

Determining the effects of transcranial alternating current stimulation on corticomotor excitability and motor performance: A sham-controlled comparison of four frequencies

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ABSTRACT

Transcranial alternating current stimulation (tACS) modulates brain oscillations and corticomotor plasticity. We examined the effects of four tACS frequencies (20 Hz, 40 Hz, 60 Hz, and 80 Hz) on motor cortex (M1) excitability and motor performance. In a randomised crossover design, 12 adults received 20-minute tACS sessions, with Sham as control. Corticomotor and intracortical excitability was measured up to 60-minutes post-tACS. Motor performance was evaluated using the Grooved Pegboard Test (GPT) and sensorimotor assessments. Our findings demonstrated frequency-dependent modulation of corticomotor excitability based on MEP amplitude. 20 Hz and 40 Hz tACS reduced MEPs, while 60 Hz and 80 Hz increased MEPs. Inhibition (cortical silent period, SP) was reduced across all tACS frequencies compared to Sham, with 20 Hz and 40 Hz showing consistent reductions, 60 Hz showing effects at post-0 and post-30, and 80 Hz at post-60. Furthermore, 60 Hz tACS decreased intracortical inhibition at post-0, while intracortical facilitation increased with 20 Hz and 60 Hz at post-0, and 40 Hz at post-60. Motor performance remained unaffected across frequencies. Regression analyses revealed that shorter SP at 60 min post 60 Hz tACS predicted faster reaction times, while greater MEP amplitudes at 60 min following 80 Hz tACS predicted improved hand dexterity. Overall, beta and gamma tACS frequencies modulate M1 excitability, with consistent effects on SP, suggesting potential use in conditions involving SP elongation, such as stroke and Huntington's disease. These findings highlight 60 Hz tACS as a potential tool for motor rehabilitation therapies.

Introduction

The primary motor cortex (M1) integrates neural inputs from motor and sensory regions and projects them to motor neurons (Bajaj et al., 2014; Rouiller et al., 1994). Due to its role in corticomotor responses and motor learning, M1 has been widely studied (Barker et al., 1985; Cirillo et al., 2011). Voluntary movement depends on coordinated neural oscillations in M1, which facilitate sensory-motor processing (MacKay, 1997). Gamma and beta oscillations dominate in M1, each playing distinct roles in motor performance (Nowak et al., 2017; Miyaguchi et al., 2018; Bologna et al., 2019).

Beta oscillations (15–30 Hz) are considered “antikinetic,” associated

with motor inhibition and postural control (Chandrasekaran et al., 2019; Brown, 2003). Prior to and during movement, beta activity in the sensorimotor cortex decreases, followed by a sharp rebound after movement ends, known as event-related synchronisation (Brown and Marsden, 1998; Baker, 2007; Pfurtscheller and Da Silva, 1999; Jurkiewicz et al., 2006). This rebound stabilises posture and prepares for the next movement phase (Androulidakis et al., 2007; Kühn et al., 2004). Beta oscillations play a role in movement planning, selection, and termination (Tzagarakis et al., 2010; Grent-t-Jong et al., 2014; Heinrichs-Graham and Wilson, 2015; Heinrichs-Graham et al., 2017), as well as movement suppression (Kühn et al., 2004; Zhang et al., 2008) and tonic contractions, where muscles remain active without producing

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movement (Bressler, 2009; Kristeva et al., 2007). The decrease in beta activity before and during voluntary movement aids smoother execution (Muthukumaraswamy, 2011).

In contrast, gamma oscillations (>30 Hz), often referred to as “motor execution signal,” are linked to movement onset and execution (Pfurtscheller et al., 1993; Pfurtscheller and Neuper, 1992; Muthukumaraswamy, 2010; Gaetz et al., 2011). As “prokinetic” signals, they facilitate movement initiation and execution (Hamada et al., 1999), becoming stronger during larger, more forceful movements but absent in sustained isometric contractions (Muthukumaraswamy, 2010). Gamma activity is sensitive to movement dynamics and encodes specific parameters like direction and speed (Muthukumaraswamy, 2011; Muthukumaraswamy, 2010; Shibata et al., 1999). These oscillations play a key role in fine-tuning motor output during dynamic tasks (Crone et al., 2006; Brücke et al., 2013). In other words, while beta activity maintains stability and suppresses unwanted movements, gamma oscillations drive active movement execution, coordinating motor output. The specific roles of beta and gamma in motor performance remain unclear. Gamma rhythms (30–80 Hz) include low, mid, and high bands (Giustiniani et al., 2019; Santarnecchi et al., 2017), each potentially serving different functions depending on the brain region and task demands (Buzsáki and Wang, 2012). Research has focused less on low and mid gamma bands (40 Hz, 60 Hz) compared to beta and high gamma oscillations (Rostami et al., 2023; Nowak et al., 2018).

There is growing evidence of a relationship between neural oscillations and corticospinal excitability, with fluctuations in EEG oscillations affecting responses to transcranial magnetic stimulation (TMS) (Berger et al., 2014; Ogata et al., 2019; Sauseng et al., 2009). Although findings have been inconsistent, these oscillations are believed to modulate excitability, highlighting the need for further investigation (Thut and Miniussi, 2009; Cai et al., 2021). Transcranial alternating current stimulation (tACS), which delivers low-intensity sinusoidal currents through scalp electrodes, offers a novel approach for modulating brain oscillations and studying the link between M1 rhythms, cortical excitability, and motor performance. (Nowak et al., 2017; Antal and Paulus, 2013; Mäki and Ilmoniemi, 2010). A meta-analysis showed tACS enhances corticomotor excitability (Rostami et al., 2023), and studies have also shown it improves motor learning, and motor performance (Rostami et al., 2023; Sugata et al., 2018).

From a behavioural perspective, tACS studies targeting beta and gamma oscillations in M1 reveal distinct effects on motor performance. Beta tACS is generally linked to performance decrements, such as slower reaction times and increased task interference (Bologna et al., 2019; Santarnecchi et al., 2017; Joundi et al., 2012; Guerra et al., 2018). In contrast, gamma-frequency tACS, especially in the high gamma range, improves motor performance, reaction times, and motor learning (Nowak et al., 2017; Sugata et al., 2018; Joundi et al., 2012). Interestingly, high gamma tACS appears to enhance motor learning more effectively than low gamma tACS (Giustiniani et al., 2019; Sugata et al., 2018). Mechanistically, beta tACS-induced changes in cortical excitability appear to be mediated by N-methyl-D-aspartate (NMDA) receptor activity (Wischniewski et al., 2019), supporting the hypothesis that Spike Timing Dependent Plasticity (STDP) underlies the effects of beta tACS (Zaehle et al., 2010; Vossen et al., 2015; Veniero et al., 2015). In contrast, gamma tACS has been shown to reduce M1 inhibitory function (short-interval intracortical inhibition), a change associated with improved motor learning (Nowak et al., 2017). This suggests that beta and gamma tACS may operate through distinct mechanisms.

Building on previous electrophysiological and behavioural research (Nowak et al., 2017; Muthukumaraswamy, 2011; Muthukumaraswamy, 2010; Santarnecchi et al., 2017; Sugata et al., 2018), it is reasonable to assume that gamma tACS applied to the M1 could enhance performance during the execution of complex motor tasks requiring the integration of visual, proprioceptive, and somatosensory information (Aoki et al., 1999). However, the systematic investigation of different tACS frequencies within the beta and gamma ranges on corticomotor excitability

and motor performance remains underexplored, highlighting a significant gap in current research that warrants further study (Rostami et al., 2023). Gamma tACS, particularly within higher frequency ranges, have been proposed to facilitate motor control during specific task windows (Nowak et al., 2017; Santarnecchi et al., 2017; Sugata et al., 2018), suggesting their potential role in clinical applications for movement disorders. Conversely, beta tACS are often associated with motor inhibition, indicating distinct functional roles for these frequencies.

To date, no inquiry has investigated the effect of beta (20 Hz) and gamma (40/60/80 Hz) tACS in conjunction with motor training on corticomotor excitability and motor performance. Given the available evidence (Muthukumaraswamy, 2010), we hypothesise that beta and gamma oscillations exert differential effects on motor performance. Specifically, we expect high and mid gamma tACS (60/80 Hz) to enhance motor performance, while low gamma (40 Hz) and beta tACS (20 Hz) may impede it. Additionally, since the mechanisms underlying corticomotor responses to beta and gamma tACS differ (Nowak et al., 2017; Wischniewski et al., 2019), it is anticipated that varying frequencies of tACS within the beta and gamma spectrums will induce distinct effects on corticomotor responses (Tavakoli and Yun, 2017; Wach et al., 2013), which may facilitate the identification of the most effective frequency of tACS to enhance motor performance and corticomotor plasticity. Additionally, exploring the causal relationships between oscillatory brain activity, corticomotor excitability, and motor behaviour in healthy individuals may offer valuable insights into the mechanisms underlying neuroplasticity.

The primary objective of the current study was to investigate whether tACS applied over the bilateral M1 at beta, low gamma, mid gamma, and high gamma frequency ranges can modulate corticomotor plasticity. To achieve this, we assessed corticomotor plasticity using single-pulse TMS (sp TMS), which included measures of corticomotor excitability, silent period, and paired-pulse TMS (pp TMS) through short interval intracortical inhibition (SICI) and intracortical facilitation (ICF). This assessment was conducted following 20 min of bilateral tACS over M1 in combination with motor training. The second objective was to examine the offline effects of beta and gamma tACS combined with motor training on motor performance. To this end, motor performance including sensorimotor function and hand dexterity, was measured using sensorimotor reaction time and the Grooved Pegboard Test (GPT), respectively following 20 min of tACS in a randomised, crossover, single-blind, sham-controlled design.

Materials and methods

Participants

Twelve healthy young adults (mean age = 32 ± 7.36 years; 6 females, 6 males) participated in the study. All participants, except one ambidextrous individual, were right-handed as assessed by the Edinburgh Handedness Inventory (EHI) (mean Laterality Quotient: 81 ± 48) (Oldfield, 1971). The EHI evaluates hand preference, calculating the Laterality Quotient (LQ) using the formula: $LQ = (R - L) / (R + L) \times 100$, where R and L represent preferences for the right and left hands, respectively. Preferences are scored as strong preference (++) = 2 points, weak preference (+) = 1 point, and no preference (+ in both) = 1 point for each hand. LQ scores indicate left-handedness (< -40), ambidexterity (-40 to +40), or right-handedness (> +40). Prior to testing, participants provided written informed consent and underwent screening to exclude those with neurological disorders, psychiatric conditions, seizures, current psychoactive medication use, upper limb injuries, or other contraindications to TMS (Keel et al., 2001). They were advised to avoid coffee and alcohol on the test day. The study received approval from the Monash University Human Research Ethics Committee (MUHREC) and adhered to the National Statement on Ethical Conduct in Human Research (2007) and the Declaration of Helsinki. Ethical approval is documented under Project ID: 32964.

Experimental design

The study employed a single-blind sham-controlled crossover design, with participants unaware of the study's precise purpose. Seventy-five percent had no prior experience with transcranial electrical stimulation (tES). Each participant completed five sessions (20 Hz, 40 Hz, 60 Hz, 80 Hz, and sham) in a randomized counterbalanced order, spaced at least 48 h apart to avoid carryover effects. To control for diurnal variations, all measurements were taken at the same time for each participant (Clow et al., 2014; Sale et al., 2007). TMS measurements were conducted at four time points: prior to (Pre), immediately after (Post 0), 30 min after (Post 30), and 60 min after (Post 60) stimulation. Motor performance was assessed at three time points: pre-stimulation, immediately post-stimulation (Post 0), and 60 min after (Post 60) stimulation (Fig. 1).

During testing, participants sat comfortably with relaxed shoulders, arms flexed at 90° at the elbows, dominant forearms midway between pronation and supination, and wrists in a neutral position. Grip strength, measured as maximum voluntary force (MVF), was assessed using a handheld grip dynamometer (Biometrics G200, Serial Number: M25789, Wilmington, DE, USA). To ensure precision, the dynamometer's handle distance was adjusted to 50 % of the distance from the tip of the middle finger to the metacarpophalangeal flexion crease at the base of the thumb.

Participants completed a warm-up protocol with grip contractions at 20 %, 50 %, and 75 % of their perceived MVF. They then performed two MVF trials, each lasting 3–5 s, with a 60-second rest between trials. Continuous verbal encouragement was provided to maximise force exertion while squeezing the dynamometer. Real-time visual feedback of force levels was displayed on a computer monitor 1 m away. The highest value recorded was taken as the MVF, and a third trial was conducted if the difference between the first two trials exceeded 5 %. Participants then underwent assessments of corticomotor excitability, intracortical excitability, and motor performance. To normalise corticomotor responses, the maximal compound wave (M_{MAX}) was measured using peripheral electrical stimulation of the dominant limb.

sEMG and TMS recording

Surface electromyography (sEMG) recordings were conducted on the dominant arm using bipolar Ag-AgCl electrodes (30 mm x 22 mm, Kendall™ electrodes, Cardinal Health, Dublin, OH, USA), placed 2 cm apart over the extensor carpi radialis longus (ECRL) muscle belly in the

proximal forearm. ECRL locations were determined using anatomical landmarks and observing muscle contractions during wrist movements (Perotto, 2011). A ground electrode was positioned ipsilaterally via a wrist strap, and all electrodes were securely taped. The ECRL was chosen because it actively contributes to wrist stabilisation during hand movements and gripping tasks, which are critical for dexterity and fine motor control required during the GPT (Ramage and Varacallo, 2018; Kidgell et al., 2013). To minimize skin resistance, a standard preparation procedure involving cleaning and abrading was performed (Gilmore and Meyers, 1983). Raw sEMG signals were amplified ($\times 1000$), band-pass filtered (high pass at 1,000 Hz, low pass at 13 Hz), digitized online at 2 kHz for 1 s, recorded and analysed using PowerLab 4/26 (ADInstruments, Bella Vista, Australia).

To assess corticomotor responses, spTMS and ppTMS were conducted using a Magstim 2002 stimulator (Magstim Co., Ltd, Whitland, UK). TMS pulses were delivered via a 90 mm circular coil to deliver a posterior-to-anterior current flow that induces an electric field perpendicular to the cortical surface (Janssen et al., 2015). The motor hotspot for the ECRL muscle in the M1 was identified using the international 10–20 system (Jasper, 1958). To elicit MEPs, the motor hotspot was pinpointed by applying suprathreshold pulses over the dominant hemisphere's motor hand area. The search began with a TMS stimulus intensity set to 50 % of the maximum stimulator output (MSO) (Ah Sen et al., 2017), based on the average active motor threshold (AMT) of around 45 % MSO (Corp et al., 2021). If no MEP was induced, the intensity was increased by 4 % increments until the largest MEP response was achieved during a 10 % MVF contraction, accompanied by a visible muscle twitch (Ah Sen et al., 2017). The optimal scalp position was marked as the motor hotspot. The AMT was defined as the minimum intensity needed to elicit MEP amplitudes exceeding 200 μV in at least five of ten presentations, as established by prior research (Kidgell et al., 2010). The AMT was reassessed and adjusted at each time point within and across testing sessions.

spTMS assessed corticomotor excitability (MEP amplitude) and inhibition (silent period duration) by delivering five pulses at 130 %, 150 %, and 170 % of AMT during 10 % of the predetermined MVF (Rogasch et al., 2009), with a 10-second interval between pulses using a metronome (Kidgell et al., 2010). Ten paired-pulse stimuli evaluated corticocortical excitability (ICF) and inhibition (SICI). For SICI, the stimulator output was set at 130 % AMT for the test response and 80 % AMT for the conditioning stimulus, with a 3 ms interstimulus interval (Kujirai et al., 1993). For ICF, the interstimulus interval was set at 10 ms (Kujirai et al., 1993). All data were collected and analysed using

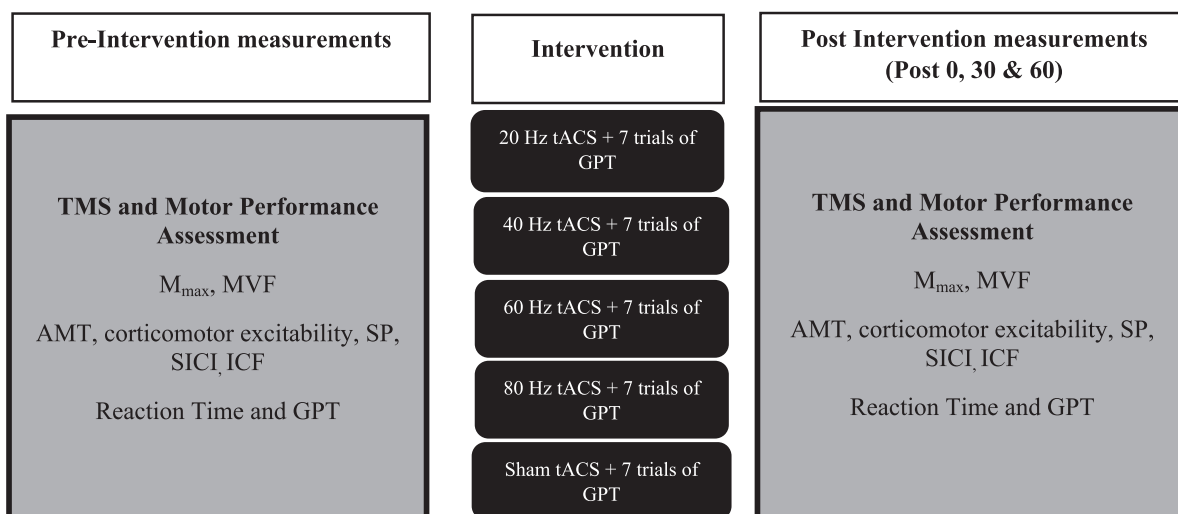


Fig. 1. Experimental Design AMT, Active motor threshold. SP, silent period. GPT, Grooved pegboard test. ICF, intracortical facilitation. M_{max} , maximal compound wave. MVF, maximum voluntary force. SICI, short-interval intracortical inhibition. tACS, transcranial Alternating Current Stimulation.

LabChart™ v8.1.24 software (ADInstruments, Bella Vista, Australia).

Maximal compound muscle action potential

Using a constant current electrical stimulator (DS8R, Digitimer, Hertfordshire, UK), we evaluated the maximal compound muscle action potential (M_{MAX}) by applying supramaximal electrical stimulation with a pulse width of 200 μ s. The cathode electrode (3.2 cm round, Axelgaard Manufacturing Co., LTD) was placed at Erb's point and the anode over the acromion. The aim was to measure the ECRL muscle response during isometric contraction at 10 % MVF, documenting changes in peripheral muscle excitability that could influence MEP amplitude as a normalisation reference for TMS. Stimulation began at low intensity and increased until the peak-to-peak amplitude of sEMG plateaued. M_{MAX} confirmation required an additional 20 % increase in current intensity, with the maximal M-wave amplitude recorded (Kidgell et al., 2013; Osborne et al., 2023). Baseline M_{MAX} recordings were initially collected, followed by measurements immediately after, and at 30 and 60 min post-tACS.

Motor performance

To evaluate tACS effects on motor performance, we employed the GPT and somatosensory reaction time tasks, measuring dexterity and sensorimotor function. Participants completed the 25-hole GPT (Lafayette Instruments, Lafayette, IN) with their dominant hand, moving pegs row by row from the left side to the right side of the pegboard using only their first two fingers, while their non-dominant hand remained flat on the table. Each participant performed three trials at three time points: pre-stimulation, immediately post-stimulation (Post 0), and 60 min post-stimulation (Post 60) after 20 min of tACS. They were verbally encouraged to complete the task quickly while maintaining accuracy.

Somatosensory testing (Brain Gauge, Cortical Metrics, Carrboro, NC), assessed reaction time, variability, and choice reaction time (Chouamo et al., 2021; Holden et al., 2020). A two-point vibrotactile stimulator delivered stimuli to the tips of digits 2 and 3, allowing participants to press a button upon perceiving the stimuli, documenting their motor response. The stimulator, controlled by Brain Gauge software, provided sinusoidal vibrotactile stimulation at amplitudes from 0 to 1000 μ m and frequencies from 0 to 200 Hz. A computer monitor displayed cues for stimulus delivery and response timing, ensuring participant engagement (Tommerdahl et al., 2019). Participants underwent three training trials to familiarise themselves with the protocol, completing an 8-minute test battery at each time point: pre-stimulation, Post 0, and Post 60.

Transcranial alternating current stimulation

tACS was administered using a NeuroConn DC-stimulator (NeuroConn, Ilmenau, Germany) with two saline-soaked rubber electrodes (35 cm²), positioned bilaterally over the M1 hotspot (Giustiniani et al., 2021; Zaghi et al., 2010). Since all participants were right-handed, the M1 hotspot for the ECRL muscle in the left hemisphere was first identified using TMS. To locate the M1 in the right hemisphere, the distance from Cz to the left M1 was measured and then applied symmetrically to the right side of Cz. tACS frequencies included 20 Hz (beta), 40 Hz (low gamma), 60 Hz (mid gamma), and 80 Hz (high gamma), with sham stimulation used as a control. For sham, electrodes were placed similarly, but the stimulator was turned off after 30 s, a method established for effective blinding in transcranial stimulation studies (Zaghi et al., 2010; Gandiga et al., 2006). Impedance was kept below 5 k Ω . The stimulation protocol involved a 30-second ramp-up and ramp-down with 20 min of 2 mA current (Rostami et al., 2023). During tACS, participants completed seven trials of the GPT as motor training, following prior instructions. They performed the GPT as quickly and accurately as possible, with 60 s of rest between trials (completion times not

recorded). An 11-point Visual Analog Scale was employed to evaluate the adverse effects resulting from either tACS or sham stimulation (Matsumoto and Ugawa, 2017).

Data and statistical analysis

The sample size ($n = 12$) was calculated using G*Power (Faul et al., 2007) based on a meta-analysis (Rostami et al., 2023) reporting an effect size of 0.36 for beta tACS on MEPs, with power (0.80) and significance level (0.05). To control for baseline fluctuations, rmsEMG data were collected 100 ms before each TMS pulse, and trials exceeding 5 ± 1 % of maximal rmsEMG were excluded. MEPs, measured in mV from the dominant ECRL, were normalised to M_{MAX} and scaled by 100. SP duration was visually assessed from MEP onset to the return of pre-stimulus rmsEMG (Cantello et al., 1992; Wilson et al., 1993). To analyse paired-pulse data across various time points, SICI and ICF ratios were calculated. SICI and ICF ratios were calculated by dividing the paired-pulse MEP by the single-pulse MEP (130 % AMT), multiplied by 100. Data analysis was performed using LabChart 8.1.28 (ADInstruments, Bella Vista, Australia).

Motor performance data, and neurophysiological data including AMT, MEPs, SPs, SICI, and ICF, were analysed using mixed-effects model implemented in Jamovi 2.0.041 with the GAMLj toolbox (Wilkinson et al., 2023). For normally distributed variables, we employed a linear mixed model (LMM), while a generalised linear mixed model (GLMM) with a gamma distribution and log link function was applied to handle non-normally distributed data. Normality was assessed by visually inspecting histograms and scatterplots of residuals (Altman and Bland, 1995; Van Belle and Kerr, 2012). Given the capacity of GLMM to handle non-normal distributions (Lo and Andrews, 2015; Salinas Ruiz et al., 2023), model selection was based on a comparison of the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), where lower values indicated a better model fit. Based on these criteria (Garson, 2019), GLMM was selected for most variables, except for SICI, which was better suited to LMM analysis.

The models included fixed effects for TIME (pre, post 0, post 30, post 60) and tACS FREQUENCY (20 Hz, 40 Hz, 60 Hz, 80 Hz, Sham), with random intercepts and slopes for participants. Statistical significance was evaluated using Wald Chi-Squared tests for GLMM and F-tests for LMM, and where significant interactions were found, Bonferroni-corrected post-hoc tests were applied.

Effect sizes were reported using Cohen's d (small: 0.2, moderate: 0.5, large: 0.8) (Garson, 2019; Cohen, 2013), with 95 % confidence intervals provided. To analyse the relationship between neurophysiological measures and motor performance, multiple linear regression analysis was conducted. To address potential multicollinearity, MEPs and SPs at 130 %, 150 %, and 170 % AMT were averaged, resulting in four independent variables: average MEP, average SP, SICI, and ICF for each condition. The dependent variables were GPT time and reaction time, both of which were normally distributed. Regression models were used to identify the neurophysiological predictors of motor performance for each tACS frequency. The significance level was established at 0.05. Mean differences are presented in text, while figures display mean \pm SEM. All graphs were generated using GraphPad Prism Software (GraphPad Software Inc., California, USA).

Results

Baseline variables (AMT, MVF, rmsEMG, MEPs, SICI, ICF, SP, reaction time, reaction time variability, choice reaction time, and speed) showed no significant differences across conditions.

Participants rated sensations (itching, tingling, burning, discomfort, fatigue, headache, warmth, facial muscle twitching, and flashes of light) on a 0–10 scale (0 = no sensation, 10 = intolerable) (Matsumoto and Ugawa, 2017). Mild tingling was reported by two participants, mild itching by four, and mild burning by three.

Regarding blinding, participants could not differentiate between active and sham stimulation, with false guesses exceeding 50 % for each condition.

Individual data for all conditions and time points are available in [Supplementary Document-2](#).

Corticomotor excitability (MEPs)

MEP 130 % AMT

Our analysis revealed significant main effects of intervention ($X^2(4) = 54, p < 0.001$), time ($X^2(3) = 14.1, p = 0.003$), and a time \times intervention interaction ($X^2(12) = 21.5, p = 0.05$). Post-hoc comparisons showed specific effects across different frequencies:

20 Hz tACS: MEP amplitude significantly decreased immediately after the intervention (MD = $-7.21, SE = 2.4, 95\% \text{ CI } [-13.22, -1.20]$; $df = 1169; p = 0.01, d = 0.41$), and 60 min post-intervention (MD = $-7.86, SE = 2.4, 95\% \text{ CI } [-13.87, -1.86]$; $df = 1169; p = 0.004, d = 0.46$), compared to sham (Fig. 2-A)

40 Hz tACS: A significant reduction in MEP amplitude was noted immediately post-stimulation compared to sham (MD = $-6.72, SE = 2.4, 95\% \text{ CI } [-12.72, -0.71]$; $df = 1169; p = 0.02, d = 0.38$) (Fig. 2-A), with a further significant decrease from baseline (MD = $-7.57, SE = 2.4, 95\% \text{ CI } [-13.33, -1.8]$; $df = 1169; p = 0.005, d = 0.33$) (Supplementary Table 8 & 9)

MEP 150 % AMT

The analysis demonstrated significant main effects of intervention ($X^2(4) = 48.2, p < 0.001$) and time ($X^2(3) = 26.5, p < 0.001$), along with a significant interaction between time and intervention ($X^2(12) = 32.2, p = 0.001$). Post-hoc comparisons revealed the following frequency-specific effects:

40 Hz tACS: A significant reduction in MEP amplitude was observed immediately post-intervention compared to Sham (MD = $-7.5, SE = 2.38, 95\% \text{ CI } [-13.45, -1.55]$; $df = 1169; p = 0.007, d = 0.36$) (Fig. 2-B). Additionally, MEP amplitude significantly decreased at post 0 (MD = $-8.60, SE = 2.38, 95\% \text{ CI } [-14.30, -2.89]$; $df = 1169; p = 0.001$) and post 30 (MD = $-7.49, SE = 2.38, 95\% \text{ CI } [-13.19, -1.78]$; $df = 1169; p = 0.005$) compared to baseline.

60 Hz tACS: At post 60, MEP amplitude showed a significant increase compared to Sham (MD = $7.67, SE = 2.38, 95\% \text{ CI } [1.72, 13.62]$; $df = 1169; p = 0.005, d = 0.32$) (Fig. 2-B).

80 Hz tACS: MEP amplitude significantly decreased at post 30 compared to baseline (MD = $-6.18, SE = 2.38, 95\% \text{ CI } [-11.89, -0.48]$; $df = 1169; p = 0.02, d = 0.3$).

In addition, following Sham tACS, MEP amplitude decreased at post 30 (MD = $-9.26, SE = 2.38, 95\% \text{ CI } [-14.97, -3.56]$; $df = 1169; p < 0.001, d = 0.46$) and post 60 (MD = $-7.17, SE = 2.38, 95\% \text{ CI } [-12.88, -1.47]$; $df = 1169; p = 0.008, d = 0.37$) compared to baseline (Supplementary Table 8 & 9).

MEP 170 % AMT

The analysis revealed significant main effects of intervention ($X^2(4) = 69.1, p < 0.001$) and time ($X^2(3) = 18.5, p < 0.001$), along with a significant time-by-intervention interaction ($X^2(12) = 37, p < 0.001$). Post-hoc comparisons showed that MEP amplitude was modulated differently across frequencies:

20 Hz tACS: A significant reduction in MEP amplitude was noted at post 30 compared to baseline (MD = $-7.43, SE = 2.87, 95\% \text{ CI } [-14.32, -0.55]$; $df = 1166; p = 0.02, d = 0.32$)

40 Hz tACS: MEP amplitude significantly decreased immediately post-intervention compared to Sham (MD = $-7.64, SE = 2.87, 95\% \text{ CI } [-14.83, -0.45]$; $df = 1166; p = 0.03, d = 0.38$) (Fig. 2-C).

60 Hz tACS: An increase in MEP amplitude was observed at post 30 compared to sham (MD = $7.41, SE = 2.87, 95\% \text{ CI } [0.22, 14.59]$; $df = 1166; p = 0.04, d = 0.38$) (Fig. 2-C)

80 Hz tACS: MEP amplitude increased significantly at post 0 (MD = $10.76, SE = 2.87, 95\% \text{ CI } [3.57, 17.94]$; $df = 1166; p = 0.001, d = 0.37$) and post 30 (MD = $7.35, SE = 2.87, 95\% \text{ CI } [0.17, 14.54]$; $df = 1166; p = 0.04, d = 0.37$) compared to Sham (Fig. 2-C).

Additionally, Sham tACS showed significant reductions in MEP amplitude at post 0 (MD = $-9.27, SE = 2.87, 95\% \text{ CI } [-16.15, -2.38]$; $df = 1166; p = 0.004, d = 0.37$), post 30 (MD = $-13.69, SE = 2.87, 95\% \text{ CI } [-20.58, -6.8]$; $df = 1166; p < 0.001, d = 0.58$), and post 60 (MD = $-11.26, SE = 2.87, 95\% \text{ CI } [-18.14, -4.37]$; $df = 1166; p < 0.001, d = 0.47$) compared to baseline (Supplementary Table 8 & 9).

In summary, our results for MEP amplitude revealed a pattern of reduction in response to 20 Hz and 40 Hz tACS, indicative of inhibitory effects. Specifically, significant decreases in MEP amplitude were observed at post 0 and post 60 for 130 % AMT and post 0 for 150 % AMT compared to Sham. Conversely, 60 Hz and 80 Hz tACS elicited increases in MEP amplitude, reflecting excitatory effects. These increases were significant at post 60 for 150 % AMT and at post 0 and post 30 for 170 %

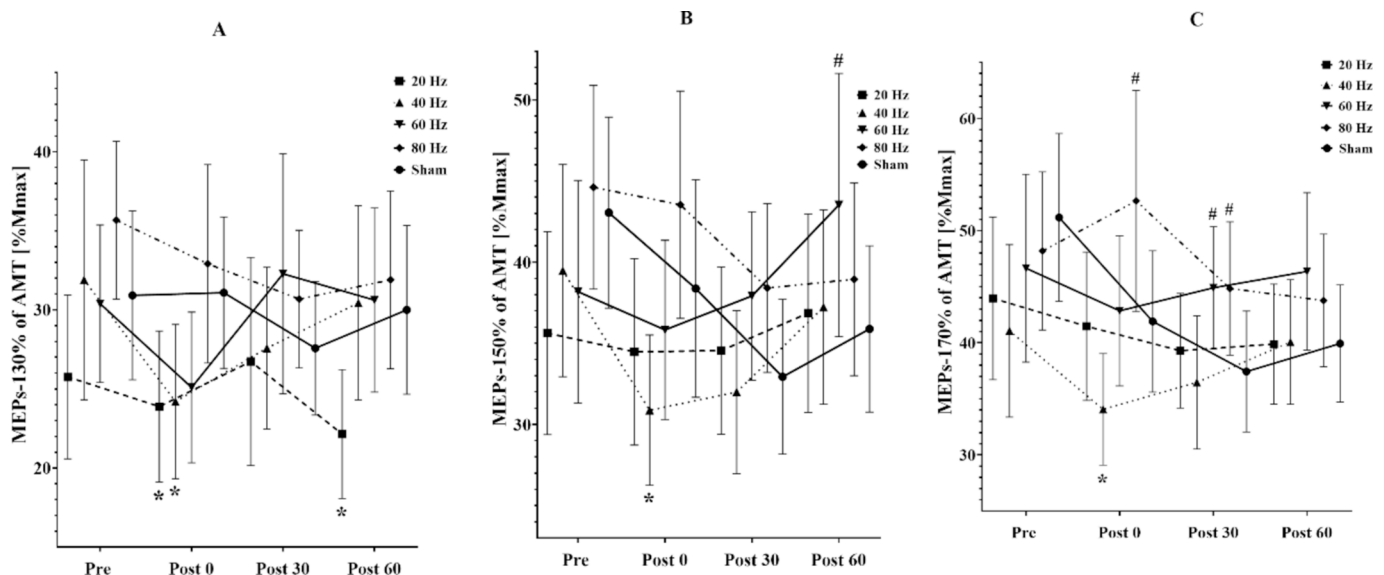


Fig. 2. Mean (\pm SEM) for the change in MEP at 130 % (A), 150 % (B), and 170 % (C) of AMT, following tACS and motor training. # indicates a significant increase in MEP amplitude compared to sham tACS ($p < 0.05$), * indicates a significant decrease in MEP amplitude compared to sham tACS ($p < 0.05$).

AMT compared to Sham.

Silent period

SP 130 % AMT

The results indicated significant main effects of intervention ($X^2(4) = 27.4, p < 0.001$), time ($X^2(3) = 20.6, p < 0.001$), and an interaction between time and intervention ($X^2(12) = 35.9, p = 0.002$). Post-hoc comparisons revealed the following frequency-specific changes:

20 Hz tACS: SP significantly decreased at post 0 (MD = -15.29, SE = 4.29, 95 % CI [-26, -4.5]; df = 1165; p = 0.002, d = 0.47), post 30 (MD = -15.79, SE = 4.2, 95 % CI [-26.49, -5.09]; df = 1165; p = 0.001, d = 0.46), and post 60 (MD = -20.3, SE = 4.25, 95 % CI [-30.95, -9.65]; df = 1165; p < 0.001, d = 0.57) compared to sham (Fig. 3-A). Additionally, SP was reduced at post 0 (MD = -12.48, SE = 4.25, 95 % CI [-22.69, -2.27]; df = 1165; p = 0.01, d = 0.37) and post 60 (MD = -12.18, SE = 4.25, 95 % CI [-22.39, -1.97]; df = 1165; p = 0.01, d = 0.32) compared to baseline

40 Hz tACS: A significant reduction in SP occurred immediately post-intervention (MD = -15.01, SE = 4.27, 95 % CI [-25.7, -4.31]; df = 1165; p = 0.002, d = 0.26) and at post 60 (MD = -14.46, SE = 4.25, 95 % CI [-25.11, -3.80]; df = 1165; p = 0.003, d = 0.37) compared to sham (Fig. 3-A). Additionally, SP decreased at post 30 (MD = -11.53, SE = 4.25, 95 % CI [-21.74, -1.32]; df = 1165; p = 0.02, d = 0.35) compared to baseline

60 Hz tACS: SP significantly declined at post 0 (MD = -18.16, SE = 4.29, 95 % CI [-28.91, -7.42]; df = 1165; p < 0.001, d = 0.59) and post 30 (MD = -15.14, SE = 4.29, 95 % CI [-24.89, -3.4]; df = 1165; p = 0.004, d = 0.43) compared to sham (Fig. 3-A). Additionally, SP was reduced at post 0 (MD = -18.49, SE = 4.25, 95 % CI [-28.69, -8.21]; df = 1165; p < 0.001, d = 0.58) and post 30 (MD = -10.48, SE = 4.27, 95 % CI [-20.73, -0.23]; df = 1165; p = 0.04, d = 0.43) compared to baseline

80 Hz tACS: A significant reduction in SP was observed at post 60 (MD = -12.48, SE = 4.25, 95 % CI [-23.13, -1.83]; df = 1165; p = 0.01, d = 0.38) compared to sham (Fig. 3-A). SP also significantly decreased at post 0 (MD = -10.21, SE = 4.25, 95 % CI [-20.42, -0.008]; df = 1165; p = 0.05, d = 0.33), post 30 (MD = -12.95, SE = 4.25, 95 % CI [-23.15, -2.74]; df = 1165; p = 0.007, d = 0.4), and post 60 (MD = -14.36, SE = 4.25, 95 % CI [-24.57, -4.15]; df = 1165; p = 0.002, d = 0.44) compared to baseline (Supplementary Table 10 & 11)

SP 150 % AMT

The results indicated significant main effects of intervention ($X^2(4) = 28.9, p < 0.001$), time ($X^2(3) = 31.1, p < 0.001$), and an interaction between time and intervention ($X^2(12) = 25.2, p = 0.01$). Post-hoc comparisons highlighted the following effects for different frequencies:

20 Hz tACS: SP significantly decreased at post 30 (MD = -19, SE = 4.64, 95 % CI [-30.61, -7.38]; df = 1166; p < 0.001, d = 0.45) and post 60 (MD = -17.81, SE = 4.64, 95 % CI [-29.43, -6.2]; df = 1166; p = 0.001, d = 0.45) compared to sham (Fig. 3-B). Additionally, SP decreased at post 0 (MD = -11.23, SE = 4.64, 95 % CI [-22.36, -0.09]; df = 1166; p = 0.04, d = 0.27) and at post 30 (MD = -13.17, SE = 4.64, 95 % CI [-24.3, -2.04]; df = 1166; p = 0.01, d = 0.39) compared to baseline.

40 Hz tACS: SP significantly decreased at post 60 (MD = -13.83, SE = 4.64, 95 % CI [-25.45, -2.21]; df = 1166; p = 0.01, d = 0.34) compared to sham (Fig. 3-B)

60 Hz tACS: A significant reduction in SP was observed at post 0 (MD = -21.88, SE = 4.68, 95 % CI [-33.11, -10.65]; df = 1166; p < 0.001, d = 0.37) and post 30 (MD = -11.69, SE = 4.68, 95 % CI [-22.92, -0.46]; df = 1166; p = 0.03, d = 0.33) compared to baseline.

80 Hz tACS: A significant decrease in SP was observed at post 60 (MD = -17.53, SE = 4.46, 95 % CI [-23.36, -0.09]; df = 1166; p = 0.04, d = 0.47) compared to sham (Fig. 3-B). Additionally, SP significantly decreased at post 0 (MD = -14.68, SE = 4.64, 95 % CI [-25.81, -3.55]; df = 1166; p = 0.005, d = 0.36), post 30 (MD = -14.81, SE = 4.64, 95 % CI [-25.94, -3.68]; df = 1166; p = 0.004, d = 0.36), and post 60 (MD = -18.96, SE = 4.64, 95 % CI [-30.09, -7.83]; df = 1166; p < 0.001, d = 0.47) compared to baseline (Supplementary Table 10 & 11)

SP 170 % AMT

The results indicated significant main effects of intervention ($X^2(4) = 25.9, p < 0.001$), time ($X^2(3) = 21, p < 0.001$), and interaction between time and intervention ($X^2(12) = 30.5, p = 0.002$). Post-hoc comparisons revealed the following effects across different frequencies:

20 Hz tACS: SP significantly decreased at post 0 (MD = -20.31, SE = 4.18, 95 % CI [-30.35, -10.27]; df = 1169; p < 0.001, d = 0.54), post 30 (MD = -13.94, SE = 4.18, 95 % CI [-23.99, -3.9]; df = 1166; p = 0.003, d = 0.38), and post 60 (MD = -12.91, SE = 4.18, 95 % CI [-22.95, -2.87]; df = 1169; p = 0.006, d = 0.35) compared to baseline

40 Hz tACS: A significant reduction in SP was observed at post 30 (MD = -13.63, SE = 4.18, 95 % CI [-24.11, -3.15]; df = 1169; p = 0.005, d = 0.31) and post 60 (MD = -12.35, SE = 4.18, 95 % CI [-22.83, -1.87]; df = 1169; p = 0.01, d = 0.26) compared to sham (Fig. 3-C).

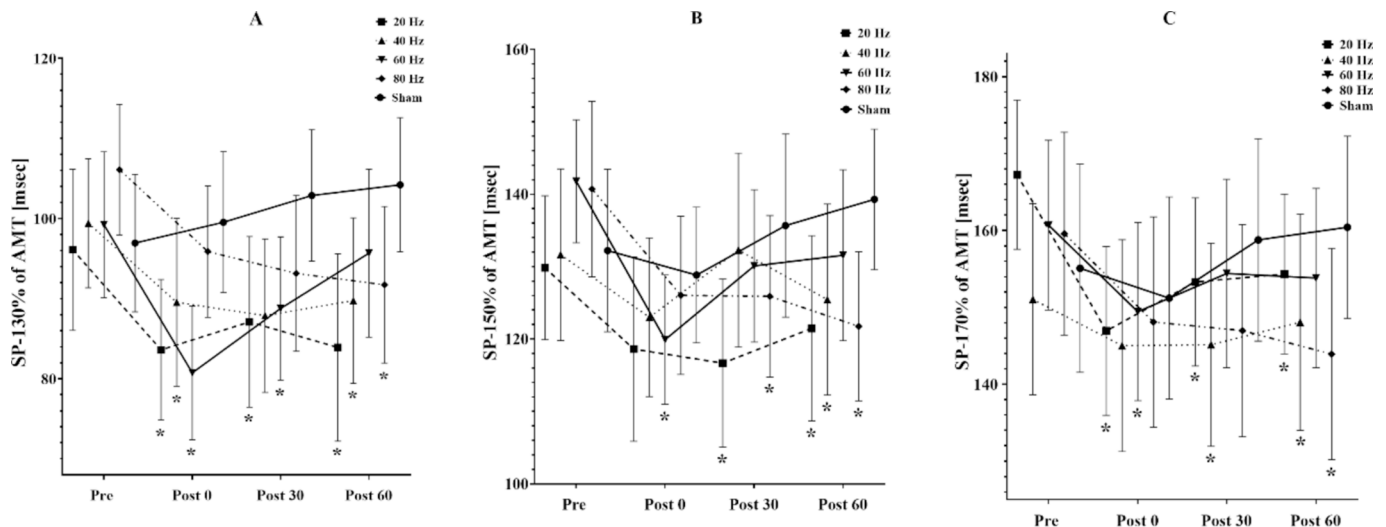


Fig. 3. Mean (\pm SEM) for the change in silent period duration (ms) at 130 % (A), 150 % (B), and 170 % (C) of AMT, following tACS and motor training. * indicates a significant decrease in SP duration amplitude compared to sham tACS ($p < 0.05$).

60 Hz tACS: SP significantly decreased at post 0 (MD = -11.25, SE = 4.18, 95 % CI [-21.29, -1.2]; df = 1169; $p = 0.02$, $d = 0.3$) compared to baseline

80 Hz tACS: SP significantly decreased at post 60 (MD = -16.5, SE = 4.18, 95 % CI [-26.98, -6.02]; df = 1169; $p < 0.001$, $d = 0.35$) compared to sham (Fig. 3-C). In addition, SP reduced at post 0 (MD = -11.5, SE = 4.18, 95 % CI [-21.54, -1.45]; df = 1169; $p = 0.01$, $d = 0.25$), post 30 (MD = -12.61, SE = 4.18, 95 % CI [-22.65, -2.57]; df = 1169; $p = 0.008$, $d = 0.27$), and post 60 (MD = -15.66, SE = 4.18, 95 % CI [-25.7, -5.62]; df = 1169; $p = 0.001$, $d = 0.34$) compared to baseline (Supplementary Table 10 & 11).

In summary, 20 Hz and 40 Hz tACS consistently showed reductions in SP across all time points and AMT levels, with more pronounced effects at post 30 and post 60 compared to Sham. In contrast, 60 Hz demonstrated SP reduction only at 130 % AMT at post 0 and post 30, while 80 Hz showed consistent SP reduction at post 60 across all intensity levels.

Intracortical excitability

Short interval intracortical inhibition

The results for SICI showed significant main effects for intervention ($F_{4, 946} = 2.45$, $p = 0.04$) and time ($F_{3, 946} = 3.41$, $p = 0.01$); as well as a significant interaction between time and intervention ($F_{12, 946} = 3.07$, $p < 0.001$). Post-hoc comparisons revealed the following effects across different frequencies:

40 Hz tACS: A significant enhancement in SICI was observed at post 30 (MD = -11.42, SE = 3.46, 95 % CI [-19.73, -3.11]; df = 946; $p = 0.003$, $d = 0.48$) compared to baseline

60 Hz tACS: A significant release in SICI was observed at post 0 (MD = 14.33, SE = 3.63, 95 % CI [5.22, 23.43]; df = 946; $p = 0.005$, $d = 0.48$) compared to sham. Additionally, SICI release was observed at post 0 (MD = 10.05, SE = 3.75, 95 % CI [-20.35, -2.6]; df = 946; $p = 0.005$, $d = 0.35$) compared to baseline (Fig. 4-A and Supplementary Table 12 & 13).

Intracortical facilitation

Regarding ICF, our analysis showed the main effect for intervention ($X^2(4) = 34.5$, $p < 0.001$), and time ($X^2(3) = 23.2$, $p < 0.001$) as well as a significant interaction between time and intervention ($X^2(12) = 51$, $p < 0.001$) following tACS. Post-hoc comparisons revealed the following effects across different frequencies:

20 Hz tACS: A significant increase in ICF was observed at post 0 (MD = 41.3, SE = 12.74, 95 % CI [9.4, 73.19]; df = 879; $p = 0.005$, $d = 0.77$) compared to sham (Fig. 4-B)

40 Hz tACS: A significant enhancement in ICF was observed at post 60 (MD = 42.35, SE = 12.85, 95 % CI [10.25, 74.45]; df = 879; $p = 0.004$, $d = 0.63$) compared to sham (Fig. 4-B). Additionally, an ICF increase was observed at post 60 (MD = 43.3, SE = 12.68, 95 % CI [120.88, 73.72]; df = 879; $p = 0.002$, $d = 0.67$) compared to baseline.

60 Hz tACS: A significant increase in ICF was observed at post 0 (MD = 35.55, SE = 12.22, 95 % CI [4.97, 66.14]; df = 879; $p = 0.01$, $d = 0.86$) compared to sham (Fig. 4-B and Supplementary Table 12 & 13)

In summary, the analysis of SICI and ICF in comparison to sham demonstrated distinct differences across frequencies. For SICI, 60 Hz tACS resulted in a significant release at post 0, while 40 Hz tACS enhanced SICI at post 30. For ICF, both 20 Hz and 60 Hz tACS induced a significant increase at post 0, and 40 Hz tACS also showed an increase at post 60.

Motor performance

Hand dexterity

Our analysis of the GPT data revealed a significant main effect for time ($F_{2, 154} = 17.85$, $p < 0.001$), indicating an improvement in hand dexterity at both post 0 and post 60. However, the main effects of intervention ($F_{4, 154} = 0.23$, $p = 0.92$) and the interaction between intervention and time ($F_{8, 154} = 0.94$, $p = 0.48$) were not significant (Fig. 5-A).

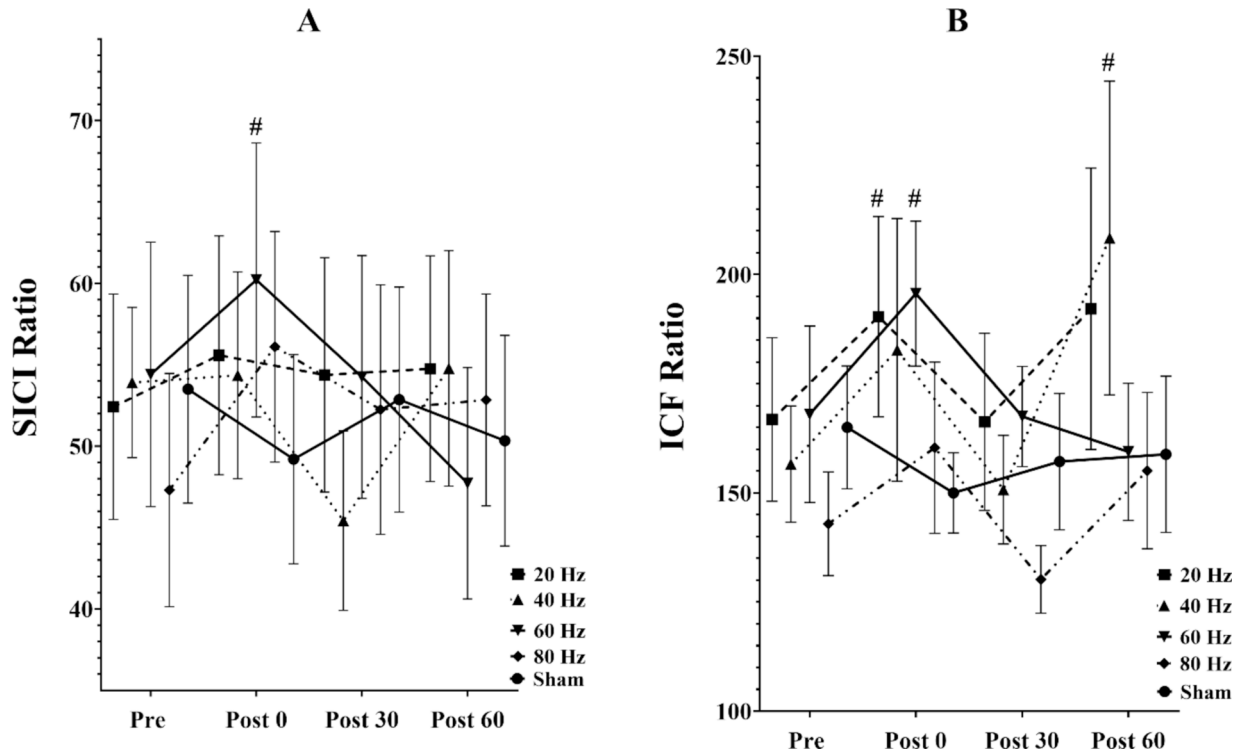


Fig. 4. Mean (\pm SEM) for the change in SICI Ratio (A) and ICF Ratio (B) following tACS and motor training. # indicates a significant increase in MEP amplitude compared to sham tACS ($p < 0.05$).

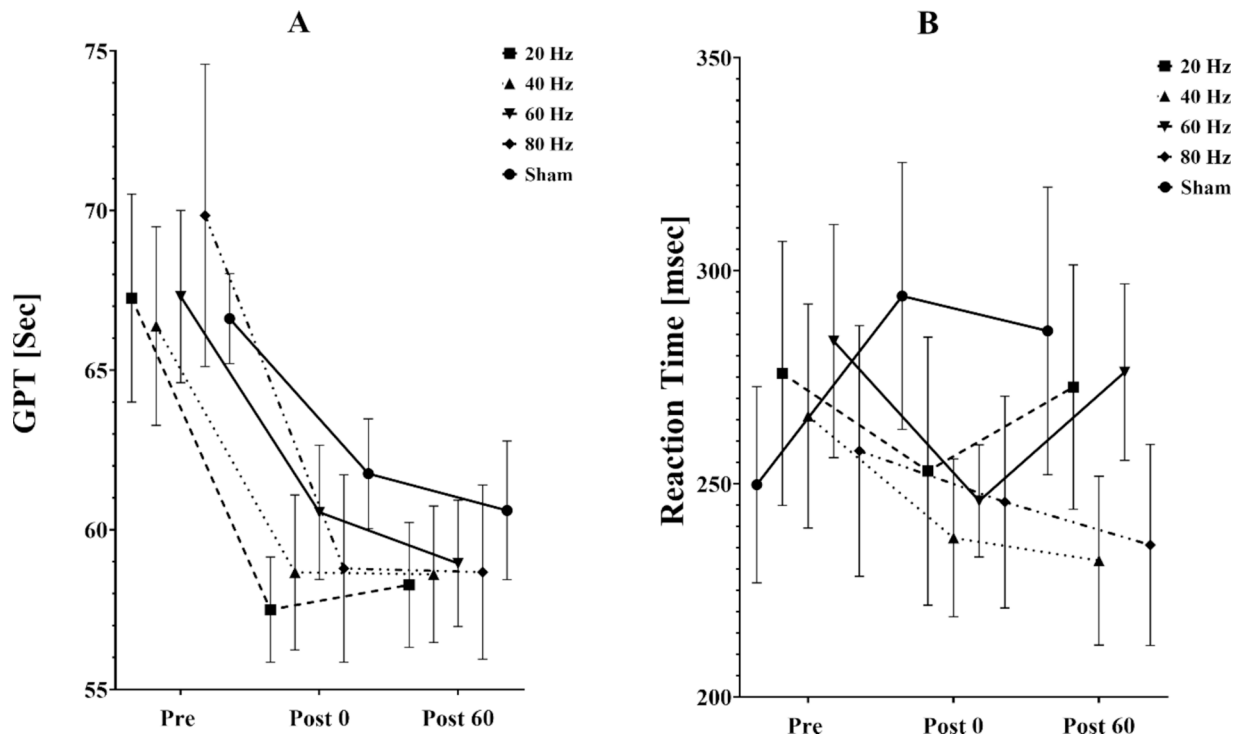


Fig. 5. Mean (\pm SEM) for the change in GPT (A) and reaction time (B) following tACS and motor training.

Sensorimotor function

The analysis of reaction time data indicated no main effects for intervention ($F_{4, 148} = 2.34, p = 0.05$), time ($F_{2, 148} = 0.72, p = 0.48$), or the interaction between intervention and time ($F_{8, 148} = 1.55, p = 0.14$) (Fig. 5-B).

No significant findings were observed for reaction time variability, and choice reaction time following different frequencies of tACS at different time points.

Predictors of motor performance

Multiple linear regression analyses were performed to determine which TMS neurophysiological measures (average MEP, average SP, SICI, and ICF) best predicted motor performance (GPT completion time

and reaction time). Separate regression models were constructed for each tACS frequency.

To assess the predictive relationships, pre/post changes in neurophysiological variables (average MEP, average SP, SICI, and ICF) were calculated as the ratio of [(post 0 and post 60) minus pre] values. Similarly, pre/post changes in motor performance measures (GPT time and reaction time) were computed as the ratio of [(post 0 and post 60) minus pre]. These change scores were then used as independent and dependent variables, respectively, in the regression models (Please refer to supplementary tables 6 and 7).

For 20 Hz, 40 Hz and sham tACS conditions, no significant coefficients were observed in the regression models for either the pre/post 0 or pre/post 60 differences in neurophysiological and motor performance measures.

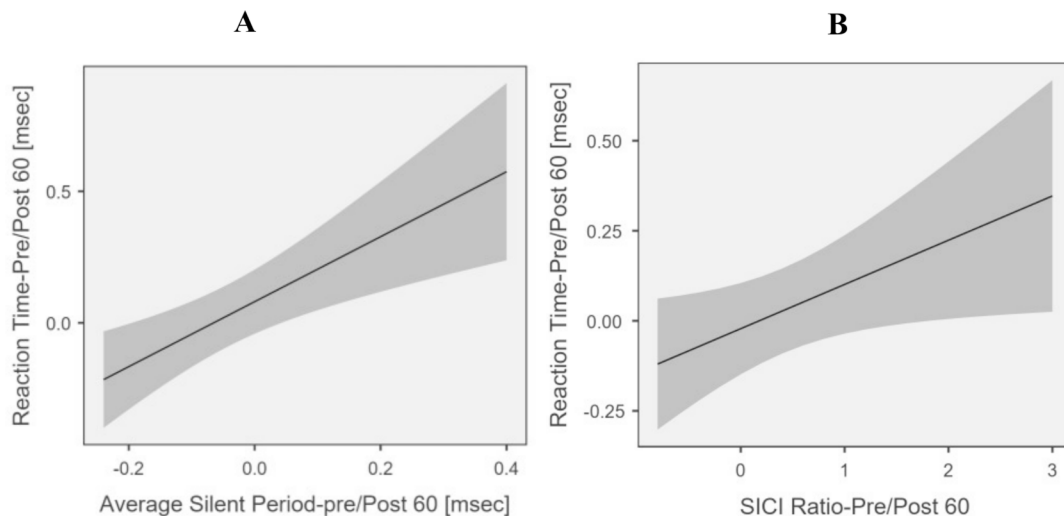


Fig. 6. Regression plots showing the relationship between Reaction Time changes (Post 60 – Pre) and SP Average changes (Post 60 – Pre) (A), and Reaction Time changes (Post 60 – Pre) and SICI changes (Post 60 – Pre) (B) following 60 Hz tACS.

Following 60 Hz tACS, the regression model examining predictors of reaction time changes (Post 60 – Pre) was statistically significant ($F(4, 7) = 6.18, p = 0.019$), explaining 77.9% of the variance in reaction time ($R^2 = 0.779$, adjusted $R^2 = 0.653$). Model fit measures included AIC = -2.54 , and BIC = 0.366 .

Post 60 – Pre changes in average SP were positively associated with reaction time changes (Estimate = 1.23 , 95% CI [$0.52, 1.94$], Standardized Estimate = 0.830 , $p = 0.005$), suggesting that shorter silent periods were related to faster reaction times (Fig. 6-A). Additionally, Post 60 – Pre changes in SICI were also positively associated with reaction time changes (Estimate = 0.123 , 95% CI [$0.007, 0.24$], Standardized Estimate = 0.461 , $p = 0.04$), indicating that greater SICI was related to slower reaction times (Fig. 6-B).

Following 80 Hz tACS, the regression model examining predictors of GPT completion time changes (Post 60 – Pre) was not statistically significant ($F(4, 7) = 3.60, p = 0.067$), but it explained 67.3% of the variance in GPT completion time ($R^2 = 0.673$, adjusted $R^2 = 0.486$). Model fit measures included AIC = -24.6 and BIC = -21.7 .

Despite the overall model not reaching statistical significance, Post 60 – Pre changes in average MEP were significantly associated with GPT completion time changes (Estimate = -0.37 , 95% CI [$-0.66, -0.08$], Standardized Estimate = -0.760 , $p = 0.018$). This result indicates that a decrease in MEP amplitude was related to faster GPT completion times, suggesting a potential relationship between reduced corticospinal excitability and improved hand dexterity performance (Fig. 7).

In summary, the regression analysis examining predictors of motor performance changes revealed frequency-specific relationships. For 20 Hz, 40 Hz, and sham tACS conditions, no significant coefficients were observed in the regression models for either the pre/post 0 or pre/post 60 differences in neurophysiological and motor performance measures. Following 60 Hz tACS, SP average changes were positively associated with reaction time changes (post 60 – pre), while SICI also showed a significant positive relationship with reaction time changes. After 80 Hz tACS, MEP average changes were negatively associated with reaction time changes and were additionally linked to GPT performance changes post-intervention.

Discussion

This study explored the effects of beta, low gamma, mid gamma, and

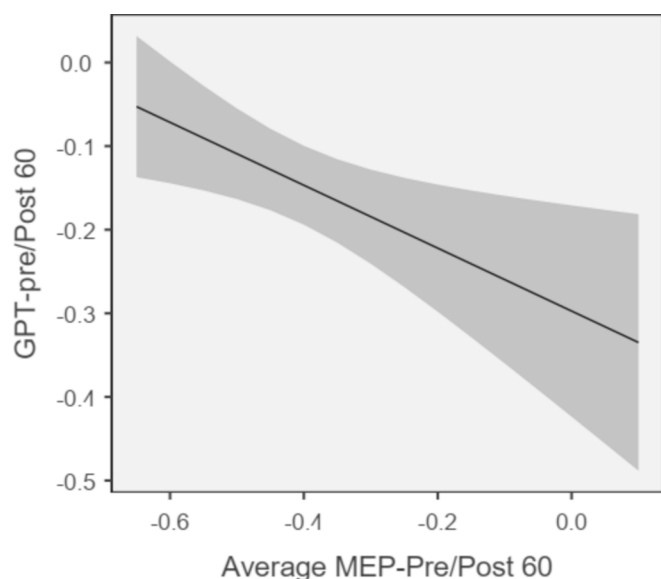


Fig. 7. Regression plots showing the relationship between GPT completion time changes (Post 60 – Pre) and MEP Average changes (Post 60 – Pre), following 60 Hz tACS.

high gamma tACS over bilateral M1 combined with motor training on corticomotor excitability and motor performance. The results indicate frequency-specific neurophysiological effects: beta and low gamma primarily reduced corticospinal excitability, while mid and high gamma increased it. All tACS frequencies shortened SP duration, and mid gamma reduced SICI, indicating reduced cortical inhibition. Beta, low gamma, and mid gamma also increased ICF, suggesting enhanced facilitation.

Despite these neurophysiological changes, no significant improvements in motor performance were observed in GPT or sensorimotor reaction time. However, a trend toward faster GPT completion across all conditions, including sham, suggests factors beyond tACS may have influenced motor performance. Reaction time decreased following stimulation across all frequencies but slowed after sham tACS, indicating that while M1 neurophysiological changes were evident, they did not directly translate into motor function improvements under these conditions.

To our knowledge, this is the first study to show that tACS in both beta and gamma ranges can modulate corticomotor and intracortical excitability, reducing SP and increasing ICF.

Neurophysiological effects of tACS at beta, low gamma, mid gamma, and high gamma frequencies

As we discussed earlier, sensorimotor oscillations in beta and gamma frequency bands are essential for motor control (Barone and Rossiter, 2021; Ulloa, 2022). Beta activity in M1 increases during tonic contractions but decreases during movement execution, emphasising its role in motor inhibition and stabilisation (Jurkiewicz et al., 2006; Muthukumaraswamy, 2010; Gaetz et al., 2011). In contrast, gamma oscillations rise during movement preparation and execution, facilitating dynamic motor tasks (Crone et al., 1998; Ball et al., 2008; Cheyne et al., 2008). Beta oscillations are linked to suppressing unnecessary movements, particularly during static tasks, while gamma aids in complex motor execution. Beta is considered 'antikinetic,' stabilising motor output, while gamma is 'prokinetic,' driving motor performance (Chandrasekaran et al., 2019; Brown, 2003; Hamada et al., 1999). In addition to the distinctions between beta and gamma frequencies, gamma oscillations, although generally associated with motor control, exhibit functional differences depending on the specific frequency band. Each narrow band within the gamma range may participate in distinct processes, thereby justifying the exploration of their individual effects. Findings from tACS studies indicate that 40 Hz stimulation results in corticospinal inhibition (Giustiniani et al., 2019). Additionally, both 35 Hz and 40 Hz tACS have been shown to slow response time (Giustiniani et al., 2019; Pollok et al., 2015), suggesting a potential suppressive effect on motor performance. In contrast, higher gamma frequencies, such as 60 Hz and 80 Hz, are more frequently associated with movement execution, motor and corticomotor facilitation (Nowak et al., 2017; Santarnecchi et al., 2017). These functional differences across gamma bands underscore the importance of investigating each frequency individually, as they may influence motor excitability and performance through distinct physiological mechanisms.

The following sections will discuss the effects of tACS at beta and gamma frequencies during a complex motor task, focusing on their impact on corticospinal excitability, motor performance, and the associations between neurophysiological measures and motor outcomes.

Beta tACS

Our findings demonstrated that 20 Hz tACS consistently decreased MEPs and SP across all post-tACS time points while increasing ICF immediately after stimulation. While several studies (Nowak et al., 2017; Bologna et al., 2019; Therrien-Blanchet et al., 2023; Splittgerber et al., 2020; Pozdniakov et al., 2021) and a recent meta-analysis (Rostami et al., 2023) reported no effect of beta tACS on corticospinal excitability, our results align with those showing reduced M1

excitability (Zaghi et al., 2010; Wang et al., 2021; Cappon et al., 2016). Conversely, another meta-analysis (Wischniewski et al., 2019) found beta tACS increased M1 excitability, suggesting that differences in stimulation intensity, duration, and electrode montage may explain these inconsistencies. We consistently observed a reduction in SP across all time points, in contrast to a previous study that reported no effect on SP (Wach et al., 2013). However, in the study by Wach et al. (2013) (Wach et al., 2013), tACS was applied with an intensity of 1 mA for 10 min. It has been suggested that longer durations and higher current intensities may be necessary to effectively modulate corticomotor responses (Rostami et al., 2023). The increase in ICF aligns with earlier findings (Guerra et al., 2016), though other studies, using lower intensities, found no effect or a reduction in ICF (Nowak et al., 2017; Zaghi et al., 2010). Notably, those studies used tACS intensities below 2 mA, unlike the current study.

Low gamma tACS

Research on 40 Hz tACS has primarily focused on cognitive functions (Manippa et al., 2024; De Paolis et al., 2024), with fewer studies investigating its effects on corticomotor excitability compared to beta and high gamma tACS. Consistent with previous findings (Giustiniani et al., 2019), our results show that 40 Hz tACS reduced MEP amplitudes immediately after stimulation, indicating acute inhibition of corticomotor excitability. Despite this, SP decreased across all time points, and ICF increased 60 min post-stimulation, suggesting that low gamma tACS influences both inhibitory and facilitatory processes in M1.

Mid gamma tACS

Similar to low gamma, mid gamma (60 Hz) frequency bands have received relatively little attention in current research. Our findings showed that 60 Hz tACS increased MEP amplitudes at 30- and 60-minutes post-stimulation, indicating delayed excitatory effects. SP reduction was observed immediately and at 30 min, along with increased ICF and SICI immediately after stimulation. At 60 min post mid gamma tACS, shorter SP was associated with faster reaction times, whereas greater SICI was linked to slower reaction times. Only one study has previously investigated the effects of mid gamma tACS over M1 on motor performance, showing a trend towards improvement (Santarnecchi et al., 2017). Additionally, 60 Hz tACS over Cz has been shown to enhance visual processing and perceptual flexibility, with BOLD signal increases in multiple brain regions (Cabral-Calderin et al., 2015; Laczó et al., 2012; Cabral-Calderin et al., 2016).

High gamma tACS

For 80 Hz tACS, MEP amplitude increased immediately after stimulation and remained elevated for up to 30 min. This contrasts with findings from Moliadze et al. (2010) (Moliadze et al., 2010), who reported no impact of 80 Hz tACS on corticomotor excitability, possibly due to their shorter 10-minute stimulation duration and lower intensity of 1 mA. Similarly, Nowak et al. (2017) (Nowak et al., 2017) found no effects with 75 Hz tACS, although they matched our stimulation duration while applying a lower intensity, which may account for differing results.

In our study, we observed a reduction in SP that persisted for up to 60 min, with decreases noted across all time points. However, we did not find significant effects on SICI or ICF, nor on motor performance. Interestingly, while Nowak's research indicated that 75 Hz tACS could modulate SICI and reduce inhibition, our findings suggest otherwise. A meta-analysis also supported the notion that high gamma tACS does not enhance motor performance (Rostami et al., 2023).

Notably, we observed a negative association between MEP amplitudes and GPT completion time, indicating that higher MEP amplitudes 60 min after high gamma tACS were linked to faster GPT performance, suggesting that increased MEP may facilitate quicker task completion.

Corticomotor excitability and MEP modulation across frequencies

Overall, our findings show that both beta and low gamma tACS produced inhibitory effects on corticomotor excitability, while mid and high gamma tACS demonstrated excitatory effects. This suggests frequency-dependent variations that don't entirely align with traditional distinctions between beta and gamma bands. One proposed mechanism for the effects of tACS involves the entrainment of cortical oscillations, primarily associated with tACS online effects. Conversely, STDP has been proposed to explain offline tACS effects (Zaehle et al., 2010; Vossen et al., 2015; Vogeti et al., 2022). A recent EEG study, which evaluated the offline effects of tACS, did not find evidence supporting the modulation for offline brain oscillation power at the stimulation site when tACS was applied over sensorimotor regions at 10 Hz and 20 Hz (Lafleur et al., 2021). Conversely, another study reported that while online application of tACS over the M1 affected corticomotor excitability, offline tACS did not produce similar effects (Pozdniakov et al., 2021). In light of the preceding information, previous meta-analyses have not discerned any distinctions in the effects of online versus offline tACS on corticomotor excitability (Wischniewski et al., 2019) and motor function (Rostami et al., 2023). In our study, tACS was applied concurrently with motor training, and we measured its aftereffects (offline effects) (Pozdniakov et al., 2021), suggesting that our findings might not depend on cortical oscillation entrainment. Instead, the persistence of these effects points toward a reliance on STDP in M1 networks (Wischniewski et al., 2019; Gallasch et al., 2018; Kasten et al., 2016; Schwab et al., 2021). The fundamental notion postulates that synaptic efficacy experiences enhancement when pre-synaptic spikes precede post-synaptic spikes, a phenomenon acknowledged as long-term potentiation (LTP). Conversely, when post-synaptic spikes precede their pre-synaptic counterparts, synaptic connections are thought to undergo a weakening process, leading to long-term depression (LTD) (Caporale and Dan, 2008; Dan and Poo, 2006).

Although previous studies have reported that beta tACS can induce NMDAR-mediated plasticity in the motor cortex and increase cortical excitability for up to 60 min (Wischniewski et al., 2019) and that 40 Hz stimulation has been shown to enhance LTP-like plasticity in the motor and prefrontal cortices, potentially through the modulation of GABAergic neurotransmission (De Paolis et al., 2024), these findings are not consistent with the current study. Our results suggest that beta and low gamma tACS may influence corticomotor excitability through different mechanisms. Consistent with previous research, mid and high gamma tACS (approximately 70 Hz and 75 Hz) may modulate corticomotor excitability by altering GABAergic neurotransmission. Evidence indicates that 70 Hz tACS can enhance LTP-like plasticity in the motor cortex by reducing GABA_A-mediated inhibition, resulting in a more pronounced excitatory response (Guerra et al., 2018). Similarly, 75 Hz tACS has been shown to decrease local GABA_A inhibition (Nowak et al., 2017). These findings suggest that alterations in GABA_A activity could be pivotal in the excitatory effects observed with mid and high gamma tACS in this study. The effects of tACS on GABAergic (inhibitory) and glutamatergic (facilitatory) neurotransmitters will be further discussed in the following section. It's worth noting that MEP amplitudes decreased across all time points, even with sham tACS, likely due to fatigue from repeated motor tasks like the GPT and holding the dynamometer, which can reduce corticospinal excitability (Kotan et al., 2015).

Inhibition and facilitation across frequencies

All administered frequencies—beta, low gamma, mid gamma, and high gamma—showed a consistent reduction in SP post-stimulation, indicating no significant frequency-dependent differences in SP modulation. Beta and low gamma tACS reduced SP across all time points, mid gamma at post 0 and post 30, and high gamma at post 60. SP, the phase of EMG quiescence following MEP onset during voluntary muscle

contraction (Chen, 2000), is governed by GABA_B receptors and reflects cortical and spinal inhibitory processes (Škarabot et al., 2019; Werhahn et al., 1995). A TMS study reinforced the strong link between GABA_B receptors and LTP, showing that prolonged SP in concussed athletes was associated with inhibited LTP plasticity (De Beaumont et al., 2012). TMS studies further suggest SP duration can serve as a proxy for M1 excitability (Mooney et al., 2016; Neva et al., 2017), with reductions indicating less inhibitory circuit activity after interventions (Udupa, 2021).

In healthy individuals, an inverse correlation has been observed between SP duration and resting MEP amplitudes, with longer SPs linked to smaller MEPs (Sfreddo et al., 2021). However, other studies, such as those by Hallett et al. suggest that SP and MEP are mediated by independent mechanisms, indicating they arise from distinct processes (Hallett, 1995; Zeugin and Ionta, 2021). In the current study, beta and low gamma tACS resulted in SP reduction alongside corticomotor inhibition, while 60 Hz tACS saw SP reduction at post 30 paired with increased excitability. After 80 Hz tACS, no MEP change occurred despite SP reduction at post 60, suggesting different mechanisms may govern SP and MEP. Additionally, Sfreddo et al. (2021) noted that SP duration has lower variability than MEP amplitude, making it a more reliable outcome measure (Sfreddo et al., 2021). This reduced variability likely explains the consistent SP changes across frequencies in our study, suggesting that SP duration offers more stable insights into neurophysiological changes compared to MEP amplitudes. Theoretically, an increase in excitability could stem from either an increased excitatory transmission or a reduced inhibitory transmission (Reis and Fritsch, 2011). While SP changes were traditionally seen as indicators of intracortical inhibition (Wilson et al., 1993; Säisänen et al., 2008; Werhahn et al., 1999), evidence points to contributions from both cortical and spinal mechanisms (Škarabot et al., 2019; Fuhr et al., 1991; Ziemann et al., 1993). The early phase of SP reflects spinal inhibition, while the later phase is mainly cortical, suggesting that spinal mechanisms may play a larger role than previously recognized (Yacyshyn et al., 2016).

Recent investigations suggest that gamma tACS modulates M1 interneuronal networks by reducing GABAergic inhibition, as shown by decreased SICI (a measure of GABA_A-mediated inhibition in M1) (Nowak et al., 2017; Guerra et al., 2018). The critical role of the GABAergic system in M1 plasticity is highlighted by evidence linking reduced GABA levels to LTP induction, with magnetic resonance spectroscopy showing decreased GABAergic inhibition following tES (Hess et al., 1996; Stagg et al., 2009). Additionally, Interneuronal networks, key components of M1 circuitry, are essential for motor learning (Guerra et al., 2018; Hamada et al., 2014). In the present study, mid gamma tACS uniquely reduced SICI immediately after stimulation. Although the reduction in SICI was accompanied by a decrease in SP, it did not lead to an increase in corticomotor excitability at this time point. In our study, both beta and gamma tACS consistently reduced SP across all three TMS intensities (130 %, 150 %, and 170 % of AMT) and at most time points. This reduction was more pronounced compared to SICI changes, which may suggest a stronger influence on spinal inhibition rather than intracortical inhibition (Säisänen et al., 2008).

Along with the GABAergic inhibitory circuit, the glutamatergic excitatory circuit is crucial for corticomotor plasticity. The balance between inhibition and excitation is essential for M1 function (Di Lazzaro et al., 2018). Changes in ICF generally reflect the facilitatory effects of glutamatergic NMDAR activity (Liepert et al., 1997; Ziemann et al., 1996). Our findings showed that beta, low gamma, and mid gamma tACS increased ICF, with 20 Hz and 60 Hz tACS showing effects immediately post-stimulation, while 40 Hz tACS effects emerged at 60 min. Similarly, recent studies have demonstrated the capacity of beta tACS to induce long-lasting plasticity in the M1 via NMDAR, resulting in diminished inhibitory transmission associated with mechanisms akin to LTP (Wischniewski et al., 2019; Tremblay et al., 2013). Though ICF increased with beta, low gamma, and mid gamma tACS, these were consistently paired with SP reductions, without a clear link to MEP amplitude. For example, after beta tACS at post 0, ICF increased, but

MEP amplitude decreased. Low gamma tACS increased ICF at post 60 with no MEP change, while mid gamma tACS increased both ICF and MEP at post 0. Thus, ICF modulation didn't directly relate to corticomotor excitability. Overall, mid gamma tACS uniquely increased corticomotor excitability, reduced inhibition (SP and SICI), and improved ICF.

Functional effects: Motor performance

Our findings revealed no significant effect of tACS at beta and gamma frequencies combined with motor training on motor performance. Previous studies have shown frequency-specific effects of tACS during motor tasks. For instance, 50 Hz tACS over the cerebellum during a serial reaction time task (SRTT) impaired performance compared to 1 Hz tACS (Giustiniani et al., 2021), and 40 Hz tACS over M1 slowed response times in sequence retrieval tasks (Giustiniani et al., 2019). Conversely, 20 Hz tACS over M1 and the supplementary motor area improved reaction times compared to 10 Hz tACS (Cappon et al., 2016). These studies suggest that the interaction between tACS and motor tasks, particularly those involving complex sensorimotor integration, may produce frequency-specific effects on performance. Additionally, Different brain regions, like M1 and the cerebellum, may also respond differently to tACS frequencies. Given the complex motor task in our study, involving visual, proprioceptive, and somatosensory integration, we hypothesized distinct effects for beta and gamma tACS. Beta oscillations typically decrease before and during voluntary movements (Engel and Fries, 2010), while gamma oscillations increase during complex motor tasks (Muthukumaraswamy, 2010). We expected beta tACS to impair, and gamma tACS to enhance, performance. However, no clear impact of tACS on motor performance was observed.

A trend of improved GPT performance was seen in all groups, including sham, likely due to training effects. However, reaction times immediately after stimulation were slower in the sham group (294 ± 103.9 ms) compared to beta tACS (253 ± 104.3 ms), low gamma tACS (237 ± 64.4 ms), mid gamma tACS (246 ± 45.5 ms), and high gamma tACS (246 ± 85.9 ms). Importantly, the oscillatory effects of tACS, such as beta and gamma entrainment, are likely limited to the duration of the stimulation (online effects). This suggests that any changes in motor performance related to the tACS online effect would only occur during its application, not afterwards, as participants engaged in motor training but their completion times across the seven trials were not recorded. Functionally relevant plastic changes in the cortical network can occur even with the training of a simple motor task (Classen et al., 1998). Motor practice has been demonstrated to augment corticomotor excitability while reducing SICI (Cirillo et al., 2011). Our study aimed to optimise plasticity in the targeted brain region and enhance the motor system's responsiveness to training by integrating tACS with motor training. This approach builds on previous findings suggesting that combining tACS with motor training can augment plastic changes, resulting in more pronounced and enduring effects (Bolognini et al., 2009). However, the lack of significant differences in motor performance across conditions suggests tACS at beta and gamma frequencies may not have the expected offline effects. One explanation could be the single-session design per frequency, with at least a 48-hour washout period. Previous studies indicate that multiple sessions of tES can improve hand dexterity (Rostami et al., 2020), highlighting the potential cumulative effects. Another reason could be the high baseline motor performance of our young, healthy participants, leaving little room for improvement (ceiling effect), consistent with findings that older adults show greater motor learning improvements after tACS (Fresnoza et al., 2020).

Regression analysis highlighted distinct predictors of motor outcomes following gamma tACS. At 60 min post mid gamma tACS, shorter SP emerged as a stronger predictor of faster reaction times compared to SICI. The standardised coefficient for SP was notably higher, indicating that SP exerted a greater influence on reaction time changes. This may

suggest that reduced inhibition, particularly spinal inhibition, reflected by shorter SP, is more critical in facilitating rapid motor responses than SICI under these conditions. Reductions in SP have been previously associated with improvements in muscle strength, force production (Hammond and Vallence, 2007; Kidgell et al., 2017; Matsugi, 2019), and faster reaction times (Paci et al., 2021).

Following high gamma tACS, MEP amplitudes at 60 min were the strongest predictor of GPT performance, with greater MEPs associated with faster task completion. This finding underscores the importance of corticospinal excitability in driving improvements in fine motor tasks. The comparatively higher standardised estimate for MEPs reinforces its dominant role over other variables in explaining motor performance changes.

These results collectively suggest that the predictive strength of neurophysiological measures varies by task type and stimulation condition, with SP and MEP amplitudes being key determinants of reaction time and fine motor performance, respectively. This task-dependent relationship highlights the complexity of motor control mechanisms modulated by gamma tACS.

However, given the limited sample size, these findings should be interpreted cautiously, and further studies are warranted to validate these predictors and their relative contributions to motor outcomes.

In this study, electrodes were placed bilaterally over M1 rather than on M1 and the contralateral supraorbital region (SOR) to minimize the risk of phosphenes, a known side effect of M1-SOR montages (Schutter, 2016; Schutter and Hortensius, 2010), which could compromise participant blinding (Rostami et al., 2023). This placement ensured stimulation targeted the motor cortex, maintaining participant blindness more effectively. While studies have noted functional connectivity between left and right M1 (Ruddy et al., 2017), this was not a focus as our task was unimanual, and interhemispheric M1-M1 interactions were not controlled. Furthermore, dual-site tACS over connected brain regions has been shown to enhance the synchronisation of oscillatory activity, which may improve connectivity and prolong effects (Fehér et al., 2022; Saturnino et al., 2017).

One potential limitation of our study was the use of EMG instead of EEG to measure MEPs, SP, SICI, and ICF. While TMS combined with EEG (TMS-EEG) allows for assessing immediate cortical responses and global network connectivity, it has been crucial in studying human M1 plasticity (Ferreri and Rossini, 2013). However, EEG has limitations in evaluating deep brain structures. Conversely, combining TMS with MRI enables the assessment of interconnected cortical and subcortical regions with a high spatial resolution during task performance, revealing behaviourally relevant interactions between brain regions (Esposito et al., 2022). Recent advancements integrating multiple neuroimaging modalities with TMS offer a more comprehensive understanding of brain plasticity and its implications for motor behaviour and Non Invasive Brain Stimulation interventions (Esposito et al., 2022). Additionally, the absence of a figure-eight coil typically preferred for sp and ppTMS protocols, may have reduced stimulation precision in this study. Lastly, measuring MEPs, SPs, SICI, and ICF from the ECRL may lack specificity for reaction time tasks that primarily involve hand flexor muscles, and using a task where extensor muscles are the prime movers could provide more targeted insights.

In conclusion, our study highlights the distinct effects of beta and gamma tACS on corticomotor excitability, and intracortical modulation. Beta and low gamma tACS consistently reduced SP, with more lasting effects at 20 Hz and 40 Hz, suggesting their potential for interventions in conditions like stroke and Huntington's disease where prolonged SP is common (Zeugin and Ionta, 2021; Kobayashi and Pascual-Leone, 2003). The reduction of SP across all gamma frequencies, along with the positive correlation between shorter SP and improved motor performance, further highlights the potential of gamma tACS, particularly in facilitating long-term motor recovery. Mid gamma tACS modulated both spTMS and ppTMS measurements, suggesting a unique capacity to induce both excitatory and inhibitory changes. The differentiation

between frequencies, where beta and low gamma had inhibitory effects and mid and high gamma showed excitatory potential, provides key insights for tailoring tACS protocols in motor rehabilitation.

CRediT authorship contribution statement

Mohamad Rostami: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Annemarie Lee:** Writing – review & editing, Validation, Supervision, Methodology. **Ashlyn K. Frazer:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Formal analysis, Data curation. **Yonas Akalu:** Writing – review & editing, Methodology, Data curation. **Ummatul Siddique:** Writing – review & editing, Investigation, Data curation. **Alan J. Pearce:** Writing – review & editing, Investigation, Conceptualization. **Jamie Tallent:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Dawson J. Kidgell:** Writing – review & editing, Validation, Supervision, Software, Project administration, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroscience.2025.01.016>.

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