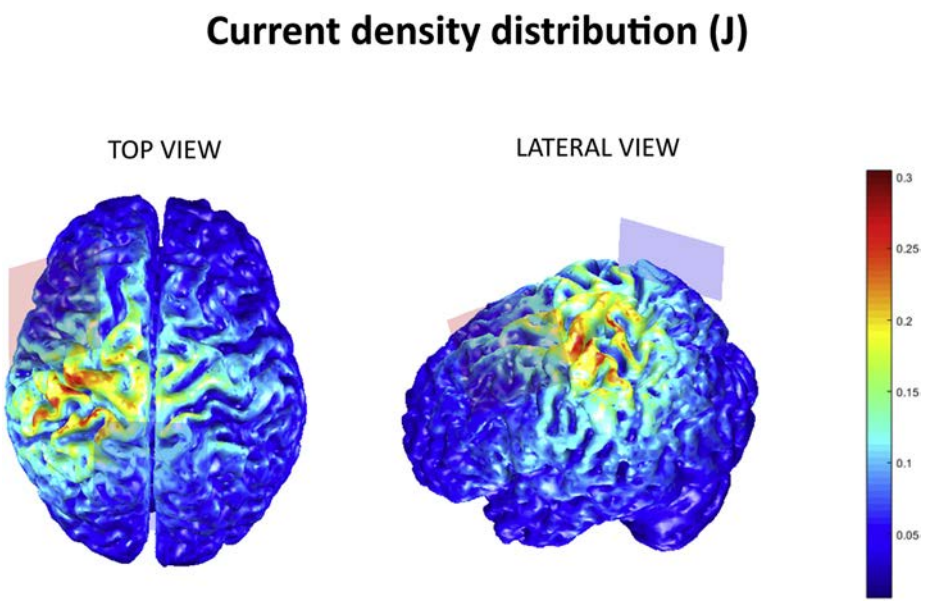

Fig. 1. Estimated current density distribution of tACS.
Top and lateral view of the estimated current density distribution produced in a representative subject receiving 1 mA tACS with the individual electrode montage used. The MATLAB toolbox Comets2 was used to compute the electric field (http://www.cometstool.com) [71].

Table 1
tACS intensity and motor thresholds.

	tACS intensity (mA)		AMT (%)			rMT (%)			MT_{1mV} (%)		
	β-tACS	γ-tACS	cTBS	cTBS-β	cTBS-γ	cTBS	cTBS-β	cTBS-γ	cTBS	cTBS-β	cTBS-γ
mean	0.78	1.00	34.7	42.0	43.8	43.9	56.9	57.9	57.8	72.1	72.8
SD	0.23	–	5.7	7.0	8.1	7.3	10.8	10.8	11.6	14.4	14.0

Transcranial alternating current stimulation (tACS) intensity, active motor threshold (AMT), resting motor threshold (RMT) and intensity used to evoke a motor evoked potential of ≈1 mV in amplitude (MT_{1mV}) for each session in Experiment 1 (mean and standard deviation - SD - values).

soon as cTBS ended (i.e. 40 s after). The tACS electrodes were not present on the scalp in the cTBS session.

Experiment 2 (Fig. 2, *middle part)* was designed to investigate the effects of γ-tACS on SICI and of β-tACS on SAI. After having determined the rMT, AMT and MT_{1mV}, 16 single-pulses, 16 $SICI_{2ms}$ and 16 $SICI_{4ms}$ were randomly recorded with tACS off and then during γ-tACS over M1. Similarly, 16 single-pulses, 16 $SAI_{22\,ms}$ and 16 $SAI_{24\,ms}$ were recorded with tACS off and then during β-tACS. The effect of γ-tACS on SICI was assessed on the same day as the cTBS-γ session, while that of β-tACS on SAI was tested on the same day as the cTBS-β session. Experiment 2 always preceded Experiment 1 by at least 15 min and tACS electrodes were mounted before determining the motor thresholds.

Experiment 3 (Fig. 2, *lower part)* was designed to verify whether γ-tACS (alone, without cTBS), was able to induce any after-effect on corticospinal excitability. γ-tACS was applied for 40 s over M1 and 48 TMS stimuli (16 single-pulses, 16 $SICI_{2ms}$ and 16 ICF) were randomly delivered at rest before and after stimulation, with a timing similar to that used in Experiment 1.

A further group of 10 subjects (6 males; mean age ± SD: 29.7 ± 2.2) underwent a control experiment, designed to test the effect of sham-tACS when combined with cTBS (cTBS-sham). Sham-tACS consisted of 70 Hz tACS activated for only 7 s before delivering cTBS. All subjects underwent cTBS-sham and cTBS-γ in two separate and randomized sessions. A neuronavigation system (SofTaxic Navigator System, EMS Italy) was used to ensure a precise TMS positioning over M1 throughout the experiment. Sixteen single-pulse MEPs were collected at T0-T3.

Data and statistical analysis

Peak-to-peak MEP amplitudes were measured by means of a customized script on Signal software and then averaged for each condition. Trials displaying EMG activity >0.1 mV in the 200 ms preceding TMS were discarded. A paired Student t-test was used to compare rMT, AMT and MT_{1mV} between sessions, and the amplitude of single-pulse MEPs, before and during tACS. Two separate repeated-measures (rm) ANOVAs with factor 'TMS protocol' were used to verify the effectiveness of SICI (3 levels: single-pulse, $SICI_{2ms}$, $SICI_{4ms}$) and SAI (3 levels: single-pulse, $SAI_{22\,ms}$, $SAI_{24\,ms}$) tested in Experiment 2. The same analysis, with 'TMS paradigm' (3 levels: single-pulse, SICI, ICF) and 'session' (3 levels: cTBS, cTBS-γ, cTBS-β) as factors, was used to confirm the efficacy of SICI and ICF protocols as tested before cTBS (T0) in Experiment 1. Raw MEP amplitudes were used for the aforementioned rmANOVAs. To test the effects of γ-tACS on SICI and β-tACS on SAI, we used two rmANOVAs with 'stimulation' (2 levels: tACS off, tACS on) and 'ISI' (2 levels: $SICI_{2ms}$ and $SICI_{4ms}$ or $SAI_{22\,ms}$ and $SAI_{24\,ms}$) as factors. RmANOVAs were also adopted to compare the after-effects of the cTBS protocol (Experiment 1) and γ-tACS (Experiment 3); in this case, we used 'time-point' (4 levels: T0, T1, T2, T3) as the factor of analysis. To test the effect of cTBS-tACS co-stimulation, we normalized the MEPs obtained after cTBS to their corresponding

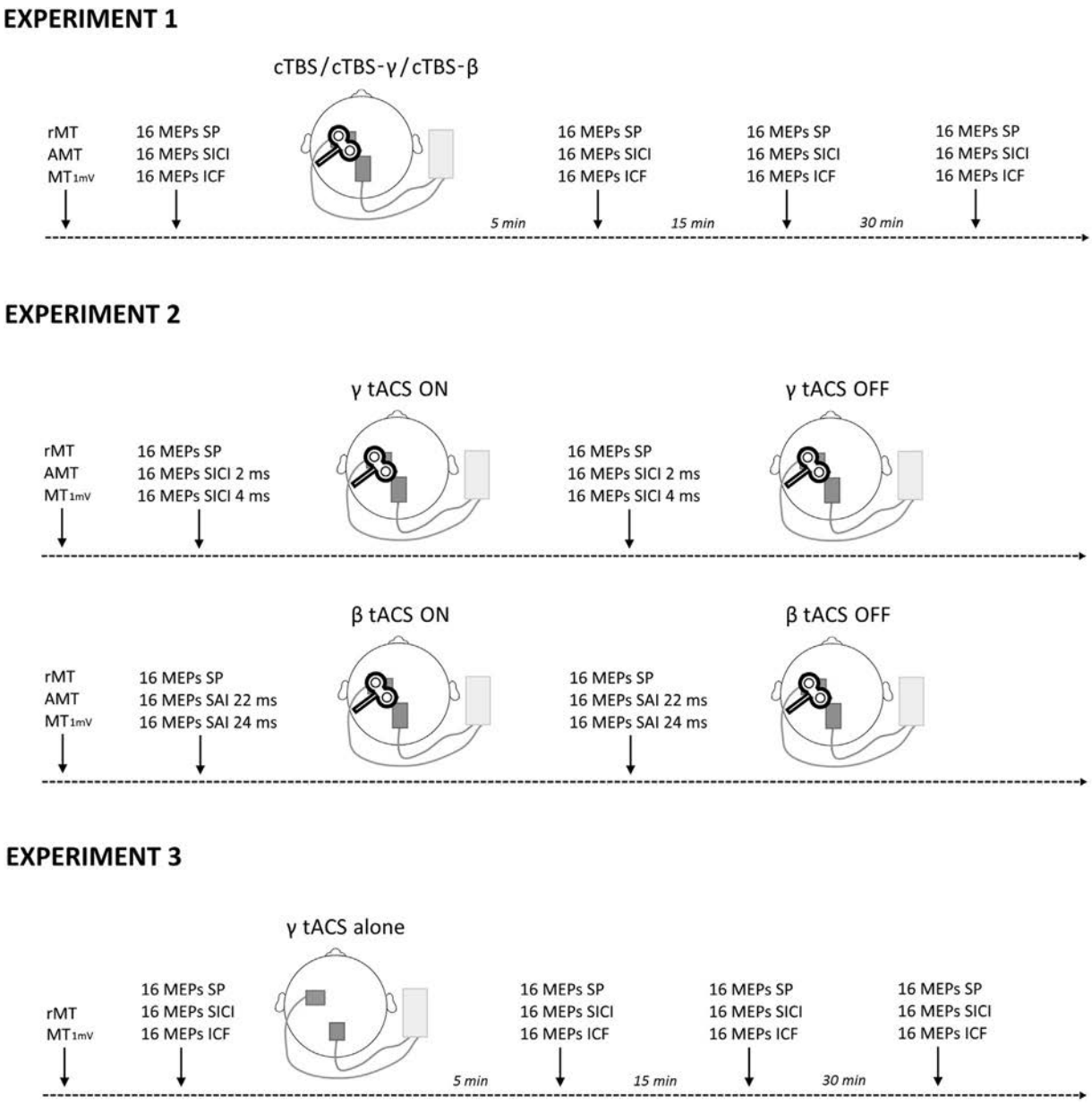

Fig. 2. Experimental design.
The TMS assessment started with the estimation of the resting motor threshold (rMT), active motor threshold (AMT) and the intensity that induced a MEP of ≈1 mV in amplitude (MT_{1mV}). *Experiment 1, effect of cTBS-tACS:* 16 single-pulse (SP) MEPs and 32 paired-pulses (16 SICI and 16 ICF) were delivered, at rest before and 5, 15 and 30 min after the continuous theta burst stimulation (cTBS) alone, or in combination with γ-tACS (cTBS-γ) or β-tACS (cTBS-β). The three different sessions were conducted in a random order at least one week apart. In this experiment, SICI was tested at ISI 2 ms. *Experiment 2, effect of γ- and β-tACS on SICI and SAI:* 16 single-pulse MEPs and 32 paired-pulses (16 SICI at ISI 2 ms and 16 SICI at 4 ms) were randomly delivered, at rest before as well as during γ-tACS. Similarly, 16 single TMS pulses and 32 paired-pulses (16 SAI at ISI 22 ms and 16 SAI at 24 ms) were delivered before and during β-tACS. *Experiment 3, after-effects of γ-tACS:* 16 single-pulse MEPs and 32 paired-pulses (16 SICI and 16 ICF) were recorded before and 5, 15 and 30 min after γ-tACS delivered alone. SICI was tested at ISI 2 ms.
Notably, tACS electrodes were mounted on the scalp before starting any TMS recording and taken off only at the end of the experiments.

pre-cTBS values. We then applied a separate rmANOVA for each TMS protocol (single-pulse, SICI and ICF) using 'session' and 'time-point' (3 levels: T1, T2, T3) as factors. For all the aforementioned rmANOVAs, SICI, ICF and SAI were expressed as the ratio between the mean conditioned and unconditioned MEP amplitude. Pearson's correlation test was used to assess neurophysiological correlations. Greenhouse-Geisser corrections were applied when a violation of sphericity was detected. Post-hoc comparisons were performed by means of paired t-tests. The level of significance was set at $p < 0.05$, with Bonferroni's correction subsequently being applied to multiple comparisons. Unless otherwise stated, all the values are presented as mean ± standard error of means (SEM). Statistical analyses were performed using SPSS Statistics for Windows (version 20.0.0; IBM).

Results

Experiment 1: effect of cTBS-tACS

rMT ($t = 1.03$, $p = 0.32$), AMT ($t = 1.38$, $p = 0.19$) and MT_{1mV} ($t = 0.57$, $p = 0.58$) were comparable in the cTBS-γ and cTBS-β sessions. The motor thresholds in the cTBS session (without tACS

electrodes) were lower than those obtained in the other sessions (Table 1 and Supplementary Fig. 1). Single-pulse MEPs, SICI and ICF were similar at T0 in the three different sessions, as shown by the non-significant interaction 'session'x'TMS paradigm' ($F_{4,68} = 1.25$, $p = 0.30$, $\eta_p^2 = 0.07$). SICI and ICF tested before the application of cTBS modulated the MEP amplitude, as demonstrated by the significant effect of the factor 'TMS paradigm' ($F_{2,34} = 70.23$, $p < 0.01$, $\eta_p^2 = 0.81$). As expected, SICI inhibited MEPs (single-pulse vs SICI: $p < 0.01$) and ICF facilitated MEPs (single-pulse vs ICF: $p < 0.01$). In the cTBS (without tACS) session, the cTBS paradigm reduced the amplitude of MEPs evoked by single-pulse TMS. The rmANOVA demonstrated a significant effect of the factor 'time-point' ($F_{3,51} = 8.25$, $p < 0.01$, $\eta_p^2 = 0.33$). The post-hoc analysis showed that MEP inhibition was maximal at T2 (T0 vs T2: $p < 0.01$), although significant also at T1 (T0 vs T1: $p = 0.03$) and T3 (T0 vs T3: $p = 0.01$). Differently, the cTBS paradigm had no effect on SICI and ICF, as shown by the non-significant effect of the factor 'time-point' (SICI: $F_{3,51} = 1.5$, $p = 0.24$, $\eta_p^2 = 0.08$; ICF: $F_{3,51} = 0.61$, $p = 0.61$, $\eta_p^2 = 0.03$).

The rmANOVA conducted on MEPs evoked by single-pulse TMS identified a significant effect of the factor 'session' ($F_{2,34} = 23.79$, $p < 0.01$, $\eta_p^2 = 0.58$, observed power = 1.0) and a 'session'x'time-point' interaction ($F_{4,68} = 4.38$, $p < 0.01$, $\eta_p^2 = 0.21$, observed power = 0.92). No effect was present of the factor 'time-point' ($F_{2,34} = 0.05$, $p = 0.95$, $\eta_p^2 < 0.01$). The post-hoc analysis on 'session' did not reveal any difference between the cTBS and cTBS-β ($p = 0.99$), whereas cTBS-γ resulted in MEP facilitation, as opposed to the expected MEP inhibition (cTBS-γ vs cTBS: $p < 0.01$; cTBS-γ vs cTBS-β: $p < 0.01$). Separate rmANOVAs conducted for the three time-points after cTBS yielded a significant effect of the factor 'session' at T1 ($F_{2,34} = 4.54$, $p = 0.02$, $\eta_p^2 = 0.21$), with a trend of differences between cTBS-γ and cTBS ($p = 0.08$), and cTBS-β ($p = 0.07$). Also, the effect was significant at T2 ($F_{2,34} = 28.10$, $p < 0.01$, $\eta_p^2 = 0.62$), with remarkable differences between cTBS-γ and cTBS ($p < 0.01$) as well as between cTBS-γ and cTBS-β ($p < 0.01$), and at T3 (factor 'session': $F_{2,34} = 7.81$, $p < 0.01$, $\eta_p^2 = 0.32$; cTBS-γ vs. cTBS: $p = 0.01$; cTBS-γ vs. cTBS-β: $p = 0.02$). The facilitatory effect of cTBS-γ was confirmed by the significant factor 'time-point' in the rmANOVA conducted on MEPs recorded in the cTBS-γ session ($F_{3,51} = 5.03$, $p = 0.01$, $\eta_p^2 = 0.23$) and by the post-hoc analysis that detected larger MEPs at T2 than at T0 ($p = 0.02$) (Fig. 3).

In contrast to the results yielded by single-pulse TMS, the trend for SICI and ICF after cTBS was similar between sessions, as shown by the non-significant effect of the factor 'session' (SICI: $F_{2,34} = 1.81$, $p = 0.18$, $\eta_p^2 = 0.10$; ICF: $F_{2,34} = 2.72$, $p = 0.1$, $\eta_p^2 = 0.14$) and the lack of any 'session'x'time-point' interaction (SICI: $F_{4,68} = 1.39$, $p = 0.25$, $\eta_p^2 = 0.08$; ICF: $F_{4,68} = 2.30$, $p = 0.11$, $\eta_p^2 = 0.12$) (Fig. 4).

Since a different mean intensity of tACS stimulation was used in the cTBS-γ and cTBS-β sessions (see Table 1), we assessed whether the lack of any effect of cTBS-β reflected the lower intensity applied. We used a median split procedure [24,30,41] and divided the participants in two groups according to the intensity of the stimulation used for β-tACS. We then conducted a rmANOVA with the within-group factor 'time-point' and the between-group factor 'stimulation intensity'. The analysis did not detect any effect of 'stimulation intensity' ($F_{1,16} = 0.02$; $p = 0.89$, $\eta_p^2 = 0.01$) or a 'stimulation intensity'x'time-point' interaction ($F_{2,32} = 0.47$; $p = 0.57$, $\eta_p^2 = 0.03$). Also, the correlation analysis demonstrated no relationship between the stimulation intensity and the effects produced by cTBS-β (average of T1-T3) ($r = -0.05$, $p = 0.85$).

Experiment 2: effect of γ-tACS on SICI and β-tACS on SAI

As expected, when tACS was off, SICI reduced the MEP amplitude ('TMS protocol': $F_{2,34} = 32.19$, $p < 0.01$, $\eta_p^2 = 0.65$) at both ISI (single-pulse vs $SICI_{2ms}$: $p < 0.01$; single-pulse vs $SICI_{4ms}$: $p < 0.01$). SAI also resulted in effective inhibition, as revealed by the significant effect of the factor 'TMS protocol' ($F_{2,34} = 57.63$, $p < 0.01$, $\eta_p^2 = 0.77$). MEPs were reduced at both ISI (single-pulse vs $SAI_{22\,ms}$: $p < 0.01$; single-pulse vs $SAI_{24\,ms}$: $p < 0.01$), though the inhibition was greater at the shorter ISI ($SAI_{22\,ms}$ vs $SAI_{24\,ms}$: $p = 0.01$).

A paired *t*-test demonstrated that single-pulse MEPs amplitude did not change during either γ-tACS (tACS off vs tACS on: $t = -1.15$, $p = 0.26$) or β-tACS (tACS off vs tACS on: $t = -0.87$, $p = 0.39$). Conversely, γ-tACS reduced SICI (factor 'stimulation': $F_{1,17} = 24.75$, $p < 0.01$, $\eta_p^2 = 0.59$) at both ISI 2 ms (tACS off vs tACS on: $p = 0.01$) and 4 ms (tACS off vs tACS on: $p < 0.01$). The γ-tACS-induced modulation of SICI was affected by ISI, as shown by the 'stimulation'x'ISI' interaction ($F_{1,17} = 4.40$, $p = 0.04$, $\eta_p^2 = 0.21$). A stronger effect was observed at $SICI_{4ms}$ than at $SICI_{2ms}$ ($p = 0.01$). β-tACS modulated SAI, as demonstrated by the significant factor 'stimulation' ($F_{1,17} = 27.94$, $p < 0.01$, $\eta_p^2 = 0.62$). SAI was reduced at both ISI 22 ms (tACS off vs tACS on: $p < 0.01$) and 24 ms (tACS off vs tACS on: $p < 0.01$), with a similar effect being observed for both intervals, as shown by the lack of any 'stimulation'x'ISI' interaction ($F_{1,17} = 2.36$, $p = 0.14$, $\eta_p^2 = 0.12$) (Fig. 5).

Correlations between the effects of γ-tACS on cTBS and SICI

Since γ-tACS modulated SICI and turned the effects of cTBS from inhibition to facilitation, we decided to assess whether these two phenomena were correlated. In order to measure γ-tACS-induced modulation of SICI, we calculated the ratio between SICI with γ-tACS 'on' and SICI with tACS 'off' at both 2 ms ($SICI_{2\ ms}$γ-tACS ON/OFF) and 4 ms ($SICI_{4ms}$γ-tACS ON/OFF). As a measure of γ-tACS-induced modulation of cTBS, we averaged the normalized values of MEPs yielded by single-pulse TMS at T1-T3. The analysis did not detect any correlation between $SICI_{2ms}$ γ-tACS ON/OFF ($r = 0.05$, $p = 0.84$) or $SICI_{4ms}$ γ-tACS ON/OFF ($r = -0.01$, $p = 0.97$) and the effect of cTBS-γ.

Experiment 3: after-effects of γ-tACS

The rmANOVA conducted on MEPs evoked by single-pulse TMS demonstrated that the amplitude did not change after γ-tACS, as shown by the non-significant effect of the factor 'time-point' ($F_{3,51} = 0.38$, $p = 0.77$, $\eta_p^2 = 0.02$). Similar results were obtained for SICI ($F_{3,51} = 1.83$, $p = 0.18$, $\eta_p^2 = 0.1$) and ICF ($F_{3,51} = 1.56$, $p = 0.21$, $\eta_p^2 = 0.08$).

Control experiment: effect of cTBS-sham tACS

A between-group ANOVA demonstrated comparable effects of cTBS-sham and cTBS (given alone) in Experiment 1, as shown by the non-significant factor 'group' ($F_{1,26} = 0.46$, $p = 0.51$, $\eta_p^2 = 0.02$) and the lack of 'group'x'time-point' interaction ($F_{2,52} = 0.39$, $p = 0.68$, $\eta_p^2 = 0.01$). A rmANOVA confirmed that the effects produced by cTBS-γ differed from those induced by cTBS-sham, as indicated by the significant factor 'session' ($F_{1,9} = 5.36$, $p = 0.04$, $\eta_p^2 = 0.37$).

Discussion

In this study, we provide new evidence demonstrating that cortical rhythms and brain plasticity interact. The main finding of this study is that γ-tACS combined with cTBS on M1 induces long-lasting MEP facilitation rather than the inhibition observed when cTBS is given alone. By contrast, β-tACS combined with cTBS does not modify the effects of cTBS on its own. Lastly, we confirmed that γ-tACS reduces SICI, though this effect does not correlate with the effects induced by γ-tACS on cTBS.

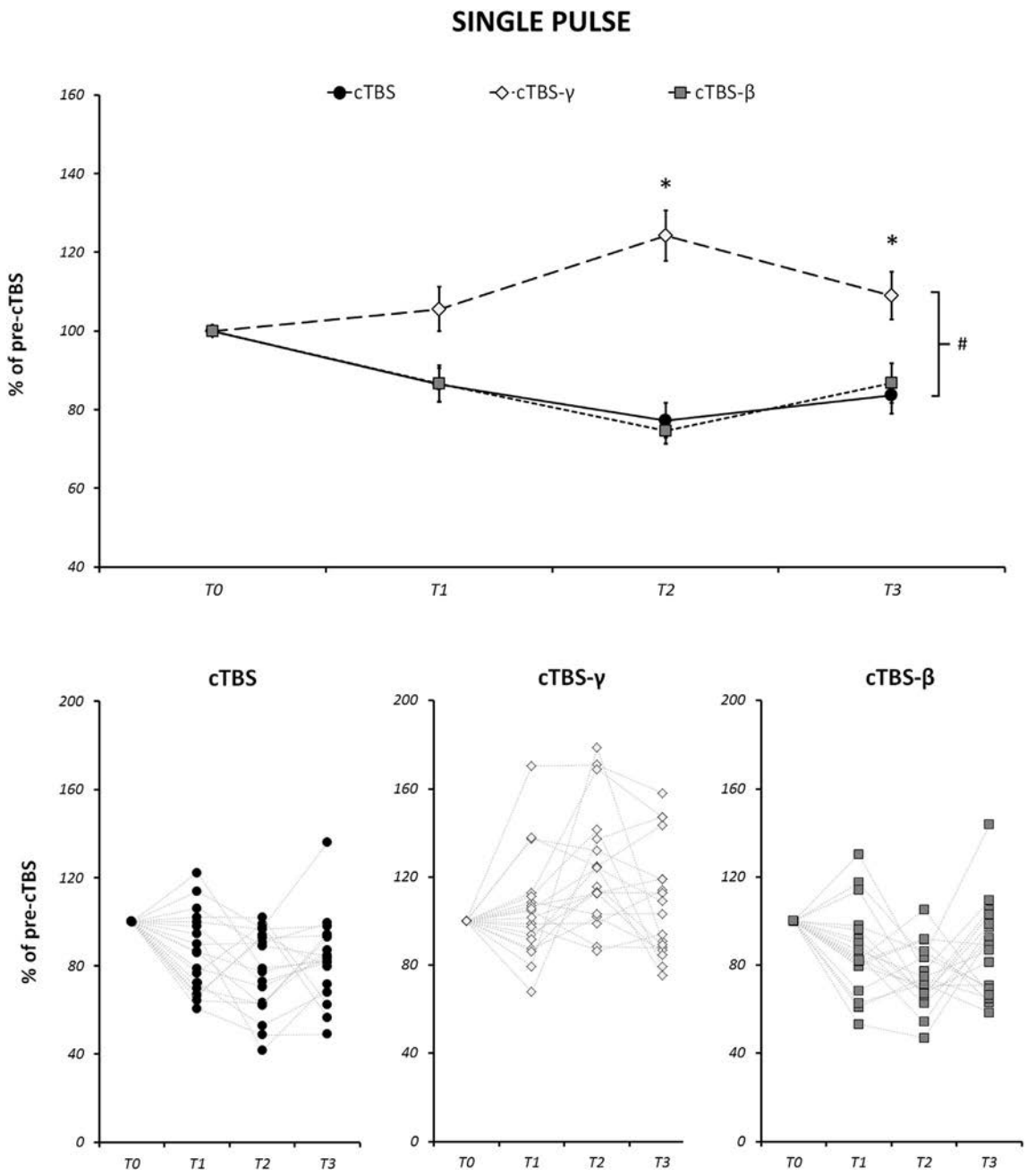

Fig. 3. Effect of tACS-cTBS on MEPs evoked by single-pulse TMS (Experiment 1).
Upper panel: γ-tACS delivered during cTBS (cTBS-γ) resulted in significant MEP facilitation as opposed to the expected MEP inhibition. No differences were detected between cTBS (alone) and cTBS-β. MEP amplitudes (average ± SEM) for each time-point after cTBS (i.e. 5 min – T1, 15 min – T2, and 30 min – T3) are compared with pre-cTBS (T0) values (set as 100%). # and * indicate differences between conditions. # = significant effect of 'session' in the rmANOVA; * = significant post-hoc t-tests after Bonferroni's correction. *Lower panel:* circles, diamonds and squares show individual data points and lines in cTBS, cTBS-γ and cTBS-β sessions, respectively.

In the experiment testing the effect of cTBS-tACS (Experiment 1), we observed an interaction between γ-tACS and cTBS, though not between β-tACS and cTBS. Therefore, we can exclude an unspecific interference on LTD-like mechanisms due to concomitant electric oscillatory-patterned stimulation. Moreover, the interaction between tACS and cTBS unlikely depends on the entrainment exerted by tACS on any resonant rhythm of M1. In the experiment testing the effect of γ-tACS on SICI and β-tACS on SAI (Experiment 2), we confirmed previous reports showing that β- and γ-tACS leave the M1 excitability unchanged [23,24,30,40,41,43,44]. Also, the experiment testing the after-effects of γ-tACS on M1 excitability (Experiment 3) disclosed that γ-tACS does not induce any marked after-effects [30,43]. These findings allow us to rule out that the interaction we observed between γ-tACS and cTBS is due merely to concurrent or long-lasting changes in corticospinal excitability induced by γ-tACS alone. Finally, the experiment testing the effect of sham-tACS on cTBS (Control experiment) showed comparable responses to cTBS given alone, allowing us to exclude a 'placebo' effect.

We thus hypothesize that the reversal of cTBS-induced LTD-like plasticity of M1 produced by γ-tACS results from a specific interaction between tACS-induced modulation of γ oscillations and the

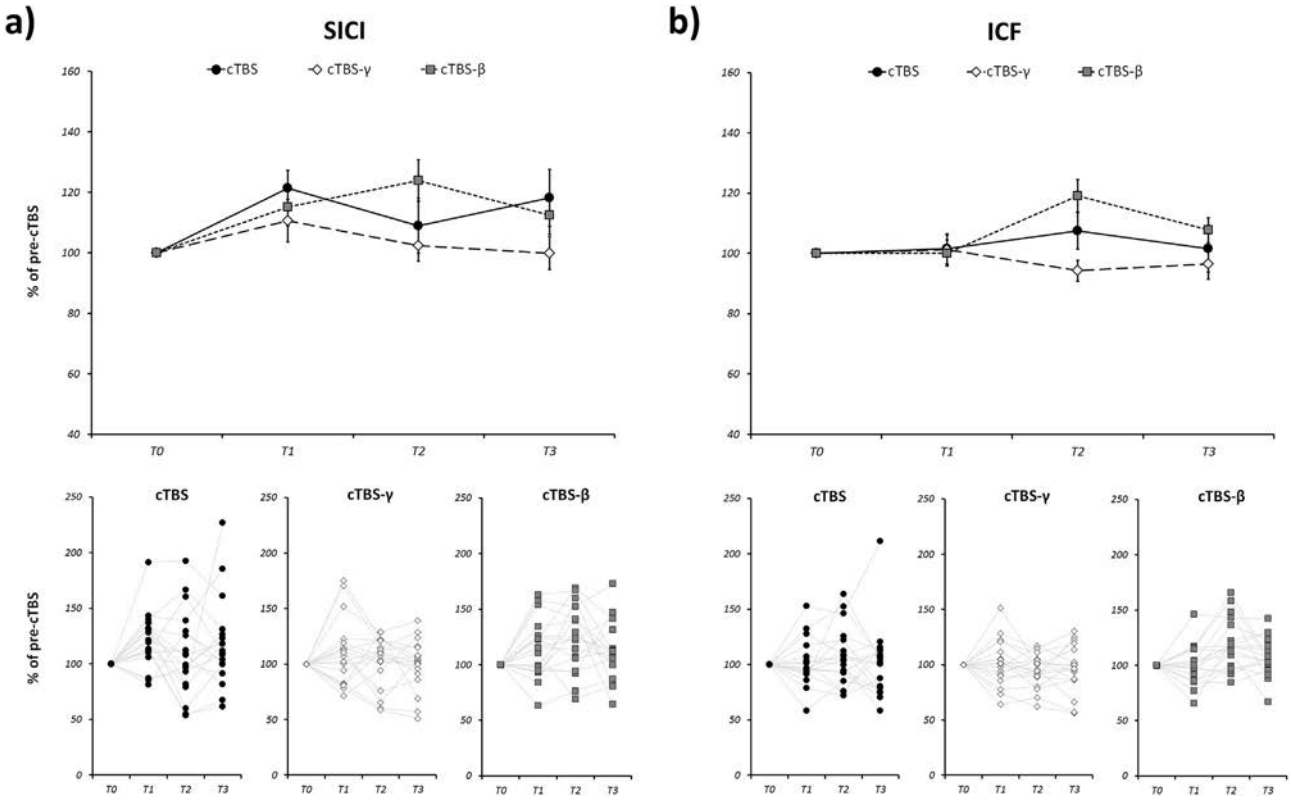

Fig. 4. Effect of tACS-cTBS on SICI and ICF (Experiment 1).
Upper panels: changes in SICI (a) and ICF (b) after cTBS did not differ in the three experimental sessions. MEP amplitudes (average ± SEM) for each time-point after cTBS are compared with pre-cTBS (T0) values (set as 100%). *Lower panels:* circles, diamonds and squares show individual data points and lines for SICI (a) and ICF (b) in the three experimental sessions.

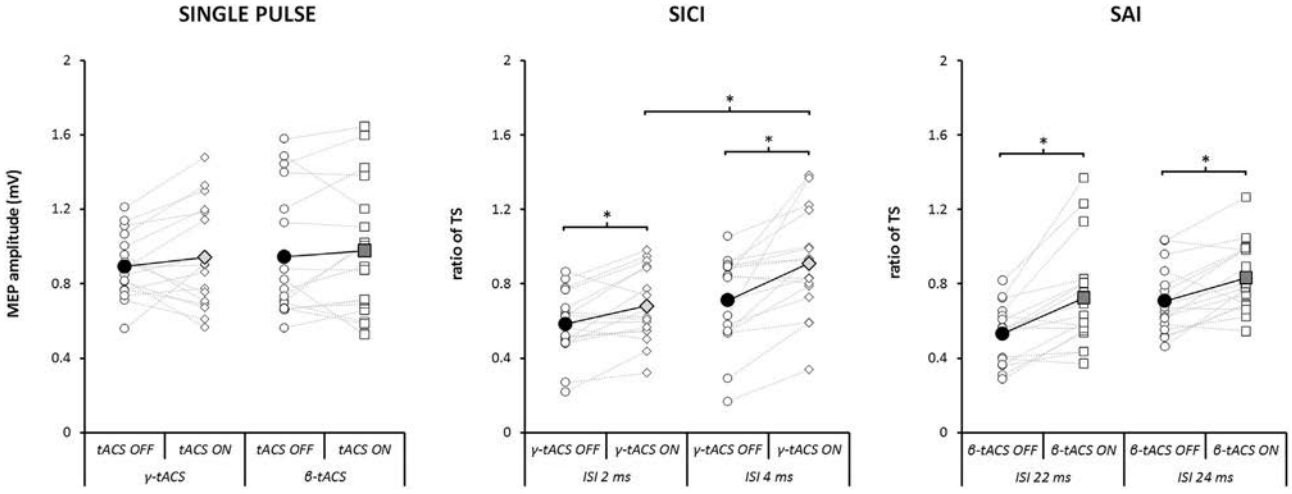

Fig. 5. Effect of γ- and β-tACS on corticospinal excitability (Experiment 2).
Left panel: γ- and β-tACS did not modify MEPs elicited by single-pulse TMS. *Central panel:* SICI was reduced by γ-tACS at ISI 2 and, even more markedly, at ISI 4 ms. *Right panel:* SAI decreased during β-tACS to a similar extent at ISI 22 and 24 ms. Empty circles, diamonds and squares show individual data. Full circles, diamonds and squares show mean data. MEPs' amplitude is displayed for single-pulse TMS data. SICI and SAI values are expressed as a ratio of the unconditioned MEP (i.e. test stimulus - TS). * = significant post-hoc t-tests.

physiological mechanisms underlying synaptic plasticity. One possible explanation for the long-lasting facilitatory effects resulting from the combination of cTBS and γ-tACS is that γ oscillations drive M1 plasticity exclusively towards LTP-like phenomena. In this scenario, the putative function of the γ rhythm in contributing to LTP-like plasticity would operate during TBS regardless of whether the pattern of TMS bursts is continuous or intermittent, as suggested by the results of our previous iTBS-tACS study [24]. In keeping with this hypothesis, *in vitro* and *in vivo* animal studies have demonstrated that cortical γ oscillations are prominently involved in the generation of LTP-like plasticity [6–8,45]. An alternative explanation is that γ oscillatory activity not only has an effect on LTP-like phenomena, but also modulates the physiological mechanisms responsible for LTD-like plasticity. This hypothesis is

supported by recent evidence from animal and human studies [15,46]. Huang and colleagues [46] demonstrated that N-methyl-D-aspartate (NMDA)-induced LTD produces a reduction of γ oscillatory activity in mouse cortex. Furthermore, the NMDA antagonist ketamine has been shown to prevent the loss of γ oscillations by inhibiting LTD [46]. Similarly, a recent TMS-EEG study on humans found that cTBS over M1 significantly reduces TMS-related spectral perturbation (a parameter that represents event-related changes in spectral power over time) in the γ frequency band [15]. Taken as a whole, these data point to a negative interaction between LTD-like plasticity mechanisms and γ oscillations in M1. This suggestion is supported by our findings: tACS, which is believed to entrain cortical rhythms and increase their power [20,47–49], might have boosted γ oscillatory activity in M1 and, in turn, disrupted the physiological mechanisms underlying LTD-like plasticity in humans.

Previous TMS-EEG studies demonstrated that a putative mechanism involved in cTBS-induced LTD-like plasticity is the increase of theta frequency oscillations [14,16]. It is therefore possible that a negative interaction between γ oscillations, enhanced by tACS, and theta oscillations, induced by cTBS, occurs in M1. A possible theta-gamma cross-frequency interaction [50] would have prevented LTD-like plasticity in M1 by decreasing cTBS-induced theta oscillations. Alternatively, the effects of γ-tACS on cTBS would reflect a non-homeostatic metaplasticity phenomenon, and in particular a 'rhythm-dependent' anti-gating phenomenon [51,52] whereby γ-tACS cancels the LTD-like effects of cTBS by modifying the balance of intracortical excitability within M1. Lastly, the effect exerted by γ-tACS on cTBS-induced plasticity would be ascribed to changes in calcium dynamics secondary to γ-tACS on M1. In this regard, a reversal effect of cTBS following the administration of nimodipine, a voltage-gated calcium channel blocker, has been reported in the literature [53]. In line with this possibility, a relevant theory suggests that the extent and dynamics of postsynaptic levels of calcium strongly affect the effective induction of synaptic plasticity [54,55].

A separate comment deserves the opposite effect produced by γ-tACS on cTBS and on iTBS-induced plasticity of M1. Indeed, unlike the present study showing a reversal of cTBS-induced after-effects, we previously demonstrated that γ-tACS boosts and prolongs the after-effects produced by iTBS [24]. This contrast can be explained given the electrophysiological evidence showing that cTBS and iTBS modulate different intracortical circuits in M1 [46,56–58]. Also, in line with the hypothesis of a different interaction between γ-tACS and circuits activated by cTBS and iTBS, we confirmed that γ-tACS reduces SICI [24,30], a well-known TMS measure of GABA-A intracortical interneuronal activity [35,36,59]. However, unlike our previous observation [24], in this study the γ-tACS-induced modulation of SICI did not correlate with the effects produced by γ-tACS-cTBS. Although neuronal elements resonant to γ rhythm are involved in circuits contributing to SICI [4,24,30], the lack of the aforementioned correlation suggests that the GABA-A-ergic interneurons tested by SICI might not contribute to the reversal effects on cTBS. Overall, these findings support the hypothesis that γ-tACS interacts with subpopulations of intracortical interneurons possibly contributing to cTBS and iTBS at different levels, thus producing opposite effects.

In the present study cTBS did not modify either SICI or ICF. A body of converging data indicates that cTBS does not induce any changes in ICF, while it reduces the GABA-A-ergic inhibition, as tested by SICI, early after the stimulation. However, the effect of cTBS on SICI has been reported as quite variable between studies [60]. Our results are generally in line with previous reports. The non-significant trend toward a reduced SICI we detected early after cTBS (Fig. 4) may be ascribed to the variability of the data.

In this study, γ-tACS modulated SICI during but not after the stimulation (Experiment 2 and 3), supporting the evidence that tACS induces robust 'ONLINE' rather than 'OFFLINE' effects on M1 [24,30,43]. We here demonstrated that the 'ONLINE' effect of γ-tACS on SICI is greater at ISI 4 than 2 ms. This result would suggest that $SICI_{4ms}$ may activate a specific subpopulation of GABA-A-ergic interneurons prominently resonant to the γ rhythm [61,62]. In line with a previous report [23], we also confirm that SAI, a measure of cholinergic neurotransmission reflecting the sensorimotor integration [39,63], is reduced during β-tACS ('ONLINE' effect – Experiment 2). However, since β-tACS did not modify the effects of cTBS, we speculate that changes in SAI do not play a crucial role in mechanisms of rhythm-dependent metaplasticity. Alternatively, the lack of β-tACS-cTBS interaction could be related to the opposite effects exerted by the β rhythm and cTBS on GABA-ergic interneurons. Indeed, whereas the increase of β oscillations triggers GABA release [64,65], the effects produced by cTBS prevent a further release of GABA [12,60], so possibly resulting in a null effect.

Finally, the present study has two limitations. First, we did not use a neuronavigation system in Experiment 1, 2 and 3. However, we adopted navigated-TMS in the control experiment, confirming our main results. Second, a recent study has suggested that transcutaneous stimulation of peripheral nerves contributes to tACS-induced motor effects [66]. Future studies using topical scalp anaesthesia are needed to verify this possibility.

Conclusions

We demonstrate that γ oscillations play a role in LTD-like plasticity in the human motor cortex. In particular, our findings show that γ-tACS negatively interacts with cTBS-induced LTD-like plasticity of M1. We also demonstrate that the effects induced by cTBS-γ tACS do not correlate with γ-tACS-induced modulation of SICI, whereas a previous observation we made showed that those induced by iTBS-γ tACS do [24]. This finding raises the hypothesis that γ-tACS interacts with subpopulations of intracortical interneurons responsible for cTBS and iTBS at different levels. Further studies are needed to evaluate possible tACS-related changes in M1 excitability and plasticity in physiological and pathological conditions characterized by altered brain plasticity or by less effective interneuronal circuits within M1 [67–70].

Conflict of interest

A.G., A.S., G.D.M., F.A., V.D.O., M.B., V.D.L., A.B. declare no competing financial interest.

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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.2019.06.029.

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