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Transcranial temporal interference stimulation (tTIS) influences event-related alpha activity during mental rotation

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Abstract

Non-invasive brain stimulation techniques offer therapeutic potential for neurological and psychiatric disorders. However, current methods are often limited in their stimulation depth. The novel transcranial temporal interference stimulation (tTIS) aims to overcome this limitation by non-invasively targeting deeper brain regions. In this study, we aimed to evaluate the efficacy of tTIS in modulating alpha activity during a mental rotation task. The effects of tTIS were compared with transcranial alternating current stimulation (tACS) and a sham control. Participants were randomly assigned to a tTIS, tACS, or sham group. They performed alternating blocks of resting and mental rotation tasks before, during, and after stimulation. During the stimulation blocks, participants received 20 min of stimulation adjusted to their individual alpha frequency (IAF). We assessed shifts in resting state alpha power, event-related desynchronization (ERD) of alpha activity during mental rotation, as well as resulting improvements in behavioral performance. Our results indicate tTIS and tACS to be effective in modulating cortical alpha activity during mental rotation, leading to an increase in ERD from pre- to poststimulation as well as compared to sham stimulation. However, this increase in ERD was not correlated with enhanced mental rotation performance, and resting state alpha power remained unchanged. Our findings underscore the complex nature of tTIS and tACS efficacy, indicating that stimulation effects are more observable during active cognitive tasks, while their impacts are less pronounced on resting neuronal systems.

KEYWORDS

event-related desynchronization, mental rotation, non-invasive brain stimulation, temporal interference stimulation, transcranial alternating current stimulation

1 | INTRODUCTION

Transcranial electrical stimulation (tES) is being researched as a promising therapeutic intervention for a diverse range of neurological and psychiatric disorders (Cho et al., 2022; Yang et al., 2021), including depression (Alexander et al., 2019; Brunoni et al., 2013; Wang et al., 2022), anxiety (Stein et al., 2020), dyslexia (Marchesotti et al., 2020; Rufener & Zaehle, 2021), schizophrenia (Brunelin et al., 2022; Pinault, 2017), attention deficit hyperactivity disorder (ADHD) (Salehinejad et al., 2019, 2020), Alzheimer's disease (Pini et al., 2022; Rajji, 2019), and stroke rehabilitation (Khan et al., 2022; Solomons & Shanmugasundaram, 2019). This non-invasive method involves the application of weak electric currents through electrodes attached to the scalp, modulating neuronal activity in underlying cortical regions, leading to both behavioral and electrophysiological changes (Antal et al., 2014; Guleyupoglu et al., 2013; Khadka & Bikson, 2023; Paulus et al., 2016; Vosskuhl et al., 2018; Zaghi et al., 2010).

One variant of tES, transcranial alternating current stimulation (tACS), applies weak sinusoidal currents to interact with endogenous brain oscillations via neural entrainment (Abd Hamid et al., 2015; Herrmann et al., 2016; Herrmann & Strüber, 2017). Entrainment refers to the synchronization of endogenous oscillations to the externally applied tACS signal, modulating ongoing rhythmic brain activity (Haegens et al., 2011; Reato et al., 2013; Thut et al., 2011). This interaction induces neuronal changes during stimulation (online effects) and persists post-stimulation (offline effects) (Kasten et al., 2016; Veniero et al., 2015; Zaehle et al., 2010). Studies attribute these offline effects to changes in spike-timing-dependent plasticity (STDP) (Vossen et al., 2015, see Vogeti et al., 2022 for a discussion). This neuronal modulation enables tACS to affect a range of cognitive processes, such as working memory (Grover et al., 2022; Hoy et al., 2015; Pahor & Jaušovec, 2018; Reinhart & Nguyen, 2019), attention (Schuhmann et al., 2019), motor function (Wischnewski, Engelhardt, et al., 2019; Wischnewski, Schutter, & Nitsche, 2019), and speech perception (Rufener et al., 2016; Zoefel et al., 2018).

Despite the effectiveness of tACS at the cortical level, a significant limitation is its shallow stimulation depth. The electrical currents remain primarily superficial and quickly diminish in intensity when reaching deeper regions of the brain (Miranda et al., 2013; Opitz et al., 2016). Consequently, in the treatment of clinical conditions such as Parkinson's disease that arise from dysfunctions in deeper brain areas (Herrington et al., 2016; Limousin & Foltynie, 2019; Volkmann, 2004), invasively implanted electrodes remain the most viable approach for deep brain stimulation.

However, recent findings highlight the potential for a new method, which may be capable of non-invasive deep brain stimulation. Grossman et al. (2017) successfully demonstrated the feasibility of transcranial temporal interference stimulation (tTIS), showing that it could induce motor activity in rodents by stimulating cortical areas. This method simultaneously applies two high-frequency ($\geq 1\,\text{kHz}$) sinusoidal electric fields $\bar{E}_1$ and $\bar{E}_2$ with a frequency offset Δf to the brain. The superposition of both fields creates an interference which results in a low-frequency amplitude-modulated waveform at Δf, which is at the "envelope" or "beat" frequency (e.g., $\Delta f = 10\,\text{Hz}$, generated via $f_1 = 1000\,\text{Hz}$, $f_2 = f_1 + \Delta f = 1010\,\text{Hz}$). This envelope frequency is within the receptive frequency range of neurons and leads to entrainment of endogenous oscillations, causing neuronal modulation (Cao et al., 2020; Conta et al., 2022; Esmaeilpour et al., 2021; Mirzakhalili et al., 2020; Rampersad et al., 2019; Wang et al., 2023). A key aspect of tTIS is that due to an inherent low-pass property, neurons are unable to entrain to oscillations $\geq 1\,\text{kHz}$ (Hutcheon & Yarom, 2000). TTIS leverages this by intentionally setting its carrier frequency f_1 above this threshold to limit its entrainment effect only to the low-frequency amplitude-modulated waveform. A further advantage of tTIS is its high focality (compared to tACS), as the locus of stimulation is limited to the area of maximum interference (i.e., where both electric fields have the same intensity). The intensity of the amplitude-modulated waveform is strongest only within this specific area, minimizing co-stimulation of adjacent areas and thereby enhancing the precision of the stimulation (Conta et al., 2021; Khatoun et al., 2021; Terasawa et al., 2022). Simulations and modeling approaches allow for the guidance of this interference point toward any region in the brain, including subcortical areas (Song 2019; Lee, 2021; Stoupis and Samaras 2022; Terasawa et al., 2022; Conta et al., 2021). The enhanced penetration depth is further facilitated by the higher conductance values of tissues for electric currents in the kHz range, enabling the currents to reach deeper regions (Gabriel et al., 1996). Therefore, tTIS could lay the foundation for non-invasive deep brain stimulation, potentially enabling the treatment of neurological deficits that currently require invasive procedures like deep brain stimulation (DBS) (Grossman et al., 2018).

A comparable method of electrostimulation was proposed half a century ago and tested for its capabilities in electro-anesthesia (Brown, 1975; Sachkov et al., 1967). While this method dubbed as "electrical interferential current therapy" was later used as a means to stimulate and treat muscle tissues (Goats 1990; Beatti et al.

2011), Grossman et al. (2017) were among the first to demonstrate its efficacy in cortical stimulation as well. Computational modeling studies deliver promising results, suggesting that tTIS can indeed induce neuronal entrainment (Karimi et al., 2019; Lee, 2021; Su et al., 2021; Zhu et al., 2022). But the body of in vivo research on tTIS in humans remains sparse and presents conflicting findings. Among the few studies, Ma et al. (2021) demonstrated improved motor functions after tTIS, while Zhu et al. (2022) observed an increased functional connectivity in the motor cortex. However, other studies using magnetoencephalography (MEG) (Conta et al., 2022) or electroencephalography (EEG) (Iszak et al., 2023) found no effect of tTIS on posterior α-power, underscoring the need for further investigation. Consequently, our aim in this study was to gather empirical evidence on the stimulation effect of tTIS in an in vivo experiment in humans to provide a proof-of-concept.

In a recent study, we investigated the efficacy of amplitude-modulated waveforms, as used in tTIS, to cause neuronal activation. For this, we used induced retinal phosphenes as an indicator for stimulation efficacy (Thiele et al., 2021). Our results revealed that unlike tACS, amplitude-modulated waveforms failed to produce phosphenes even at intensities significantly higher than those required for tACS, which was also replicated in Iszak et al. (2023). These findings align with existing literature suggesting that amplitude-modulated waveforms necessitate greater stimulation intensities for effective neuronal activation compared to sinusoidal alternating currents, as used in tACS (Esmaeilpour et al., 2021; Rampersad et al., 2019). We concluded that although effects in the form of neuronal *activation* may not be achievable, the potential for neuronal *modulation* remains. Therefore, in the present study, we evaluated the efficacy of tTIS in humans by analyzing its capability for causing neuronal modulations.

For this, we induced and measured changes in cortical alpha activity after stimulation with tTIS. Studies on alpha oscillations generally refer many cognitive functions to alpha activity, including perception (Romei et al., 2012), intelligence (Doppelmayr et al., 2002), or top-down control (Sherman et al., 2016). The prevailing understanding of the role of alpha activity in cognition is that it directs the flow of information by gating task-irrelevant or distracting information, thereby allowing for more focused attention on task-relevant information (Foxe & Snyder, 2011; Klimesch et al., 2011). Consequently, an increase in alpha activity within a region is observed when there is active suppression of interfering information or processes. Conversely, a decrease in alpha activity is thought to facilitate information processing and cognitive performance (Foxe & Snyder, 2011; Haegens et al., 2011; Jensen

& Mazaheri, 2010; Rihs et al., 2009; Sauseng et al., 2005; Zumer et al., 2014). TACS studies can use this link to their advantage by modulating alpha activity to enhance information processing (Schutter & Wischnewski, 2016). Studies have validated this concept using Shepard's mental rotation task (Shepard & Metzler, 1971), with tACS in the alpha range significantly improving task performance compared to sham stimulation (Kasten et al., 2018; Kasten & Herrmann, 2017). Building on these findings, the objective of this study was to explore whether tTIS could produce a similar effect. Specifically, we aimed to increase alpha power using tTIS, with the goal of enhancing performance in a mental rotation task. To differentiate between true stimulation effects and effects due to time-on-task, we included a sham stimulation group as a control. Additionally, a tACS group was included as a benchmark of stimulation effects using this paradigm (Kasten et al., 2018; Kasten & Herrmann, 2017) allowing for a direct comparison of the stimulation efficacy of tTIS and tACS.

We quantified the stimulation effect by calculating event-related spectral perturbation (ERSP) (Makeig et al., 2004; Pfurtscheller & Aranibar, 1977; Pfurtscheller & Da Silva, 1999) in the alpha band (8–13 Hz). ERSP measures the change in spectral power, or oscillatory activity, triggered by an event, like the presentation of a visual stimulus. This measurement distinguishes between two phenomena: an increase in spectral power, known as event-related synchronization (ERS); and a decrease in spectral power, referred to as event-related desynchronization (ERD). Klimesch et al. (2007) argue that an ERD in the alpha band is associated with a release of inhibitory processes, allowing for subsequent neuronal activation and facilitation of information processing (see also Pfurtscheller, 1997). This hypothesis has been supported by studies using transcranial magnetic stimulation (TMS) (Klimesch et al., 2003) and more recently, by studies using tACS to increase ERD and improve performance in a mental rotation task (Kasten et al., 2018; Kasten & Herrmann, 2017). However, conversely, some studies not using brain stimulation techniques have instead reported improved performance with reduced ERD, postulating a neural efficiency hypothesis, which suggests that skilled individuals use fewer brain resources during task performance (Chen et al., 2013; Riečanský & Katina, 2010). Given our use of brain stimulation techniques, we hypothesize our results to be in line with those found in the studies of Kasten et al. (2018; 2017), expecting an ERD increase in tTIS and tACS groups compared to the sham group, as well as a corresponding improvement in mental rotation performance.

Numerous studies have demonstrated the neuronal modulation effect of tACS and its associated increase in alpha power (Berger et al., 2018; Kasten et al., 2016; Veniero et al., 2015; Zaehle et al., 2010). Considering that

a mental rotation task naturally leads to significant alpha modulations by suppressing alpha activity during task execution, this could potentially disrupt the stimulation's entrainment effect. To measure the stimulation effect without the confounding influence of a complex cognitive task, we additionally included resting blocks utilizing a simple vigilance task, a setup also utilized by other studies (Conta et al., 2022; Kasten et al., 2018; Kasten & Herrmann, 2017; Zaehle et al., 2010). We hypothesized a significantly stronger increase in resting state alpha power from pre- to poststimulation in the tTIS and tACS groups compared to the sham group.

2 | METHODS

2.1 | Participants

Given that no studies on the effects of tTIS on mental rotation have been conducted, we could only approximate the required sample size. We based our estimate on a previous study by Kasten and Herrmann (2017), which reported an effect size of $\eta^2 = 0.27$ for two groups (stimulation vs. sham). Using these parameters, we conducted a power analysis with G*Power (Ver. 3.1.9.7, Faul et al., 2007), setting an alpha error probability of 0.05 and a power of 0.95 for a t test between two independent means. This analysis suggested a required sample size of 16 participants per group. While we recognize that this is only an approximate solution, it provided a reasonable starting point for our research. In total, we recruited 67 participants who were randomly assigned to either the tTIS, tACS, or sham group. Of the 67 participants, 48 were eligible for data analysis. This was, on the one hand, due to technical issues (a coding error in the Matlab stimulation function) leading to the exclusion of nine individuals from the data analysis. Additionally, 10 participants were excluded due to the absence of a discernible peak in the alpha band (8–13 Hz) during the first block of the resting task, which was crucial to extract the individual alpha frequency (IAF) (see Electrical Stimulation) for subsequent stimulation. As a result, our analysis included data from 48 participants, divided into three stimulation conditions: tACS ($n=18$; 11 female, 7 male; mean age = 23.7, SD age = 4.52), tTIS ($n=16$; 10 female, 6 male; mean age = 21.8, SD age = 2.46), and sham ($n=14$; 11 female, 3 male; mean age = 22.9, SD age = 2.85).

Eligible participants for this study had to meet the following criteria: no history of epileptic seizures or psychiatric or neurological disorders, no metal or electric implants in their body, free of medication affecting the central nervous system, non-smoking, and normal or corrected-to-normal vision. Before the experiment, participants were informed about the experimental procedure and the potential adverse effects of electrostimulation and were required to give written informed consent. This study was approved by the local ethics committee of the University Clinic of Magdeburg and conducted in accordance with the guidelines of the Declaration of Helsinki.

2.2 | EEG

EEG data were acquired using passive Ag-AgCl electrodes (EasyCap, Brain Products, Gilching, Germany) positioned at Fz, Pz, P7, and P8 following the international 10–20 system. The reference electrode was placed on the tip of the participant's nose, while the ground electrode was positioned at AFz. In addition, electrodes were placed vertically (VEOG) and horizontally (HEOG) to the right eye and referenced to the nose electrode, to control for eye movements and eyeblinks. To increase electrode to skin conductivity, we applied a conductive paste (Abralyt 2000 abrasive electrolyte-gel, Brain Products, Gilching, Germany), ensuring impedances remained below 5 kΩ. Data were sampled at a rate of 1000 Hz using a BrainAmp DC amplifier (Brain Products, Gilching, Germany).

2.3 | Electrical stimulation

We used a battery-operated stimulator system (DC-Stimulator Plus, NeuroConn GmbH, Ilmenau, Germany) connected to a PC via a digital-to-analog converter (NI USB-6212, National Instruments, Austin, TX, USA) to generate and send the stimulation signal through a custom Matlab (version 2020a, Mathworks, Natick, USA) script. The stimulation was administered using surface conductive rubber electrodes (NeuroConn GmbH, Ilmenau, Germany) attached to the subject's head using an adhesive, electrically conductive paste (Ten20, D.O. Weaver, Aurora, CO, USA). Electrode impedances were kept below 5 kΩ to ensure optimal conductivity.

As studies suggest that stimulation in the alpha band is much more effective if the stimulation frequency matches the participants' IAF (Huang et al., 2021; Kasten et al., 2019; Schutter & Wischnewski, 2016), we determined the IAF based on the EEG data recorded in the first resting block at EEG electrode Pz and used it as the stimulation frequency.

For the tACS and sham groups, we used a parieto-occipital electrode montage consisting of a 5 × 7 cm electrode placed over Cz and a 4 × 4 cm electrode placed over Oz, with a stimulation intensity of 1 mA peak-to-peak. This montage has shown to increase power in the alpha range in posterior areas (Kasten et al., 2019)

and to improve performance in a mental rotation task (Kasten et al., 2018; Kasten & Herrmann, 2017). Using SimNIBS 3.0 (Thielscher et al., 2015), we simulated the electric field of this montage to confirm sufficient electric field strengths ($>0.2\,V/m$) were being delivered to the targeted posterior brain areas (see Figure 1c Left). Participants in the tACS group received 20 min of stimulation in total, split between the Rest$_{Stimulation}$ and Rotation$_{Stimulation}$ blocks, whereas those in the sham group received stimulation for only 30 s at the beginning of a stimulation block. Stimulation intensities were ramped up and down for 10 s at the beginning and end, respectively.

For tTIS, we used a custom SimNIBS script based on the formula proposed by Grossman et al. (2017) to determine a tTIS montage targeting approximately the same posterior regions as our tACS montage. Our simulations indicated that two pairs of two round electrodes (34 mm diameter) each allow for stimulation of posterior brain areas (see Figure 1c Right). The first pair of electrodes was positioned with one electrode on P4 and the other between I1 and O1. The second pair was arranged with one electrode on P3 and the other placed between I2 and O2. Since tTIS requires a higher stimulation intensity to achieve a comparable stimulation efficacy as tACS (Esmaeilpour et al., 2021), we used a stimulation intensity of 2 mA peak-to-peak for stimulation with tTIS. This is still a safe (Cassarà et al., 2022; Piao et al., 2022) and tolerable stimulation intensity, as tTIS uses high-frequency stimulation, to which somatosensory perception is less sensitive (Fertonani et al., 2015; Hsu et al., 2021; Zeng et al., 2019) and thus can be tolerated by participants without adverse effects. Anecdotally, many participants in our study reported not feeling tTIS at all. We selected a carrier frequency of 1 kHz balancing the need to maximize stimulation efficacy and minimizing unintended stimulation effects related to the carrier frequency (Esmaeilpour et al., 2021; Grossman et al., 2017; Rampersad et al., 2019). For the envelope frequency, we used the IAF. Using tTIS, the envelope is determined by the difference in stimulation frequencies of E_1 and E_2. This resulted in stimulation frequencies of $f_1 = 1000\,Hz$ and $f_2 = 1000\,Hz + IAF$. As was the case for tACS, the stimulation duration for tTIS was 20 min in total, split between the Rest$_{Stimulation}$ and Rotation$_{Stimulation}$ blocks, with the stimulation being ramped up at the beginning and down at the end over a period of 10 s.

2.4 | Data analysis

The acquired electrophysiological data were processed and analyzed using Matlab 2020a (The MathWorks Inc.,

Natick, MA, USA) in conjunction with the Fieldtrip toolbox (Oostenveld et al., 2011). Statistical analysis was performed using JASP version 0.17.1 (JASP Team, 2023) and Jamovi version 2.3 (The Jamovi project 2022).

To assess behavioral performance in the mental rotation task, measures of task accuracy, that is, correct answers and reaction time (RT), were analyzed. One-way analyses of variance (ANOVAs) were conducted on accuracy and RT of the Rotation$_{Baseline}$ Block, with the between-subject factor *Stimulation* (tTIS, tACS, sham) to identify potential baseline differences. Subsequently, group differences in task performance before, during, and after stimulation were examined using repeated measures ANOVAs (rmANOVAs). The rmANOVAs included the within-subject factor *Block* (Rotation$_{Baseline}$, Rotation$_{Stimulation}$, Rotation$_{Poststim}$) and the between-subject factor *Stimulation* (tTIS, tACS, sham). Further, to analyze the effects of stimulation on behavioral performance and adjust for individual baseline differences, we've calculated change measures ΔAccuracy (Accuracy in Rotation$_{Poststim}$ − Accuracy in Rotation$_{Baseline}$) and ΔRT (RT in Rotation$_{Poststim}$ − RT in Rotation$_{Baseline}$). This shows whether performance increased or decreased, comparing the pre- and poststimulation performance, to help us understand changes due to stimulation, regardless of initial performance levels. Change measures, ΔAccuracy and ΔRT, were then analyzed using separate ANOVAs using between-subject factor *Stimulation* (tTIS, tACS, sham).

In our ANOVAs, we report both partial eta squared (η_p^2), which shows the variance explained in our model but may overestimate effects, and generalized eta squared (η_G^2), which offers consistent effect sizes across studies but is less specific to our design. This approach balances detailed insights with broader comparability.

For EEG analysis of alpha activity, we focused on electrode Pz for the analysis similar to previous studies (Kasten et al., 2016; Kasten & Herrmann, 2017; Zaehle et al., 2010). To analyze changes in resting state alpha activity, data of all stimulation-free resting blocks (Rest$_{Baseline}$, Rest$_{Poststim\ 1}$, Rest$_{Poststim\ 2}$, Rest$_{Poststim\ 3}$) were analyzed. EEG data collected during the Rest$_{Stimulation}$ block could not be analyzed due to significant stimulation artifacts. Blocks were epoched into 1-second non-overlapping segments. Segments containing major artifacts (e.g., muscle artifacts) were removed after visual inspection via fieldtrips ft_rejectvisual function. Afterward, power in the IAF band (IAF $+/-1\,Hz$) was calculated by performing fast Fourier transforms (FFTs) using a Hanning window and 2-second zero padding. In addition, using the *fitting oscillations & one-over f* (FOOOF) method (Donoghue et al., 2020), data were split into periodic and aperiodic components to
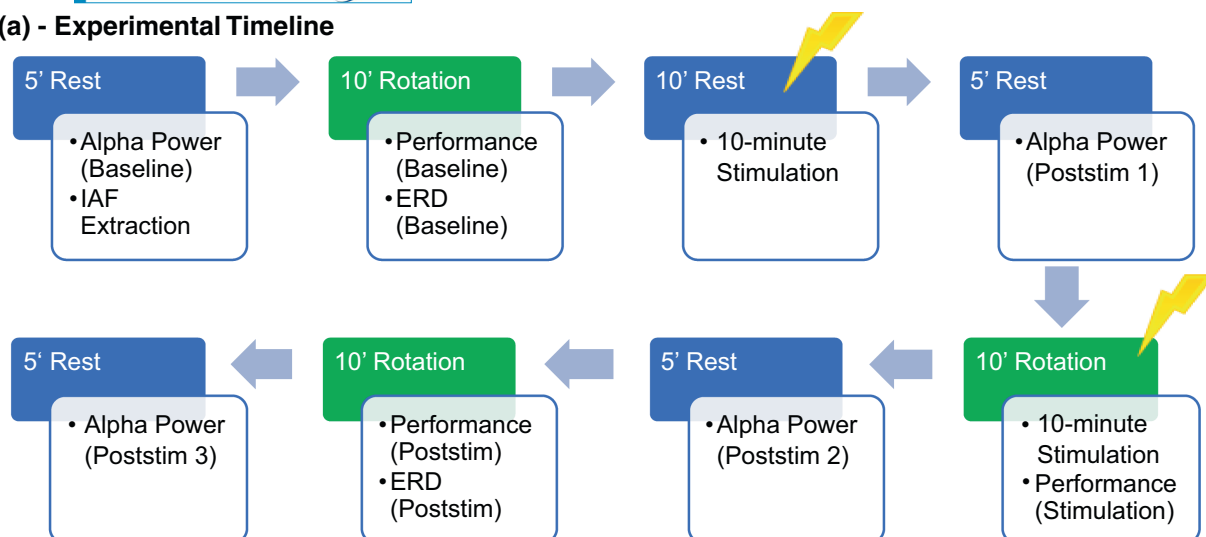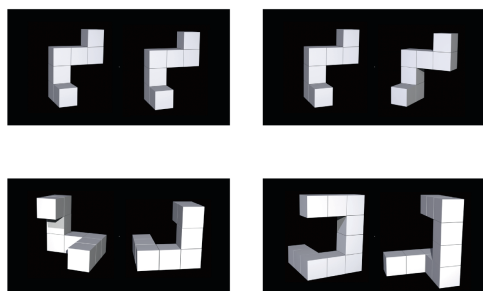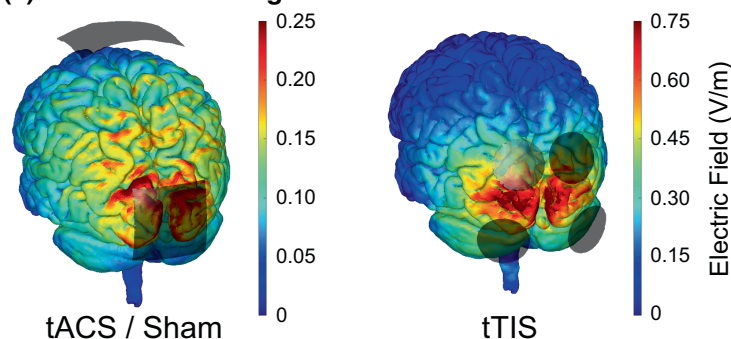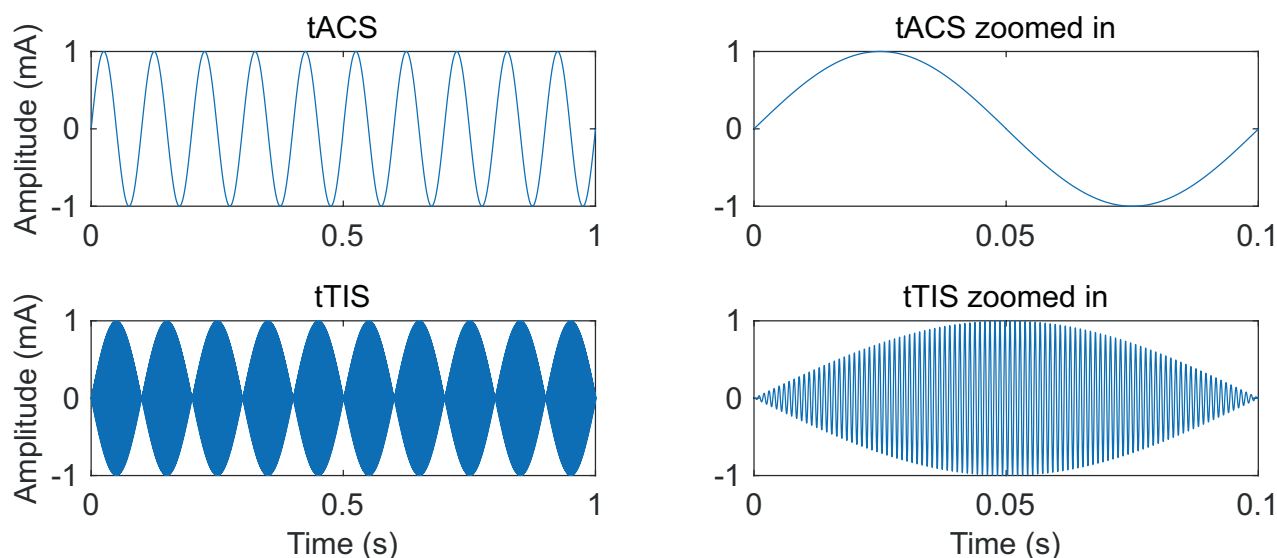
FIGURE 1 Experimental design. (a) Experimental Timeline. Chronological sequence of events during the experiment. Participants began with a resting block, followed by alternating blocks of mental rotation and resting blocks. Stimulation was administered during the second resting block and the second mental rotation block (indicated with a lightning symbol). (b) Example Task Set. Illustration of example task sets used in the study. Geometric figures, based on Shepard's mental rotation task, were presented to participants. They were required to determine whether the figures were mirrored or not. (c) Electrode Montages. Depending on the (random) group assignment, participants received either tACS, sham, or tTIS. (d) Stimulation Signal Exemplified. The figure demonstrates the stimulation signals used in the study. On the left side, 10 Hz tACS sine waves are compared to a tTIS amplitude-modulated waveform with a 10 Hz envelope frequency. The right side provides a zoomed-in view of the waveforms, highlighting the high-frequency carrier component of tTIS.

distinguish rhythmic activity from concurrent power-spectral 1/f modulations. For data analysis, only periodic components were analyzed, as these reflect frequency-specific rhythmic activity and are free of power changes affecting all frequency bands, which can be caused, for instance, by technical issues such as changes in electrode impedances. The periodic component in the IAF Band was then analyzed using an rmANOVA with the within-subject factor *Block* (Rest$_{Baseline}$, Rest$_{Poststim\ 1}$, Rest$_{Poststim\ 2}$, Rest$_{Poststim\ 3}$) and between-subject factor *Stimulation* (tTIS, tACS, sham) to detect changes in resting state alpha power. Additionally, we calculated a change measure, $\Delta Alpha_{Rest}$ (=Alpha power in Rest$_{Poststim3}$ − Alpha power in Rest$_{Baseline}$), and conducted an ANOVA with the between-subject factor *Stimulation* (tTIS, tACS, sham). This analysis focused specifically on increases in alpha activity, independent of individual alpha levels.

To capture changes in the IAF-band during the mental rotation task, ERSP was calculated for baseline and poststim mental rotation blocks. Again, data acquired during the stimulation block could not be analyzed due to the stimulation artifact. Data in the mental rotation blocks were segmented into 10-second epochs, spanning from 3 s before to 7 s after stimulus presentation. Epochs containing major artifacts were rejected after visual inspection using fieldtrips *ft_rejectvisual* function. Remaining epochs were analyzed using FFTs with a Hanning-tapered sliding window with a fixed length of 1 s moving in steps of 50 ms along each segment and 2-second zero padding (as in Kasten & Herrmann, 2017). Afterward, ERSP values were calculated as:

$$ERSP_t = \frac{R_t - A_t}{R_t} \times 100$$

In this formula, *R* is defined as the power during a reference period, specifically before the stimulus is presented. In our study, *R* was the power in the IAF band (IAF +/− 1 Hz) calculated from −2 to 0 s relative to stimulus onset. On the other hand, *A* is defined as the power of the frequency of interest during a test period, which is after the stimulus presentation. For *A*, we defined it as the power in the IAF band from 0 to 3 s following stimulus onset. Furthermore, *t* is defined as the trial number, as we calculated the ERSP on a trial-by-trial basis, based on prior studies (Kasten & Herrmann, 2017; Nakayashiki et al., 2014). To acquire an average ERSP for a block, ERSPs of all trials were averaged in each block for each subject. Resulting positive values indicate an ERD, reflecting a drop in power in the frequency band of interest at stimulus onset, whereas negative values indicate an ERS, reflecting an increase in power at stimulus onset. Based on previous

work (Kasten et al., 2018; Kasten & Herrmann, 2017), we expected to observe an ERD. To explore potential differences in baseline ERD between stimulation groups, the ERD in the baseline block was analyzed using an ANOVA with between-subject factor *Stimulation* (tTIS, tACS, sham). ERD values were then fed into an rmANOVA with within-subject factor *Block* (Rotation$_{Baseline}$, Rotation$_{Poststim}$) and between-subject factor *Stimulation* (tTIS, tACS, sham). Again, a change measure ΔERD (ERD in Rotation$_{Poststim}$ − ERD in Rotation$_{Baseline}$) was calculated and subjected to an ANOVA with between-subject factor *Stimulation* (tTIS, tACS, sham) to titrate changes in ERD from pre- to poststimulation.

Finally, we investigated if changes in task performance were correlated with changes in ERD values. To achieve this, we correlated ΔERD with $\Delta Accuracy$ and ΔRT. Prior to further analysis, we confirmed that all variables exhibited normal distribution based on the Shapiro–Wilk test (ΔERD: $W = 0.985$, $p = .796$; $\Delta Accuracy$: $W = 0.972$, $p = .31$; ΔRT: $W = 0.973$, $p = .337$). Subsequently, we performed Pearson's correlational analysis to examine the potential influence of changes in ERD on changes in task performance measures.

For rmANOVA results we report partial eta squared (η_p^2) to focus on effect size within our chosen design, as well as generalized eta squared (η_G^2) to facilitate comparing effect sizes across studies.

3 | RESULTS

3.1 | Experimental design

The experimental tasks were displayed on a Samsung SyncMaster SA450 placed at a distance of approximately 100 cm from the participants. For the experimental presentation, we utilized Psychtoolbox 3 (Kleiner et al., 2007) which was implemented using Matlab 2020a (The MathWorks Inc., Natick, MA, USA).

During the experiment, participants engaged in alternating resting blocks and mental rotation blocks (see Figure 1a). During the resting blocks (Rest$_{Baseline}$, Rest$_{Stimulation}$, Rest$_{Poststim\ 1}$, Rest$_{Poststim\ 2}$, Rest$_{Poststim\ 3}$), participants engaged in a simple vigilance task as employed by previous studies (Kasten & Herrmann, 2017; Zaehle et al., 2010). In this task, participants were shown a fixation cross at the center of the screen, which could rotate by 45 degrees for a duration of 500 ms. The onset of the rotation varied, occurring randomly between 30 and 40 s. Upon noticing the rotation, participants were required to press a response button within a 2-second window following the stimulus onset. This task served a dual purpose: maintaining the subjects' attention and facilitating the

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collection of clean EEG data. Resting blocks consisted of a 4-minute vigilance task followed by a 1-minute break. The exception was the $\text{Rest}_{\text{Stimulation}}$ block, whose duration was doubled to 10 min to accommodate the necessary 10-minute stimulation period.

In mental rotation blocks ($\text{Rotation}_{\text{Baseline}}$, $\text{Rotation}_{\text{Stimulation}}$, $\text{Rotation}_{\text{Poststim}}$), participants performed a Shepard's mental rotation task (Shepard & Metzler, 1971) which involved presenting two geometrical figures (see Figure 1b) that could be (1) rotated and/ or (2) mirrored in relation to each other. Participants were tasked with mentally rotating the figures to matching angles, in order to determine whether the figures were mirrored or not. The figures could be rotated relative to each other by 0°, 50°, 100°, or 150°, with larger rotation angles increasing the task's difficulty. Participants indicated their responses by pressing the "J" key for mirrored trials and the "n" key for non-mirrored trials. Each rotation block comprised 48 trials, with 12 trials per rotation angle. Half of the trials contained mirrored figures. A trial began with the presentation of a fixation cross in the middle of the screen for 3 s, followed by the presentation of the geometric figures which lasted for 7 s. Participants were instructed to answer as fast and accurately as possible. A mental rotation block consisted of a 4-minute task, followed by a 1-minute break, then another 4-minute task, and a concluding 1-minute break. The stimuli for the task were selected from a published open-source stimulus set (Ganis & Kievit, 2015). During the $\text{Rotation}_{\text{Stimulation}}$ block, participants received 10 min of stimulation.

At the beginning of the experiment, participants completed a questionnaire to assess exclusion criteria and were informed about the planned experimental procedure and tasks. Following this, the montages for electrical stimulation (see Figure 1c) and EEG were set up. Participants then engaged in the alternating blocks of resting and mental rotation tasks. Depending on the group, electrical stimulation of either tTIS, tACS, or sham (see Figure 1d) was administered in the second resting block and in the second rotation task block (see Figure 1a). At the end of the experiment, participants filled out a questionnaire about possible adverse effects of the stimulation (nausea, headache, sensations of pain/burning/itching/reddening at the stimulated area) (Brunoni et al., 2011). Afterward, participants were debriefed about the aim of this study and reimbursed for their time, either with course credit or monetarily.

3.2 | Resting-state alpha power

Analysis of resting-state alpha power revealed a main effect *Block* [$F(3,135) = 22.27$, $p < .001$, $\eta_p^2 = 0.331$, $\eta_G^2 = 0.051$]. Subsequent post-hoc t tests indicated an increase in alpha power throughout the experiment [$\text{Rest}_{\text{Baseline}}$ vs. $\text{Rest}_{\text{Poststim 1}}$, $\text{Rest}_{\text{Baseline}}$ vs. $\text{Rest}_{\text{Poststim 2}}$, $\text{Rest}_{\text{Baseline}}$ vs. $\text{Rest}_{\text{Poststim 3}}$, $\text{Rest}_{\text{Poststim 1}}$ vs. $\text{Rest}_{\text{Poststim 2}}$, $\text{Rest}_{\text{Poststim 1}}$ vs. $\text{Rest}_{\text{Poststim 3}}$: all $t(45) \geq 3.263$, $p_{\text{tukey}} \geq 0.011$], with the exception of the comparison between blocks $\text{Rest}_{\text{Poststim 2}}$ and $\text{Rest}_{\text{Poststim 3}}$ [$t(45) = 0.671$, $p_{\text{tukey}} = 0.908$] (see Figure 2a). Neither a significant main effect of *Stimulation* on resting state alpha power [$F(2,45) = 1.19$, $p = .314$, $\eta_p^2 = 0.050$, $\eta_G^2 = 0.045$] nor an interaction between *Stimulation* × *Block* [$F(6,135) = 0.931$, $p = .475$, $\eta_p^2 = 0.040$, $\eta_G^2 = 0.004$] were observed. The ANOVA on $\Delta\text{Alpha}_{\text{Rest}}$ did not reveal a main effect *Stimulation* [$F(2,45) = 1.15$, $p = .327$, $\eta_p^2 = 0.048$]. In sum, these findings indicate that alpha power did increase over the course of the experiment, but this increase did not differ between stimulation groups.

3.3 | Mental rotation accuracy

The analysis of baseline accuracy in the $\text{Rotation}_{\text{Baseline}}$ block did not reveal a statistically significant main effect for *Stimulation* [$F(2,45) = 1.38$, $p = .263$, $\eta_p^2 = 0.058$], indicating comparable baseline performance between groups. The rmANOVA across all mental rotation blocks (see Figure 2b) demonstrated a significant main effect *Block* [$F(2,90) = 7.14$, $p < .001$, $\eta_p^2 = 0.137$, $\eta_G^2 = 0.046$]. Post-hoc tests revealed this to be due to a statistically significant improvement in accuracy from $\text{Rotation}_{\text{Baseline}}$ to $\text{Rotation}_{\text{Poststim}}$ [$t(45) = 3.77$, $p_{\text{tukey}} = .001$] but no statistically significant difference in accuracy between $\text{Rotation}_{\text{Baseline}}$ and $\text{Rotation}_{\text{Stimulation}}$ [$t(45) = 1.96$, $p_{\text{tukey}} = .135$] or between $\text{Rotation}_{\text{Stimulation}}$ and $\text{Rotation}_{\text{Poststim}}$ blocks [$t(45) = 1.81$, $p_{\text{tukey}} = .176$]. We found no main effect *Stimulation* on accuracy [$F(2,45) = 1.27$, $p = .291$, $\eta_p^2 = 0.053$, $\eta_G^2 = 0.038$] nor a *Block* × *Stimulation* interaction [$F(4,90) = 1.34$, $p = .260$, $\eta_p^2 = 0.056$, $\eta_G^2 = 0.018$]. For descriptive results of the mental rotation accuracy, see Table 1. The analysis of $\Delta\text{Accuracy}$ did not reveal a main effect *Stimulation* [$F(2,45) = 0.653$, $p = .525$, $\eta_p^2 = 0.028$], indicating that all groups experienced comparable increases in task accuracy.

Notably, accuracy levels in the $\text{Rotation}_{\text{Poststim}}$ block approached the ceiling across all stimulation groups, offering minimal room for observable improvements attributable to stimulation. This suggests that the lack of significant stimulation effects could be attributed to ceiling effects, limiting the ability to draw conclusions about the impact of stimulation on task accuracy. Collectively, the findings suggest that while accuracy on the mental rotation task significantly increased throughout the experiment, the rate of this improvement did not vary across the different stimulation groups. Therefore, it is most plausible that the observed improvement stems from a training effect rather than the stimulation itself.
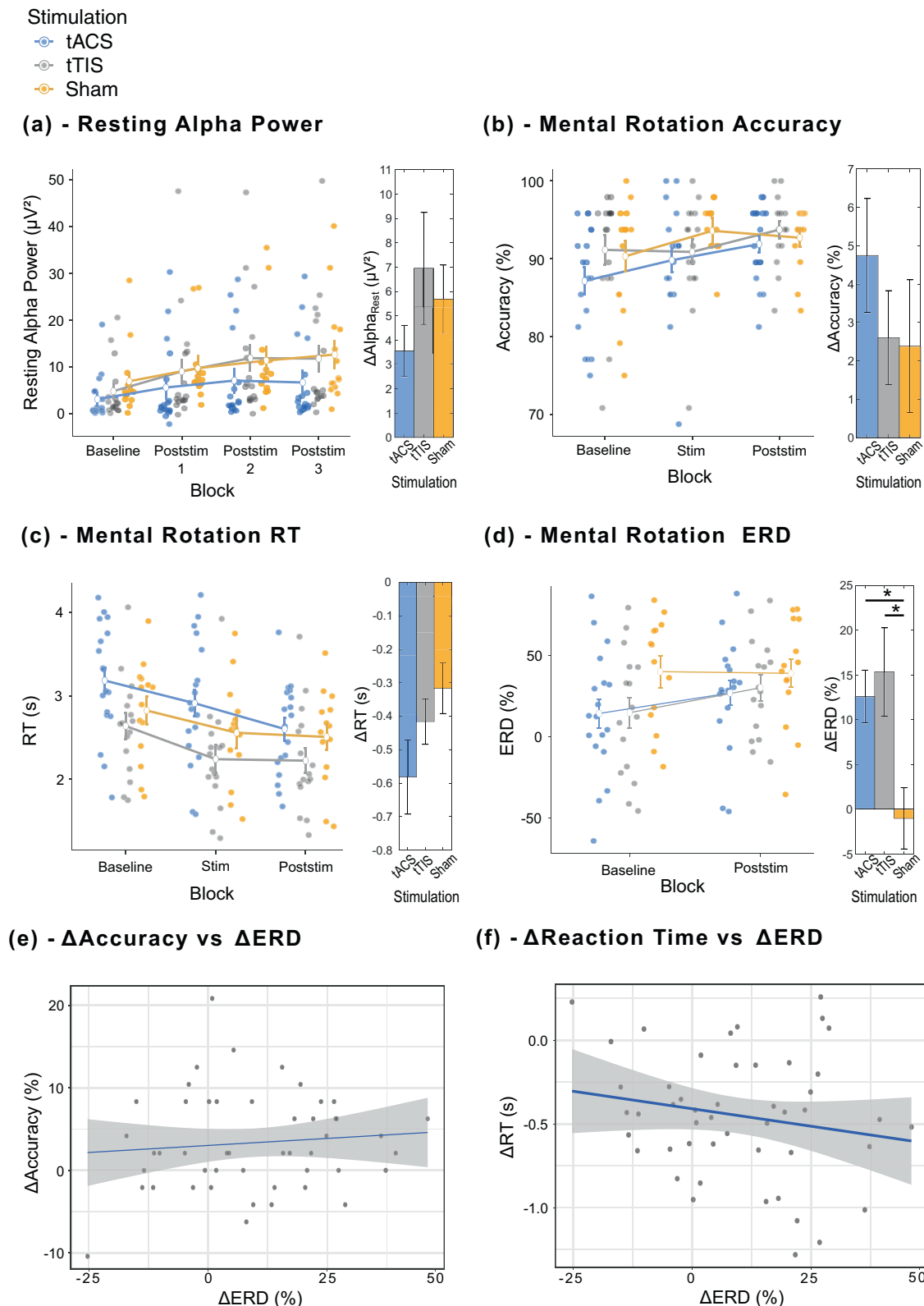
FIGURE 2 Overview of main results. (a) Mental rotation accuracy improves from the Baseline to the Poststim block, with no statistically significant differences observed between stimulation groups. (b) Similarly, reaction time in the mental rotation task shows improvement from the Baseline to the Poststim block. (c) In resting blocks, alpha power increases over the course of the experiment from Baseline to Poststim 2, where alpha activity plateaus and does not further increase in Poststim 3. No significant differences were observed between stimulation groups. (d) In the mental rotation task, ERD values increased from Baseline to Poststim blocks for tTIS and tACS groups, while remaining stable for the sham group. (e, f) Correlation analysis reveals no significant correlation between changes in ERD and changes in task accuracy (e) or RT (f).

TABLE 1 Descriptive statistics of behavioral data during mental rotation.

Stimulation	Block	Accuracy (%)				RT (s)			
		Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
tTIS	Baseline	91.1	7.70	70.8	97.9	2.64	0.59	1.75	4.06
	Stimulation	90.9	6.97	70.8	100.0	2.24	0.62	1.29	3.92
	Poststim	93.7	4.37	83.3	100.0	2.22	0.62	1.33	3.71
tACS	Baseline	87.2	7.15	75.0	95.8	3.18	0.68	1.78	4.18
	Stimulation	89.8	7.39	68.8	100.0	2.91	0.76	1.58	4.21
	Poststim	91.9	4.89	81.3	97.9	2.60	0.55	1.67	3.76
Sham	Baseline	90.3	7.43	75.0	100.0	2.82	0.60	1.79	3.89
	Stimulation	93.6	3.32	85.4	97.9	2.56	0.61	1.52	3.75
	Poststim	92.7	3.98	83.3	95.8	2.51	0.58	1.43	3.51

Abbreviations: Poststim, poststimulation, SD = standard deviation.

TABLE 2 Post-hoc analysis of the significant *Block × Stimulation* interaction effect on RT during mental rotation.

Block	Stimulation		Block	Stimulation	Mean diff.	SE	df	t	p_{tukey}
Baseline	tTIS	-	Stim	tTIS	0.40	0.08	45	5.27	<.001
Baseline	tTIS	-	Poststim	tTIS	0.42	0.09	45	4.59	0.001
Stim	tTIS	-	Poststim	tTIS	0.02	0.08	45	0.23	1.000
Baseline	tACS	-	Stim	tACS	0.27	0.07	45	3.82	0.011
Baseline	tACS	-	Poststim	tACS	0.58	0.09	45	6.80	<.001
Stim	tACS	-	Poststim	tACS	0.31	0.07	45	4.26	0.003
Baseline	Sham	-	Stim	Sham	0.27	0.08	45	3.31	0.044
Baseline	Sham	-	Poststim	Sham	0.32	0.10	45	3.27	0.048
Stim	Sham	-	Poststim	Sham	0.05	0.08	45	0.60	1.000

Abbreviations: df, degrees of freedom; mean diff., mean difference; Poststim, poststimulation; p_{tukey}, p-value with Tukey correction; SE, standard error; t, t value.

3.4 | Mental rotation reaction time

Analysis of baseline differences of RT in the Rotation$_{Baseline}$ block revealed a statistically significant main effect *Stimulation* [$F(2,45) = 3.31$, $p = .046$, $\eta_p^2 = 0.128$]. Post-hoc *t*tests indicated that reaction times in the tACS group were significantly slower than in the tTIS group [$t(45) = 2.52$, $p_{tukey} = .040$], but no differences were found between tTIS and sham [$t(45) = 0.81$, $p_{tukey} = .70$] or tACS and sham groups [$t(45) = 1.60$, $p_{tukey} = .255$]. Since this was RT in the Rotation$_{Baseline}$ block, where no stimulation had yet been administered, the observed differences are likely a random effect due to randomly assigning slower participants to the tACS group, faster subjects to the tTIS group, or a combination of both scenarios.

Comparing RT between all mental rotation blocks (see Figure 2c), we observed a main effect *Block* on RT [$F(2,90) = 45.67$, $p < .001$, $\eta_p^2 = 0.504$, $\eta_G^2 = 0.083$] with post-hoc tests indicating an improvement in RT from Rotation$_{Baseline}$ to Rotation$_{Stimulation}$ [$t(45) = 7.13$, $p_{tukey} < .001$], Rotation$_{Baseline}$ to Rotation$_{Poststim}$

[$t(45) = 8.33$, $p_{tukey} < .001$], and Rotation$_{Stimulation}$ to Rotation$_{Poststim}$ [$t(45) = 2.81$, $p_{tukey} = .020$]. Further, a main effect *Stimulation* was found [$F(2,45) = 3.32$, $p = .045$, $\eta_p^2 = 0.129$, $\eta_G^2 = 0.118$]. Post-hoc analysis revealed this to be due to the tACS group having significantly slower RTs compared to the tTIS group [$t(45) = 2.57$, $p_{tukey} = .035$], which is in line with the found baseline difference between these groups. No difference was found between tTIS and sham [$t(45) = 1.19$, $p_{tukey} = .464$] or tACS and sham groups [$t(45) = 1.26$, $p_{tukey} = .426$]. Additionally, we observed a significant *Block × Stimulation* interaction on RT [$F(4,90) = 2.56$, $p = .044$, $\eta_p^2 = 0.102$, $\eta_G^2 = 0.010$]. Post-hoc tests revealed that all stimulation groups exhibited improvements in RT from the Rotation$_{Baseline}$ to the Rotation$_{Stimulation}$ block, as well as from the Rotation$_{Baseline}$ to the Rotation$_{Poststim}$ block (see Table 2 for full post-hoc results). However, the tTIS and sham groups reached a plateau in RT improvement during the Rotation$_{Stimulation}$ block and did not show further improvement from Rotation$_{Stimulation}$ to Rotation$_{Poststim}$. In contrast, the tACS group displayed continued RT improvement even after stimulation, showing further enhancements in the

Rotation$_{Poststim}$ block. For descriptive results of the RT, see Table 1. The analysis of ΔRT did not reveal a main effect *Stimulation* [$F(2,45)=2.20$, p$=.123$, $\eta_p^2=0.089$], meaning no differential decrease in RT between stimulation groups could be observed.

Taken together, reaction times significantly improved over the course of the experiment, with RT in the tTIS and sham groups reaching a plateau during stimulation, while the tACS group continued to improve even post-stimulation. It is important to note that the tACS group initially had the slowest RT, thereby having the greatest potential for improvement. This suggests that the difference observed between the tACS group and both the tTIS and sham groups could be attributed to the latter groups reaching an RT ceiling earlier in the Rotation$_{Stimulation}$ block, whereas the tACS group may have required the duration of the Rotation$_{Poststim}$ block to catch up.

3.5 | Mental rotation ERD

The analysis of baseline differences in ERD between stimulation groups did not reveal significant differences [$F(2,45)=2.34$, $p=.108$, $\eta_p^2=0.094$]. The analysis of changes in ERD across mental rotation blocks revealed a main effect *Block* [$F(1,45)=16.15$, $p<.001$, $\eta_p^2=0.264$, $\eta_G^2=0.017$]. This was due to an increase in ERD from the Rotation$_{Baseline}$ to the Rotation$_{Poststim}$ block (see Figure 2d). This indicates a notable shift in task-relevant oscillatory activity. Though there was no statistically significant main effect *Stimulation* on ERD [$F(2,45)=1.41$, $p=.254$, $\eta_p^2=0.059$, $\eta_G^2=0.056$], we observed a significant *Stimulation × Block* interaction [$F(2,45)=4.80$, $p=.013$, $\eta_p^2=0.176$, $\eta_G^2=0.010$]. Post-hoc *t*tests revealed this interaction to be driven by an increase in ERD from the Rotation$_{Baseline}$ to the Rotation$_{Poststim}$ block for the

tTIS [$t(45)=3.99$, $p_{tukey}=.003$] and tACS [$t(45)=3.47$, $p_{tukey}=.014$] groups. In contrast, the sham group did not exhibit a change in ERD [$t(45)=0.251$, $p_{tukey}=1.00$] (see Figure 3). To further titrate if the increases in ERD differed between stimulation groups, the change measure ΔERD was analyzed. This revealed a significant difference among the stimulation groups [$F(2,45)=4.80$, $p=.013$, $\eta_p^2=0.176$], as was expected based on the significant interaction effect in the prior rmANOVA. Post-hoc analysis revealed that both the tTIS [$t(45)=2.91$, $p_{tukey}=.015$] and tACS [$t(45)=2.48$, $p_{tukey}=.043$] groups experienced significantly greater ERD increases compared to the sham group, with no notable difference between tTIS and tACS [$t(45)=0.52$, $p_{tukey}=.861$]. This suggests that both verum stimulations showed increased ERDs compared to sham, while no significant differences between verum stimulation conditions were evident.

Additionally, we performed a correlational analysis to determine if an increase in ERD values corresponded with an improvement in behavioral performance. This did not reveal a significant correlation between ΔAccuracy and ΔERD [$r(46)=.095$, $p=.259$] (see Figure 2e), nor between ΔRT and ΔERD [$r(46)=.021$, $p=.556$] (see Figure 2f). This leads to the conclusion that the change in ERD was not accompanied by a change in behavioral performance.

3.6 | Exploratory analyses

Analyzing only ERDs has the disadvantage that one key information is missing: As the ERD is itself a ratio between the power in a reference period (i.e., the time period before stimulus presentation) and test period (i.e., the time period after stimulus presentation), it remains unclear if a rise in ERD is driven by a rise in power in the reference period, a loss of power in the test period or a combination
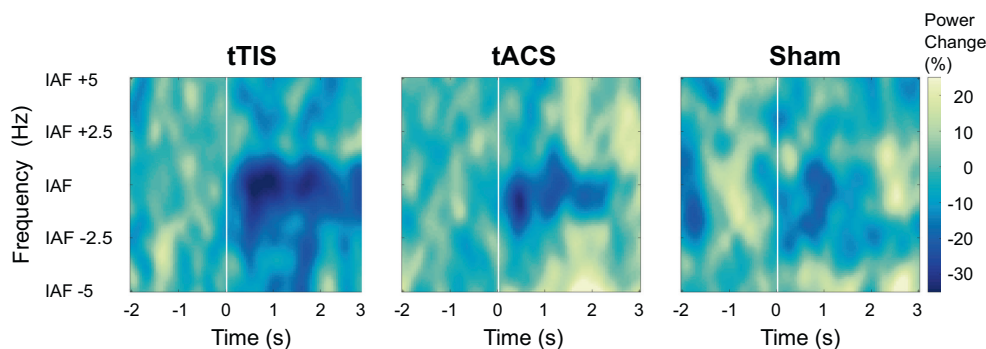

FIGURE 3 Time-Frequency Representations (TFRs) depicting changes in ERD: Contrasted is power at the IAF between the Baseline and the Poststim block. TFRs were aligned at the IAF and averaged across participants within each stimulation group. The reference period for relative baseline correction was defined as the range from −2 to 0 before stimulus onset, as indicated by the white bar. The verum stimulation groups (tTIS, tACS), exhibit a distinct decrease in power around the IAF in the poststim block compared to the baseline block, resulting in increased ERD. The sham group does not exhibit this change in ERD.

of both. To test this, alpha power (IAF+−1 Hz) was extracted for each trial for the reference period (2 to 0 s before stimulus presentation) and test period (0 to 3 s after stimulus presentation) and averaged for each block. Subsequently, we calculated changes in task alpha activity based on the Rotation$_{Baseline}$ and the Rotation$_{Poststim}$ blocks (ΔAlpha = Alpha$_{Poststim}$ − Alpha$_{Baseline}$) separately for both the reference period and the test period. Then, we performed correlational analyses between ΔERD and ΔAlpha separately for the reference and the test period. This revealed a trend for a positive correlation between ΔAlpha in the reference period with ΔERD [$r(46) = 0.279$, $p = .055$] (see Figure 4b), but no significant correlation between

ΔAlpha in the test period with ΔERD [$r(46) = -0.181$, $p = .217$] (see Figure 4a). This suggests that the changes in ERD are more likely due to power changes in the reference period than in the test period.

To further titrate stimulation effects on ΔAlpha$_{Rotation}$, we fed it into an rmANOVA with the factors *Period* (Reference, Test) and the between-subject factor *Stimulation* (tACS, tTIS, sham). This revealed a significant main effect *Period* [$F(1,45) = 6.10$, $p = .017$, $\eta_p^2 = 0.119$, $\eta_G^2 = 0.052$] which is based on a significantly higher alpha increase in the reference period than in the test period (see Figure 4c). However, neither the main effect *Stimulation* [$F(2,45) = 1.36$, $p = .267$, $\eta_p^2 = 0.057$, $\eta_G^2 = 0.035$] nor the
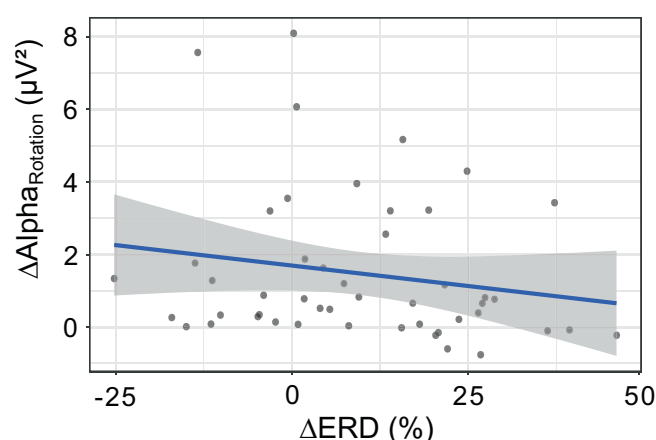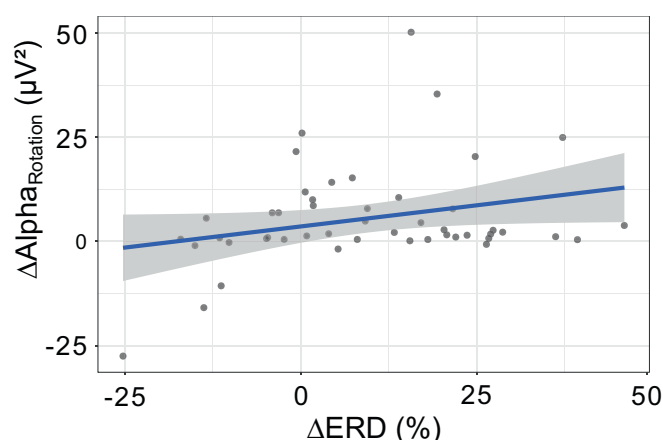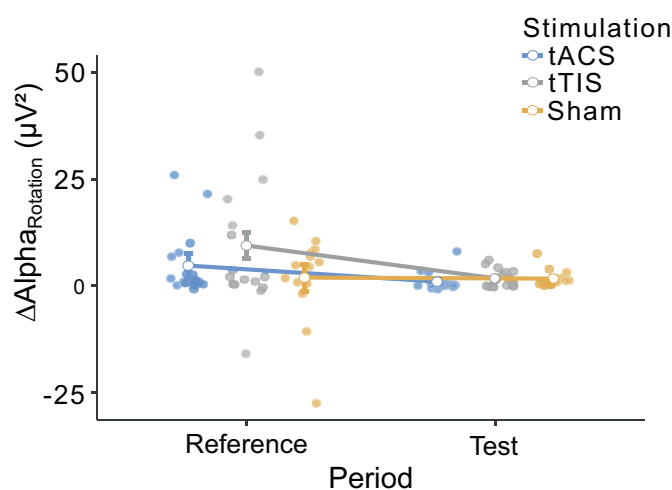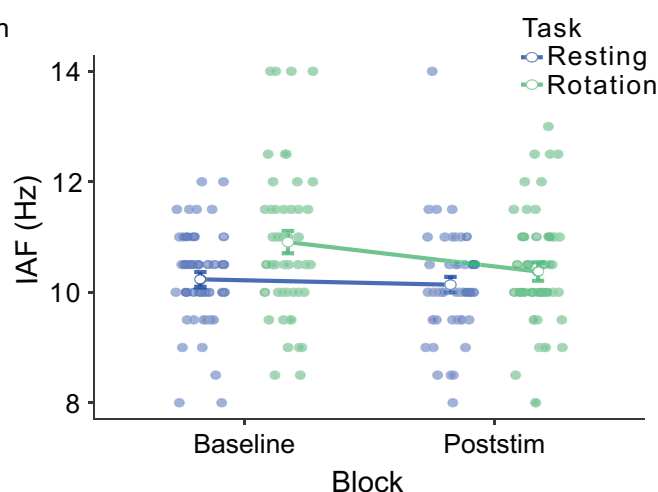

FIGURE 4 Overview of Exploratory Results. (a, b) Correlational analysis of ERD and alpha activity changes. Analysis focused on the difference in ERD (ΔERD) and alpha activity changes (ΔAlpha = Alpha$_{Poststim}$ − Alpha$_{Baseline}$) during (a) the test period (0 to 3 s after stimulus presentation) and (b) the reference period (−2 to 0 s before stimulus presentation). Results indicated no significant correlation between ΔAlpha in the test period and ΔERD, but a trending significance was observed between ΔAlpha in the reference period and ΔERD. (c) Analysis of alpha changes during mental rotation split between reference and test periods. This indicates that alpha increases were significantly higher in the reference period compared to the test period. There was no difference between stimulation groups. (d) Analysis of IAF across tasks and blocks. The IAF remained stable in resting blocks, whereas in rotation tasks, it was significantly elevated compared to resting blocks and showed a significant slowing from baseline to the poststimulation block.

interaction effect *Period × Stimulation* [$F(1,45) = 1.76$, $p = .183$, $\eta_p^2 = 0.073$, $\eta_G^2 = 0.031$] reached significance. This suggests that although the reference period appears to be the primary factor influencing ERD changes, attributing the stimulation effect exclusively to either the reference or test period is overly simplistic. It likely indicates a complex interplay between stimulation effects and alpha activity alterations across both periods.

Further, we examined the changes in IAF over the course of the experiment aiming to assess the stability of IAF and to post-hoc verify the accuracy of the stimulation frequency. IAFs were extracted from the baseline blocks (Rest$_{Baseline}$, Rotation$_{Baseline}$) and the poststimulation blocks (Rest$_{Poststim\ 3}$, Rotation$_{Poststim}$). Descriptive analysis revealed varying IAF frequencies [$M_{RestBaseline} = 10.2\ Hz$, $SD_{RestBaseline} = 0.91\ Hz$, $M_{RestPoststim} = 10.1\ Hz$, $SD_{RestPoststim} = 0.99\ Hz$, $M_{RotationBaseline} = 10.9\ Hz$, $SD_{RotationBaseline} = 1.38\ Hz$, $M_{RotationPoststim} = 10.4\ Hz$, $SD_{RotationPoststim} = 1.14\ Hz$]. To analyze these differences, we employed an rmANOVA with within-subject factors of *Block* (Baseline, Poststim) and *Task* (Resting, Rotation). This revealed a significant main effect of *Block* on IAF [$F(1,47) = 17.71$, $p < .001$, $\eta_p^2 = 0.274$, $\eta_G^2 = 0.019$], attributed to a slowing of IAF from baseline to poststim blocks (see Figure 4d). Additionally, a significant main effect of *Task* was observed [$F(1,47) = 18.08$, $p < .001$, $\eta_p^2 = 0.278$, $\eta_G^2 = 0.044$], indicating a faster IAF during the mental rotation task compared to the resting block. There was no significant interaction of *Block × Task* [$F(1,47) = 1.92$, $p = .172$, $\eta_p^2 = 0.039$, $\eta_G^2 = 0.008$].

4 | DISCUSSION

To this day, studies researching in vivo effects of tTIS are still sparse, which is true for murine models but especially in humans. Our current study contributes a proof-of-concept and new evidence for the neuromodulatory effect of tTIS in humans. We demonstrate an outlasting electrophysiological effect of tTIS in the form of an increase of ERD in the alpha range during a mental rotation task. Building on prior work that demonstrated the neuromodulatory potential of tACS on parieto-occipital alpha activity (Kasten et al., 2018; Kasten & Herrmann, 2017), we extend these findings to tTIS. Though contrary to our hypothesis, we observed no stimulation effect on mental rotation performance or resting alpha activity.

To further clarify the specific impact of the stimulation on ERD, we have conducted an additional analysis aimed at determining whether the stimulation effect could be attributed distinctly to alpha changes either in the reference or the test period or a combination of both (as discussed in Kasten & Herrmann, 2017). This analysis uncovered

a significantly larger change in alpha power during the reference period than in the test period. Though importantly, we observed no interaction effect between the period-specific changes in alpha activity and the stimulation applied, which stands in contrast to the distinct interaction effect we identified between ERD changes and the stimulation. This suggests that while the alterations in ERD are primarily attributable to the reference period, these alterations alone cannot fully account for the effects of the stimulation. One possible explanation may be that the stimulation effect does not originate from changes in either period individually, but rather from an interaction between changes occurring in both periods.

Even though no specific stimulation effect was evident in the reference period, our correlational analysis suggests that the significant increase in alpha activity during this period might be the primary influence on the overall ERD changes observed. This elevated alpha activity sets the stage for a more marked drop in alpha activity when the stimulus is presented, suggesting that the dynamics within the reference period play a crucial role in shaping the brain's oscillatory response to stimuli. Generally speaking, the ERD is well known to be associated with task performance (Haegens et al., 2011; Kasten & Herrmann, 2017; Klimesch et al., 2003; Neubauer et al., 1995). Klimesch et al. (2003) used repetitive transcranial magnetic stimulation (rTMS) to apply stimulation time-locked to the reference period, in turn boosting alpha activity to result in an increase in ERD and task performance. Though they did not measure ERD, studies by Zoefel et al. (2011) and Hanslmayr et al. (2005) used neurofeedback training to demonstrate a performance advantage of increased parieto-occipital alpha activity on a mental rotation task. The rationale is based on the presumption that alpha range oscillations play a crucial role in regulating information flow. Specifically, high alpha oscillations represent the natural resting or idling state of certain brain areas. However, when a region becomes relevant to a task, alpha oscillations decrease, signaling that the area is transitioning to a state of active information processing, with the change in alpha activity quantified by ERD.

However, in our study, we did not observe an improvement in behavioral performance despite the increased ERD. One potential explanation for this discrepancy is the presence of a behavioral ceiling effect. This is particularly evident in task accuracy, where all groups achieved near-perfect hit rates in the poststim block. This indicates that participants, including those in the sham group, performed the task with ease, leaving little room for the potential enhancing effect of the stimulation to manifest in improved performance. Thus, the comparable improvement in task performance across all three group rather indicates a significant learning effect,

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covering any specific effects of stimulation. To detect the specific benefits of stimulation on mental rotation, future studies should consider increasing the task difficulty. Interestingly, our findings, which indicate no significant effect of stimulation on reaction times, are consistent with existing literature that also did not observe a performance improvement following an increase in alpha activity (Klimesch et al., 2003).

A potential limitation in measuring stimulation effects during the mental rotation task is the experimental design, which may have led to an underestimation of the true stimulation effects. Specifically, our experimental design positioned the Rest$_{Poststim\ 2}$ Block in between the Rotation$_{Stimulation}$ and Rotation$_{Poststimulation}$ Blocks, resulting in a 5-minute delay between applied stimulation and measuring its effect on mental rotation. We cannot rule out that the stimulation effect is only strongest immediately after stimulation; thus, this delay could theoretically mean that the peak stimulation impact was not fully present during the Rotation$_{Poststimulation}$ block. Future studies should prioritize examining stimulation effects on mental rotation tasks by immediately following stimulation with a task to accurately assess the outcomes.

Contrary to our initial hypothesis, we did not observe any stimulation effect on alpha activity during the vigilance task. Though the alpha activity experienced an increase between resting blocks, the rate of this increase was consistent across all stimulation groups, indicating that the tTIS and tACS groups did not exhibit greater increases in alpha activity compared to the sham group. This suggests that the observed increase in alpha power over time might be attributed to an increase in mental fatigue throughout the experiment, which is known to increase alpha activity (Hsu & Wang, 2013; Käthner et al., 2014; Trejo et al., 2015), rather than a direct effect of the stimulation. In relation to tACS, our results did not align with the expected increase in alpha activity following parieto-occipital tACS, a well-documented effect in existing literature (Kasten et al., 2016; Kasten & Herrmann, 2017; Neuling et al., 2013; Vossen et al., 2015; Zaehle et al., 2010). Several reasons could account for the absence of observed stimulation effects. One consideration is the electrode montage's efficacy in targeting alpha oscillation generators. Despite using an established tACS montage and verifying field strengths at the region of interest (ROI) with SimNIBS simulations, the possibility of a non-optimal montage cannot be entirely dismissed. Furthermore, uncontrolled intra- and interindividual variations, including suboptimal brain states at the time of stimulation (Bergmann, 2018), could have influenced our results.

However, these potential explanations do not fully account for the discrepancy for a lack of stimulation effect on resting alpha activity and our observed stimulation effect on ERD or task-related alpha activity. It is possible that the alternation between resting and rotation blocks introduced significant interference, given the rotation task's requirement for constant adjustments in alpha activity. This hypothesis is supported by similar findings from Kasten and Herrmann (2017), who employed a similar design featuring alternating rest and task phases and were not able to demonstrate changes in resting alpha activity but were able to observe alterations in task-related alpha activity. Still, our study leaves open questions regarding the precise relationship between stimulation and alpha activity, underlining the necessity for further research to disentangle these complex dynamics.

While computational modeling studies have shown promising outcomes, indicating that tTIS can lead to neuronal entrainment (Karimi et al., 2019; Lee, 2021; Su et al., 2021; Zhu et al., 2022), some research highlights the potential for enhancing its effectiveness. These studies specifically propose enhancing tTIS by adopting an electrode configuration that utilizes multiple pairs of electrodes. This approach aims to increase the intensity at the target site and improve focality, potentially amplifying stimulation efficacy (Cao & Grover, 2019; Howell & McIntyre, 2021; Huang et al., 2020; Huang & Parra, 2019; Zhu et al., 2019). To validate these theoretical improvements, future research should investigate these strategies through in vivo studies.

A potential limitation of this study is the observed lack of robustness of the IAF. The aim of this study was to apply stimulation at each subject's IAF, as the Arnold tongue principle suggests that the efficacy of oscillatory stimulation can be enhanced when the target frequency and the applied frequency are as close as possible (Huang et al., 2021; Kasten et al., 2019; Schutter & Wischnewski, 2016). However, our exploratory analysis revealed that IAF fluctuates over the course of the experiment, a finding that aligns with other studies (Benwell et al., 2019; Stecher et al., 2017; Vossen et al., 2015). In this study, we estimated the IAF based on resting-state activity in the initial baseline resting block. Hence, the optimal stimulation frequency might have shifted by the time stimulation began. Furthermore, these studies suggest that IAF can vary depending on whether the neuronal system is at rest or under load. Accordingly, we might have misestimated the IAF for the mental rotation task, which led to the application of non-optimal stimulation frequencies. Future studies should consider (1) extracting the IAF immediately before the application of stimulation and (2) using a task that closely resembles the cognitive

demands of the target task, to reduce the mismatch between stimulation and target frequency and thus enhance stimulation efficacy. Additionally, adopting closed-loop methods (Karabanov et al., 2016) that adjust stimulation parameters in real-time based on the current brain state (Bergmann, 2018) could offer a more sophisticated approach to optimizing stimulation effectiveness.

In our study, we employed an inactive control stimulation (sham stimulation which was applied for only 30 seconds), which allowed us to differentiate between stimulation effects and effects not based on electrostimulation. Some other tTIS studies (Conta et al., 2022; Wessel et al., 2023) instead opt for an active control condition, where a high-frequency condition without a frequency offset ($\Delta f = f_1 - f_2 = 2000\,\text{Hz} - 2000\,\text{Hz} = 0\,\text{Hz}$) is utilized, allowing to measure stimulation effects specific to the amplitude modulation and potential confounding effects due to the high-frequency signal of the stimulation. Indeed, recent studies are debating a potential effect of the high-frequency signal in the form of a conduction block in off-target areas, which should be considered (Mirzakhalili et al., 2020; Wang et al., 2023), though this is mainly when using high-intensity, suprathreshold tTIS. However, an active control is not necessary to differentiate between entrainment effects and non-specific stimulation effects. We hypothesized that true entrainment would specifically boost power at the frequency of amplitude modulation (IAF), without affecting neighboring frequencies. In contrast, a non-specific stimulation effect would likely cause a broad increase across the frequency spectrum, raising overall power. Our results, as visualized in Figure 3, confirm that the power increase is indeed localized to the IAF and thus frequency-specific, as per the entrainment principle. Nonetheless, future studies should ideally incorporate both an active as well as an inactive control condition to measure and control stimulation-unrelated effects (sham stimulation), non-specific stimulation effects due to the high-frequency signal (active control) as well as true entrainment effects due to the amplitude modulation (verum stimulation).

5 | CONCLUSION

This study offers early electrophysiological evidence for tTIS's in vivo effect on humans. We observed increased ERD during a mental rotation task after both tTIS and tACS stimulation, but no increase in alpha power at rest. This indicates that manifestation of tTIS's effects requires an active task-engaged neuronal network. Although higher ERD has been associated with enhanced information processing in prior studies, we did not see this translate to improved performance in the mental rotation task, likely due to a ceiling effect. Future research should focus on identifying the best stimulation parameters and brain states for modulating behavior through tACS and tTIS.

CONFLICT OF INTEREST STATEMENT
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT
The data sets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

DECLARATION OF AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS
During the preparation of this work, the authors used ChatGPT-4 in order to improve readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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