Journal of NeuroEngineering and Rehabilitation

RESEARCH

Open Access

Frequency-specific modulation of motor cortical excitability by transcranial alternating current stimulation

Lei Tingting[1,2†], Chen Lilin[1,3†], Wang Chuangjia[1†], Si Jiamen[4], Zhang Shuxian[1], Ai Yinan[1], Liu Hanjun[5*] and Zheng Haiqing[1*]

Abstract

Background Transcranial alternating current stimulation (tACS) is a non-invasive technique that modulates neural oscillations, yet its specific effects on cortical excitability are not well-understood. This study investigated the effects of tACS on neuroplasticity in the primary motor cortex (M1) across different frequencies.

Methods In this randomized, sham-controlled, crossover study, 18 healthy young adults received β-tACS γ-tACS, and sham stimulation over the M1. Neurophysiological responses were assessed using motor evoked potentials (MEPs), electroencephalograms (EEG), and transcranial evoked potentials (TEPs) to determine the frequency-specific effects of tACS on cortical excitability and neuroplasticity.

Results γ-tACS significantly enhanced cortical excitability, as reflected by larger MEP amplitudes compared to both β-tACS and sham stimulation. In addition, γ-tACS resulted in significantly smaller M1-P15 amplitudes in TEP than other stimulation conditions. In contrast, β-tACS did not produce significant changes in either MEPs or TEPs compared to sham stimulation.

Conclusion These findings provide evidence that tACS induces frequency-dependent effects on cortical excitability and neuroplasticity within the M1. This selective modulation of cortical excitability with γ-tACS suggests its potential as a therapeutic intervention for optimizing motor function and rehabilitation.

Trial registration This study was registered in the Chinese Clinical Trial Registry (ChiCTR2300074898, date of registration: 2023/08/18).

Keywords Transcranial alternating current stimulation, Primary motor cortex, Moter evoked potentials, TMS evoked potentials, Neural modulation.

†Lei Tingting, Chen Lilin and Wang Chuangjia contributed equally to this work.

*Correspondence:
Liu Hanjun
lhanjun@mail.sysu.edu.cn
Zheng Haiqing
zhenghq2@mail.sysu.edu.cn

[1]Department of Rehabilitation Medicine, the Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510630, Guangdong, China
[2]Department of Cardiovascular Medicine, Xi'an Central Hospital, Xi'an, Shanxi, China
[3]School of optometry, The Hong Kong Polytechnic University, Hong Kong, China
[4]Southern Medical University, Guangzhou, Guangdong, China
[5]Department of Rehabilitation Medicine, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, Guangdong, China

Background

Stroke is a leading cause of death and long-term disability worldwide, imposing significant economic and social burdens due to the extensive costs of treatment and rehabilitation [1]. Post-stroke survivors often experience persistent motor dysfunction, severely impairing their quality of life [2]. In recent years, non-invasive brain stimulation (NIBS) techniques have emerged as promising interventions for post-stroke motor impairments due to their non-invasive nature, ease of application, and potential for standardized clinical protocols [3]. Among the various NIBS techniques, transcranial magnetic stimulation (TMS) [4], transcranial direct current stimulation (tDCS) [5], and transcranial alternating current stimulation (tACS) [6] have been the focus of extensive research. In particular, tACS has gained attention as a promising method for modulating neural activity in a frequency-specific manner [7]. Unlike tDCS, which modulates neuronal excitability by inducing membrane depolarization or hyperpolarization through direct currents [8], tACS operates by using alternating, biphasic currents that change polarity at specific frequencies [9]. This approach enables tACS to interact with endogenous neural oscillations, influencing brain activity without directly altering membrane potential [10]. Such frequency-specific modulation of neural oscillations positions tACS as a versatile tool for modulating brain circuits involved in various cognitive [11] and motor functions [12]. However, the therapeutic potential of tACS in motor rehabilitation remains uncertain, particularly regarding how different stimulation frequencies modulate motor cortical activity.

Previous research has shown the frequency-dependent effects of tACS on neural function [13]. For instance, Bologna et al. [14] found that β-tACS impaired motor learning acquisition, while γ-tACS enhanced performance during motor training. These findings, along with other studies [15–18], emphasize the important role of stimulation frequency in shaping the effects of tACS on motor learning and cortical excitability. Specifically, while γ-tACS appears to facilitate movement, β-tACS is generally associated with motor inhibition [19–22]. However, inconsistencies across studies [15, 23–24] have been observed, highlighting the need for further investigation into the specific effects of tACS on motor function and its potential therapeutic applications. In particular, determining the optimal stimulation frequency for promoting motor recovery remains an open question.

To this end, this study investigated the effects of tACS on cortical excitability and neuroplasticity across different frequency bands in healthy participants. By comparing the effects of β-, γ-, and sham-tACS conditions, we sought to elucidate the neurophysiological mechanisms underlying frequency-dependent modulation of cortical activity. By employing a comprehensive set of neurophysiological measures that included motor evoked potentials (MEPs), electroencephalography (EEG), and transcranial evoked potentials (TEPs), this study aimed to provide new insights into the optimal tACS parameters in modulating M1 neuroplasticity, ultimately informing its potential for post-stroke motor rehabilitation.

Methods

Participants

A total of 18 healthy, right-handed adults (6 males and 12 females, aged 23.33 ± 1.80 years) were recruited for this study. Participants were excluded if they had: (1) a history of neurological or psychiatric disorders, (2) drug or alcohol addiction, (3) severe cardiopulmonary illness, (4) cognitive impairment, (5) inadequate sleep the night before the experiment, (6) recent consumption of neuroexcitatory substances or medications, and (7) contraindications to tACS, such as epilepsy or intracranial metal implants. All participants provided written informed consent prior to their participation in the study. No participants withdrew from the study. Ethical approval was obtained from the Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University (PJ2020MI-K180-01). This study is part of the registered research project (ChiCTR2300074898), which aims to investigate the effects and mechanisms of tACS in both healthy individuals and clinical populations. As an initial step, the present manuscript reported findings from the healthy cohort.

Measurement of electrophysiological indicators

Motor evoked potentials (MEPs)

Corticospinal excitability was assessed using a TMS device (YIRUIDE, YRD CCY-I, Wuhan, China). Participants were seated comfortably while the TMS coil was positioned over the left M1. The motor hotspot was identified as the scalp location that produced the largest MEP in the first dorsal interosseous (FDI) muscle, recorded by surface electromyography (EMG). The resting motor threshold (RMT) was defined as the minimum stimulation intensity required to evoke MEPs with a peak-to-peak amplitude greater than 50 μV in at least 5 out of 10 trials. TMS was then delivered at 120% of the RMT for ten trials, and both the amplitude and latency of MEPs were measured for analysis.

Resting-state electroencephalogram (RS-EEG)

RS-EEG was recorded using a 64-channel, TMS-compatible EEG cap (EGI, MicroCelGeodesic Sensor Net, USA) in accordance with the International 10–20 EEG System. Participants were asked to close their eyes while listening to while noise through headphones. EEG signals were recorded at a sampling rate of 1,000 Hz, with impedance levels maintained below 5 KΩ by applying GT10 medical

conductive paste (GREENTEK). Recordings were made over two minutes in a resting-state condition.

TMS evoked potentials (TEP)

TEPs were recorded to assess cortical plasticity by combining TMS with EEG. The same 64-channel EEG setup was used as in RS-EEG recordings. Single-pulse TMS was applied to the identified motor hotspot at 120% of the RMT, with an inter-stimulus interval of 2 s. A total of 200 TMS pulses were delivered, with EEG signals recorded concurrently during TMS application at a sampling rate of 1,000 Hz.

Transcranial alternating current stimulation (tACS)

tACS was administered using a VOLCAN device (VC-8000 F, Nanjing, China) with a 4 × 1 high-definition (HD) electrode montage. The central electrode was placed over the motor hotspot, with four return electrodes positioned around it. A biphasic alternating current waveform was used, with impedance kept below 1 KΩ and a current intensity of 2 mA applied for 20 min. Prior to each session, the stimulation intensity was increased gradually from 1 mA to 2 mA to ensure participant comfort. Sham stimulation consisted of a 15-second ramp-up period and a ramp-down period, with 30 s of electrical stimulation in between to mimic the tACS experience.

Experimental procedures

This study was performed in a randomized, sham-controlled, crossover design. Each participant underwent three experimental sessions in a randomized order: β-tACS (20 Hz), γ-tACS (70 Hz), and sham-tACS (20/70 Hz), with a washout period of one week (no deviations) between sessions to minimize carryover effects (Fig. 1). Randomization sequences were concealed in sealed opaque envelopes, and investigators involved in data collection and analysis were blinded to group assignments. The blinding was successfully implemented during the experimental process, and relevant data can be found in the supplementary materials. During each session, participants were seated comfortably with their head and arms supported, and MEPs were recorded at baseline to assess corticospinal excitability. Subsequently, tACS was applied to the identified motor hotspot for 20 min. Following stimulation, RS-EEG and TEPs were recorded, and MEP threshold, amplitude, and latency were reassessed to determine post-stimulation changes.

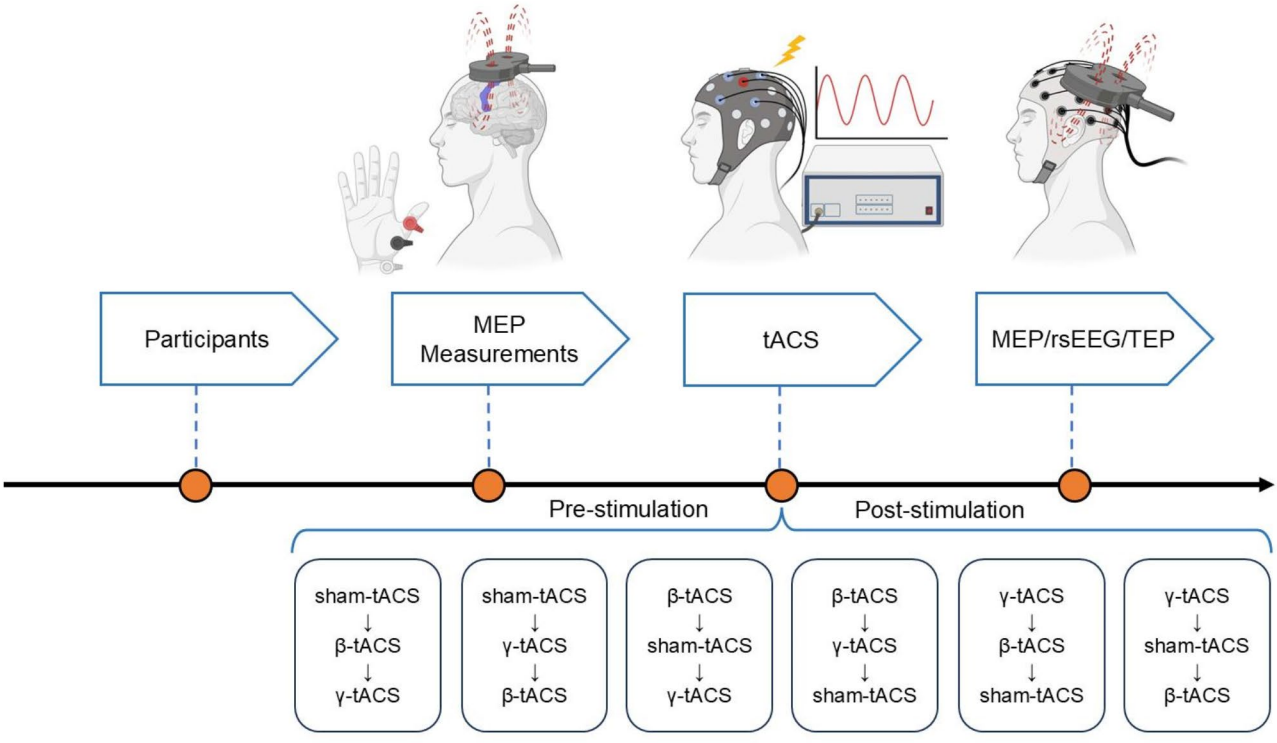

Fig. 1 Schematic representation of the study procedure. Prior to each session, MEPs were assessed to establish baseline values and determine the motor spot. Participants were then randomly assigned to one of three stimulation conditions: γ-tACS, β-tACS, or sham-tACS, applied over the primary motor cortex (M1). Following each stimulation session, electrophysiological measures were reassessed. The entire process was repeated after a washout period of at least one week to minimize carryover effects. MEPs: motor evoked potentials. tACS: transcranial alternating current stimulation; blue: β-tACS over the left M1, green: γ-tACS over the left M1, orange: sham

Calculations

Data analysis was performed using MATLAB (R2022a, MathWorks, USA) with the EEGLAB and TESA toolboxes for EEG- and TMS-related analyses, respectively.

MEP preprocessing

MEP data underwent an initial visual inspection to exclude trials contaminated by EMG noise. MEP amplitudes at 120% RMT were averaged for each tACS condition (pre- and post-stimulation). The modulatory effect of tACS was quantified as the ratio of post- to pre-stimulation MEP amplitudes for each session.

Rs-EEG preprocessing

RS-EEG data were processed using the EEGLAB toolbox in MATLAB. Data filtering included a bandpass filter (0.1–80 Hz) and a notch filter (49–51 Hz) to eliminate power line noise. EEG signals were re-referenced to the bilateral mastoid electrodes, and epochs were defined from − 1000 to 1000 ms relative to each event. Baseline correction was applied using the 500 ms window before event onset. Channels with artifacts were identified visually and interpolated. Independent component analysis (ICA) was employed to remove artifacts from eye movements. Wavelet transform analyses were applied to the C3 electrode and its four surrounding channels, followed by statistical comparisons across conditions.

TEP preprocessing

The TESA toolbox was used for TEP data processing. EEG signals were segmented into epochs from − 200 to 500 ms relative to TMS pulses. Artifacts within − 10 to 10 ms of the TMS pulse were interpolated, and FastICA was utilized to remove muscle and electrical artifacts induced by TMS. A band-pass filter (1–100 Hz) and a band-stop filter (49–51 Hz) were then applied, followed by a second round of ICA to eliminate remaining artifacts. The data were re-referenced to the bilateral mastoid, and the amplitudes and latencies of TEP components were extracted from the C3 electrode and its surrounding channels for statistical analysis.

Statistical analyses

Statistical analyses were performed using SPSS software (v. 25.0, IBM Corp., Armonk, NY). Normality was assessed using Shapiro-Wilk test, and homogeneity of variance was examined with Levene's test. Quantitative data were expressed as mean ± standard deviation ($\bar{x} \pm s$). A univariate general linear model was used for analysis of variance (ANOVA) in this crossover design, and post-hoc comparisons were performed with Least Significant Difference (LSD) correction. When the assumption of homogeneity of variance was violated, Welch's ANOVA was applied and post hoc comparisons were conducted using the Games-Howell test. An alpha level of $p < 0.05$ was considered statistically significant. Graphical representations of the data were generated using OriginPro (Version 2024b, OriginLab Corporation, Northampton, MA, USA).

Results

γ-tACS modulates corticospinal excitability

The effects of tACS on corticospinal excitability were evaluated by analyzing the pre- and post-stimulation ratios of RMT and 120% MEP amplitudes and latencies across different stimulation conditions. Baselines variable (pre-stimulation) stability is confirmed as detailed in the supplementary materials. To ensure normality, the pre-post ratio of the MEP amplitude data was log-trasnformed (i.e. ln (MEP Amp_{post}/MEP Amp_{pre})) before statistical analyses. As shown in Fig. 2C, there were no significant changes in the RMT ratios across tACS conditions ($F(2, 51) = 0.496$, $p = 0.612$, $\eta^2 = 0.019$), indicating that tACS did not alter baseline excitability threshold. However, there was a significant main effect of tACS condition on the ratios of 120% MEP amplitude (Welch's

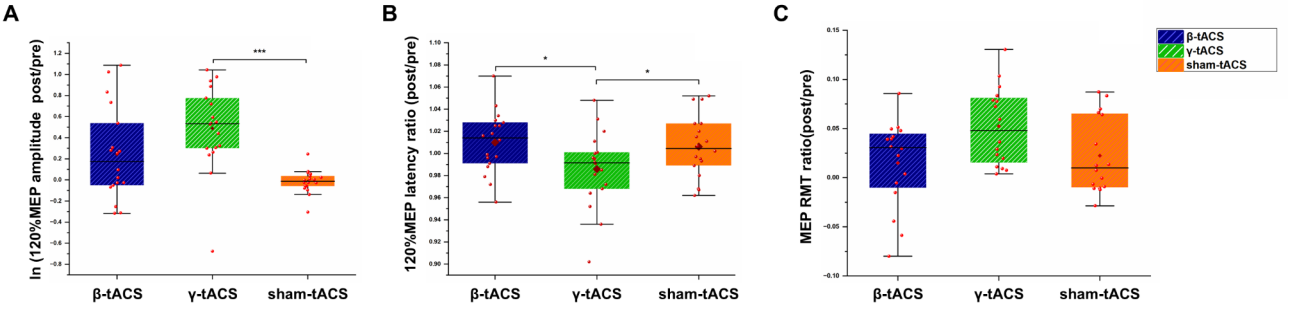

Fig. 2 Modulation of motor cortex excitability by tACS. **(A)** Alteration of Ln (120% MEP amplitude post/pre ration) under the three stimulation conditions. γ-tACS significantly increased 120% MEP amplitude compared to sham-tACS, while β-tACS did not show a significant effect; **(B)** Post/pre modulation of 120% MEP latency across the three conditions. γ-tACS significantly reduced 120% MEP latency compared to sham-tACS, with no significant effect observed for β-tACS; **(C)** Comparison of post/pre ratios of MEP RMT across γ-tACS, β-tACS, and sham-tACS conditions, showing no significant differences between the conditions. (*$P < 0.05$; ***$P < 0.001$)

F(2, 25.468) = 14.790, $p < 0.001$, η^2=0.268), where γ-tACS led to increased MEP amplitudes than sham-tACS ($p < 0.001$) (Fig. 2A). In addition, there was a significant main effect of tACS condition on the ratios of 120% MEP latency (F(2, 51) = 3.314, $p = 0.044$, $\eta^2 = 0.115$), indicating that γ-tACS resulted in shorter MEP latencies than both sham-tACS ($p = 0.049$) and β-tACS ($p = 0.020$) (Fig. 2B). We also analyzed the potential influence of gender on the experimental effects. The results indicated that gender did not significantly modulate the effects of stimulation on most neurophysiological measures, as detailed in the supplementary materials.

γ-tACS modualtes M1-μ rhythm

To examine the effect of tACS on neural oscillations, we performed spectral analyses of RS-EEG data. A significant main effect of tACS condition was observed in the alpha band (Welch's F(2, 27.854) = 4.877, $P = 0.015$, $\eta^2 = 0.162$). As shown in Fig. 3A, γ -tACS led to a significant increase in alpha power compared to sham-tACS ($p = 0.017$). In contrast, β-tACS did not induce a significant change in alpha power. EEG topographical maps further show an increase in alpha oscillation localized to the sensorimotor cortex following both β-tACS and γ-tACS conditions compared to sham-tACS (Fig. 3B).

γ-tACS modulates M1-P15 TEP

Analyses of TEPs revealed significant differences in the M1-P15 amplitudes across different tACS conditions (F(2, 33) = 4.069, $p = 0.026$, η^2=0.198) (Fig. 4A and C). As shown in Fig. 4D, the M1-P15 amplitudes following γ-tACS were significantly reduced compared to sham-tACS ($p = 0.010$). Similarly, β-tACS also led to significantly smaller M1-P15 amplitudes than sham-tACS ($p = 0.047$). However, the differences between β-tACS and γ-tACS were not statistically significant ($p = 0.506$).

Discussion

This study investigated the frequency-dependent effects of tACS on corticospinal excitability and cortical activity in M1. The results showed that γ-tACS led to a significant increase in MEP amplitudes and a reduction in MEP latencies. Moreover, γ-tACS significantly increased alpha power in the sensorimotor cortex. In addition, we observed a significant decrease in M1-P15 TEP amplitudes following γ-tACS and β-tACS. These results provide evidence for the frequency-specific interactions between tACS and cortical activity, suggesting that γ-tACS, in particular, may effectively modulate cortical excitability and oscillatory patterns within the motor system.

tACS modulates corticospinal excitability

Our results found that γ-tACS over M1 significantly increased MEP amplitudes and reduced MEP latencies compared to sham-tACS. These results are in line with those reported by Naro et al. [25] that showed similarly increased MEP amplitudes following γ-tACS over the cerebellum, suggesting enhanced excitability in both the cerebellar-cortical pathway and the corticospinal tract. Similarly, Zhang et al. [26] reported increased pharyngeal MEP amplitude after γ-tACS over the motor cortex, further supporting the frequency-specific effects of tACS on corticospinal pathways. However, some previous studies reported no significant changes in corticospinal excitability following γ-tACS [27–28]. A potential explanation for these discrepancies lies in differences in stimulation intensity. Our study employed a higher current intensity (2 mA), whereas Feurra et al. [27] and Nowak et al. [28] used lower current intensities (less than 1.3 mA). This aligns with findings from a meta-analysis [29] suggesting that tACS below 1 mA often fails to elicit significant changes in MEP amplitude. Additionally, variations in electrode montage (e.g. high-definition configurations)

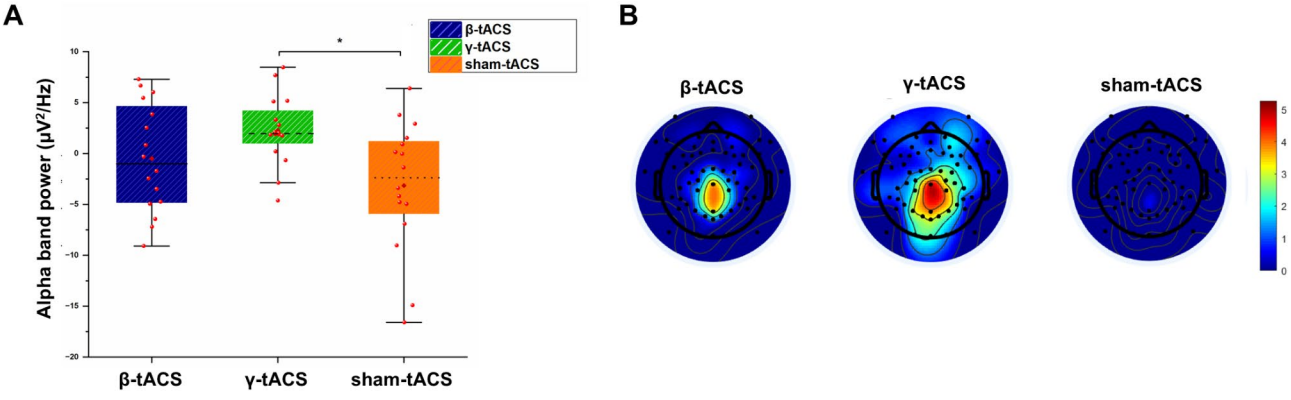

Fig. 3 Changes in resting-state electroencephalogram following tACS over M1. **(A)** Comparison of alpha band power in C3 channel and four surrounding channels across different conditions. γ-tACS significantly increased the alpha band power compared to sham-tACS, whereas β-tACS showed no significant effect; **(B)** Topographical maps of alpha oscillations under each stimulation condition, showing the spatial distribution of alpha band power across the scalp. (*P<0.05)

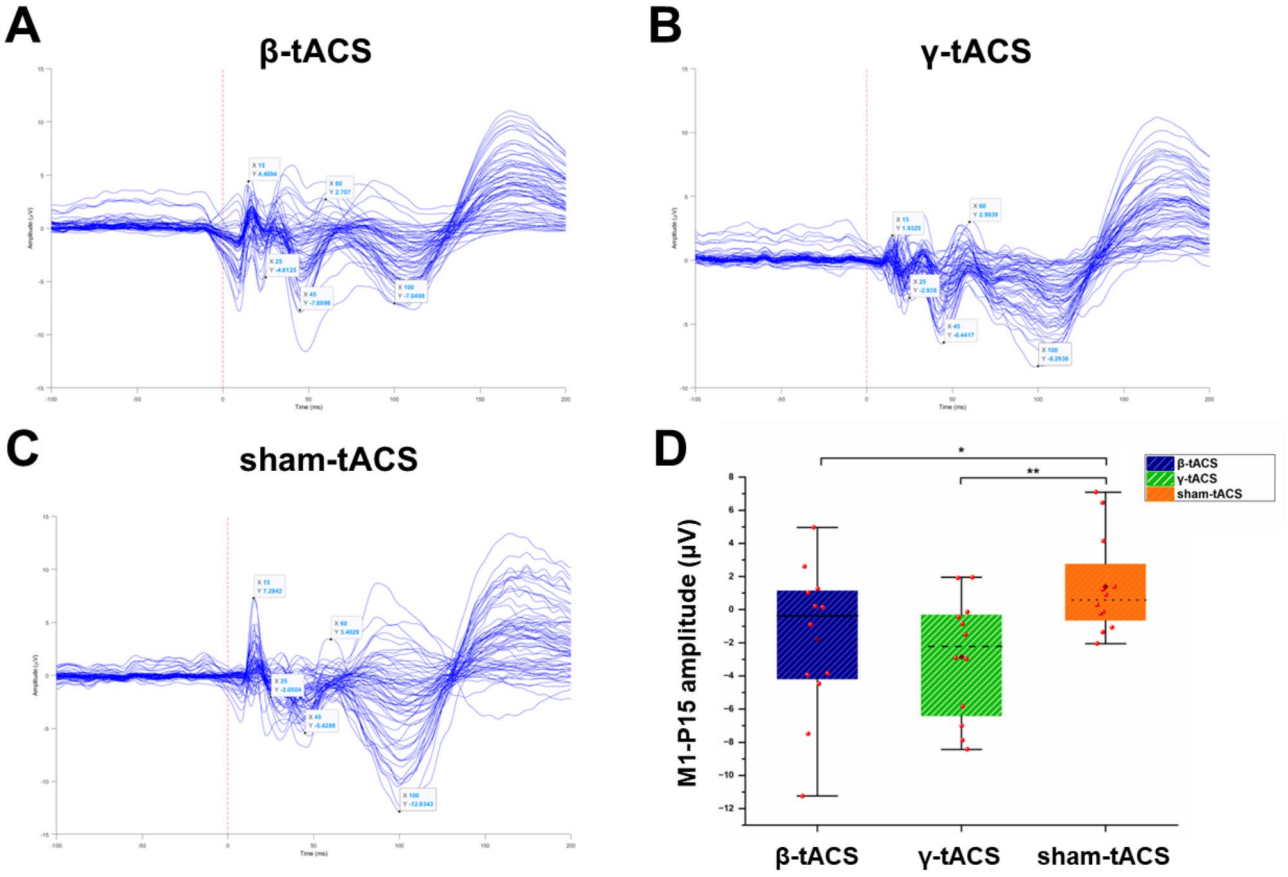

Fig. 4 Cortical reactivity to single-pulse TMS. **(A)∼(C)** Butterfly plot of TEPs across all EEG channels (blue lines, 64 channels), X indicated the latency of the TEP component, and Y indicates the amplitude of the TEP component; **(D)** Comparison of the M1-P15 amplitudes across different stimulation conditions. Both β-tACS and γ-tACS significantly reduced the amplitude of the M1-P15 component compared to sham-tACS. (*P<0.05, **P<0.01). TEP: TMS evoked potential

may enhance the focality and efficacy of tACS [30–32]. These findings underscore the importance of optimizing stimulation parameters to maximize the efficacy of tACS, as noted by Johnson et al. [33] in non-human primate studies.

The observed effects of γ-tACS on corticospinal excitability may be related to spike-timing dependent plasticity (STDP) [34], a process in which the precise timing of pre- and post-synaptic potentials determines synaptic strengthening or weakening. When pre-synaptic spikes precede post-synaptic activity, long-term potentiation (LTP) is induced, whereas the opposite timing leads to long-term depression (LTD) [35–36]. In this context, γ-tACS may enhance LTP-like plasticity by aligning oscillatory brain activity with the optimal timing for synaptic strengthening. Further supportive evidence comes from Guerra et al. [37–38], who found that γ-tACS but not β-tACS enhanced and prolonged LTP-like plasticity induced by intermittent theta burst stimulation (iTBS) over M1 [39] and reversed LTD-like plasticity induced by cTBS [40]. These findings may be attributed to the distinct roles of beta and gamma oscillations in motor control, with beta oscillations predominantly associated with motor inhibition [39–40] and gamma oscillations involved in movement preparation and execution [39, 41–43].

GABAergic interneurons play a critical role in regulating cortical excitability and plasticity, particularly in the context of STDP [44]. The interaction between γ-tACS and gamma-resonant GABAergic interneurons in M1 may contribute to the observed increases in cortical excitability and neuroplasticity [37–38]. However, to date, only one cross-sectional study examined the potential relationship between GABAergic activity and tACS, showing that alpha-frequency tACS did not significantly alter corticospinal excitability or GABAergic activity, as measured by MEPs and short-interval intracortical inhibition (SICI) [45]. Notably, this study was limited to alpha-frequency tACS, leaving the effects of tACS with other frequency bands on GABAergic activity unexplored.

In the present study, we extended this line of research by examining the effects of β- and γ-tACS on GABAergic activity using TEPs. TEPs reflects the balance between

cortical excitation and inhibition and have been linked to GABAergic interneuron function [46]. Alterations in TEPs have been observed in patients with neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), where GABAergic dysfunction is a hallmark feature [47]. Our findings found both β- and γ-tACS led to a reduction in M1-P15 TEP amplitudes, suggesting that these frequencies may modulate GABAergic activity. This supports the notion that β- and γ-tACS can regulate cortical excitability and plasticity through their effects on GABAergic interneurons.

Alternation in resting-state EEG

To further investigate the effects of tACS on neural oscillations, we analyzed RS-EEG following stimulation. While no significant changes were observed in beta or gamma oscillations, we found a significant increase in alpha power localized in the S1, particularly in the γ-tACS condition. These alpha oscillations, often referred to as mu rhythms, are closely linked to sensorimotor processing and cortical excitability [48], suggesting that γ-tACS may exert broader modulatory influences beyond M1.

Our findings are consistent with those of Gundlach et al. [49–50], who found that tACS can modulate somatosensory mu-rhythms and reduce functional connectivity in S1. This suggests that γ-tACS influences the sensorimotor loop, where sensory inputs from S1 shape motor output via M1. Functional MRI studies have extensively documented the critical role of sensory feedback in modulating motor activity [51–53], suggesting that γ-tACS may enhance motor function indirectly through sensory modulation. The observed increase in alpha power in S1 may reflect a shift in cortical excitability, potentially affecting downstream motor function [54–57]. Although our study did not establish a direct causal link between alpha modulation and motor excitability, previous studies by Thies et al. [58], Bergmann [59], and Zrenner [60] have reported a positive correlation between enhanced mu-alpha power and increased MEP amplitude. These findings suggest γ-tACS may facilitate motor cortical plasticity by enhancing sensorimotor interactions, a mechanism that warrants further exploration.

Alternations in TEP

TMS-EEG provides a direct measure of cortical excitability, offering valuable insights into the effects of γ-tACS on motor cortical function. In our study, γ-tACS led to a significant decrease in the M1-P15 TEP amplitudes, suggesting a modulation of transcallosal inhibition [61]. This finding is consistent with findings from Zazio et al. [62] that showed a positive correlation between M1-P15 amplitudes and the ipsilateral silent period (iSP), indicating that the P15 component reflects inhibitory processes across the corpus callosum. The attenuation of the M1-P15 amplitude following γ-tACS suggests that this stimulation protocol may reduce transcallosal inhibition from the unaffected hemisphere, potentially facilitating motor recovery by restoring interhemispheric balance. This mechanism is consistent with neuromodulation strategies aimed at promoting post-stroke motor recovery by rebalancing interhemispheric excitability. Previous TMS studies have demonstrated that reducing transcallosal inhibition can enhance motor function in stroke patients, particularly when targeting interhemispheric asymmetry [63]. Our findings thus contribute to this growing body of evidence, suggesting that γ-tACS may hold therapeutic potential for stroke rehabilitation by modulating interhemispheric dynamics.

Clinical potential of tACS

Our study found that γ-tACS had a more pronounced modulatory effect on motor cortical excitability than β-tACS, suggesting that its potential clinical relevance for post- stroke motor rehabilitation. Neuromodulation techniques such as TMS [63] and tDCS [64] have been extensively studied in stroke rehabilitation, primarily targeting interhemispheric coordination to restore excitability balance between the affected and unaffected hemispheres. In contrast, tACS offers a distinct advantage by modulating neural oscillations and synchronizing brain activity at functionally relevant frequencies [65]. This frequency-specific modulation may provide a more physiologically relevant approach to enhancing motor plasticity. To date, research on tACS for post-stroke rehabilitation has primarily reported benefits in gait function [66], aphasia [67], and spatial attention deficits [68]. Compared to TMS and tDCS, tACS has unique advantages, including lower seizure risk [69], higher cost-effectiveness, and reduced discomfort [70]. Therefore, further studies are necessary to directly compare the therapeutic efficacy of tACS, TMS, and tDCS, particularly regarding their effects on STDP and GABAergic neuronal activity [71–73].

Limitations

There are several limitations of this study that should be acknowledged. First, our study specifically focused on immediate effects of tACS on cortical excitability and neuroplasticity. Given that such transient neurophysiological changes are typically not robust enough to induce measurable behavioral effects, we did not include a motor task assessment. Future studies should incorporate multi-session tACS protocols and motor task assessments to link tACS-induced neuroplasticity to functional improvements. Secondly, We collected only 10 MEP trials per condition, and during the experiment, we included the visual exclusion of trials contaminated by

EMG noise. Due to technical limitations, we are unable to provide the specific percentage of trials excluded. This may impact the reliability of motor cortical excitability assessments. Increasing the number of trials and implementing methods to record excluded trials in future studies would enhance measurement stability and improve the robustness of findings. Finally, while EEG provides valuable insights into neural oscillatory dynamics, its limited spatial resolution remains challenges. Integrating EEG with functional imaging techniques could provide a more comprehensive understanding of the neural mechanisms underlying tACS effects.

Conclusions

In summary, this study found that γ-tACS over the M1 enhanced corticospinal excitability and modulated sensorimotor activity, suggesting its potential to influence both motor and sensory networks for sensorimotor integration. Additionally, the reduction in the M1-P15 TEP amplitudes suggest a potential role of γ-tACS in modulating interhemispheric inhibition, which may contribute to rebalancing cortical excitability in motor networks. These results underscore the therapeutic potential of γ-tACS as a non-invasive tool for enhancing neuroplasticity, particularly in the context of post-stroke motor rehabilitation.

Abbreviations

tACS	transcranial alternating current stimulation
M1	primary motor cortex
MEPs	motor evoked potentials
EEG	electroencephalogram
RS-EEG	resting-state electroencephalogram
TEPs	transcranial evoked potentials
NIBS	non-invasive brain stimulation
TMS	transcranial magnetic stimulation
tDCS	transcranial direct current stimulation
FDI	first dorsal interosseous
RMT	resting motor threshold
EMG	electromyography
HD	high-definition
ICA	independent component analysis
ANOVA	analysis of variance
LSD	least Significant Difference
STDP	spike-timing dependent plasticity
LTP	long-term potentiation
LTD	long-term depression
iTBS	intermittent theta burst stimulation
cTBS	continuous theta burst stimulation
fMRI	functional magnetic resonance imaging

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12984-025-01610-2.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

Lei Tingting: Conceptualization, Methodology, Investigation, Formal analysis, Data Curation, Writing - Original Draft, Visualization; Chen Lilin: Conceptualization, Methodology, Investigation, Formal analysis, Data Curation, Writing - Review & Editing, Visualization; Wang Chuangjia: Investigation, Formal analysis, Data Curation, Writing - Original Draft, Visualization, Writing - Review & Editing; Si Jiamen: Investigation; Zhang Shuxian: Investigation; Ai Yinan: Resources; Liu Hanjun: Writing - Review & Editing; Zheng Haiqing: Conceptualization, Methodology, Validation, Resources, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

Funding

This work was supported by the National Key R&D Program of China (Grant No. 2023YFC3603800, 2023YFC3603804); the National Natural Science Foundation of China (Grant: NO. 82272605); and the Science and Technology Projects in Guangzhou (Grant:2024A03J0177).

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (No. RG2023-279-02), and all the subjects volunteered to participate and signed informed consent forms.

Consent for publication

Consent to publish was obtained from all the participants.

Competing interests

The authors declare no competing interests.

Received: 18 November 2024 / Accepted: 17 March 2025
Published online: 27 March 2025

References

1. GBD 2016 Stroke Collaborators. Global, regional, and National burden of stroke, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet Neurol. 2019;18(5):439–58. https://doi.org/10.1016/S1474-4422(19)30034-1.
2. Winstein CJ, Stein J, et al. Guidelines for adult stroke rehabilitation and recovery: A guideline for healthcare professionals from the American heart association/american stroke association. Stroke. 2016;47(6):e98–169.
3. Li KP, Wu JJ, Zhou ZL, et al. Noninvasive brain stimulation for neurorehabilitation in Post-Stroke patients. Brain Sci. 2023;13(3):451. https://doi.org/10.3390/brainsci13030451. Published 2023 Mar 6.
4. Bai Z, Zhang J, Fong KNK. Effects of transcranial magnetic stimulation in modulating cortical excitability in patients with stroke: a systematic review and meta-analysis. J Neuroeng Rehabil. 2022;19(1):24. https://doi.org/10.1186/s12984-022-00999-4. Published 2022 Feb 22.
5. Orrù G, Conversano C, Hitchcott PK, Gemignani A. Motor stroke recovery after tDCS: a systematic review. Rev Neurosci. 2020;31(2):201–18. https://doi.org/10.1515/revneuro-2019-0047.
6. Yang S, Yi YG, Chang MC. The effect of transcranial alternating current stimulation on functional recovery in patients with stroke: a narrative review. *Front Neurol*. 2024;14:1327383. Published 2024 Jan 10. https://doi.org/10.3389/fneur.2023.1327383
7. Wischnewski M, Alekseichuk I, Opitz A. Neurocognitive, physiological, and biophysical effects of transcranial alternating current stimulation. Trends Cogn Sci. 2023;27(2):189–205. https://doi.org/10.1016/j.tics.2022.11.013. Epub 2022 Dec 19. PMID: 36543610; PMCID: PMC9852081.
8. Yavari F, Jamil A, Mosayebi Samani M, Vidor LP, Nitsche MA. Basic and functional effects of transcranial electrical stimulation (tES)-An introduction. Neurosci Biobehav Rev. 2018;85:81–92. https://doi.org/10.1016/j.neubiorev.2017.06.015. Epub 2017 Jul 6. PMID: 28688701.

9. Tavakoli AV, Yun K. Transcranial alternating current stimulation (tACS) mechanisms and protocols. Front Cell Neurosci. 2017;11:214. https://doi.org/10.3389/fncel.2017.00214. PMID: 28928634; PMCID: PMC5591642.
10. Elyamany O, Leicht G, Herrmann CS, Mulert C. Transcranial alternating current stimulation (tACS): from basic mechanisms towards first applications in psychiatry. Eur Arch Psychiatry Clin Neurosci. 2021;271(1):135–56. https://doi.org/10.1007/s00406-020-01209-9. Epub 2020 Nov 19. PMID: 33211157; PMCID: PMC7867505.
11. Nissim NR, Pham DVH, Poddar T, et al. The impact of gamma transcranial alternating current stimulation (tACS) on cognitive and memory processes in patients with mild cognitive impairment or Alzheimer's disease: A literature review. Brain Stimul. 2023;16(3):748–55. https://doi.org/10.1016/j.brs.2023.04.001.
12. Del Felice A, Castiglia L, Formaggio E, et al. Personalized transcranial alternating current stimulation (tACS) and physical therapy to treat motor and cognitive symptoms in Parkinson's disease: A randomized cross-over trial. Neuroimage Clin. 2019;22:101768. https://doi.org/10.1016/j.nicl.2019.101768.
13. Fertonani A, Miniussi C. Transcranial Electrical Stimulation: What We Know and Do Not Know About Mechanisms. Neuroscientist. 2017;23(2):109–123. doi: 10.1177/1073858416631966. Epub 2016 Jul 8. PMID: 26873962; PMCID: PMC5405830.
14. Bologna M, Guerra A, Paparella G, et al. Berardelli A. Transcranial alternating current stimulation has Frequency-Dependent effects on motor learning in healthy humans. Neuroscience. 2019;411:130–9. https://doi.org/10.1016/j.neuroscience.2019.05.041. Epub 2019 May 30. PMID: 31152934.
15. Antal A, Boros K, Poreisz C et al. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. Brain Stimul. 2008;1(2):97–105. https://doi.org/10.1016/j.brs.2007.10.001. Epub 2007 Dec 3. PMID: 20633376.
16. Pollok B, Boysen AC, Krause V. The effect of transcranial alternating current stimulation (tACS) at alpha and beta frequency on motor learning. Behav Brain Res. 2015;293:234–40. https://doi.org/10.1016/j.bbr.2015.07.049. Epub 2015 Jul 28. PMID: 26225845.
17. Krause V, Meier A, Dinkelbach L, et al. Beta band transcranial alternating (tACS) and direct current stimulation (tDCS) applied after initial learning facilitate retrieval of a motor sequence. Front Behav Neurosci. 2016;10:4. https://doi.org/10.3389/fnbeh.2016.00004. PMID: 26834593; PMCID: PMC4722123.
18. Sugata H, Yagi K, Yazawa S, et al. Modulation of motor learning capacity by transcranial alternating current stimulation. Neuroscience. 2018;391:131–9. https://doi.org/10.1016/j.neuroscience.2018.09.013. Epub 2018 Sep 20. PMID: 30244032.
19. Joundi RA, Jenkinson N, Brittain JS, et al. Driving oscillatory activity in the human cortex enhances motor performance. Curr Biol. 2012;22(5):403–7. https://doi.org/10.1016/j.cub.2012.01.024.
20. Pogosyan A, Gaynor LD, Eusebio A, et al. Boosting cortical activity at Beta-band frequencies slows movement in humans. Curr Biol. 2009;19(19):1637–41. https://doi.org/10.1016/j.cub.2009.07.074.
21. Moliadze V, Antal A, Paulus W. Boosting brain excitability by transcranial high frequency stimulation in the ripple range. J Physiol. 2010;588(Pt 24):4891–904. https://doi.org/10.1113/jphysiol.2010.196998.
22. Wach C, Krause V, Moliadze V, et al. Effects of 10 hz and 20 hz transcranial alternating current stimulation (tACS) on motor functions and motor cortical excitability. Behav Brain Res. 2013;241:1–6. https://doi.org/10.1016/j.bbr.2012.11.038.
23. Moisa M, Polania R, Grueschow M, et al. Brain network mechanisms underlying motor enhancement by transcranial entrainment of gamma oscillations. J Neurosci. 2016;36(47):12053–65. https://doi.org/10.1523/JNEUROSCI.2044-16.2016.
24. Gonzalez Andino SL, Michel CM, Thut G, et al. Prediction of response speed by anticipatory high-frequency (gamma band) oscillations in the human brain. Hum Brain Mapp. 2005;24(1):50–8. https://doi.org/10.1002/hbm.20056.
25. Naro A, Bramanti A, Leo A, et al. Effects of cerebellar transcranial alternating current stimulation on motor cortex excitability and motor function. Brain Struct Funct. 2017;222(6):2891–906. https://doi.org/10.1007/s00429-016-1355-1.
26. Zhang M, Cheng I, Sasegbon A, et al. Exploring parameters of gamma transcranial alternating current stimulation (tACS) and full-spectrum transcranial random noise stimulation (tRNS) on human pharyngeal cortical excitability. Neurogastroenterol Motil. 2021;33(9):e14173. https://doi.org/10.1111/nmo.14173.
27. Feurra M, Pasqualetti P, Bianco G, Santarnecchi E, Rossi A, Rossi S. State-dependent effects of transcranial oscillatory currents on the motor system: what you think matters. J Neurosci. 2013;33(44):17483–9. https://doi.org/10.1523/JNEUROSCI.1414-13.2013.
28. Nowak M, Hinson E, van Ede F, et al. Driving human motor cortical oscillations leads to behaviorally relevant changes in local $GABA_A$ Inhibition: A tACS-TMS study. J Neurosci. 2017;37(17):4481–92. https://doi.org/10.1523/JNEUROSCI.0098-17.2017.
29. Wischnewski M, Schutter DJLG, Nitsche MA. Effects of beta-tACS on corticospinal excitability: A meta-analysis. Brain Stimul. 2019;12(6):1381–9. https://doi.org/10.1016/j.brs.2019.07.023f.
30. Kuo HI, Bikson M, Datta A, et al. Comparing cortical plasticity induced by conventional and high-definition 4 × 1 ring tDCS: a neurophysiological study. Brain Stimul. 2013;6(4):644–8. https://doi.org/10.1016/j.brs.2012.09.010.
31. Heise KF, Kortzorg N, Saturnino GB, et al. Evaluation of a modified High-Definition electrode montage for transcranial alternating current stimulation (tACS) of Pre-Central areas. Brain Stimul. 2016;9(5):700–4. https://doi.org/10.1016/j.brs.2016.04.009.
32. Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: improved Spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul. 2009;2(4):201–e2071. https://doi.org/10.1016/j.brs.2009.03.005.
33. Johnson L, Alekseichuk I, Krieg J, Doyle A, Yu Y, Vitek J, Johnson M, Opitz A. Dose-dependent effects of transcranial alternating current stimulation on Spike timing in awake nonhuman primates. Sci Adv. 2020;6(36):eaaz2747. https://doi.org/10.1126/sciadv.aaz2747.
34. Caporale N, Dan Y. Spike timing-dependent plasticity: a hebbian learning rule. Annu Rev Neurosci. 2008;31:25–46. https://doi.org/10.1146/annurev.neuro.31.060407.125639.
35. Vossen A, Gross J, Thut G. Alpha power increase after transcranial alternating current stimulation at alpha frequency (α-tACS) reflects plastic changes rather than entrainment. Brain Stimul. 2015;8(3):499–508. https://doi.org/10.1016/j.brs.2014.12.004.
36. Wischnewski M, Schutter DJLG. After-effects of transcranial alternating current stimulation on evoked delta and theta power. Clin Neurophysiol. 2017;128(11):2227–32. https://doi.org/10.1016/j.clinph.2017.08.029.
37. Guerra A, Suppa A, Bologna M, et al. Boosting the LTP-like plasticity effect of intermittent theta-burst stimulation using gamma transcranial alternating current stimulation. Brain Stimul. 2018;11(4):734–42. https://doi.org/10.1016/j.brs.2018.03.015.
38. Guerra A, Suppa A, Asci F, et al. LTD-like plasticity of the human primary motor cortex can be reversed by γ-tACS. Brain Stimul. 2019;12(6):1490–9. https://doi.org/10.1016/j.brs.2019.06.029.
39. Pfurtscheller G, Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol. 1999;110(11):1842–57. https://doi.org/10.1016/s1388-2457(99)00141-8.
40. Picazio S, Veniero D, Ponzo V, et al. Prefrontal control over motor cortex cycles at beta frequency during movement Inhibition. Curr Biol. 2014;24(24):2940–5. https://doi.org/10.1016/j.cub.2014.10.043.
41. Brown P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. Mov Disord. 2003;18(4):357–63. https://doi.org/10.1002/mds.10358.
42. Cheyne D, Bells S, Ferrari P, Gaetz W, Bostan AC. Self-paced movements induce high-frequency gamma oscillations in primary motor cortex. NeuroImage. 2008;42(1):332–42. https://doi.org/10.1016/j.neuroimage.2008.04.178.
43. Cheyne DO. MEG studies of sensorimotor rhythms: a review. Exp Neurol. 2013;245:27–39. https://doi.org/10.1016/j.expneurol.2012.08.030.
44. Schulz A, Miehl C, Berry MJ 2nd, Gjorgjieva J. The generation of cortical novelty responses through inhibitory plasticity. Elife. 2021;10:e65309. https://doi.org/10.7554/eLife.65309.
45. Vallence AM, Dansie K, Goldsworthy MR, McAllister SM, Yang R, Rothwell JC, Ridding MC. Examining motor evoked potential amplitude and short-interval intracortical Inhibition on the up-going and down-going phases of a transcranial alternating current stimulation (tacs) imposed alpha Oscillation. Eur J Neurosci. 2021;53(8):2755–62. https://doi.org/10.1111/ejn.15124. Epub 2021 Feb 5.
46. Tremblay S, Rogasch NC, Premoli I, Blumberger DM, Casarotto S, Chen R, Di Lazzaro V, Farzan F, Ferrarelli F, Fitzgerald PB, Hui J, Ilmoniemi RJ, Kimiskidis VK, Kugiumtzis D, Lioumis P, Pascual-Leone A, Pellicciari MC, Rajji T, Thut G, Zomorrodi R, Ziemann U, Daskalakis ZJ. Clinical utility and prospective of TMS-EEG. Clin Neurophysiol. 2019;130(5):802–44. https://doi.org/10.1016/j.clinph.2019.01.001. Epub 2019 Jan 19.
47. van den Bos MAJ, Menon P, Pavey N, Higashihara M, Kiernan MC, Vucic S. Direct interrogation of cortical interneuron circuits in amyotrophic lateral

sclerosis. Brain 2024 Oct 10:awae317. https://doi.org/10.1093/brain/awae317. Epub ahead of print.
48. Samaha J, Iemi L, Haegens S, Busch NA. Spontaneous brain oscillations and perceptual Decision-Making. Trends Cogn Sci. 2020;24(8):639–53. https://doi.org/10.1016/j.tics.2020.05.004.
49. Gundlach C, Müller MM, Hoff M, et al. Reduction of somatosensory functional connectivity by transcranial alternating current stimulation at endogenous mu-frequency. NeuroImage. 2020;221:117175. https://doi.org/10.1016/j.neuroimage.2020.117175.
50. Gundlach C, Müller MM, Nierhaus T, Villringer A, Sehm B. Modulation of somatosensory alpha rhythm by transcranial alternating current stimulation at Mu-Frequency. Front Hum Neurosci. 2017;11:432. https://doi.org/10.3389/fnhum.2017.00432. Published 2017 Aug 25.
51. Stepniewska I, Preuss TM, Kaas JH. Ipsilateral cortical connections of dorsal and ventral premotor areas in new world Owl monkeys. J Comp Neurol. 2006;495(6):691–708. https://doi.org/10.1002/cne.20906.
52. Taniwaki T, Okayama A, Yoshiura T et al. Reappraisal of the motor role of basal ganglia: a functional magnetic resonance image study [published correction appears in J Neurosci. 2003;23(21):7966]. *J Neurosci*. 2003;23(8):3432–3438. https://doi.org/10.1523/JNEUROSCI.23-08-03432.2003
53. Dum RP, Strick PL. The origin of corticospinal projections from the premotor areas in the frontal lobe. J Neurosci. 1991;11(3):667–89. https://doi.org/10.1523/JNEUROSCI.11-03-00667.1991.
54. Vidoni ED, Acerra NE, Dao E, Meehan SK, Boyd LA. Role of the primary somatosensory cortex in motor learning: an rTMS study. Neurobiol Learn Mem. 2010;93(4):532–9. https://doi.org/10.1016/j.nlm.2010.01.011.
55. Zagha E, Casale AE, Sachdev RN, McGinley MJ, McCormick DA. Motor cortex feedback influences sensory processing by modulating network state. Neuron. 2013;79(3):567–78. https://doi.org/10.1016/j.neuron.2013.06.008.
56. Umeda T, Isa T, Nishimura Y. The somatosensory cortex receives information about motor output. Sci Adv. 2019;5(7):eaaw5388. https://doi.org/10.1126/sciadv.aaw5388. Published 2019 Jul 10.
57. Kristeva R, Chakarov V, Wagner M, Schulte-Mönting J, Hepp-Reymond MC. Is the movement-evoked potential mandatory for movement execution? A high-resolution EEG study in a deafferented patient. NeuroImage. 2006;31(2):677–85. https://doi.org/10.1016/j.neuroimage.2005.12.053.
58. Thies M, Zrenner C, Ziemann U, Bergmann TO. Sensorimotor mu-alpha power is positively related to corticospinal excitability. Brain Stimul. 2018;11(5):1119–22. https://doi.org/10.1016/j.brs.2018.06.006.
59. Bergmann TO, Lieb A, Zrenner C, Ziemann U. Pulsed facilitation of corticospinal excitability by the sensorimotor μ-Alpha rhythm. J Neurosci. 2019;39(50):10034–43. https://doi.org/10.1523/JNEUROSCI.1730-19.2019.
60. Zrenner C, Kozák G, Schaworonkow N, et al. Corticospinal excitability is highest at the early rising phase of sensorimotor μ-rhythm. NeuroImage. 2023;266:119805. https://doi.org/10.1016/j.neuroimage.2022.119805.
61. Bai Z, Zhang JJ, Fong KNK. Intracortical and intercortical networks in patients after stroke: a concurrent TMS-EEG study. J Neuroeng Rehabil. 2023;20(1):100. https://doi.org/10.1186/s12984-023-01223-7. Published 2023 Aug 2.
62. Zazio A, Barchiesi G, Ferrari C, Marcantoni E, Bortoletto M. M1-P15 as a cortical marker for transcallosal inhibition: A preregistered TMS-EEG study. *Front Hum Neurosci*. 2022;16:937515. Published 2022 Sep 16. https://doi.org/10.3389/fnhum.2022.937515
63. Bai Z, Zhang J, Fong KNK. Effects of transcranial magnetic stimulation in modulating cortical excitability in patients with stroke: a systematic review and meta-analysis. J Neuroeng Rehabil. 2022;19(1):24.
64. Orrù G, Conversano C, Hitchcott PK, Gemignani A. Motor stroke recovery after tDCS: a systematic review. Rev Neurosci. 2020;31(2):201–18.
65. Riddle J, Frohlich F. Targeting neural oscillations with transcranial alternating current stimulation. Brain Res. 2021;1765:147491.
66. Kitatani R, Koganemaru S, Maeda A, Mikami Y, Matsuhashi M, Mima T, Yamada S. Gait-synchronized oscillatory brain stimulation modulates common neural drives to ankle muscles in patients after stroke: A pilot study. Neurosci Res. 2020;156:256–64.
67. Xie X, Hu P, Tian Y, Wang K, Bai T. Transcranial alternating current stimulation enhances speech comprehension in chronic post-stroke aphasia patients: A single-blind sham-controlled study. Brain Stimul. 2022 Nov-Dec;15(6):1538–40.
68. Schuhmann T, Duecker F, Middag-van Spanje M, Gallotto S, van Heugten C, Schrijnemaekers AC, van Oostenbrugge R, Sack AT. Transcranial alternating brain stimulation at alpha frequency reduces hemispatial neglect symptoms in stroke patients. Int J Clin Health Psychol. 2022 Sep-Dec;22(3):100326.
69. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009;120(12):2008–39.
70. Fertonani A, Ferrari C, Miniussi C. What do you feel if I apply transcranial electric stimulation? Safety, sensations and secondary induced effects. Clin Neurophysiol. 2015;126(11):2181–8.
71. Turrini S, Fiori F, Chiappini E, Lucero B, Santarnecchi E, Avenanti A. Corticocortical paired associative stimulation (ccPAS) over premotor-motor areas affects local circuitries in the human motor cortex via hebbian plasticity. NeuroImage. 2023;271:120027. https://doi.org/10.1016/j.neuroimage.2023.120027. Epub 2023 Mar 15. PMID: 36925088.
72. Lenz M, Galanis C, Müller-Dahlhaus F, Opitz A, Wierenga CJ, Szabó G, Ziemann U, Deller T, Funke K, Vlachos A. Repetitive magnetic stimulation induces plasticity of inhibitory synapses. Nat Commun. 2016;7:10020. https://doi.org/10.1038/ncomms10020. PMID: 26743822; PMCID: PMC4729863.
73. Hassanzahraee M, Nitsche MA, Zoghi M, Jaberzadeh S. Determination of anodal tDCS duration threshold for reversal of corticospinal excitability: an investigation for induction of counter-regulatory mechanisms. Brain Stimul 2020 May-Jun;13(3):832–9. https://doi.org/10.1016/j.brs.2020.02.027. Epub 2020 Feb 26. PMID: 32289714.

Publisher's note