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Publication Date

2022-06-01

DOI

10.1016/j.bbr.2022.113894

Peer reviewed

HHS Public Access

Author manuscript

Behav Brain Res. Author manuscript; available in PMC 2022 October 25.

Published in final edited form as:

Behav Brain Res. 2022 June 25; 428: 113894. doi:10.1016/j.bbr.2022.113894.

Research outside of the laboratory: Longitudinal at-home neurostimulation

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Abstract

The use of noninvasive transcranial electrical stimulation (tES) has rapidly increased over the past two decades. Yet, tES continues to be largely implemented in laboratory and rehabilitation settings, thereby limiting accessibility to the broader population. We have previously demonstrated that transcranial alternating current stimulation (tACS) in the theta (4–7 Hz) band improves cognitive control, such as multitasking, in younger adults following a single tACS session, as well as in older adults following three tACS sessions. Here, the goal was to extend our in-lab results by 1) assessing the feasibility for at-home tACS and 2) evaluating whether five tACS sessions may yield continuing improvements in multitasking ability in young adults. Participants (aged 18 – 34 years) received bilateral prefrontal tACS while engaged in an adaptive multitasking training over five consecutive days in their home settings. Participants were randomly assigned to receive either 20-minutes of theta or delta tACS during daily multitasking training. Prior to and on the day immediately following five days of tACS, we assessed performance on single task, multitask, and sustained attention ability with analyses of variance statistics. 92.1% of participants were able to self-administer tACS at home without researcher assistance. However, we observed that both theta and delta tACS groups exhibited improvements in both single and multitask performance. Compared to previously collected data, five days of theta tACS was comparable to one day of theta tACS. However, theta tACS has continued benefits in older, but not younger adults as evidenced by previous research. Both groups similarly improved in sustained attention. These results demonstrate that laboratory paradigms utilizing neurostimulation can be effectively deployed in a home environment without direct support from research personnel. Moreover, these results suggest that while theta tACS may facilitate multitasking improvements over one session, multiple sessions of theta tACS results in diminishing returns in young adults. Additional research will be required to confirm if delta activity plays an important role in multitasking ability.

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Conflict of Interests: A.G. is an advisor and shareholder in Neuroelectrics, who provided the neurostimulation device employed in the current study. A.G. is co-founder, shareholder, BOD member, and advisor for Akili Interactive, which is the application used as a training task in the current study. T.Z. is a scientific advisor for Humm, which makes a neurostimulation device not used in the current study.

Keywords

transcranial alternating current stimulation; multitasking; cognitive training; remote research

1.0 Introduction

Multitasking is a complex expression of cognitive control abilities that is prevalent in everyday life, yet it is well established that task performance declines when several tasks are conducted simultaneously[1]. Despite this multitasking cost, successful multitasking remains an important and commonly sought-after ability in our information rich environments. Compounding the cost of multitasking, the influence of distractors disproportionally affects older adults as compared to younger adults[2]. Fortunately, through repeated multitasking practice and learning, the cost of multitasking can be reduced in older adults, which is marked by increased frontal theta (4–7 Hz) oscillatory activity[3]. To explore the causal role of frontal theta activity in multitasking ability, we demonstrated that a single session of transcranial alternating current stimulation (tACS) during multitasking in younger adults also led to an increase in multitasking performance when stimulation was applied to the prefrontal cortex (PFC) in the theta band[4,5]. More recently, we observed similar benefits in older adults' multitasking ability following three sessions of theta tACS, compared to delta tACS, with benefits sustaining 1 month following the end of training[6]. Therefore, frontal theta activity plays an important role in facilitating this cognitive control-based skill, multitasking.

The strength of noninvasive tACS is that it is safe[7,8], can modulate cognitive functioning through neural entrainment of oscillations[9], and is cost-efficient compared to alternative interventions. If the use of neurostimulation is to be broadly applicable to the general population, protocols must be able to scale to ecologically valid environments outside of laboratory settings. While there is some variability in the reliability of applying tACS to improve cognition (reviewed in: [10]), we have had repeated in-laboratory success using neurostimulation to enhance multitasking in older[6] and younger adult populations[4,5,11]. Here, we established the proof-of-concept for a self-administered neurostimulation paradigm, while participants engaged in an adaptive five-day tablet-based multitasking training paradigm without direct researcher assistance.

Beyond assessing feasibility of at-home neurostimulation, we also directly tested whether the repeated application of theta tACS may yield continued improvements in multitasking ability. We previously observed that longitudinal neurostimulation[6,12] improved cognition in healthy older adults as compared to control stimulation, supporting the additive benefits of multiple sessions of neurostimulation (reviewed in: [13]). Therefore, we hypothesized that repeated sessions of theta tACS would follow this pattern in healthy younger adults and yield continuing performance improvements.

2.0 Materials and Methods

2.1 Participants.

In this study (ClinicalTrials.gov identifier: NCT04231825), 40 young adult participants (Mean age: 25.2, standard deviation (SD): 4.38, 25 females) completed the baseline, home-training, and follow-up sessions of this study over the course of one-week. All participants provided informed consent as approved by the University of California, San Francisco Institutional Review Board and were compensated $20 per hour for participation with a $50 bonus for completion of the study. Participants had no history of neurological or psychiatric disease, were not currently on medications that modulate neural excitability, and had corrected-to-normal vision. All participants were native English speakers. Participants were randomly assigned to one of two stimulation frequency groups, which received 20 minutes of 6 Hz (Mean age: 25.8, SD: 4.56, 12 females) or 1 Hz tACS (Mean age: 24.55, SD: 4.21, 13 females) over five consecutive days. The participants, researchers, and outcomes assessor were all blinded to the tACS conditions.

2.2 Neurostimulation.

The tACS was delivered through a Starstim device (Neuroelectrics, Spain) with NG Pistim electrodes (contact area: 3.14 cm^2) placed over the PFC at 1 mA (baseline to peak; 2mA peak-to-peak) with a 180-degree phase offset. Perceptual phosphenes are a common side effect in studies employing tACS, however these are unlikely to occur in the delta-theta frequency range at 1 mA as opposed to tACS provided in the alpha-gamma range[14,15]. Indeed, participants did not report phosphenes, in line with our previous research targeting the prefrontal cortex with delta and theta tACS[4–6]. Participants applied the electrodes themselves within a neoprene EEG head cap where the only two holes in the cap corresponded to the electrode locations F3 and F4. These stimulation sites were selected to maximally target midline frontal theta oscillations, which were observed to underlie gains in multitasking on NeuroRacer[3]. During the initial baseline session, we instructed participants in how to align the headcap, set up the tACS battery and electrodes, apply gel, and how to operate AKL-T01. Participants were given step-by-step instructions to self-apply conductive gel within the Pistim electrodes in front of a mirror, which screw open for easy access to the scalp underneath. Of note, the headcap only had two holes for electrode placement, thereby minimizing the possibility of placement error. Following a self-monitored impedance check, participants were able to begin stimulation by pressing “BEGIN” and participants were instructed to not do this until AKL-T01 was started. The tACS control software did not allow participants to manipulate the stimulation protocol. The current was ramped up and down over the course of 10 seconds at the beginning and end of 20 minutes of stimulation, respectively. Participants began the stimulation then immediately began the training task on five consecutive days. Researchers were able to remotely monitor adherence to the tACS sessions. At the end of stimulation each day participants were probed as to whether they experienced pain, unpleasant sensation under the electrodes, or changes in cognition/mood. If participants reported yes to any of these an email would be immediately sent to the research staff. Any responses of yes would be reported to the IRB.

2.3 Baseline & follow-up session.

To measure multitasking performance, participants were assessed in the laboratory with NeuroRacer, a gamified task where they must continuously perform visuomotor tracking (driving a car) while simultaneously performing visual discrimination (detect a target sign) with a button press (for details see: [3]). On both in-lab sessions (baseline and follow-up), participants first completed thresholding of the visual discrimination (sign) and visuomotor tracking (drive) tasks, to establish a difficulty level where participants scored ~80% accuracy. Target signs appeared every 2–3 seconds and lasted for 400 ms. Next, in a counterbalanced order, participants completed two runs of only the NeuroRacer sign task, two runs of only the NeuroRacer drive task, and three multitasking runs of the NeuroRacer sign and drive task together. Furthermore, participants had to respond within their individual reaction time window as determined by single task thresholding during the baseline session to be counted as correct (participant range: 320 – 490 ms). Perceptual discrimination performance was measured during each multitasking run using a metric of discrimination (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(hits)–Z(false alarms). Finally, we calculated multitasking cost by measuring the difference in d' between sign only and multitask runs within each session ((multitask d'/sign only d')-1). The total number of signs to respond to on both the sign only and multitask tasks portions totaled 216 trials with 33% target trials.

Following the NeuroRacer tasks, participants completed a computerized continuous performance task (CPT) that tests sustained attention ability. The CPT is a well-validated modified version of the Test of Variables of Attention (TOVA; [16]), which tests sustained attention by measuring reaction time (RT) and reaction time variability (RTV) to stimuli (white squares) which appear on a black background on either the top or bottom half of the screen[3,17–19]. Participants were instructed to press the space bar as quickly as possible when the white square appeared on the top half, but not the bottom half of the screen. The ratio of targets to non-targets was 25%.

2.4 Training sessions.

On five consecutive days, participants began the self-applied tACS and immediately engaged in the training task, *AKL-T01* (Akili Interactive Labs, Inc). AKL-T01 is a proprietary system based on the NeuroRacer paradigm that challenges cognitive control by requiring multitasking[20]. Importantly, AKL-T01 employs algorithms that continuously adapts to individual drive and target performance in real time with feedback provided. During the initial baseline session, we instructed participants in how to connect the iPad we provide to their home WiFi network and launch the AKL-T01 app on the tablet. Each participant was provided a unique login number and password so that they could resume their progress on the following day. The tablets automatically uploaded data in real time so that the researchers could monitor progress and adherence to the training schedule. AKL-T01 requires both visuospatial tracking with concurrent feature discrimination. During AKL-T01, participants guided a character down a path by tilting the iPad similar to a steering wheel (visuospatial tracking) in order to avoid barriers in the road that subtract from their navigation score. As participants avoided multiple barriers in succession, the

speed of the character increased and upon collision with a barrier the character speed decreased. At the same time, participants engaged in a feature discrimination task, where they tapped on the screen in response to target items (e.g., green fish) and ignored all distractors (e.g., blue fish). Targets appeared every 2–3 seconds with 500 ms jitter of onset. AKL-T01 was developed on the iPad with high-quality graphics and rewards designed to be more engaging than standard laboratory cognitive tasks. As participants correctly tapped targets and withheld responses from nontargets, the target speed increased, which limited the amount of time to respond and be correct. As participants incorrectly tapped the screen to nontargets or were too slow to respond to targets, the target speed decreased, allowing for more time to respond and be marked correct. During each AKL-T01 mission, participants completed five missions per day, which lasted 20 minutes, the same length as the 20-minute tACS protocol. Participants were instructed to administer the tACS and play AKL-T01 at the same time of day during all five training sessions without taking significant breaks between each mission. However, as participants were able to take momentary pauses between runs before advancing, the total duration of each AKL-T01 session varied slightly, but never less than the duration of tACS (M = 21.4 min). Researchers were able to remotely monitor adherence to the training sessions as timestamped data was uploaded online during each session. Given the adaptive nature of AKL-T01, which maintains accuracy as participants improve, we did not analyze performance between groups on the training task.

3.0 Results

3.1 Feasibility & Compliance.

Of the 47 participants enrolled in the study, 3 participants did not adhere to the stimulation schedule and were dropped from the study. Additionally, 1 participant was dropped due to COVID-19 lockdowns. 3 additional participants experienced hardware problems and were not able complete the study. Finally, two participants had performance that were calculated as outliers per Tukey's rule, which is calculated as more than 1.5 interquartile ranges (IQRs) below the first quartile and 1.5 IQRs above the 3rd quartile of the primary outcome measure, change in multitasking d'. Together, we retained 38 participants (19 per group) for data analysis. Of these participants, only three participants (7.9%) needed assistance in applying tACS to themselves at home. All three participants had issues beginning tACS due to Bluetooth or WiFi connectivity issues with the Windows tablet that is used to signal the tACS device to begin stimulation, but were able to maintain the stimulation schedule with remote researcher assistance. The remaining participants (35/38, 92.1%) had no issues conducting the remote neurostimulation paradigm independently. Side effects were reported as barely noticeable, in line with our in-lab research [REFs]. There was no difference in total minutes spent on AKL-T01 between the groups as this data is automatically uploaded following each session (Daily training minutes: 6 Hz avg: 21.5, 1 Hz avg: 21.58, $p = 0.76$). To ensure there was no substantial difference in the start time of the tACS and the AKL-T01 training task, we calculated the difference in the time stamps of the start of tACS stimulation and the start of the initial level of AKL-T01 per day. The average delay between the start of AKL-T01 and tACS was 25.7 seconds (SD: 17.7, range: 4.0 – 67.2) for the 6 Hz group and 25.9 seconds (SD: 26.3, range: 2.8 – 115.0) for the 1 Hz group ($p = 0.98$).

3.2 Training Results: NeuroRacer.

Prior to and following five consecutive days of at-home AKL-T01 training with paired self-administered neurostimulation, we assessed performance in the laboratory on the same tasks performed at baseline. To first test the effect of tACS with AKL-T01 training on the single task (visual discrimination, sign only) performance during NeuroRacer, we conducted a repeated-measures analysis of variance (rm-ANOVA) with the factor of time point (baseline, follow-up) on target discriminability (d') with the between-subjects factor of tACS frequency (6 Hz, 1 Hz). The results revealed a significant main effect of time ($F_{1,36}$ = 17.46, $p < 0.001$, $\eta_p^2 = 0.33$), such that both groups had improved d' scores following the at-home neurostimulation (Table 1), however there was not a significant time x group interaction ($F_{1,36} = 2.97$, $p = 0.09$, $\eta_p^2 = 0.08$). To further investigate whether this main effect of time was disproportionally due to a single group, we conducted a paired-samples t-test for each group on the baseline and follow-up single task d' scores. We observed that the 1 Hz group had a significant difference between the time points ($t_{18} = 6.12$, $p < 0.001$, Cohen's d = 1.40) and the 6 Hz group did not ($t_{18} = 1.4$, $p = 0.178$, Cohen's d = 0.32).

To directly test the impact of tACS on multitasking performance d' between groups we conducted a rm-ANOVA with the factor of time point (baseline, follow-up) on multitasking target discriminability (d') with the between-subjects factor of tACS frequency (6 Hz, 1 Hz). The results revealed a significant main effect of time ($F_{1,36} = 16.52$, $p < 0.001$, $\eta_p^2 = 0.31$; Figure 2), such that both groups improved following the at-home neurostimulation (Table 1), however no time x group interaction ($F_{1,36} = 1.86$, $p = 0.18$, $\eta_p^2 = 0.05$). To further investigate whether this main effect of time was disproportionally due to a single group, we conducted a paired-samples t-test for each group on the baseline and follow-up single task d' scores. We observed that both the 6 Hz ($t_{18} = 2.57$, $p = 0.019$, Cohen's d = 0.59) group and 1 Hz ($t_{18} = 3.19$, $p = 0.005$, Cohen's d = 0.73) group had a significant improvement in multitasking performance pre- to post-tACS.

The other primary outcome measure was an assessment of the change in multitasking cost on NeuroRacer (discriminability (d') cost at follow-up – baseline). Cost is calculated by comparing the reduction in d' between multitasking and single task performance within each session ((multitask d'/sign only d')-1). To assess the effect of tACS on multitasking ability, we conducted a rm-ANOVA with the factor of time point (baseline, follow-up) on multitasking cost with the between-subjects factor of tACS frequency (6 Hz, 1 Hz). The results revealed no significant main effect of time ($F_{1,36} = 0.03$, $p = 0.86$, $\eta_p^2 < 0.01$) or time x group interaction ($F_{1,36} = 0.11$, $p = 0.74$, $\eta_p^2 = 0.003$).

3.3 Transfer Results: Sustained Attention.

The secondary outcome measure was the assessment of sustained attention ability using CPT and measured by change in RT and RTV from baseline during the follow-up session. To investigate the effect of tACS condition on sustained attention, we conducted a rm-ANOVA with the factor of time point (baseline, follow-up) on CPT RT with the between-subjects factor of tACS frequency (6 Hz, 1 Hz). The results revealed a significant main effect of time ($F_{1,36} = 15.94$, $p < 0.001$, $\eta_p^2 = 0.31$), but no time x group interaction ($F_{1,36} < 0.01$, $p = 0.97$, $\eta_p^2 < 0.01$). To further investigate whether this main effect of time was

disproportionally due to a single group, we conducted a paired-samples t-test for each group on the baseline and follow-up CPT RTs. We observed that both the 6 Hz (t_{18} = 2.81, p = 0.012, Cohen's d = 0.64) group and 1 Hz (t_{18} = 2.84, p = 0.011, Cohen's d = 0.65) group had a significant improvement in RT pre- to post-tACS (Table 2). Next, we conducted the same rm-ANOVA on RTV and observed a main effect of time ($F_{1,36}$ = 7.94, p = 0.008, η_p^2 = 0.18), but no time x group interaction ($F_{1,36}$ = 0.64, p = 0.43, η_p^2 = 0.02). To further investigate whether this main effect of time was disproportionally due to a single group, we conducted a paired-samples t-test for each group on the baseline and follow-up CPT RTV. We observed that both the 6 Hz (t_{18} = 2.41, p = 0.027, Cohen's d = 0.55) group and 1 Hz (t_{18} = 2.83, p = 0.007, Cohen's d = 0.45) group had a significant improvement in RTV pre- to post-tACS.

3.4 Exploratory Analyses: tACS Length.

Next, we wanted to investigate whether multiple sessions of at-home theta tACS led to greater multitasking improvements on NeuroRacer as compared to a single in-lab session. Therefore, we sought data from a recent study where we employed both 6 Hz and Sham tACS as comparisons[5]. This previous study had the same electrode locations (F3-F4), age group (ages 18–35), and outcome measure in NeuroRacer. In this study participants completed 16 NeuroRacer multitasking runs with a short break between runs 8 and 9. During NeuroRacer tACS (theta or sham) was applied during runs 3–6 and 10–14 with sham tACS applied during the first and last two runs of each half of the task so that EEG could be recorded to assess neural changes. Importantly, this was a single day study so we assess multitasking on the initial two (1, 2) pre-tACS multitasking runs and the final two (15, 16) post-tACS multitasking runs. We compared the change in multitasking d' on the NeuroRacer runs pre-tACS to post-tACS with an independent samples t-test and observed no statistical difference between the two theta tACS groups (t_{36} = 0.007, p = 0.99, Cohen's d = 0.002; In-Lab 6 Hz d' Δ: 0.23 (SD: 0.55), At-Home 6 Hz d' Δ: 0.23 (SD: 0.38); Figure 3). The same numerical gains between the At-Home and In-Lab theta tACS groups demonstrates that multiple sessions of theta tACS did not lead to additive benefits that we expected. We then sought to investigate whether the At-Home theta tACS group had greater gains than the In-Lab Sham group from the same study. An independent samples t-test was conducted on the change in multitasking d' on NeuroRacer runs pre-tACS to post-tACS and observed a significant difference between the groups (t_{36} = 2.29, p = 0.028, Cohen's d = 0.74; In-Lab Sham d' Δ: −0.08 (SD: 0.44); Figure 3). These comparisons demonstrate that theta tACS is able to effectively improve multitasking as compared to sham stimulation, however multiple sessions of At-Home theta tACS did not yield additive benefits as compared to a single In-Lab session.

3.5 Exploratory Analyses: Age.

The initial analyses yielded results that were unexpected from our initial hypothesis, as the 6Hz tACS group had fewer gains in performance than 1Hz tACS (albeit an insignificant difference). In previous research in healthy older adults (Mean age: 67.15, SD: 5.19), we observed that 6Hz tACS led to greater multitasking gains following 3 sessions of tACS during NeuroRacer[6]. Although older adults trained on NeuroRacer, which is different than AKL-T01 in graphical content and physical interface, the task demands were similar

by design. Furthermore, the baseline and follow-up assessments in both studies utilized NeuroRacer multitasking. In this additional study, healthy older adults had the same electrode locations (F3-F4) and tACS frequencies (theta, delta). Similar in design to the in-lab intervention included in the Exploratory Analysis above[5], participants completed 16 runs of NeuroRacer multitasking with tACS applied during runs 3–6 and 10–14, however this was repeated on three consecutive days as opposed to a single day. We assessed multitasking on the initial pre-tACS NeuroRacer runs and the final two post-tACS NeuroRacer runs. To investigate the effect of age on tACS effects, we conducted a rm-ANOVA with the factor of time (pre-tACS, post-tACS) and the between-subjects factors of tACS group (6 Hz Younger, 6 Hz Older, 1 Hz Younger, 1 Hz Older). The results Revealed a significant main effect of time ($F_{1,74} = 67.46$, $p < 0.001$, $\eta_p^2 = 0.48$) and a significant time x group interaction ($F_{1,36} = 4.47$, $p = 0.023$, $\eta_p^2 = 0.15$). To investigate this interaction further, we compared the two theta tACS groups (Younger, Older) with an independent samples t-test and observed a significant difference in multitasking d' gains between the groups ($t_{37} = 4.11$, $p < 0.001$, Cohen's $d = 1.32$). Repeating this comparison for the two 1 Hz groups (Younger, Older) revealed no significant difference in NeuroRacer multitasking d' change ($t_{37} = 0.54$, $p = 0.59$, Cohen's $d = 0.17$; Figure 4).

4.0 Discussion

In this remote multitasking training study, 38 young adults completed a five-day adaptive cognitive training protocol with self-applied neurostimulation (6 Hz, 1Hz) at home without researcher assistance. We believe that demonstrating the feasibility of tACS and cognitive training in home settings is particularly valuable given concerns such as global pandemics and the inaccessibility of research environments to much of the general public. Here, only in three of 38 participants was researcher support required to troubleshoot problems, thereby providing important proof-of-concept for future unsupervised remote tACS applications. Interestingly, we observed improved performance on the NeuroRacer single task, multitask, and on the CPT sustained attention response time metrics. Based on our previous research[3–5], we hypothesized that 6 Hz tACS during multitasking training would demonstrate the greatest gains in our outcome measures, relative to 1 Hz tACS. However, we observed that both groups improved performance on these tasks.

In an exploratory analysis to ascertain whether multiple days of theta tACS yielded greater multitasking improvements than a single session, we compared our current results to a previously collected data set where participants were randomized to receive one day of theta tACS or sham tACS. Results showed comparable performance improvements regardless of whether one day or five days of theta tACS was applied. Although both the one-day and five-day theta tACS groups outperformed one day of sham tACS, the question remains whether five days of sham tACS would yield performance comparable to five days of theta tACS. We believe that this would be the case, as we know that multiple days of NeuroRacer training without tACS will lead to performance improvements (i.e., practice/training effects)[3]. Therefore, the utility of theta tACS appears to accelerate the learning process so that peak performance may be achieved in a shorter time period. In young adults, the maximal benefit of theta tACS was achieved after one session, as five days of tACS did not result in any further improvement. However, we have recently shown that multitasking

ability in older adults continually improves after three days of theta tACS, although the third day exhibited diminishing returns[6]. Here, we directly compared five days of theta tACS in young adults to three days of theta tACS in older adults and showed that older adults indeed benefitted more from multiple days of stimulation. Furthermore, the multitasking performance of the older adults following tACS is notably similar to the younger adults prior to training, a pattern previously observed following a month of NeuroRacer training without tACS[3]. As with the first use of NeuroRacer[3], younger and older adults begin with drastically different multitasking performances despite the difficulty of the tasks individually adjusted prior to multitasking. Younger adults need fewer sessions of theta tACS to reach their multitasking ceiling, whereas it takes multiple sessions in older adults to reach comparable multitasking performance (6 and 1 Hz Young pre d': 1.12 (SEM: 0.10), 6 Hz Old post d': 1.07 (SEM: 0.19).

The fact that young adults do not benefit from more than one session of theta tACS leads us to speculate that the additional sessions of theta tACS in younger adults were unnecessary because frontal theta activity may have served to facilitate task learning[21–24]. As such, frontal theta activity, and theta tACS by extension, may be important only during the acquisition of the mechanics required during the cognitive control tasks. However, once the task is learned (e.g., rules, motor mapping, etc.) frontal theta activity may play a less prominent role[25], resulting in limited utility of multi-day theta tACS as multitasking (and the associated game mechanics) becomes more natural to perform. This would not only explain why theta tACS did not continually improve performance in young adults (who are generally adept at learning new video games/technologies), but it would account for why older adults benefitted from multiple theta tACS sessions – because older adults are slower to learn new skills[26,27].

Interestingly, delta tACS facilitated the numerically greatest multitask improvements when applied across multiple sessions. Delta tACS is rarely applied with the goal of improving cognition. However, it is known that frontal delta activity is involved in modulating visual cortical activity during top-down guided visual attention in younger adults[28]. Indeed, delta oscillations are often associated with temporal attention[29–31], which facilitates the ability to anticipate impending targets for optimal performance[32]. Specifically, delta phase is thought to entrain with the expected timing of predictable stimuli[33–39]. Given that the targets presented during the multitasking occurred with a somewhat predictable timing (every 2–3 sec), it may be hypothesized that delta tACS facilitated temporal attention ability.

We believe that there are at least two other possible explanations for why theta tACS did not improve single task or multitask performance more so than delta tACS in young adults. First, it is possible that the 6 Hz stimulation frequency chosen in the current study was not optimal for the younger adult age group. It is known that behavioral improvements are greatest when tACS is at or near each individual's intrinsic oscillatory peak[6,40–43]. However, we did not collect baseline EEG data and could not determine individual theta peaks, leaving open the possibility that individual frequency-tuned tACS would benefit younger adults more than a set frequency; whereas delta tACS may provide a peak-irrelevant benefit while engaged in multitasking. Second, our previous research employed a non-adaptive version of NeuroRacer as a training task. Although AKL-T01 and NeuroRacer are similar by design

(visual discrimination with simultaneous visuo-motor tracking), we have not previously attempted to utilize AKL-T01 with concurrent neurostimulation. It is important to note that AKL-T01 adaptively changes the target difficulty with each correct or incorrect response and the driving speed is also adapted as driving obstacles are hit or avoided. Furthermore, NeuroRacer requires participants to only remain on the road, whereas AKL-T01 has both a bending river to navigate, but also target gates and hazards that must be hit or avoided. Given that neurostimulation effects are sensitive to the networks that are engaged while stimulation is applied[44], and different brain networks are known to be utilized during the same task but alternate difficulty levels[45–48], it may be that frontal delta activity played an important role in adapting cognitive control ability to updating task demands.

To date, few neurostimulation studies occur outside of a clinic or lab. Such research is primarily conducted in clinical populations[49–57], where researchers were generally present via teleconferencing (reviewed in: [58]). Here we take an important step forward to show that even a virtual presence may not be required for a successful remote-based study, particularly in healthy populations. The caveat is that participants in this study were trained on how to use the equipment in-lab, and all outcomes were assessed in-lab to ensure quality control of outcome data. Furthermore, participants were remotely monitored through the tablet software to ensure compliance and assess safety (side-effects), which were reported through the digital interface. Nonetheless, this study continues to advance neuroscience technologies beyond the lab so that future research may begin to address fundamental questions of brain function in more ecologically valid environments.

4.1 Conclusion.

This study provides novel proof-of-concept for the feasibility of remote neurostimulation without the presence of researchers. Demonstrating the potential of remote neurostimulation in ecologically valid environments is especially important for those with difficulties accessing traditional research facilities or when minimizing human contact for health reasons (e.g., pandemics). Given the rapidly growing use of neurostimulation in research, rehabilitation, and commercial enterprises, establishing the feasibility in novel remote environments allows for future basic research and translational applications with fewer geographic restrictions. Future research will be required to ascertain when different frequencies of stimulation may be best suited for specific aspects of a task, such as learning (via theta) and cognitive control (via delta).

Acknowledgements:

We would like to thank Amber Kang, Avery E. Ostrand, Elizabeth L. Johnson, Joaquin A. Anguera, and Peter E. Wais for their contributions to data collection and interpretation of data. We would also like to thank Akili Interactive Labs for providing tablets with AKL-T01 for use during the tACS sessions. Finally, we would like to thank Whitmire Vo for drawing figures 2–4, which reminds of us our past as technology continues to move science into the future.

Funding:

This work was supported by the National Science Foundation (grant #1829473), the National Institute on Aging (R21AG062395), and generous donations from the Neuroscape Network.

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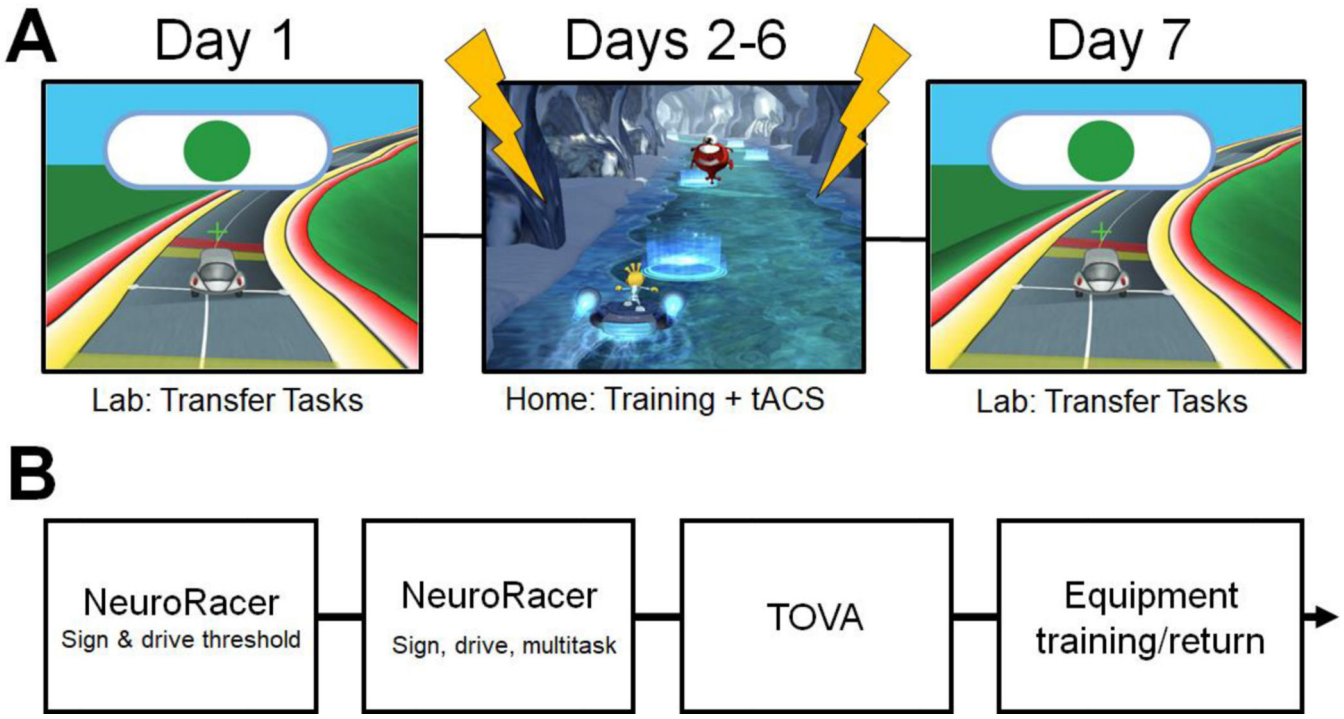

Figure 1.

The training paradigm and order of tasks. A) Timeline of events depicting in lab thresholding and transfer task performance on days 1 and 7. Consecutive days of self-administered tACS occur in conjunction with AKL-T01 on the five days in between the transfer tasks sessions. B) Order of the untrained tasks conducted in lab to assess near transfer gains at the baseline and follow-up sessions.

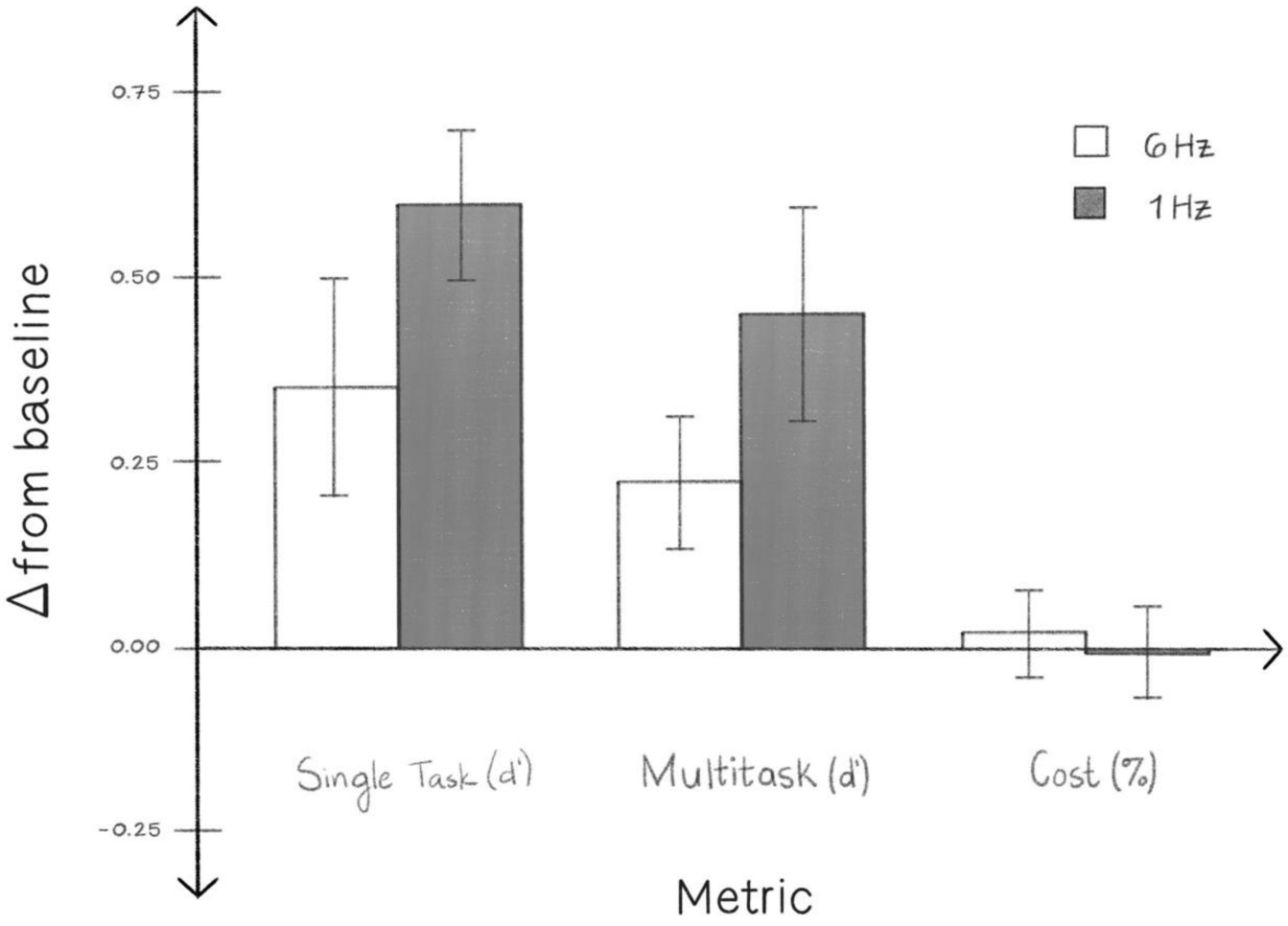

Figure 2.

Change in NeuroRacer performance during the in-laboratory follow-up session compared to the baseline session in sign only d', multitasking d', and multitask cost percentage. Error bars represent the standard deviation of the mean.

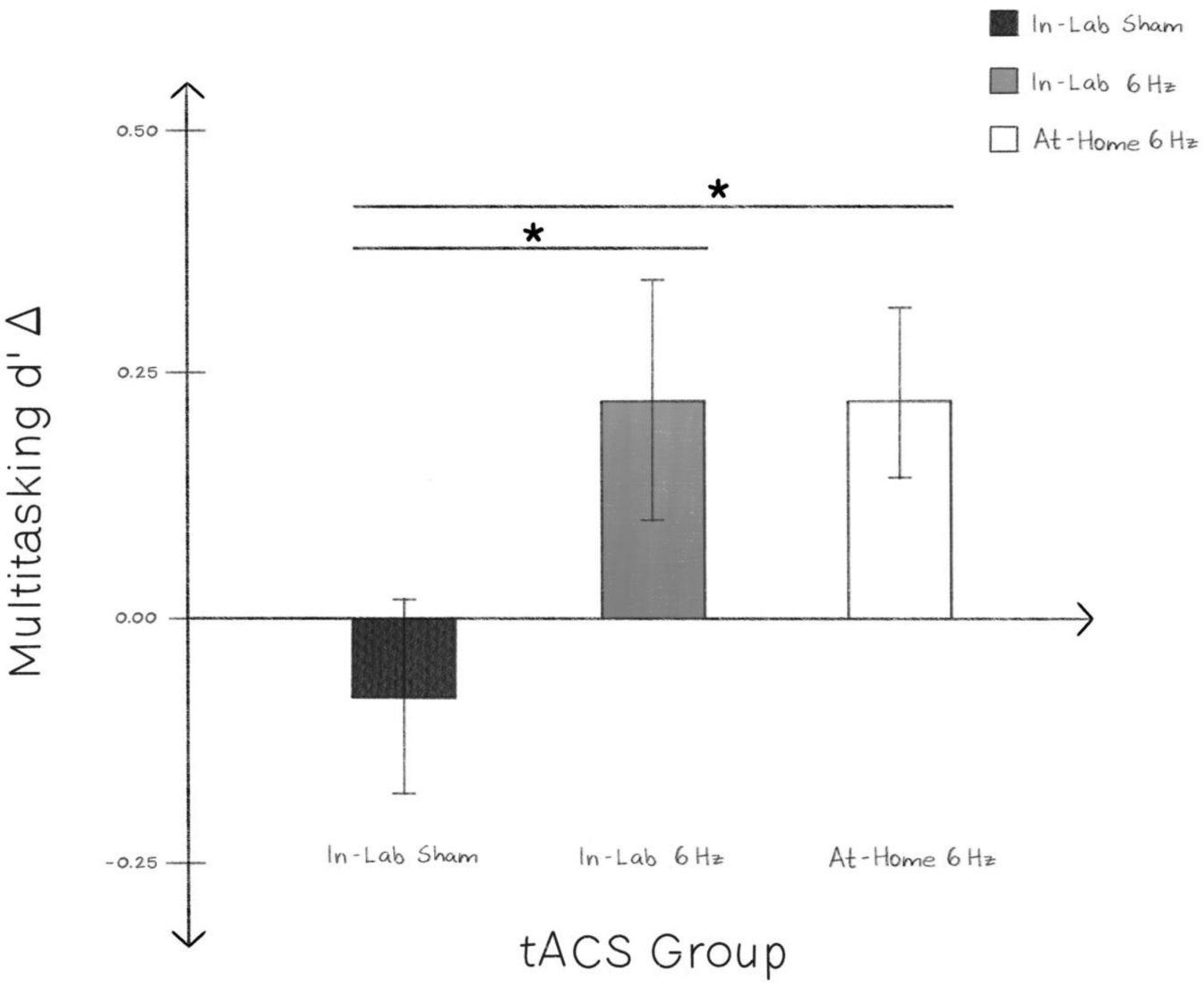

Figure 3.

Comparison of multitasking gains following tACS interventions in three different groups of young adults. Two groups received 6 Hz stimulation, with one occurring at home and the other in the laboratory. Each group that received theta (6 Hz) tACS had significant gains as compared to the Sham group. Error bars represent the standard deviation of the mean.

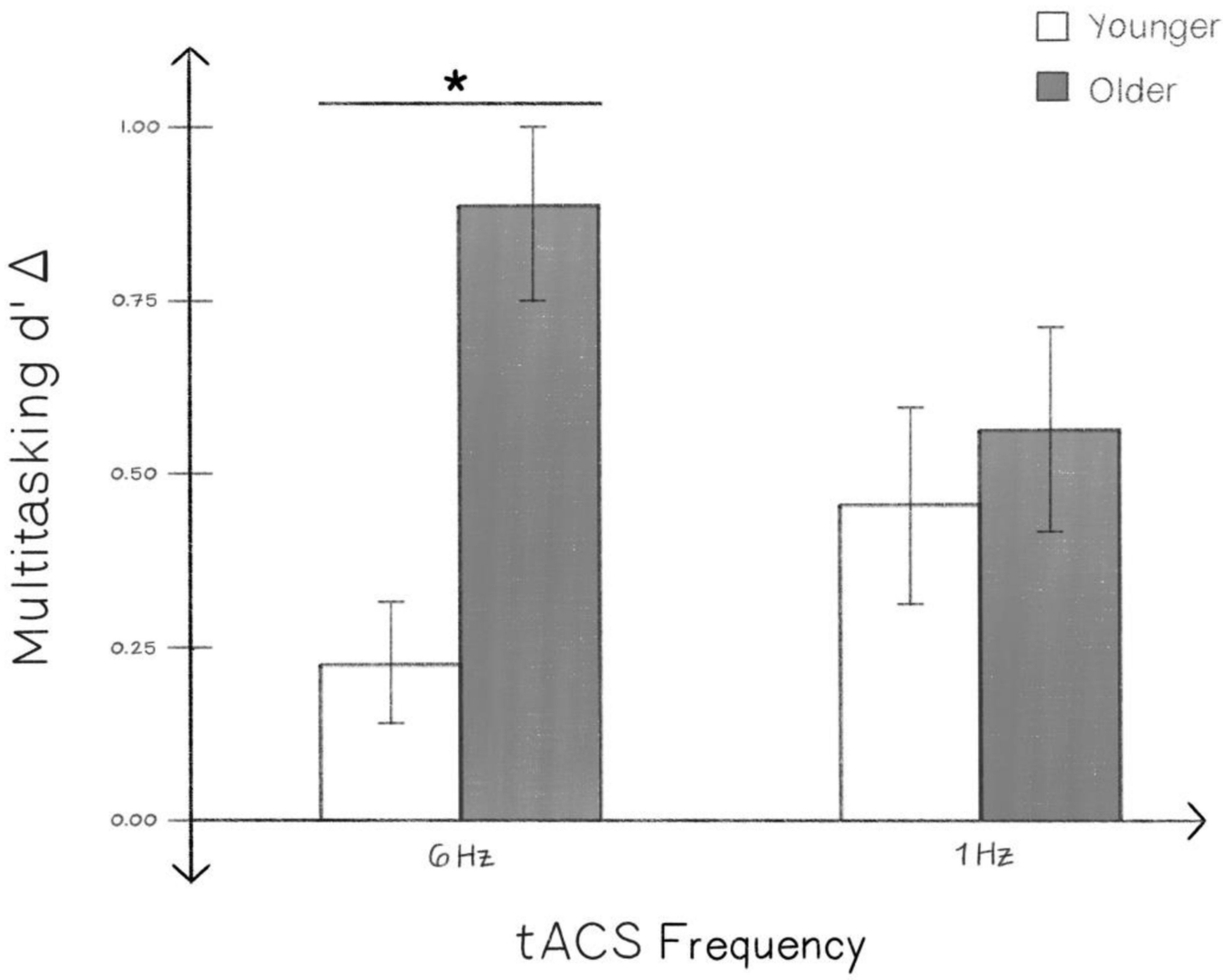

Figure 4.

A comparison of NeuroRacer multitasking performance improvement following one week multitask training paired with tACS in healthy older and younger adults. Younger adults received five sessions of tACS and AKL-T01 training whereas older adults received three sessions of tACS and NeuroRacer training. Both groups were assessed on NeuroRacer in the laboratory as the outcome measure during days where no stimulation occurred. Error bars represent the standard deviation of the mean.

Table 1.

Performance on NeuroRacer at baseline and follow-up sessions. Values listed in parentheses represent the standard error of the mean.

Group	Sign Only (d')		Multitasking (d')		Multitasking Cost (%)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
6 Hz	1.69 (0.15)	2.04 (0.22)	0.98 (0.14)	1.21 (0.17)	47.0% (0.09)	44.9% (0.07)
1 Hz	2.06 (0.14)	2.66 (0.15)	1.24 (0.13)	1.69 (0.18)	39.6% (0.05)	40.2% (0.06)

Table 2.

Reaction time and reaction time variability on the sustained attention CPT task. Data reported for the baseline and follow-up sessions for each for the tACS groups. Values listed in parentheses represent the standard error of the mean.

Group	CPT Reaction Time		CPT Reaction Time Variability	
	Baseline	Follow-up	Baseline	Follow-up
6 Hz	317.52 (8.67)	298.44 (9.61)	72.95 (6.60)	57.81 (6.00)
1 Hz	317.98 (6.62)	298.86 (5.65)	62.59 (3.73)	54.16 (4.52)

Table 3.

NeuroRacer multitasking d' values at pre-tACS and post-tACS time points for all groups mentioned. Exploratory analyses on tACS length (Section 3.4) include data from younger adult groups who trained in-lab in the top two rows[5]. Exploratory analyses on participant age (Section 3.5) include data from older adults who trained in-lab on the bottom two rows[6]. The data from the current manuscript are presented in the middle two rows. All values in parentheses represent the standard deviation of the mean.

Study	Age	Stimulation Frequency	Training Location	Multitasking (d') Avg	
				Pre-tACS	Post-tACS
Hsu et al. 2017	Younger	6 Hz	In-Lab	1.20 (0.59)	1.43 (0.49)
Hsu et al. 2017	Younger	Sham	In-Lab	1.01 (0.46)	0.93 (0.53)
At-Home tACS	Younger	6 Hz	At-Home	0.98 (0.14)	1.21 (0.17)
At-Home tACS	Younger	1 Hz	At-Home	1.24 (0.13)	1.69 (0.18)
Zanto et al. 2021	Older	6 Hz	In-Lab	0.18 (0.35)	1.07 (0.81)
Zanto et al. 2021	Older	1 Hz	In-Lab	0.39 (0.52)	0.95 (0.79)