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Individual differences in neuroanatomy and neurophysiology predict effects of transcranial alternating current stimulation

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Abstract

Background: Noninvasive transcranial electrical stimulation (tES) research has been plagued with inconsistent effects. Recent work has suggested neuroanatomical and neurophysiological variability may alter tES efficacy. However, direct evidence is limited.

Objective: We have previously replicated effects of transcranial alternating current stimulation (tACS) on improving multitasking ability in young adults. Here, we attempt to assess whether these stimulation parameters have comparable effects in older adults (aged 60–80 years), which is a population known to have greater variability in neuroanatomy and neurophysiology. It is hypothesized that this variability in neuroanatomy and neurophysiology will be predictive of tACS efficacy.

Methods: We conducted a pre-registered study where tACS was applied above the prefrontal cortex (between electrodes F3-F4) while participants were engaged in multitasking. Participants were randomized to receive either 6-Hz (theta) tACS for 26.67 minutes daily for three days (80 minutes total; Long Exposure Theta group), 6-Hz tACS for 5.33 minutes daily (16-minutes total; Short Exposure Theta group), or 1-Hz tACS for 26.67 minutes (80 minutes total; Control group). To account for neuroanatomy, magnetic resonance imaging data was used to form individualized models of the tACS-induced electric field (EF) within the brain. To account for neurophysiology, electroencephalography data was used to identify individual peak theta frequency.

Results: Results indicated that only in the Long Theta group, performance change was correlated with modeled EF and peak theta frequency. Together, modeled EF and peak theta frequency accounted for 54% – 65% of the variance in tACS-related performance improvements, which sustained for a month.

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Declaration of Interests: T.Z. is a scientific advisor for HUMM, which makes a neurostimulation device not used in the current study. A.G. is a scientific advisor for Neuroelectrics, which makes the neurostimulation device employed in the current study. As such, A.G. was not involved in data collection or analysis.

Conclusion: These results demonstrate the importance of individual differences in neuroanatomy and neurophysiology in tACS research and help account for inconsistent effects across studies.

Keywords

transcranial alternating current stimulation; computational modeling; theta band; multitasking

Introduction

The use of noninvasive neurostimulation techniques to modify cognitive function in basic research, clinical, and rehabilitation settings has grown exponentially over the past two decades. Two of the most commonly applied techniques are variants of transcranial electrical stimulation (tES): transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). Despite the broad use of tDCS, the effects on cognitive performance are inconsistent, leading to poor reliability in outcomes and limited reproducibility of findings (1–3). Although less research has employed tACS compared to tDCS, similar problems exist within the tACS literature (4–6). Together, the field of tES is disproportionately affected by publication bias and the ‘file-drawer problem’ of null findings (7). Despite this, the successes of tES in research settings (8, 9) have inspired widespread applications in uncontrolled do-it-yourself environments (10) and commercial products (11). Therefore, if tES were ever to become a reliable tool for scientists, a viable therapeutic for patients, or a safe consumer product, it is necessary to understand the source of this variability to control tES effects – both inside and outside of laboratory settings.

When implementing tES, one of the most important parameters to be determined is the intensity at which to stimulate. Generally, researchers select a stimulating current between 1mA and 2mA (12, 13), with very few exceptions. Intensity is set in this range because it is well tolerated, it can modulate motor cortex excitability, and alter cognitive function (13, 14). As such, it is common to select an intensity within this range (often arbitrarily) and provide that same intensity to every participant (i.e., one-size-fits-all). Unfortunately, there is a fundamental problem with this approach. Computational modeling of the induced electric fields (EF) from tES has indicated that differences in skull thickness, cerebrospinal fluid, subcutaneous fat, gyral pattern, and local tissue heterogeneities yield differences in resistivity that will differentially impede current flow to the cortex (15–17). The consequence of this anatomical variability can lead to 1.5 to 3-fold differences in the induced EF in cortex (18, 19) and these computational models have been validated (20–22). Thus, applying the same tES intensity to all participants will yield dramatically different EF magnitudes induced in the cortex across participants. This is critically important because tES effects are intensity specific, such that low intensities can have inhibitory effects, whereas higher intensities can be excitatory (23, 24). Yet, direct evidence that modeled EF in the brain can predict tES effects on cognitive function is needed.

When implementing tACS, another important parameter to select is the frequency of stimulation. It is thought that tACS modulates cognitive function via a combination of neural entrainment and resonance, which results in the recruitment of neurons into a local

multitasking to last for at least a month. Importantly, it was hypothesized that frontal theta tACS effects will be related to individual differences in modeled EF and baseline peak theta frequency.

To address these hypotheses, we conducted a pre-registered, double-blinded study, in which 60 older adults (aged 60 – 80 years) were randomized into 1 of 3 groups: Long Theta exposure, Short Theta exposure, and Control groups. The Long Theta group was considered our primary experimental group, whereas the Short Theta group was to assess effects of tACS duration, and the Control group was to assess frequency specificity. Here, we employed the same tACS paradigm and parameters (intensity, frequency, duration) as we previously used with young adults (32, 33), but did so on three consecutive days. This permits us to assess the potential for cumulative effects over time, which may be more effective than a single tES session (40). The entire experimental procedure was conducted over 6 days: 5 consecutive days with a 1-month follow-up. On the first day of the experiment, MRI data was collected, participants underwent a thresholding procedure for the single task components of the multitasking paradigm, and single task performance of the multitasking paradigm was assessed at the threshold level. For days 2–4 (tACS days 1–3), participants were engaged in the multitasking paradigm while tACS was applied with concurrent EEG. Participants then returned for a 1-day and a 1-month follow up visit to assess the sustainability of the potential tACS effects on multitasking performance. Results converged to show that high individual variability precluded a group effect of tACS on performance. More importantly, individual differences in neuroanatomy and neurophysiology predicted tACS effects, specifically in the Long Theta group.

Materials and methods

Registration.

This study was pre-registered on the Open Science Framework (<https://osf.io/zxbku>).

Participants.

Sixty older adults aged between 60 and 80 years were recruited for this study. All participants gave informed consent as approved by the University of California San Francisco Institutional Review Board. Participants were randomized into 1 of 3 groups: Long Theta (mean age = 66.5, SD = 5.0), Short Theta (mean age = 65.6, SD = 5.6), and Control (mean age = 67.9, SD = 5.4) groups (all $p > 0.40$). Both participants and researchers were blinded to the group assignments. Participants had no history of neurological or psychiatric disease (e.g. seizures), no history of brain tumors, were not taking medications that modulate brain excitability (e.g. neuroleptic, anti-depressant, stimulant, hypnotic), no amblyopia, strabismus, or color blindness, and did not have a pacemaker. To ensure participants were cognitively healthy and not different between groups, the average score on the Montreal Cognitive Assessment was compared. No significant differences between groups were observed (Long Theta: $M = 27.1$, $SD = 2.5$; Short Theta: $M = 26.6$, $SD = 3.2$; Control: $M = 26.1$, $SD = 2.7$; all $p > 0.19$). Additionally, all participants scored within 2 SD of standardized scores on 12 tests of neuropsychological and physical function: California Verbal Learning Test-II, animal fluency, digit symbol, Patient Health

Questionnaire, Delis-Kaplan Executive Functioning System Trails, Number and Number-Letter, Stroop, Measurement of Everyday Cognition, Ishihara Color Deficiency test, physical assessments (chair sitting and standing speed), hearing, and visual acuity. Participants received \$20 per hour for participation and a \$50 bonus for completion of the study.

Experimental procedure.

A multitasking paradigm, NeuroRacer (31), was conducted with concurrent tACS. Each participant was assessed on 5 consecutive days (Monday through Friday) and then again 1 month later (4th Monday after 1st session; see Figure 1). All experimental sessions were conducted at the same time of day for each participant. On the first day of the experiment, MRI data was collected, participants underwent a thresholding procedure for the single task components of the multitasking paradigm, and single task performance of the multitasking paradigm was assessed at the threshold level. Prior to the start of NeuroRacer on the second day, baseline performance on a sustained attention and working memory tasks were assessed (data not discussed here). For the rest of days 2–4 (tACS days 1–3), participants were engaged in the multitasking paradigm while tACS was applied with concurrent EEG. Participants then returned for a 1-day and a 1-month follow up visit to assess the sustainability of the potential tACS effects on multitasking, sustained attention, and working memory (only multitasking data assessed here). Participants sat 57 cm from a CRT monitor used for stimulus presentation during all computerized tasks. To achieve double blinding, the researcher who interacted with the participants was separated from another research who interacted with the computer that applied the tACS parameters and collected the EEG data. Additionally, participants were unaware of the stimulation condition they were assigned to, and a survey of side effects was collected to ensure a comparable perceptual experience (Supplementary Table 1).

Multitasking: NeuroRacer.

The NeuroRacer paradigm was developed using the OpenGL Utility Toolkit (GLUT; <http://www.opengl.org/resources/libraries/glut/>) to serve as a challenging multitasking video game that assesses visual (sign) discrimination while simultaneously performing visuomotor tracking (driving a car; see (31) for details). The visuomotor tracking task required participants to control a constantly moving car in the center of the road within yellow and red boundaries at a fixed speed as the road turned horizontally and moved up and down hills. The speed of the car was determined during the thresholding session performed on the first day of the study so that participants did not perform at ceiling or floor. Participants always drove the car with their left thumb on a joystick. The visual (sign) discrimination task required participants to press a button with their right thumb on the same controller as the driving joystick (Logitech controller, USA). Participants responded only to green circle targets and were instructed to ignore all other distractor non-targets (blue and red objects, pentagons and squares, and circles that were not green). The difficulty of the sign discrimination task was determined by a thresholding procedure performed on the first day. Participants were thresholded to maintain ~80% accuracy, which was achieved by manipulating the response time window. Responses outside the thresholded window were considered incorrect. When multitasking, signs appeared above the car and were randomly presented for 400 ms every 2, 2.5, or 3 seconds. Participants received feedback via a fixation

cross that was always present between the car and where the signs appeared. After each sign presentation, the color of the crosshair changed for 50 ms to green when correct or red when incorrect. Each NeuroRacer run lasted for 3 minutes and during each day of tACS, participants completed 16 runs. During each run, participants were randomly presented 24 targets and 48 non-targets. Participants were given a 30-minute break after the 8th run. During the 1-day follow-up (Friday) and 1-month follow-up, participants completed 8 NeuroRacer runs. This was done for two reasons: 1) only 8 runs of data from the tACS sessions were analyzed (see below) and 2) to minimize potential fatigue.

Transcranial alternating current stimulation.

The tACS was delivered through a Starstim device (Neuroelectronics, Spain) with Ag/AgCl electrodes (3.14 cm²) placed at bilateral prefrontal cortex (F3, F4) at 1 mA (baseline to peak; 2mA peak-to-peak) with a 180-degree phase offset. This montage and phase offset was used based on our prior research using this paradigm, which showed that a 180-degree (anti-phase) offset yielded greater changes in performance than 0-degree (in-phase) stimulation (32, 33). Current was ramped up and down over the course of 10 seconds at the beginning and end of stimulation, respectively. To avoid tACS artifact contamination of the EEG signal, half of the 16 multitasking runs on each day had stimulation for 20 seconds prior to beginning the task and EEG recording (runs 1,2,7–10,15,16). This enabled the tACS to ramp up (begin) and down (end) prior to task engagement and prior to EEG recording. For the remaining 8 runs (3–6, 11–14), the Long Theta group received 6 Hz tACS for the full 3-minute multitasking run duration, the Control group received 1 Hz tACS for 3-minutes, and the Short Theta group received 20 seconds of stimulation (ramp up/down) in line with the other 8 runs. Therefore, participants in the Long Theta and Control groups received 26.7 minutes of tACS each day for a total of 80 minutes across the experiment, while the Short Theta group received 5.3 minutes of tACS each day for a total of 16 minutes across the experiment. For control, 1 Hz was selected because we had no theoretical reason to believe it would affect performance. After each of the 16 runs, participants filled out a survey rating potential side effects on a scale from 0–10: headache, neck pain, scalp pain, tingling, itching, burning sensation, alertness, sleepiness, trouble concentrating, acute mood change, and phosphenes.

Magnetic resonance imaging.

All data was collected by a Siemens 3T MAGNETOM Trio MRI. High-resolution T1 (1.4 × 1.4 × 1.4 mm voxel size, FOV = 270 × 270 mm, TR = 2300 ms, TE = 2.75 ms, FA = 9°) and T2 (1.4 × 1.4 × 1.4 mm voxel size, FOV = 270 × 270 mm, TR = 4000 ms, TE = 207 ms, FA = 160°) scans were acquired.

Electrical field modeling.

Current modeling was performed using the Realistic vOlumetric Approach to Simulate Transcranial Electric Stimulation (ROAST, version 3.0) software to map the EF (V/m) distribution throughout the brain (41). ROAST is an open-source MATLAB-based, automated pipeline that applies Statistical Parametric Mapping software (SPM; <http://www.fil.ion.ucl.ac.uk/spm/software/spm12>) segmentation to the head and neck. Following segmentation (42), typical isotropic electrical conductivities are assigned to the tissues and

electrodes (white matter: 0.126 Siemens/meter (S/m), grey matter: 0.276 S/m, CSF: 1.65 S/m, bone: 0.01 S/m, skin: 0.465 S/m, air: 2.5e-14 S/m, gel: 0.3 S/m, and electrode: 5.9e7 S/m), typical boundary conditions are assigned to the surfaces, and simulation of current flow is achieved by solving the Laplace equation ($\nabla \cdot (\sigma \nabla V) = 0$), where V is potential and σ is conductivity. Current modeling was conducted on each T1 and T2 scan using a 6-compartment model including gray matter, white matter, CSF, skin, bone, and air with the default SPM12 segmentation settings. To facilitate comparisons between participants, the structural files and electrical field results were then fit to the MNI-152 standard head using the Linear Image Registration Tool (43, 44) within the FMRIB Software Library (FSL) toolbox (Analysis Group, FMRIB, Oxford, United Kingdom (45)).

Electroencephalography.

EEG data was collected with a Starstim 32-channel system (Neuroelectronics, Spain) with a sampling rate of 500 Hz. One electrode was used as an electrooculogram channel and the remaining 31 channels were distributed across the scalp (P8, T8, CP6, F8, AF4, C4, P4, AFz, Fp2, Fp1, Fpz, Fz, F4, Cz, PO8, PO3, O1, Oz, O2, PO4, Pz, PO7, FCz, P3, C3, F3, AF3, F7, CP5, T7, P7; 10–20 EEG system). The stimulating electrodes (F3, F4) also recorded EEG during the runs where no stimulation occurred after the initial 20 seconds. Although not discussed here, 60 seconds of resting EEG data was collected at three time points during each tACS session: 1) prior to the beginning of NeuroRacer, 2) during the 30-minute break before the 9th run of NeuroRacer, and 3) following the last NeuroRacer run (Tuesday-Thursday only).

Preprocessing was conducted with custom MATLAB (R2020a; MathWorks, Natick, MA) scripts in conjunction with the Fieldtrip toolbox (46). Raw EEG data were passed through a 0.5–50 Hz two-pass Butter-worth infinite impulse response (IIR) bandpass filter. EEG data was segmented into epochs beginning 1 second prior to and following sign onset and the data was demeaned. Channels with greater than 2 standard deviations away from the mean of all channels and epochs with greater than $\pm 500 \mu\text{V}$ activity were removed. Data was then referenced to the average EEG signal. Independent component analysis (ICA) was then used to remove components consistent with eye blinks and eye movement (mean components removed = 2.09, SD = 0.32). Trials were then rejected if data exceeded a $\pm 75 \mu\text{V}$ threshold. After rejection, an average of 464.03 (SD = 17.68) trials remained for analysis per day. Lastly, channels that were previously removed were reconstructed using interpolation from the nearest neighbor electrodes (average number of electrodes interpolated = 4.40, SD = 0.32). Data from both stimulus types were included for all cleaning and analyses (target and non-target signs).

EEG analysis.

To assess possible neuroplastic changes following tACS, measures of event-related spectral perturbations (ERSP) were computed for the 8 non-tACS runs (i.e., runs 1, 2, 7–10, 15, 16). This ensures tACS artifacts are not in the EEG data. Also, this balances the number of the trials analyzed between the tACS days and the follow-up days (where no tACS was applied and 8 runs were collected). Spectral decomposition was performed per channel using a multitapering approach with the Fieldtrip toolbox (46) for Matlab (MathWorks,

Inc., Natick, MA). Epochs of data were zero-padded (10-seconds) and the multitaper time-frequency spectrum was calculated by sliding a 500-ms window in 10-ms increments at each frequency (3 – 50 Hz, 1/4 Hz fractional bandwidth, rounded up). For ERSP analysis, frequencies were defined as theta (3–8 Hz), alpha (8–12 Hz), beta (12–30 Hz). Normalized (ERSP) power was defined as the log ratio of post-stimulus power relative to baseline power ($10 \cdot \log_{10}(\text{post-sign power} / \text{baseline power})$). The baseline was selected as –500 to –100 ms prior to sign onset. In line with our previous tACS+EEG research using this paradigm (32, 33), analyses focused on the average ERSP within the time period between 300 and 500 ms post stimulus onset in 2 regions of interest (ROIs): one frontal and one posterior. This time window and ROIs were selected based our prior research indicating maximal theta power during this task (31–33). The frontal ROI included electrodes AFz, AF3, AF4, Fz, F3, F4, while the posterior ROI included electrodes Pz, P3, P4, P7, P8, PO3, PO4, PO7, PO8, Oz, O1, and O2. To identify individual peak theta frequency, we used the irregular-resampling auto-spectral analysis (IRASA) method (47) on the frontal ROI from epoched data during the pre-tACS runs. This method distinguishes rhythmic activity from the arrhythmic 1/f power spectrum, which would otherwise bias estimates of oscillatory activity, then identifies the local maxima in the set frequency range. Although the lower theta band limit is typically set at 4 Hz, peak theta frequency was identified as the maximum peak between 3 Hz and 8 Hz to accommodate a few participants who exhibited a peak at 3.4 Hz, and to avoid edge effects in peak detection for those at the high and low ends of the range. This is in line with prior research assessing peak theta activity in healthy adults (48), clinical populations (49), and animals (50).

Behavioral analysis.

To determine the effects of tACS on multitasking performance, we evaluated perceptual discrimination performance during each multitasking run using a metric of discrimination performance (d'), which was estimated for each participant by comparing hit (correct responses to target signs) rates and false alarm (responses to non-targets) rates and calculated as $d' = Z(\text{hits}) - Z(\text{false alarms})$. Baseline performance for d' was obtained from the average of the first two runs of tACS Day 1 (Tuesday). Performance on all other runs where tACS was not applied during the task were averaged together to obtain a measure of multitasking performance post-tACS. By focusing on offline tACS effects, we control for three factors. First, this ensured that tACS artifacts did not contaminate the EEG signal. Second, it enabled a comparable assessment between performance and EEG data. Third, because the Short Theta group did not receive the same amount of stimulation as the Long Theta and Control groups, this approach controls for any potential acute effects of stimulation. Importantly, offline (or carry-over) effects of tES are a well-documented phenomena (51–55), which we have previously observed using this protocol (32, 33, 56).

Statistics.

Statistical analyses were conducted in JASP (57). To determine if significant differences exist between groups following tACS, change scores in multitasking performance and ERSP activity were calculated by subtracting baseline data (i.e., runs 1 and 2 tACS day 1). These change scores were submitted to an analysis of covariance (ANCOVA) with Day (tACS Day 1, tACS Day 2, tACS Day 3, 1-Day Follow-Up, 1-Month Follow-Up)

and Group (Long Theta, Short Theta, and Control) as factors. Age, sign difficulty, and drive difficulty served as covariates. Sign difficulty and drive difficulty were obtained from the NeuroRacer thresholding procedure following the MRI (for details of the sign/drive difficulty metrics, see (31)). A Greenhouse-Geisser correction was applied when appropriate. Post-hoc comparisons were assessed with t-tests. Pearson's r was used for all correlations. When modeled EF from each voxel in the brain was correlated with changes in performance, a cluster-based correction was applied using a Monte Carlo simulation to account for multiple comparisons. All other correlations were corrected with the false-discovery rate method (58). For the region of interest analysis, two masks were created (Supplementary Figure 1). The first mask was used to assess gray matter and was created from the MNI structural atlas for the frontal lobe (30% threshold). The second mask was used to assess white matter and was created from the Harvard-Oxford subcortical structural atlas for cerebral white matter within the frontal lobe (30% threshold). These masks were created using FSLeves (v0.34; (59)) and contained 16% overlap to capture anatomical variability. For statistical analyses, modeled EF data was normalized to MNI space and averaged together within these masks. Based on manual inspection of the individual EF maps, any modeled EF value above 0.25 V/m was not included in analysis as high EF values were only found in cerebrospinal fluid surrounding the gray matter.

Results

Compliance & Tolerability.

All participants tolerated tACS well. Side effects were measured by a post-stimulation questionnaire following each of the 16 runs of NeuroRacer, on each of the three stimulation days (summarized in Supplementary Table 1). Ratings from each of these 11 potential side effects were consistent between groups and reported to be mild or not noticeable. All participants completed the week-long training session and five participants failed to complete the 1-month follow up session (three in the Control group, two in the Short Theta group).

Multitasking Performance.

It was hypothesized that theta tACS while engaged in a multitasking challenge would improve multitasking performance on that challenge, and would also show sustained benefits for one month. To assess effects of tACS, d' from the sign discrimination task during multitasking was analyzed in line with our previous research with this paradigm (31–33). Performance during the first two runs on the first day of tACS were averaged together for a baseline metric and subtracted from the mean of all other runs per day. This was done because we are interested in the effects of tACS as a function of change from baseline. Of note, no baseline differences were observed between groups ($F_{2,54} = 1.31$, $p = 0.28$, $\eta_p^2 = 0.05$). Figure 2 summarizes the change in d' relative to this baseline for each group across the five experimental sessions. Differences between the groups were assessed via an analysis of covariance (ANCOVA) with Day (tACS Day 1, tACS Day 2, tACS Day 3, 1-Day Follow-Up, 1-Month Follow-Up) and Group (Long Theta, Short Theta, and Control) as factors. Age, sign difficulty, and drive difficulty served as covariates. Results showed no main effects for Day ($F_{2,8,140} = 1.70$, $p = 0.17$, $\eta_p^2 = 0.03$) or Group ($F_{2,49} = 1.59$, $p = 0.21$,

$\eta_p^2 = 0.06$). Additionally, no Day x Group interaction was observed ($F_{5,7,140} = 0.56$, $p = 0.75$, $\eta_p^2 = 0.02$). Of note, when only the Long Theta and Control groups were assessed, the main effect of Group trended towards significance ($F_{1,32} = 4.08$, $p = 0.052$, $\eta_p^2 = 0.11$), but not the main effect of Day ($F_{2,8,88} = 1.13$, $p = 0.34$, $\eta_p^2 = 0.03$) or the Day x Group interaction ($F_{2,8,88} = 0.55$, $p = 0.63$, $\eta_p^2 = 0.03$). Although the theta stimulation groups showed numerically greater performance improvements compared to the control group (Fig. 2A), high individual variability prevented the groups from exhibiting statistical differences (Fig. 2B).

Modeled Electric Field and Performance.

It was hypothesized that anatomical differences would yield variable modeled EF within the brain, which would positively correlate with theta-tACS effects on multitasking performance. To assess whether tACS effects were related to the amount of modeled EF within the brain, a linear regression was conducted between the modeled EF at each voxel and the change in d' from baseline to post-tACS Day 3. Results showed a positive correlation between the modeled EF and the change in d' only in the Long Theta group, such that participants who had the highest modeled EF in the brain exhibited the greatest improvement in multitasking performance (Fig. 3; cluster corrected). The distribution of r -values across the brain shows some voxels reached significance in the Short Theta and Control groups (Fig. 3B), but relatively few voxels in those groups remained significant after correcting for multiple comparisons (Fig. 3C). Moreover, no negative correlations remained after cluster correction (Fig. 3C). Supplementary Table 2 details the regions that exhibited a correlation between EF and change in performance for the Long Theta group. Similar results were observed between the modeled EF and the change in d' baseline to the 1-day follow-up and the 1-month follow-up (see Supplementary Table 2). These relationships between modeled EF and performance were largely absent in the Short Theta and Control groups (Fig. 3, middle and bottom rows). Interestingly, the majority of the brain regions exhibiting a correlation with performance were located within the frontal lobe and its associated white matter.

To explore the robustness of these results within the Long Theta group, two frontal lobe masks were created, one for gray and one for white matter (see Methods). Individual average EF within these masks were submitted to separate linear mixed models with Day (Post-tACS Day 3, 1-Day Follow-Up, 1-Month Follow-Up), and modeled EF as fixed effects variables, Subjects as random effects grouping factor, and change in d' as the dependent variable. Results showed a significant relationship between performance and modeled EF (EF_{gray} : $F_{1,18} = 15.51$, $p < 0.001$; EF_{white} : $F_{1,18} = 14.38$, $p = 0.001$), but not Day ($F_{2,38} = 0.81$, $p = 0.22$). To further characterize these effects, modeled EF within the gray and white matter frontal cortex masks were averaged together and correlated with change in performance. In line with the voxel-wise analysis, results exhibited a significant correlation post-tACS day 3 ($r = 0.53$, $p_{\text{fdr}} = 0.017$; Fig. 4, left panel), at the 1-day follow-up ($r = 0.58$, $p_{\text{fdr}} = 0.012$; Fig. 4 center panel) and 1-month follow-up ($r = 0.67$, $p_{\text{fdr}} = 0.003$; Fig. 4, right panel).

While it is intriguing that there is a relationship between modeled EF and change in performance only in the Long Theta group, it is unclear whether this relationship is driven

by the specific type of stimulation applied to that group, or if there is a group difference in anatomy that would give rise to systematic differences in the modeled EF. To address the potential for group differences in anatomy, voxel-based morphology (VBM) analyses were conducted using the Computational Anatomy Toolbox (CAT12, <http://dbm.neuro.uni-jena.de/cat>), which is an extension toolbox of SPM12. We then compared total intracranial volume, total gray matter, and total white matter between groups using unpaired t-tests. Results indicated no differences between groups in any of the anatomical markers of interest (all $p > 0.25$; Supplementary Table 3). Next, we assessed whether the modeled EF was different between groups across the whole brain and within the prefrontal cortex. No group differences in the modeled EF were observed (all $p > 0.14$; Supplementary Table 3). This supports visual inspection of the modeled EF between groups (Supplementary Figure 2), which would indicate the same brain regions were stimulated to a similar extent. Together, anatomical or modeled EF differences between groups are not likely responsible for the observed relationship between modeled EF and performance change selectively in the Long Theta group.

Electroencephalography and Performance.

Based on our prior research (32, 33), it was hypothesized that frontal oscillatory activity within the theta, alpha, and beta bands would positively correlate with theta-tACS related changes in multitasking performance. To address this, a linear mixed model was created for each of the frequency bands of interest (theta, alpha, beta) with change in oscillatory (ERSP) activity (tACS Day 3 minus baseline Day 1) from the Long Theta group and Day (Post-tACS Day 3, 1-Day Follow-Up, 1-Month Follow-Up) as fixed effects variables, Subjects as random effects grouping factor, and change in d' as the dependent variable. Results showed no relationship between change in performance and change in frontal oscillatory activity within any of the frequency bands (ERSP_{theta}: $F_{1,17.4} = 1.14$, $p = 0.30$; ERSP_{alpha}: $F_{1,9.0} = 0.31$, $p = 0.59$; ERSP_{beta}: $F_{1,16.5} = 1.25$, $p = 0.28$). Similarly, no relationship between change in performance and Day was observed (Day_{theta}: $F_{2,33.8} = 0.42$, $p = 0.66$; Day_{alpha}: $F_{2,35.4} = 0.38$, $p = 0.69$; Day_{beta}: $F_{2,36.1} = 0.06$, $p = 0.94$).

It was also hypothesized that posterior beta activity would be increased following theta tACS. To address this, posterior beta activity (ERSP) during the first two runs on tACS Day 1 were averaged together for a baseline metric and subtracted from the mean of all other runs per day. This was done because we are interested in the effects of tACS as a function of change from baseline. Beta activity was then submitted to an ANCOVA with Day (tACS Day 1, tACS Day 2, tACS Day 3, 1-Day Follow-Up, 1-Month Follow-Up), Group (Long Theta, Short Theta, and Control), and ROI (Frontal, Posterior) as factors. Age, sign difficulty, and drive difficulty served as covariates. Results exhibited a main effect of ROI ($F_{1,47} = 5.34$, $p = 0.025$, $\eta_p^2 = 0.10$) such that frontal electrodes exhibited greater desynchronization (more negative change). A Group x ROI was also observed ($F_{2,47} = 3.27$, $p = 0.047$, $\eta_p^2 = 0.12$). Supporting our a priori hypothesis, post-hoc analysis of the interaction indicated that the Long Theta group exhibited a greater increase in posterior beta activity compared to the Control group ($t_{37} = 2.06$, $p = 0.047$; Supplementary Fig. 3A). Although the Long Theta group exhibited a numerically larger increase in posterior beta activity compared to the Short Theta group, this difference was not significant ($t_{38} = 1.44$, p

= 0.16). No other main effects or interactions were observed for beta activity (Group: $F_{2,47} = 1.07$, $p = 0.35$, $\eta_p^2 = 0.04$; Day: $F_{3,3,152.8} = 0.68$, $p = 0.58$, $\eta_p^2 = 0.01$; Group x Day: $F_{6,5,152.8} = 0.58$, $p = 0.76$, $\eta_p^2 = 0.02$; Day x ROI: $F_{1,8,85.7} = 0.19$, $p = 0.81$, $\eta_p^2 = 0.00$; Group x Day x ROI: $F_{3,6,85.7} = 0.62$, $p = 0.63$, $\eta_p^2 = 0.03$).

Whereas the above analyses focused on our primary (and pre-registered) hypotheses, here we will conduct exploratory assessments on other measures of interest. Specifically, ERSP data from the theta and alpha bands were assessed similar to the pre-registered beta ERSP analysis above. Data from the first two runs on the first day of tACS were averaged together for a baseline metric and subtracted from the mean of all other runs per day. This was done because we are interested in the effects of tACS as a function of change from baseline.

Theta, alpha, and beta activity was then submitted to an ANCOVA with Day (tACS Day 1, tACS Day 2, tACS Day 3, 1-Day Follow-Up, 1-Month Follow-Up), Group (Long Theta, Short Theta, and Control), and ROI (Frontal, Posterior) as factors. Age, sign difficulty, and drive difficulty served as covariates.

Results from the theta ERSP analysis exhibited no main effects (Group: $F_{2,47} = 0.67$, $p = 0.52$, $\eta_p^2 = 0.03$; Day: $F_{2,8,130.9} = 0.22$, $p = 0.87$, $\eta_p^2 = 0.01$; ROI: $F_{1,47} = 0.02$, $p = 0.88$, $\eta_p^2 = 0.00$) or interactions (Group x Day: $F_{5,6,130.9} = 0.76$, $p = 0.59$, $\eta_p^2 = 0.03$; Group x ROI: $F_{2,47} = 0.50$, $p = 0.61$, $\eta_p^2 = 0.02$; Day x ROI: $F_{2,7,127.2} = 1.18$, $p = 0.32$, $\eta_p^2 = 0.02$; Group x Day x ROI: $F_{5,4,127.2} = 0.73$, $p = 0.61$, $\eta_p^2 = 0.03$). Although there was no Group main effect or interaction, it is interesting to note that the Long Theta group exhibited numerically greater increases in theta activity compared to the Control group, and to a lesser extent, greater than the Short Theta group (Supplementary Fig. 4).

Results from the alpha ERSP analysis exhibited a main effect of ROI ($F_{1,47} = 4.69$, $p = 0.035$, $\eta_p^2 = 0.09$) such that posterior electrodes exhibited a greater decrease. A Group x ROI was also observed ($F_{2,47} = 3.52$, $p = 0.038$, $\eta_p^2 = 0.13$). Interestingly, our previous research in young adults exhibited a trend toward a significant increase in frontal alpha. Here, we show a similar trend toward a significant increase in frontal alpha in the Long Theta group compared to the Short Theta ($t_{38} = 1.88$, $p = 0.068$) and Control groups ($t_{37} = 1.78$, $p = 0.068$; Supplementary Fig. 3B). No other main effects or interactions were observed for alpha activity (Group: $F_{2,47} = 2.75$, $p = 0.07$, $\eta_p^2 = 0.11$; Day: $F_{3,5,164.9} = 0.30$, $p = 0.86$, $\eta_p^2 = 0.01$; Group x Day: $F_{7,0,164.9} = 0.48$, $p = 0.85$, $\eta_p^2 = 0.02$; Day x ROI: $F_{2,9,136.0} = 1.47$, $p = 0.23$, $\eta_p^2 = 0.03$; Group x Day x ROI: $F_{5,8,136.0} = 1.30$, $p = 0.26$, $\eta_p^2 = 0.05$).

Baseline Electroencephalography and Performance.

Given that previous research has suggested a relationship between intrinsic oscillatory frequencies and effects of tACS (28–30), we assessed whether the peak baseline theta frequency correlated with tACS-related changes in multitasking performance. Visual inspection of the data revealed an inverted-U relationship between peak theta frequency at baseline and change in performance pre- to post-tACS in the Long Theta group (Fig.5A). We then computed the absolute distance of each individual's peak theta frequency from 6 Hz at baseline for subsequent analysis. A linear mixed model was used with Peak Theta Distance in the Long Theta group and Day (Post-tACS Day 3, 1-Day Follow-Up, 1-Month

Follow-Up), as fixed effects variables, Subjects as random effects grouping factor, and change in d' as the dependent variable. Results showed a significant relationship between change in performance and Peak Theta Distance ($F_{1,18} = 26.21$, $p < 0.001$), but not with Day ($F_{2,36} = 0.18$, $p = 0.83$). To better characterize this effect, a Pearson correlation was conducted between the change in d' (tACS Day 3 minus baseline) and the absolute peak theta distance from 6 Hz. Results show that only the Long Theta group exhibited a relationship between peak baseline theta frequency deviation and multitasking performance (Fig. 5B). Specifically, in the Long Theta group, participants with a peak theta frequency at baseline that was close to the stimulation frequency (6 Hz) were the ones who exhibited the greatest improvements in multitasking performance post-tACS (Day 3; $r = -0.68$, $p_{\text{fdr}} = 0.004$). Of note, the peak theta frequency distance from 6 Hz in the Long Theta group also correlated with the change in performance at the 1-Day Follow-up ($r = -0.66$, $p_{\text{fdr}} = 0.006$) as well as the 1-Month Follow-Up ($r = -0.69$, $p_{\text{fdr}} = 0.004$).

Modeled Electric Field and Electroencephalography.

Due to the relationship between modeled EF and performance in the Long Theta group, we conducted an exploratory analysis to assess whether the modeled EF was also associated with changes in frontal oscillatory activity. To assess this, individual average EF within frontal lobe gray and white matter masks were separately submitted to a linear mixed model with Day (Post-tACS Day 3, 1-Day Follow-Up, 1-Month Follow-Up) and modeled EF as fixed effects variables, Subjects as random effects grouping factor, and change in frontal ERSF activity as the dependent variable. Results indicated no relationship between modeled EF and change in theta ($EF_{\text{gray}}: F_{1,17.2} = 0.15$, $p = 0.70$; $EF_{\text{white}}: F_{1,17.3} = 0.17$, $p = 0.69$; Day: $F_{2,36.4} = 3.35$, $p = 0.046$), alpha ($EF_{\text{gray}}: F_{1,17.9} = 0.03$, $p = 0.87$; $EF_{\text{white}}: F_{1,18.0} = 0.00$, $p = 0.95$; Day: $F_{2,37.0} = 1.08$, $p = 0.35$), or beta activity ($EF_{\text{gray}}: F_{1,17.8} = 0.25$, $p = 0.63$; $EF_{\text{white}}: F_{1,18.0} = 1.04$, $p = 0.32$; Day: $F_{2,37.1} = 0.73$, $p = 0.49$).

Multiple Regression Models.

Given that both modeled EF and baseline theta frequency were related to subsequent tACS-related changes in multitasking performance, we sought to characterize their combined explanatory value. To achieve this, an exploratory analysis was conducted using a multiple linear regression with change in d' as the dependent variable and modeled EF (averaged over frontal lobe gray and white matter masks) as well as peak theta frequency distance from 6 Hz as the two predictor variables. Results showed in the Long Theta group that modeled EF and peak theta frequency were able to account for 54% of the variance in Day 3 multitasking improvements, 54% of the 1-Day Follow-Up variance, and 65% of the 1-Month Follow-Up variance (Table 1). These models were unable to significantly predict changes in performance in the Short Theta or Control groups. Although the models are influenced most by peak theta deviation, these combined models account for more variance (54%–65%) compared to using peak theta (44%–48%) or modeled EF (28%–45%) alone.

Discussion

Here we assessed the effects of 6 Hz (theta) tACS above the prefrontal cortex in older adults that were engaged in a multitasking paradigm over 3 consecutive days. Based on

our prior research (32, 33), it was hypothesized that frontal theta tACS would improve multitasking ability, increase posterior beta activity, changes in performance would correlate with changes in spectral band EEG power, and all of which would sustain for a month. Although we observed an increase in posterior beta activity, effects on performance and correlations between performance and spectral power were not observed at the group level, due in part to high inter-individual variability. It was also hypothesized that variable tACS effects would be related to individual differences in neuroanatomy that would yield different tACS-induced EF in the brain. Results supported this hypothesis, such that participants in the Long Theta stimulation group exhibited the greatest improvements in multitasking when the modeled EF was largest, particularly in the frontal lobe. This relationship was not observed in the Short Theta or Control groups. Additionally, it was hypothesized that variable tACS effects would also be related to individual differences in the baseline peak theta frequency. This too was observed, such that the Long Theta group, and not the Short Theta or Control groups, exhibited the greatest improvements in multitasking when their baseline peak theta frequency was closest to the stimulation frequency (6 Hz; i.e., smallest deviation). Together, modeled EF and baseline frequency were able to jointly account for 54%–65% of the variance in tACS effects, which includes both acute and sustained effects 1 day and 1 month later.

The field of tES research has been burdened with variable effects that create replicability problems (1, 2, 4, 5, 7, 28). Even meta-analyses of tES effects do not always agree (3, 7). Fortunately, we have been able to replicate our own research in healthy young adults (32, 33). However, the current results demonstrated that applying tACS parameters from young adult research does not yield comparable effects in healthy older adults. Knowing that age-related neuronal atrophy lowers the modeled EF in the brain (35, 36) and that individual differences in neuroanatomy results in 1.5 to 3-fold differences in the tES-induced EF in the brain (18, 19), we hypothesized that theta tACS would yield the greatest benefits in older adults who received the highest EF in the brain. Although we were able to support this hypothesis, we did not observe the hypothesized improvement at the group level similar to our previous research with younger adults. These results support prior research indicating tES effects are lessened in older, compared to younger, adults (37). Importantly, we show that these weakened effects in the aging population are due in part to a lower current density reaching the brain. Given that low intensities can have inhibitory effects, whereas higher intensities can be excitatory (23, 24), age-related differences in the EF may also explain research indicating opposing effects of tES, where younger adults exhibit excitatory effects and older adults exhibit inhibitory effects (60). Thus, future tES studies in populations with known cortical atrophy should not necessarily use a tES intensity that is intended for young adults. Ideally, individualized models should be used to tailor the tES intensity for each participant. If MRI-based modeling is not feasible, and if tES intensity cannot be determined from a comparable population, researchers may consider using an intensity from a young adult study and then apply a correction to estimate the average decrease in EF due to aging-based changes in neuroanatomy. This correction may be calculated through the use of freely available modeling software (41, 61, 62) and age-appropriate brain templates (63).

Despite the computational modeling work indicating the importance of individual neuroanatomy on tES current density, few studies attempt to account for this potential

confound, likely due to the cost and time required to collect MRI data. In the few studies that have collected both MRI and tDCS data, larger modeled EF was associated with greater tDCS-related improvements in working memory (64) as well as a decrease in GABA and an increase in functional connectivity (65). Additionally, increased tDCS efficacy has been related to cortical volume (66) and cortical thickness (67), which are known to affect the modeled EF in the brain. Here, we extend these findings from tDCS research to the application of tACS, such that participants with a higher modeled EF experience the greatest multitasking benefits. These results support recent work demonstrating that the modeled EF from tACS correlates with greater changes in neural activity in humans (68, 69) and non-human primates (70). Here, we build on this research to show modeled EF correlates with behavioral performance, despite not observing the hypothesized relationship between performance and neural activity. Additional research will be required to understand the complex interplay between non-invasive neurostimulation, the affects it has on neural activity, and subsequent consequences for behavior.

It is interesting to note that both tDCS and tACS effects appear to be similarly sensitive to the amount of current that reaches the brain. Each of these methodologies is thought to operate via distinct mechanisms of action, which could result in differing responses to different EF intensities. Whereas tDCS is thought to elicit increases or decreases in cortical excitability (71), tACS is thought to modulate cognitive function via a combination of neural entrainment and resonance (25, 26) (also see (72)). As such, it cannot be assumed that both tDCS and tACS effects would exhibit similar responses to EF intensity. This relationship is particularly important in light of criticism that the tES-induced EF is insufficient to modulate neural activity and subsequent behavior, regardless of whether tDCS or tACS (3, 73) is applied. Demonstrating that the effects of tDCS and tACS are both related to amount of modeled EF within the brain provides some evidence that these tES tools are indeed able to modulate neural activity and associated behavior. Yet, the precise EF magnitude necessary for desired effects is still to be determined.

In addition to the importance of neuroanatomy in predicting the effects of tES, intrinsic oscillatory activity is thought to play a role in tACS effects. While some studies have applied stimulation at individual peak frequencies (74, 75), it was only assumed that this would yield optimal effects. Only more recently has evidence shown that tACS effects may be most prominent when the stimulation is close to the individual's endogenous peak oscillatory activity (28–30). Here, we provide supporting evidence indicating that tACS effects were greatest in participants who had baseline peak theta frequencies closest to the 6 Hz stimulation frequency. Individual peak theta frequency deviation accounted for 44% - 48% of the variance of tACS effects on performance. On the other hand, individual differences in the average modeled EF across the entire prefrontal cortex accounted for 28% - 45% of the variance. When combined, modeled EF and peak theta frequency deviation accounted for 54% - 65% of the variance in tACS-induced performance change. Although neuroanatomy and neurophysiology were able to account for a reasonable amount of variance, it is possible that this could be improved by characterizing measures of neuroanatomical and neurophysiological connectivity. The strength of both structural and functional connectivity between brain regions has been associated with individual differences in response to tES (76, 77). Thus, future tES research would greatly benefit from accounting for multiples

differences in neuroanatomy and neurophysiology that lower inter-individual variability in tES effects. This tailoring of stimulation parameters to the individual participant would increase the reliability of desired tES effects and facilitate replicability of studies across labs. This is also important knowledge given the rise in commercial and off-label use of these tools.

Yet, neuroanatomy and neurophysiology are only two of many possible sources of tES variability. Baseline performance ability has been shown to affect stimulation efficacy, where participants with low initial performance exhibited improvements but those with high initial performance did not benefit from stimulation (78, 79). Another potential source of variability is psychological state. For example, tES outcomes have been shown to be affected by anxiety (80) as well as task (or reward) motivation (81). Furthermore, expectation for how stimulation may affect performance is rarely characterized, yet the placebo effect is well known to affect performance outcomes and may be exacerbated with tES (82). Related to psychological state, the cognitive state of a participant can also affect tES outcomes. Cognitive state refers to the physiological mechanisms that are engaged during stimulation. Numerous studies have shown effects of stimulation are contingent on cognitive state, with greater tES effects when the stimulation is applied on-line (i.e., when participants are engaged in the task; (83). Finally, it is worth mentioning that cortical excitability likely plays an important role in tES effects. Genetic factors that alter dopamine concentrations are known to modulate tES outcomes (84, 85), as well as the presence of a brain-derived neurotrophic factor polymorphism (86). Additionally, changes in cortical excitability due hormonal fluctuations from the menstrual cycle can influence tES (87). Although the effects of circadian rhythms on tES have not been assessed to our knowledge, circadian-based changes in cortical excitability contribute to transcranial magnetic stimulation responsivity (88), which may extend to tES.

Other factors have been suggested to account for differences in tES effects, but these are not likely unique sources of variability. For example, tES has yielded different effects based on gender (89, 90). However, computational modeling has demonstrated that neuroanatomical differences between genders can result in systematic differences in the amount of tES current that reaches the cortex (91). Additionally, hormonal differences, as mentioned above, could also account for differential tES effects based on gender. Therefore, it is unlikely that gender influences tES variability beyond differences in neuroanatomy and cortical excitability (e.g., neurotransmitter concentrations / hormonal levels). Aging also plays a factor in tES outcomes (92, 93). Yet, aging is associated with neuroanatomical differences (34) as well as changes in cortical excitability (94) and baseline cognitive performance differences (95) that all can contribute to variable tES effects. It is unclear whether age can account for additional tES variability once these factors are controlled. Similar to aging, brain health is thought to play a role in tES outcomes based on disease progression (96) or extent of brain injury (97). However, it is likely that this variability can also be attributed to individual differences in neuroanatomy. Additional research will be needed to ascertain whether gender, aging, or brain health contributes to tES variability beyond the known factors listed above: neuroanatomy, neurophysiology, baseline ability, psychological state, cognitive state, and cortical excitability.

In the current study, we accounted for several sources of tACS variability. First, we were able to account for baseline differences by thresholding participants prior to task engagement to equate for these individual differences. Next, cognitive state was controlled by engaging all participants in the same task during stimulation. Finally, cortical excitability was partially controlled by collecting data from participants at the same time of day, every day. Therefore, it is possible that our ability to account for such a high amount of variability via modeled EF and peak theta frequency stems from the fact that we controlled for other sources of variability. Unfortunately, cortical excitability was not well controlled. Individual differences in circadian rhythms lead to individual differences in the optimal time of day (98). Because we did not test for the optimal time to test each individual, this could theoretically affect baseline performance and subsequent tACS effects. Additionally, we did not collect magnetic resonance spectroscopy, menstrual cycle / postmenopausal hormonal levels, or genetic data to help inform cortical excitability differences between participants. Beyond the limitations in controlling for cortical excitability, we did not assess psychological state, such as baseline anxiety, motivation, or expectation of effects, or measures of structural/functional connectivity. Future research will aim to characterize these additional factors to better account for individual differences that may elicit more consistent tACS outcomes.

Despite our attempts to control for multiple sources of inter-subject variability, we did not observe group-level effects on performance similar to our previous tACS research in young adults. We attribute this to the fact that we attempted to apply tACS parameters used in healthy young adults in an older adult population who is known to have greater variability in neuroanatomy and neurophysiology. Although we demonstrated a relationship between tACS effects and neuroanatomy and neurophysiology, it could be argued that a group effect may still have been observed with a larger sample size (99). Indeed, increased population variability can contribute to lowered statistical power (100). Nonetheless, we were able to increase posterior beta activity at the group level, similar to our previous young adult studies (32, 33). It remains unclear why frontal theta tACS alters posterior beta activity, but this result is robust enough to observe it across three experiments (twice in young adults, once in older adults).

Finally, it is worth noting that EF modeling can only provide an approximation of the true electric field within the brain. Results from EF modeling can vary depending on the accuracy of the head model segmentation, the number of compartments included in the model (e.g., skin, skull, CSF, gray matter, white matter, air), and the conductivities assigned to the compartments (17, 19, 20, 22). Although it is commonplace to use the same conductivity values across individuals for each tissue type, it is known that variability exists in the conductivity between individuals (101, 102). Therefore, EF models might be improved by estimating individual conductivity values using magnetic resonance electrical impedance tomography (MREIT; 108, 109). However, additional research is needed to characterize the extent to which MREIT may benefit EF models, and whether such a technique may be used to further reduce variability of tES effects.

To summarize, there are many factors that contribute to tES outcomes. Yet, many of these factors are unaccounted for in tES research, which leads to large individual variability that

lowers the replicability of these studies. Here, we provide important evidence that tACS effects are related to the individual's neuroanatomy and neurophysiology. Specifically, the greatest effects of tACS on performance were observed in individuals with the highest modeled EF within the prefrontal cortex, as well as in those who exhibited an intrinsic peak theta frequency that was closest to the stimulation frequency. Future tACS research may benefit from using individual computational models to determine stimulation intensity as well as measuring intrinsic oscillatory activity to determine an individualized stimulation frequency. In addition, controlling for baseline ability, cortical excitability, as well as psychological and cognitive states will lower individual variability in tACS effects and increase replicability across studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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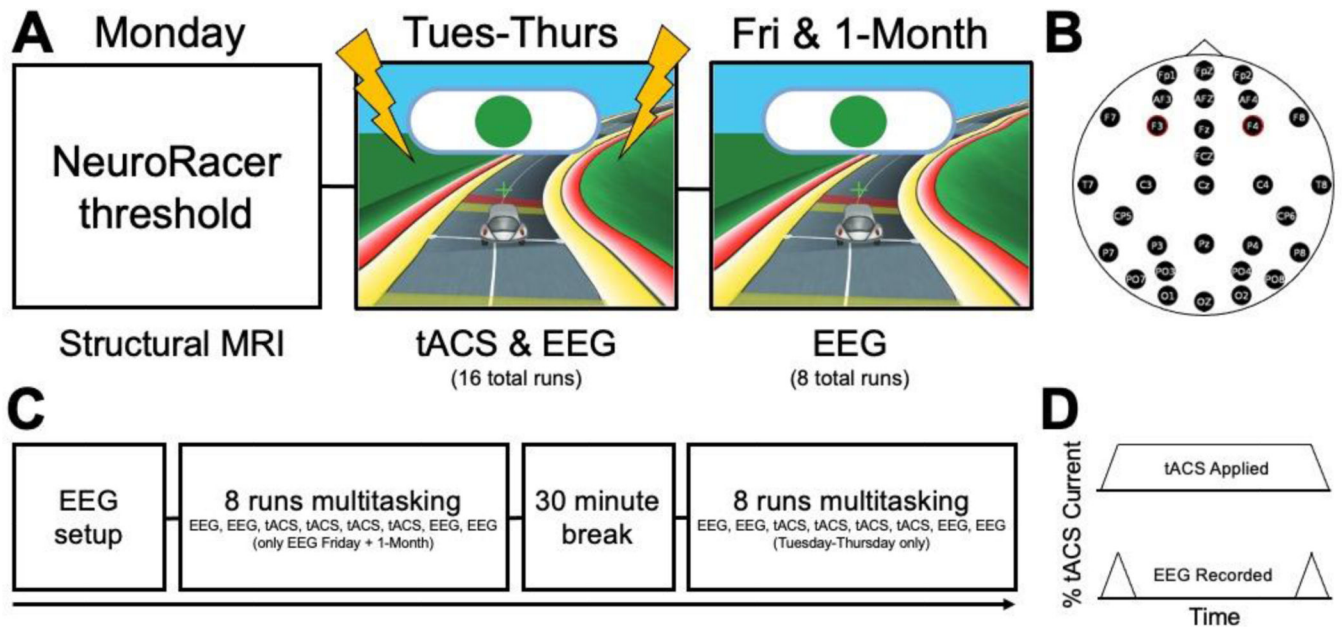


Figure 1. Study paradigm and timeline. (A) The protocol during the initial week and 1-month follow up. (B) The electrodes used during EEG and the two that served as both EEG and tACS marked in red (F3, F4). (C) The daily order of operations for all sessions where EEG was conducted and/or tACS was applied. (D) The amplitude during tACS sessions during each NeuroRacer run (top) and the control sessions where EEG was recorded following perceived tACS stimulation (bottom).

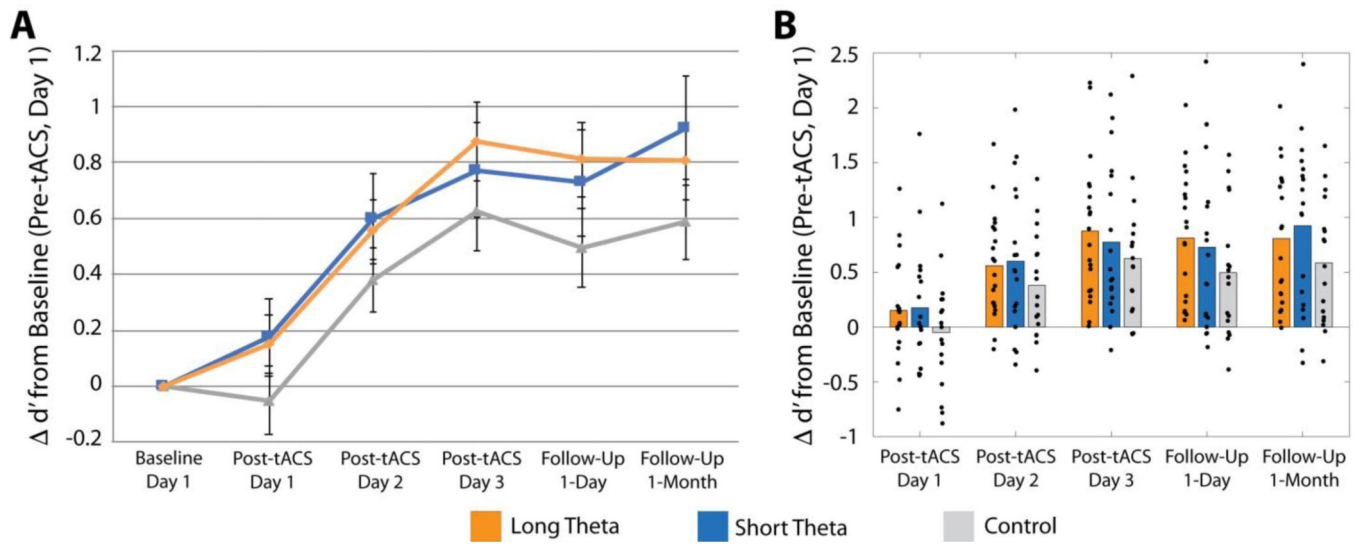


Figure 2. Mean change in performance over time with (A) standard error of the mean and (B) individual data points. Note: no error bars are present for Baseline Day 1 because all data are referenced to it as a change score.

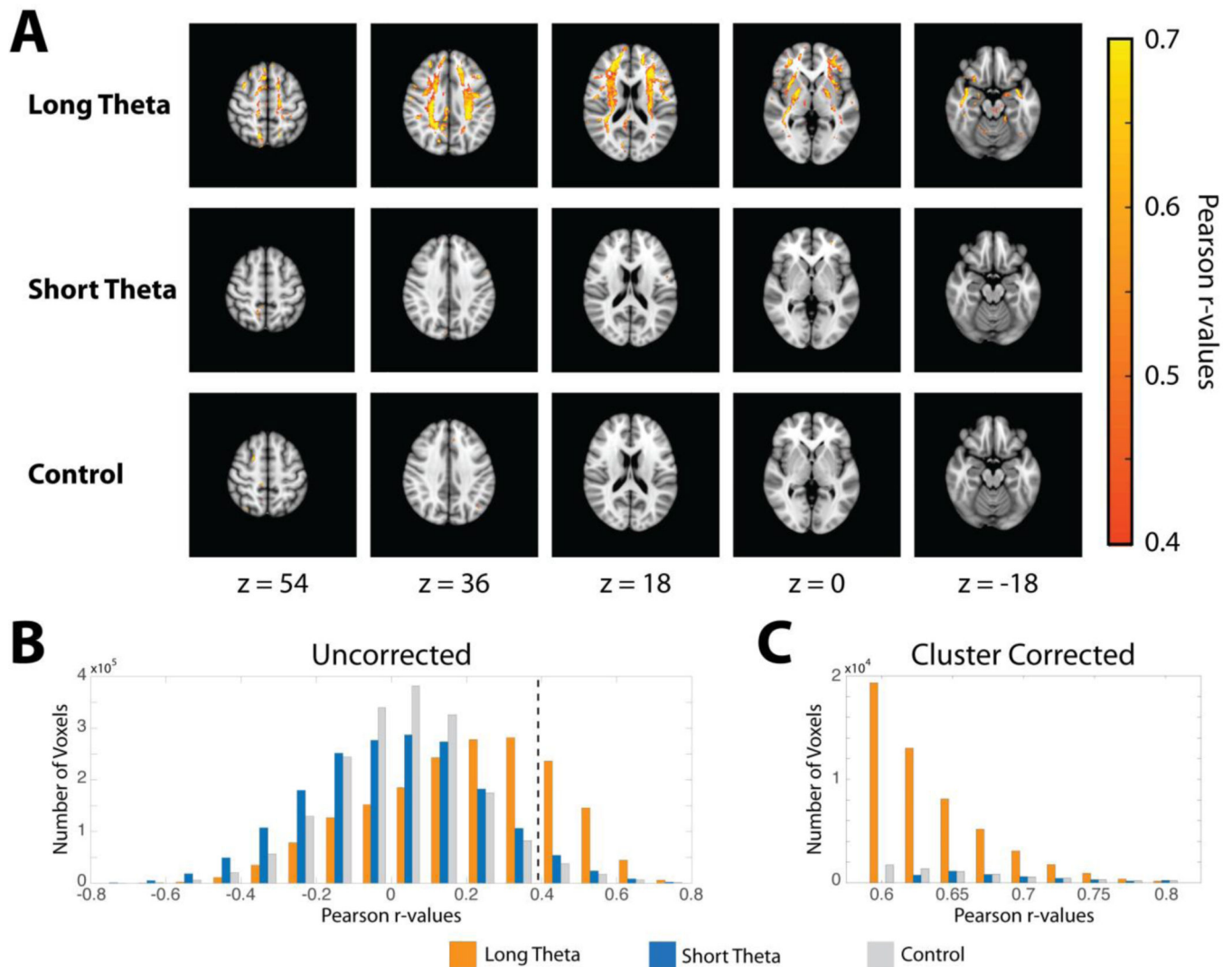


Figure 3. Relationship between modeled EF and tACS effects on performance. (A) Colored voxels exhibit a significant correlation between the modeled EF and the change in performance from baseline day 1 to post-tACS day 3. Coordinates are in MNI space. (B) Distribution of all Pearson r-values for each group, across the entire brain (gray + white matter). Dashed line indicates cutoff for $p < 0.05$ uncorrected for multiple comparisons. (C) Distribution of significant r-values after cluster correction.

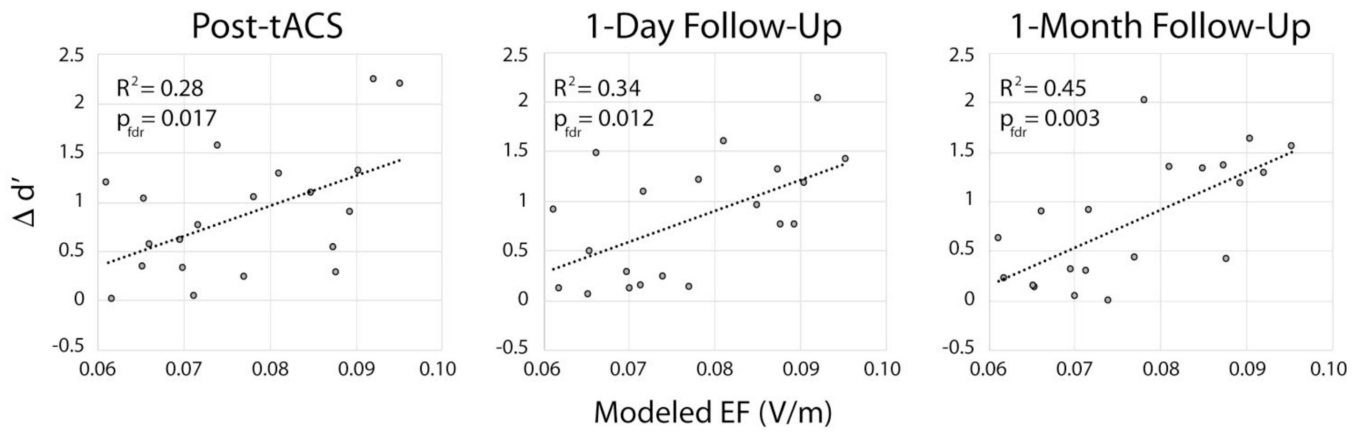
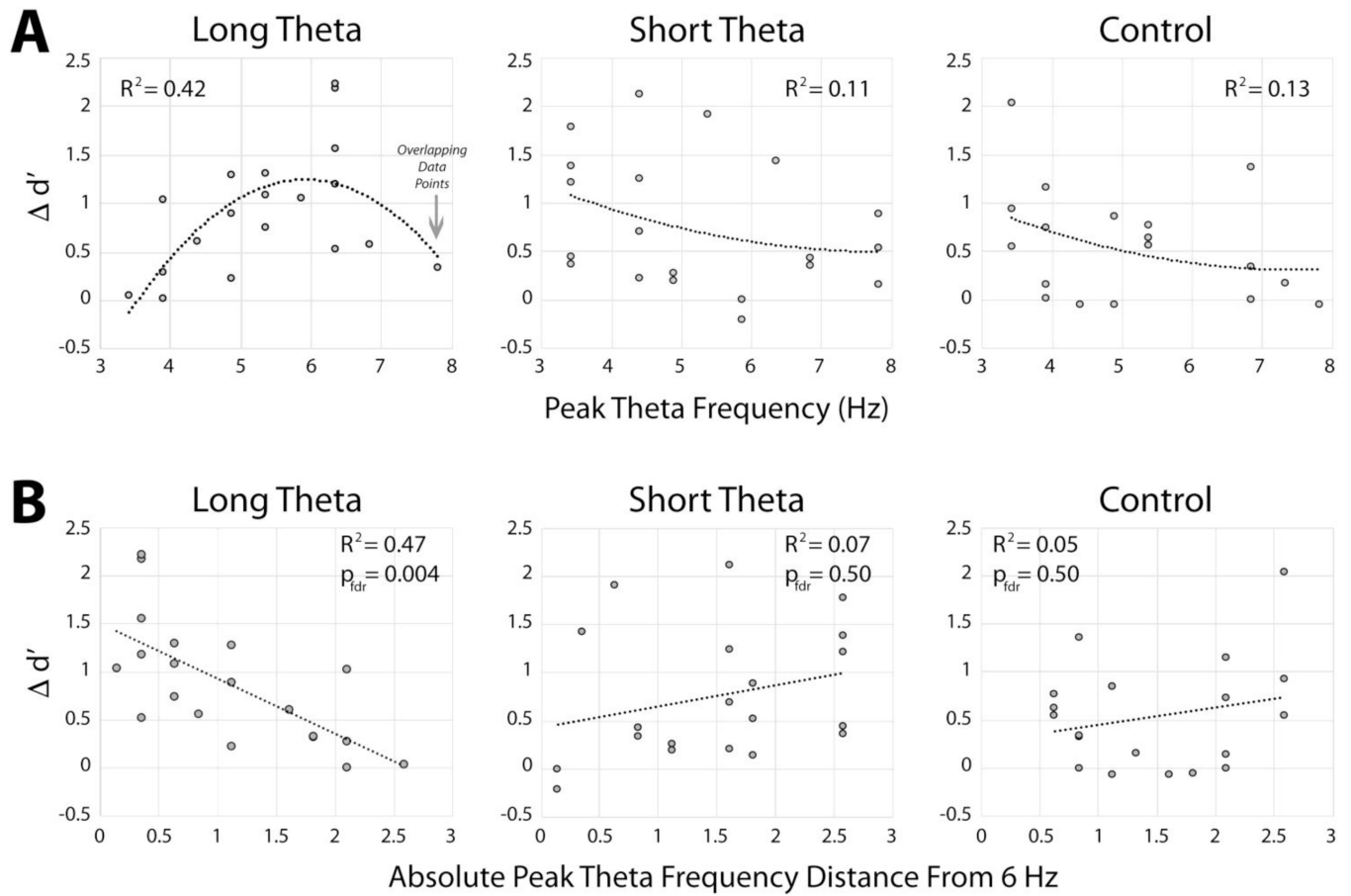


Figure 4. Relationship between tACS effects on performance and modeled EF within the frontal lobe.

**Figure 5.**

Relationship between peak theta frequency and tACS effects on performance. (A) Change in d' (tACS Day 3 – baseline) plotted against peak theta frequency at baseline and fit with a 2nd order polynomial function. (B) Correlation between the change in d' and the absolute distance from 6 Hz of each individual's peak theta frequency at baseline is only significant in the Long Theta group.

Table 1.

Results of linear regression models.

Group	Model / Predictors	Post-tACS Day 3			1-Day Follow-Up			1-Month Follow-Up		
		R ²	t	P _{thr}	R ²	t	P _{thr}	R ²	t	P _{thr}
Long Theta	Regression	0.538	---	0.001 **	0.544	---	0.001 **	0.648	---	<0.001 **
	Theta	---	-3.09	0.011 *	---	-2.82	0.012 *	---	-3.09	0.011 *
	EF PFC	---	1.60	1.00	---	2.00	0.093	---	2.94	0.027 *
Short Theta	Regression	0.001	---	1.00	0.007	---	1.00	0.060	---	1.00
	Theta	---	0.02	1.00	---	-0.08	1.00	---	0.08	1.00
	EF PFC	---	-0.02	1.00	---	0.02	1.00	---	0.24	1.00
Control	Regression	0.094	---	1.00	0.173	---	1.00	0.390	---	1.00
	Theta	---	0.19	1.00	---	0.87	1.00	---	-1.77	1.00
	EF PFC	---	0.19	1.00	---	1.16	1.00	---	2.68	0.060

The model summary is listed along with the individual predictors: peak theta frequency distance and modeled EF in PFC. Significant results highlighted in bold.

* =
p < 0.05

** =
p < 0.01