

## Research report

## Replacing tDCS with theta tACS provides selective, but not general WM benefits

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## HIGHLIGHTS

- Working memory (WM) improves after multiple sessions of tDCS.
- Improvement is associated with enhanced theta and decreased alpha.
- We tested whether 1 session of tACS would elicit the same WM benefits.
- Frontoparietal slow theta (4.5 Hz), but not fast (7 Hz), or bifrontal tACS improved object WM.
- No benefit of tACS extended to spatial WM.

## ARTICLE INFO

## Keywords:

tDCS  
tACS  
Working memory  
Theta  
Alpha

## ABSTRACT

Working memory (WM) can be improved after repeated training sessions paired with noninvasive neurostimulation techniques. Previously, we reported that WM training paired with tDCS succeeded behaviorally by enhancing anterior-posterior theta phase coherence and reducing alpha power. Here, in two experiments we tested several theta and alpha frequencies and two transcranial alternating current stimulation (tACS) montages in an effort to *shortcut* WM training while preserving behavioral gains. In Experiment 1, in separate sessions participants received online tACS at two frequencies derived from the previous study with the respective goal of improving and impairing WM performance. We selected the mean group peak value theta (7 Hz) to benefit WM and alpha (11 Hz) to impair WM. Stimulation (tACS) over right frontoparietal sites (F4-P4) during 3-back WM tasks (object, spatial) produced no behavioral consequences. In Experiment 2 we stimulated at a slower theta frequency (4.5 Hz), which was also significant in our prior study, and tested whether frontoparietal or bifrontal montages would be more effective at improving WM. This experiment revealed selectively improved object WM after right frontoparietal tACS alone. In summary, one session of tACS failed to produce the magnitude or breadth of WM gains observed after 4–10 tDCS-WM training sessions. In short, despite looking for loopholes we found little tACS savings.

## 1. Introduction

Working memory (WM) provides a mental workspace permitting most cognitive tasks (e.g., Conway et al., 2003; Kane and Engle, 2002). Strikingly, WM is capacity limited (e.g., Cowan, 2001). Consequently, there is interest in enhancing, or restoring WM. Yet, WM resists improvement, and there is considerable debate regarding the benefits of WM training (reviewed in: Karbach et al., 2015; Melby-Lervåg and Hulme, 2013; Morrison and Chein, 2011; Owen et al., 2010; Sala and Gobet, 2017; Shipstead et al., 2012; von Bastian and Eschen, 2016; von Bastian and Oberauer, 2014). Recently, studies pairing WM training

with noninvasive transcranial direct current stimulation (tDCS) reported durable behavioral improvement and transfer to untrained tasks (reviewed in: Berryhill, 2017; Berryhill and Martin, 2018). A major problem is that the underlying mechanism of tDCS-augmented WM gains remains poorly understood.

To address this, we previously conducted a 4-day WM training with frontoparietal tDCS study and pre- and post- training EEG recording (Jones et al., 2017). WM improved beyond the gains provided by training alone. EEG revealed that post- training, the active tDCS group selectively showed heightened frontal-posterior theta-alpha phase locking (4.5–8.5 Hz, peak: 7 Hz) during WM maintenance. We

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<https://doi.org/10.1016/j.brainres.2019.146324>

Received 9 May 2019; Received in revised form 2 July 2019; Accepted 3 July 2019

Available online 04 July 2019

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interpreted this as strengthened connectivity, which we argued was important in improving WM performance. The sham tDCS group showed no neural or behavioral changes. This finding is consistent with others' reporting superior WM performance associated with greater phase coupling (Liebe et al., 2012; Sauseng et al., 2004; Schack et al., 2005). After training the active tDCS group also showed reduced posterior alpha power during WM maintenance. As others showed alpha power increases with greater task demands (Jensen and Tesche, 2002; Manza et al., 2014), we interpreted the decrease as evidence of improved task efficiency (Jones et al., 2017).

Unlike tDCS, transcranial alternating current stimulation (tACS) can entrain neural oscillations (Antal and Paulus, 2013; Herrmann et al., 2013). In the few studies applying tACS to WM tasks, stimulation site and frequency are key parameters (reviewed in: Albouy et al., 2018). TACS can improve WM performance after theta tACS to parietal cortex (P3 or P4), but is less reliable when targeting left prefrontal sites (F3; Jausovec and Jausovec, 2014; Alekseichuk et al., 2016). Importantly, recent research reports that simultaneous focal tACS to both left prefrontal and left temporal areas improves WM in healthy older adults, whereas each tACS to either the left prefrontal or temporal region in isolation has no benefit (Reinhart and Nguyen, 2019). Slowing intrinsic theta via tACS may improve WM capacity by enabling coupling with more gamma oscillations per theta peak (Vosskuhl et al., 2015). In contrast, tACS that synchronizes gamma to the theta trough removes any benefit of theta tACS (Alekseichuk et al., 2017; Polania et al., 2012). Thus, tACS likely modulates WM performance through frontoparietal networks, with effects depending on tACS frequency, stimulation site, and task demands.

Our goal was to test whether entraining the frequencies altered by tDCS and WM training would permit one session of tACS to provide similar WM benefits, but in less time. We predicted that stimulating frontoparietal theta (7 Hz) would improve WM performance compared to sham (but see: Wolinski et al., 2018). Second, as reduced alpha power was associated with improved WM we predicted that 11 Hz tACS would impair WM performance. To test whether observations would generalize across WM task demands we included spatial and object conditions. Finally, we collected an independent measure of WM, as WM capacity can predict responsiveness to tDCS (Berryhill et al., 2014; Jones and Berryhill, 2012). Experiment 2 tested whether tACS at a slower theta frequency (4.5 Hz), which had also been significant in our previous study, would elicit superior WM effects. Recent findings emphasize the role of theta rhythms in sustained attention (e.g. Fiebelkorn and Kastner, 2019; Fiebelkorn et al., 2018) and improved WM (Meiron and Lavidor, 2014). It was also significant in our study (Jones et al., 2017). We also tested whether a frontoparietal, or bifrontal montage was superior for tACS during object and spatial WM performance. The bifrontal montage is more common and associated with WM benefits (Hsu et al., 2019; Hsu et al., 2017; Meiron and Lavidor, 2014; Ruf et al., 2017; reviewed in: Berryhill and Martin, 2018). We predicted 4.5 Hz tACS across montages would improve WM.

## 2. Results: Experiment 1

We calculated the discriminability index ( $d'$ ) per session and task as there were unequal numbers of target and non-target trials. This imbalance can introduce response bias, to which  $d'$  is resistant (Hoy et al., 2015; Hoy et al., 2016). To answer whether right frontoparietal tACS affected WM performance we subjected  $d'$  values to a 3 (tACS: sham, 7 Hz, 11 Hz)  $\times$  2 (task: object, spatial) repeated-measures ANOVA. There was a significant tACS condition  $\times$  task interaction ( $F_{1, 29} = 3.63$ ,  $p = .04$ , partial  $\eta^2 = 0.10$ ; Fig. 1B); post-hoc Tukey tests showed no pairwise differences ( $ps > 0.53$ ). There were no main effects ( $ps > 0.54$ ). The median correct RTs were faster on the object task ( $F_{1, 29} = 8.37$ ,  $p = .04$ , partial  $\eta^2 = 0.22$ ), but no other effects reached significance ( $ps > 0.41$ ). We subjected OSPAN scores to median split (high WM capacity mean: 40.6 (SD: 2.13), low WM

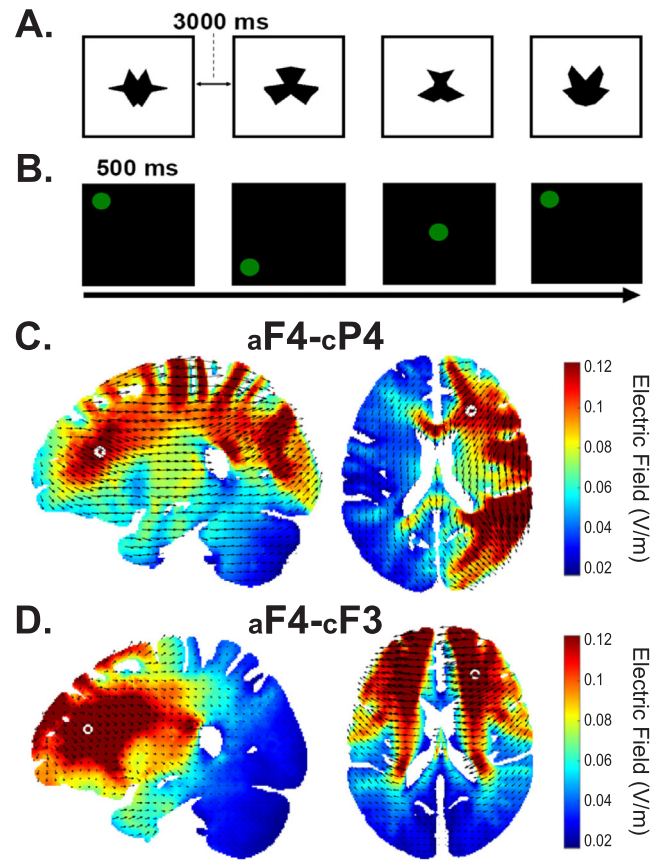


Fig. 1. Example trial sequences of the A) object and B) spatial 3-back tasks. For each image, a button press response indicated whether the current stimulus matched the stimulus presented 3-items earlier. C, D) Current modeling the tACS montages: frontoparietal (C), and bifrontal (D).

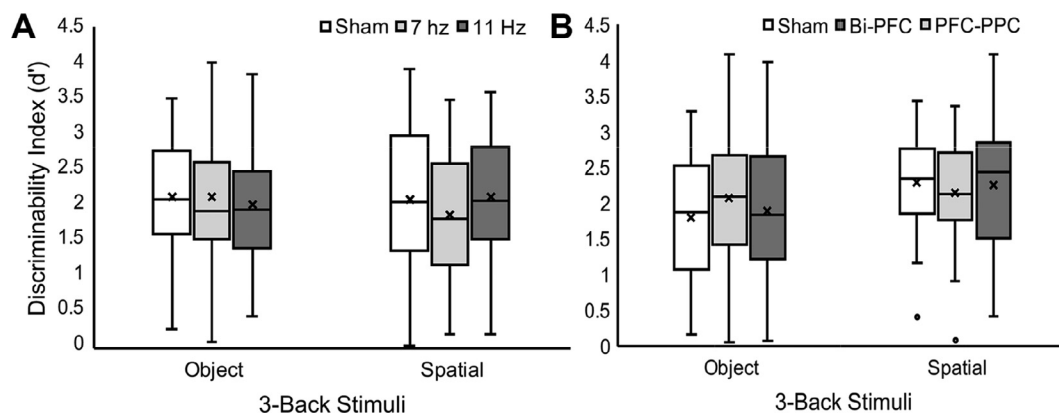
capacity mean: 29.73 (SD: 4.64)). ANOVAs including WM capacity group found no significant effects on  $d'$  ( $ps > 0.53$ ) or RT ( $p > .45$ ).

## 3. Results: Experiment 2

A repeated-measures ANOVA of  $d'$  evaluated tACS montage (bifrontal, frontoparietal, sham)  $\times$  WM task (object, spatial). Performance was better on the spatial task ( $F_{1, 37} = 5.97$ ,  $p = .02$ , partial  $\eta^2 = 0.14$ ). No main effect of montage emerged ( $p > .84$ ). There was a significant montage  $\times$  task interaction ( $F_{1, 37} = 4.85$ ,  $p = .01$ , partial  $\eta^2 = 0.12$ ; Fig. 1C). Frontoparietal tACS improved object WM ( $t_{37} = 2.33$ ,  $p = .03$ ) but impaired spatial WM ( $t_{37} = 1.43$ ,  $p = .16$ ). Bifrontal tACS had no effect (both  $ps > 0.38$ ). RTs revealed a main effect of task ( $F_{1, 37} = 9.99$ ,  $p < .01$ , partial  $\eta^2 = 0.21$ ), but no interaction ( $p > .13$ ). WM capacity (high WMC mean: 39 (SD: 2.52), low WMC mean: 27.68 (SD: 5.36)) revealed no significant effects for  $d'$  (both  $ps > 0.09$ , see Fig. 2B) or RTs ( $ps > 0.44$ ).

## 4. Discussion

Shortcuts are appealing; arguably no more so than for improving cognition. The goal of this project was to bypass onerous longitudinal WM training paradigms by replacing multiple WM training sessions paired with tDCS with just one session of tACS. The previous tDCS and WM training study revealed enhanced frontoparietal phase locking synchrony that tACS could mimic because it can modulate oscillations. We thought we could leverage our EEG observations characterizing the mechanistic changes in neural activity that drove behavioral shifts, but we failed overall. Our results revealed behavioral improvement on WM



**Fig. 2.** A) Experiment 1: Discriminability ( $d'$ ) scores for each tACS frequency and task. The significant interaction shows that 7 Hz frontoparietal tACS lowered performance on the spatial stimuli and 11 Hz tACS also lowered spatial performance. B) Experiment 2: Discriminability ( $d'$ ) scores for each tACS montage and task. Frontoparietal tACS (4.5 Hz) improved object WM and impaired spatial WM. Error bars represent 95% confidence intervals.

performance paired with frontoparietal theta, such that slower theta (4.5 Hz) was more effective than faster theta (7 Hz). Other manipulations had no effect, including bifrontal theta tACS that we predicted would improve WM and frontoparietal 11 Hz tACS that we predicted would disrupt WM. Finally, there was some task selectivity such that the subtle effects were not uniformly generalized across spatial and object WM tasks. The spatial impairment may have occurred due to interference in right frontoparietal endogenous oscillations with the 4.5 Hz tACS. Furthermore, spatial tasks are believed to rely on fronto-temporal connections (reviewed in: Herweg and Kahana, 2018) and the exogenous frontoparietal tACS may have disrupted this connection. Below we discuss several relevant points and suggestions to guide future efforts at leveraging one neuromodulatory approach to improve another.

One primary concern is that the tACS protocols were ineffective. Of the key paradigm parameters, we eliminate the concern of the duration of tACS effects because of foundational work demonstrating that 10 min of tACS produces changes lasting 30 min (Neuling et al., 2013). Our online (during task) stimulation lasted 15 min to correspond with the full length of the WM tasks. Stimulation intensity was low (1 mA) and this may be a major issue for mid- to higher- level cognitive tasks and frontal stimulation sites. We applied low intensity stimulation because of the truly distracting phosphene participants reported above 1 mA. This is a known phenomenon attributed to retinal responses and makes frontal alpha tACS problematic (Schutter and Hortensius, 2010). A third concern is that the WM tasks might have been too easy, given the high  $d'$  values. Although the 3-back is challenging, adaptive WM tasks may better maintain an equal level of difficulty across participants, especially given the within-subject design. Finally, we note that these data fail to replicate a similar paradigm that found significant theta tACS (4.5 Hz) induced WM benefits when applied to bilateral PFC locations (Meiron and Lavidor, 2014), as well as other research that improved multitasking with bilateral PFC theta tACS (6 Hz; Hsu et al., 2019; Hsu et al., 2017). This failure to replicate may have occurred due to differences in experimental paradigms and task demands. Specifically, despite the same electrode locations as the Hsu et al publications, their electrodes were smaller, their frequency differed (6 Hz), as did their task focused on attentional multitasking. The differences between the current manuscript and the Meiron & Lavidor study include their use of smaller electrodes (4x4 cm), a slight difference in electrode placement (between F3/4 and AF3/4), and an easier task (2-back word recognition). Their study also was between subjects and the two groups of 12 participants were exclusively female by design. Thus, as in tDCS designs, the tACS field may be vulnerable to replication difficulty.

Given the difficulties in reliability and reproducibility in both neurostimulation and cognitive training studies, Bayesian analyses provide advantages over reports relying only on  $p$ -values (Rouder et al., 2012).

Importantly, parametric statistics are particularly vulnerable to sampling error. The Bayes Factor (BF), which represents the likelihood the data under one hypothesis as compared to another (such as the null), allows for both reporting of the hypothesized effect as well as evidence for a null hypothesis. Traditional  $p$ -values cannot distinguish between evidence for the null hypothesis and lack of evidence for the hypothesized effect (reviewed in: Dienes, 2014). In cognitive studies, Bayesian analyses are often applied to investigate evidence of transfer following WM training (De Simoni and von Bastian, 2018; Guye and von Bastian, 2017) and to report that the effectiveness of such interventions is often lower than reported (reviewed in: Dougherty et al., 2016; Lampit et al., 2014). Therefore, given the null results in Experiment 1, a subsequent Bayesian repeated measures ANOVA in the same manner as the traditional ANOVA provided a consistent interpretation. There is strong evidence of a null effect of tACS ( $BF_{10} = 0.11$ ). Furthermore, we predicted an interaction of tACS and WM task and for this prediction there was no supporting evidence ( $BF_{10} = 0.38$ ). We note that our experimental design was not optimized for Bayesian analyses. Importantly, however, the take home message remains consistent regardless of the statistics leveraged in these analyses: tACS is not the fast-track brain hack of the future.

Neuromodulation remains an emerging field challenged by a large parameter space. Importantly, the mechanism underlying tACS differs from that of tDCS and there are important differences in their application (Antal and Herrmann, 2016). Thus, directly applying the observations from a tDCS study to a tACS protocol likely requires translation. However, there is reasonable value in doing so, after all both work by modulating neural activity to effect behavior. For example, tDCS can improve performance on sustained attention WM tasks (Andrews et al., 2011; Mulquiney et al., 2011; Zaehle et al., 2011). Similarly, a single session of 6 Hz tACS can be effective at improving performance on divided attention tasks (Hsu et al., 2019; Hsu et al., 2017). Across all neuromodulatory approaches, it may be essential to apply the appropriate frequency for each individual (Ali et al., 2013; Gulbinaite et al., 2017; Reinhart and Nguyen, 2019). This view is in line with the recent research demonstrating WM does not improve after a uniform tACS frequency administered to all participants, but it can when the tACS frequency is tailored to an individual endogenous theta peak (Reinhart and Nguyen, 2019).

In conclusion, the one-size-fits-all approach to neurostimulation is a suboptimal strategy for ensuring reliable benefits across homogenous populations. Going forward, pairing neurostimulation with neural measurements such as pre- and post-EEG recordings can clarify the neural mechanism(s) driving behavioral benefits. Tailoring stimulation protocols per known individual variables that modulate the effectiveness of tACS will maximize the cognitive benefits gained from neurostimulation interventions and reduce the variability when using



neurostimulation techniques. Identifying and addressing these factors requires consideration before attempting to improve WM with neurostimulation. This gap in knowledge is preventing reproducibility and a deeper understanding of the mechanisms that determine the effectiveness of both neurostimulation and WM training protocols.

## 5. Methods

### 5.1. Participants

**Experiment 1:** 30 right-handed neurotypicals participated (mean age (SD): 24.60 (6.54) years, 23 females). The University of Nevada Institutional Review Board approved both experiments. Participants provided informed consent and received \$20. Three participants were excluded due to below chance performance; 1 participant failed to return.

**Experiment 2:** 38 right-handed neurotypicals participated (mean age: 24.5, SD: 5.48, 25 females). Two participants were excluded due to below chance performance.

### 5.2. WM tasks

**3-Back Tasks.** Participants completed blocks of spatial and object 3-back tasks (Fig. 1). *Spatial* trials: participants remembered stimulus locations (green circles: 3°) across nine locations (500 ms), interleaved with delays (3000 ms). Participants indicated whether the current location matched the location shown two presentations earlier (match: 'J', non-match: 'F'). There were 45 practice and 138 experimental trials (66% non-match, 7 min). *Object* trials: identical but stimuli were centrally-located symmetrical polygons (Jiang et al., 2000). The WM tasks started immediately after the tACS begun in order to be conducted in an online manner.

**Operation Span.** Participants completed the Automated Operation Span (OSpan) (Unsworth et al., 2005) task as an independent measure of WM. Arithmetic problems are interleaved with letter sequences.

### 5.3. Transcranial alternating current stimulation

**Experiment 1:** Each session (3, counterbalanced), participants received 15 min of: 7 Hz tACS (in phase, 6300 cycles, 100 cycles fade in/out), 11 Hz tACS (in phase, 0 degrees phase angle offset, 9900 cycles, 100 cycles fade in/out), or sham tACS. Stimulation ramped over 20-seconds (0 to 1 mA). During sham, stimulation returned to 0 mA. Piloting at 1.5 mA (4 participants, 11 Hz) revealed distracting phosphenes (Matsumoto and Ugawa, 2017), and no participant reported any major adverse effects as a result of any stimulation condition when probed after each session. A second experimenter entered the condition code to preserve double-blinding. Electrodes lay over right PFC (F4) and PPC (P4). Each 5x5 cm electrode was encased in a saline-soaked sponge.

**Experiment 2:** During 3 counterbalanced sessions (> 24 h washout) participants received sham or 15 min of 1 mA 4.5 Hz tACS over right frontoparietal (F4, P4), or bifrontal (F3, F4) sites. Current was in phase, 4050 cycles, 100 cycles fade in/out. Participants and experimenter were double-blinded as to condition and no participants reported that they believed that they received sham stimulation on after any session.

## Declaration of Competing Interest

The authors declare no competing financial interests.

## Acknowledgments and Funding

Funding was provided by NSF [OIA 1632849, OIA 1632738 to MB]. The content is solely the responsibility of the authors and does not represent the official views of any funding agency.

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