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Efficacy of Transcranial Alternating Current Stimulation in the Enhancement of Working Memory Performance in Healthy Adults: A Systematic Meta-Analysis

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ABSTRACT

Background: Transcranial alternating current stimulation (tACS)—a noninvasive brain stimulation technique that modulates cortical oscillations in the brain—has shown the capacity to enhance working memory (WM) abilities in healthy individuals. The efficacy of tACS in the improvement of WM performance in healthy individuals is not yet fully understood.

Objective/Hypothesis: This meta-analysis aimed to systematically evaluate the efficacy of tACS in the enhancement of WM in healthy individuals and to assess moderators of response to stimulation. We hypothesized that active tACS would significantly enhance WM compared with sham. We further hypothesized that it would do so in a task-dependent manner and that differing stimulation parameters would affect response to tACS.

Materials and Methods: Ten tACS studies met the inclusion criteria and provided 32 effects in the overall analysis. Random-effect models assessed mean change scores on WM tasks from baseline to poststimulation. The included studies involved varied in stimulation parameters, between-subject and within-subject study designs, and online vs offline tACS.

Results: We observed a significant, heterogeneous, and moderate effect size for active tACS in the enhancement of WM performance over sham (Cohen's d = 0.5). Cognitive load, task domain, session number, and stimulation region showed a significant relationship between active tACS and enhanced WM behavior over sham.

Conclusions: Our findings indicate that active tACS enhances WM performance in healthy individuals compared with sham. Future randomized controlled trials are needed to further explore key parameters, including personalized stimulation vs standardized electroencephalography frequencies and maintenance of tACS effects, and whether tACS-induced effects translate to populations with WM impairments.

Keywords: Cognition, cortical oscillations, meta-analysis, tACS, working memory

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Working memory (WM)—the capacity for temporary storage and manipulation or reorganization of information held online—facilitates many higher-level cognitive functions (eg, learning, language, problem solving).[1] As a largely frontal lobe-mediated cognitive process, WM is linked to fluid intelligence and is involved in decision-making and goal-directed behaviors that are fundamental to everyday life.[2,3] Unfortunately, this critical cognitive ability typically decreases with age, even among healthy older adults, which can negatively affect quality of life, limit functional independence, and increase mortality rates among the older adult population.[4,5]

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Recent years have witnessed growing interest in the use of noninvasive brain stimulation (NIBS) techniques as interventions aimed at cognitive enhancement, maintenance of cognition, or slowing of age-related cognitive changes.[6–12] Most WM NIBS studies to date have used transcranial direct current stimulation (tDCS), which applies a direct current that affects the resting membrane potential of neurons.[13] In contrast, transcranial alternating current stimulation (tACS) is a form of NIBS that safely and painlessly alters cortical oscillations, rhythmic patterns of electrophysiological activity of the brain, in a frequency-specific manner.[14,15] Similarly to tDCS, tACS influences cortical excitability and brain activity but differs from tDCS by the application of alternating sinusoidal electrical currents (in-phase or antiphase) using electrodes placed over the scalp.[16,17] The mechanism of action involves entrainment of endogenous neural oscillations as a function of rhythmic shifts in membrane potentials to the set frequency of stimulation,[18–22] differing from tDCS. Frequency of tACS can be applied at a standard value across participants, or personalized (electroencephalography [EEG]-informed) to an individual's peak frequency of interest. tACS can synchronize (or desynchronize, depending on phase) neural oscillations to modulate cortical rhythms that underlie cognitive processes, manipulate brain activity, and affect behavior.[23–25] In addition to being dependent on phase and frequency of stimulation, effects of tACS on brain oscillations have also been shown to be task/state-dependent, in that the activities one engages in at the time of stimulation directly influence the effects elicited by stimulation.[23,25–27] Furthermore, evidence suggests that multiple sessions of tACS entrainment can elicit enduring neuroplastic changes and subsequent physiologic and behavioral aftereffects,[16,18,28,29] underscoring the therapeutic potential of tACS.[15]

Neural oscillations play an important role in a variety of cognitive functions, including WM.[27] Mounting evidence from EEG and magnetoencephalography studies indicates that WM is associated with synchronous activity across multiple frequency bands independently (eg, theta, alpha, beta, and gamma) in addition to cross-frequency coupling between theta and gamma (eg, theta-nested gamma).[30–34] Theta oscillations are thought to be involved in the organization of sequentially ordered WM items, whereas gamma-band oscillations appear to correspond to general maintenance of WM information.[35,36] Previous research has suggested that cross-frequency coupling between low (theta) and high (gamma) frequencies enables the processing of information held in WM, including the sequential ordering and maintenance of stimuli.[29,30,37,38] Disruption of theta frequency has been shown to impair WM performance.[39] A growing body of research suggests that tACS can enhance cognitive processes that underlie WM function in healthy individuals.[22,31,32,40,41] For instance, a study in healthy participants found that tACS applied at individualized theta frequency during a WM task increased short-term memory capacity in the active vs sham group.[42] Recent research has suggested that active frontotemporal theta tACS can enhance WM performance in healthy older adults to levels comparable with those of young adults.[32] There is also evidence that specific frequency bands are relevant to different features of WM, such as the positive association between gamma-band frequency (> 40 Hz) and performance at higher cognitive loads of WM tasks in healthy individuals.[30,31,43,44] The ability to manipulate cortical oscillations to a standardized frequency or personalized to an individual makes tACS a promising tool to alter the brain activity that underlies cognition.

However, although studies using tACS to enhance WM have shown promise, there exists variability in the response to tACS that is not yet well understood.[45] Moreover, the efficacy of tACS in enhancing WM in healthy individuals has not yet been explored in sufficiently large cohorts to be considered definitive. Therefore, the aim of this meta-analysis was to assess the efficacy of tACS in the enhancement of WM performance (eg, accuracy or reaction time) in healthy participants. Potential moderators of treatment effects such as stimulation parameters (including frequency of stimulation, number of sessions, duration, stimulation region, subject-specific frequency vs standard frequency), WM task demands (eg, cognitive load), verbal vs spatial tasks, and participant demographics were also explored, to determine potential moderator effects on tACS response. We hypothesized that active tACS vs sham would significantly enhance WM task performance and improve behavioral outcomes. We also hypothesized that tACS-induced effects on behavioral performance would be revealed in a task-dependent manner.

MATERIALS AND METHODS

This systematic meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[46,47]

Literature Search Strategy

One reviewer (Nicole R. Nissim) carried out literature searches to identify studies assessing tACS in the context of WM performance in healthy individuals. Articles were identified through a computerized literature search using the data bases Embase, PubMed, Web of Science, Cochrane Central Register of Controlled Trials, and clinicaltrials.gov. The search terms included for titles, abstracts, and keywords were "transcranial alternating current stimulation" OR "tACS" OR "oscillatory activity" AND "working memory" OR "executive function" OR "cognition." The search was limited to published research articles between January 1960 and March 2022 written in English. Using this approach, we identified 509 articles from Embase, PubMed, Web of Science, and Cochrane Central Register of Controlled Trials, and 24 records from ClinicalTrials.gov. The PRISMA flow diagram displays the procedures for study identification as seen in Figure 1. Additional thorough manual reviews of the articles were performed as described in Figure 1.

Eligibility: Inclusion/Exclusion

Articles were eligible for inclusion if the studies they reported 1) enrolled healthy human subjects; 2) involved administration of tACS either online or offline (eg, during or before behavioral assessments); 3) assessed WM performance before, during, or after stimulation; and 4) had > two participants. Between-subject studies with active vs sham trials and baseline data were included, in addition to within-subject crossover study designs. The rationale for requiring pre- and poststimulation data was to increase the validity and stability of WM performance across studies that assessed different cognitive aspects of WM and included heterogeneous stimulation protocols. The following factors excluded articles from meta-analysis: 1) case studies of a single participant; 2) studies involving clinical populations; 3) review articles; 4) studies involving nonalternating waveforms of transcranial electrical stimulation (tES); 5) studies that involved pharmacologic or other additional interventions; or 6) studies that assessed tACS only in

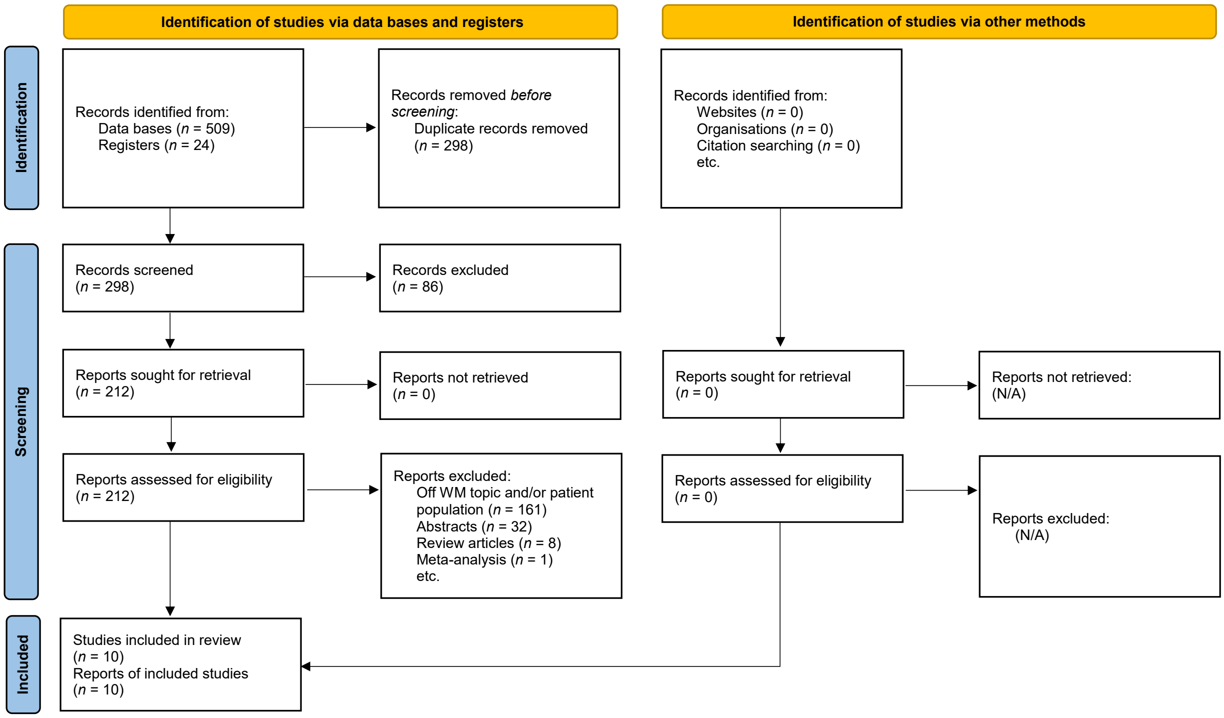

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart for the search and selection of studies. N/A, not applicable. [Color figure can be viewed at www.neuromodulationjournal.org]

motor or sensory contexts. Common reasons for excluding articles were duplication within the literature search, tACS applications in noncognitive domains, studies involving other brain stimulation techniques, review articles, or limited statistical reporting (eg, conference abstracts).

Literature Data Extraction

Manuscripts (titles, abstracts, and full texts) were independently screened by four of the authors (Nicole R. Nissim, Darrian C. McAfee, Shanna Edwards, and Amara Prato). Any disagreements during the selection process were resolved through collaborative discussion and consensus. The final selected studies are summarized in Table 1 and the study demographics in Table 2. For articles that met the inclusion criteria, the information extracted was author and publication year, study design, sample size, participant demographics (eg, age, sex, and education when reported), cognitive task, cognitive domain of the task (ie, verbal vs spatial WM task), mean performance and SDs (accuracy and/or reaction time) at baseline, during tACS, or after stimulation to calculate change score, and stimulation parameters including duration, frequency band, number of sessions, electrode location and size, region of stimulation (ie, frontal vs parietal vs frontoparietal vs frontotemporal), hemisphere (ie, bilateral vs left vs right), and personalized vs standard frequency.

Data Analyses

The Comprehensive Meta-Analysis software version 3 (CMA, Englewood, NJ) was used to perform analyses. To account for heterogeneity across studies due to differences in methods and sample characteristics, the random-effects model approach was used for all analyses.[55] The main outcome measures, accuracy, or reaction time on WM assessments were defined as the mean percent correct response or mean latency (millisecond) determined from the change score (baseline to poststimulation). For all studies, change in performance was calculated by comparing the mean accuracy or latency achieved before with during or after active and/or sham stimulation. If the means and SDs were not reported, effect sizes were calculated from reported univariate *F*-tests, *t*-statistics, or *p* values. In the event studies reported that active vs sham differences were not statistically significant, but did not report the direction of the effect, the direction was coded as negative to provide more conservative effect size estimates. Effect sizes were classified as small ($d \geq 0.20$), medium ($d \geq 0.5$) or large ($d \geq 0.80$), corresponding to previous conventions.[56] To determine whether statistical significance was achieved, CIs and *z*-transformations of the effect size were used. The criterion for statistical significance was achieved for mean effects within the 95% CI that did not span zero, providing evidence that tACS has a reproducible, robust effect on WM in healthy adults. Cochran Q-statistic, which computes the sum of the squared deviations from the estimate of each study from the overall meta-analysis estimate,[57] was used to assess how much of the total variability could be attributed to heterogeneity among the selected studies or whether variations in findings were due to chance alone.[58] Behavioral performance was analyzed across 32 effects in an overall omnibus analysis spanning different WM tasks. The data assignments used across all effects were paired groups (difference, *p*), paired groups (*N*, *t*-value), and independent groups (means, SDs). The number of effects is defined as *k;* Cohen's d is defined as *d*.

To assess factors that might influence response to tACS, we explored moderator variables that might affect behavioral outcomes in subgroup moderator analyses. Performance was further assessed on behavioral tasks with multiple effects. The categorical variables examined were WM task domains (three levels: identifying letters (verbal) vs spatial location vs object recognition (nonverbal),

Table 1. Data Summary of Included Studies in the Meta-Analysis.

Author, year	Study design	Session number	Duration (min)	Stimulation frequency	Electrode location (anode, cathode[s])	Electrode size	Concurrent task	Task	Task domain	Measure	Outcome
Meiron and Lavidor,[48] 2014	Between-subject	1	20	4.5 Hz; theta	Bilateral DLPFC (F3/F4)	4 × 4 cm	Online	N-Back	Verbal	Accuracy, RT	WM accuracy significantly improved
Jaušovec and Jaušovec,[40] 2014	Within-subject	2	15	personalized; theta	Left parietal (P3), right eyebrow	5 × 7 cm; 10 × 7 cm	Offline	Visual array comparison task	Spatial	Accuracy, RT	WM storage capacity significantly improved
Jaušovec et al,[49] 2014	Within-subject	2	15	personalized; theta	Left parietal (P3), right eyebrow	5 × 7 cm	Offline	Corsi block tapping task (FW/BW); Digit span (FW/BW)	Verbal-spatial	Accuracy	WM storage capacity significantly improved
Hoy et al,[31] 2015	Within-subject	1	20	40 Hz; gamma	Left frontal (F3), right supraorbital area	5 × 7 cm	Offline	N-Back	Verbal	Accuracy	Larger performance improvement in active vs sham, not statistically significant
Borghini et al,[50] 2018	Within-subject	4	20	10 Hz; alpha	Bilateral parietal (P3/P4)	5 × 7 cm	Online	Retro-cue WM paradigm	Spatial	Accuracy	WM recall accuracy significantly improved
Jones et al,[51] 2019	Within-subject	1	15	4.5 Hz; theta	Right DLPFC (F4), right parietal (P4)	5 × 5 cm	Offline	N-Back	Object	Accuracy	Object WM significantly improved
Bender et al,[52] 2019	Within-subject	2	12	4 Hz; theta	Right parietal (P4); Oz, Cz, and T8	19.6 cm^2; 4.9 cm^2 return	Online	Delayed match-to-sample	Visuo-spatial	Accuracy	WM storage capacity significantly improved
Reinhart and Nguyen,[32] 2019	Within-subject	1	25	personalized; theta	Left frontal (F3), left temporal (T3)	12 mm diameter, Ag/AgCl	Online	Change detection task	Object	Accuracy, RT	WM accuracy significantly improved
Biel et al,[53] 2022	Between-subject	1	14	6 Hz; theta	Left frontal (F3), left parietal (P3); Cz, focal	2.5 cm diameter	Online	Delayed Letter Recognition Task	Verbal	Accuracy, RT	Performance in demanding task significantly improved
Thompson et al,[54] 2021	Within-subject	1	20	35 Hz; gamma	Bilateral parietal (P3/P4)	5 × 7 cm	Online	Retro-cue WM paradigm	Visuo-spatial	Accuracy	WM recall accuracy significantly improved

Table 2. Study Sample Demographics.

Author, y	Sample size	Age (y)	Percent female	Education (mean year)
Meiron and Lavidor,[48] 2014	24	21.5	100	12.67 Active; 12.43 Sham
Jaušovec and Jaušovec,[40] 2014	12	20.6	66.6	–
Jaušovec et al,[49] 2014	12	20.5	75	–
Hoy et al,[31] 2015	18	29.3	50	16.23
Borghini et al,[50] 2018	25	69.1	44	16.2
Jones et al,[51] 2019	38	24.5	66	–
Bender et al,[52] 2019	14	21.9	85	–
Reinhart and Nguyen,[32] 2019	42	68.8	52	17
Biel et al,[53] 2022	24	21.3	58.3	–
Thompson et al,[54] 2021	51	24.1	58.8	–

cognitive load on N-Back task (1-Back vs 2-Back vs 3-Back vs 2-Back over 1-Back), accuracy vs reaction time, study design (between-subject vs within-subject), stimulation frequency (Hz), number of sessions (one vs two vs four), stimulated hemisphere (bilateral vs left vs right), stimulation region (frontal vs parietal vs frontoparietal vs frontotemporal), and online vs offline task performance. Meta-regression was performed to explore characteristics of continuous variables, including stimulation duration and participant demographics (mean age, education, percentage female vs male).

Publication bias was evaluated by visual assessment of the funnel plot, which provides a graphic scatter plot of the effect-size estimates from each study plotted against the result. A relatively symmetrical funnel plot indicates absence of publication bias, whereas an asymmetrical shape indicates bias among the included studies.[59] Egger's regression was used to quantify a statistical measure of the funnel plot.[60] An adjusted rank-correlation test was calculated according to the methods of Begg and Mazumdar.[51] The classic fail-safe *N* was used as a measure to identify the number of additional negative studies that would be needed to negate the current findings.[61]

RESULTS

From the initial data base search, we identified ten articles[31,32,40,48–54] that met our inclusion criteria and provided 32 effects (*k = 32)* included in the meta-analysis. All articles involved tACS, with 16 effects involving subject-specific frequency and 16 effects set at a standard frequency. The overall sample size across all effects included *n* = 695 healthy participants who underwent tACS during WM task performance (online) or tACS in between task assessments (offline). Study details are shown in Table 1.

Effects Across all tACS Studies and WM Tasks

Omnibus Analysis

The omnibus analysis of overall effects from active tACS across all WM tasks resulted in a significant and moderate improvement in behavioral performance over sham (k = 32; d = 0.514; 95% CI = 0.349–0.680; z = 6.105; p = 0.0001). Analysis of homogeneity indicated that specific study effect sizes were significantly heterogeneous (Q-stat = 91.47; df = 32; p = 0.0001). Given the variability across tasks, study-specific effect sizes, and differences in tACS parameters, moderator analyses were performed to better account for the observed heterogeneity. The study statistics and corresponding forest plot for the omnibus analysis are provided in Figure 2.

Moderator Analyses

Effect of Cognitive Load: N-Back Task

Assessment of cognitive load and its relationship with tACS revealed a significant difference such that 2-Back over 1-Back showed the greatest effect (k = 1, d = 1.709, 95% CI = 0.822–2.597, p <0.0001), followed by 2-Back (k = 4, d = 1.067, 95% CI = 0.376–1.76, p = 0.002), 1-Back (k = 2, d = 0.839, 95% CI = 0.373–1.304, p <0.0001), and 3-Back (k = 2 d = 0.072, 95% CI = -0.53 to 0.67, p = 0.813) (Q-stat = 10.32; df = 3; p = 0.02). This suggests that tACS effects on WM behavior are beneficial for the more challenging 2-Back over 1-Back condition but do not reliably influence the highest-level difficulty (ie, 3-Back [p > 0.05]).

Task Domains: Verbal, Spatial, and Object

Analysis of WM task domains included three levels: verbal, spatial, and object. We defined verbal tasks as those that used language-related stimuli, including single letters. Spatial tasks tested subjects on the location of visual stimuli, whereas object tasks tested recognition of sequentially presented visual stimuli. Active tACS had a significant and larger improvement in verbal WM tasks (k = 16; d = 0.720; 95% CI = 0.498–0.942) than in tasks testing spatial location (k = 6; d = 0.321; 95% CI = −0.154 to 0.796) and object recognition (k = 5; d = 0.238; 95% CI = −0.095 to 0.571) (Q-stat = 6.520; df = 2; p = 0.04).

Task Accuracy vs Reaction Time

Contrasts assessing accuracy (k = 25; d = 0.622; 95% CI = 0.453–0.790) vs reaction time (k = 7; d = -0.008; 95% CI = -0.247 to 0.231) revealed that accuracy was significantly and moderately enhanced from active tACS, whereas reaction time (d = 0.622) slowed as a function of stimulation (p = 0.0001).

Number of tACS Sessions

Contrasts assessing number of sessions indicated a significant, heterogeneous result suggesting that a higher number of sessions imparts greater benefit to WM behavior for active over sham stimulation (four sessions: k = 2; d = 0.750; 95% CI = 0.435–1.063; two sessions: k = 14; d = 0.735; 95% CI = 0.454–1.016; one session: k = 16; d = 0.301; 95% CI = 0.109–0.494) (Q-stat = 9.211; df = 2; p = 0.01).

Target Region of Stimulation

Contrasts assessing stimulation region revealed a significant effect between parietal, frontal, frontoparietal, and frontotemporal stimulation (k = 15, 5, 8, 4, respectively), in which parietal received

Study name	SD in means	SE	Variance	Lower limit	Upper limit	Z-Value	*p* Value
Meiron, 2014	1.265	0.447	0.200	0.388	2.141	2.828	0.005
Meiron, 2014a	0.418	0.413	0.170	-0.391	1.226	1.012	0.312
Jaušovec, 2014 (1)	1.137	0.370	0.137	0.411	1.863	3.070	0.002
Jaušovec, 2014a (1)	-0.312	0.296	0.087	-0.891	0.268	-1.055	0.292
Jaušovec, 2014b (1)	-0.049	0.289	0.083	-0.615	0.517	-0.170	0.865
Jaušovec, 2014 (2)	0.719	0.324	0.105	0.084	1.354	2.220	0.026
Jaušovec, 2014a (2)	0.635	0.316	0.100	0.015	1.256	2.008	0.045
Jaušovec, 2014b (2)	1.709	0.453	0.205	0.822	2.597	3.775	0.000
Jaušovec, 2014c (2)	0.785	0.330	0.109	0.138	1.432	2.377	0.017
Jaušovec, 2014d (2)	0.672	0.320	0.102	0.046	1.299	2.103	0.035
Jaušovec, 2014e (2)	0.897	0.342	0.117	0.227	1.566	2.623	0.009
Jaušovec, 2014f (2)	0.785	0.330	0.109	0.138	1.432	2.377	0.017
Jaušovec, 2014g (2)	2.208	0.535	0.286	1.159	3.257	4.125	0.000
Jaušovec, 2014h (2)	0.672	0.320	0.102	0.046	1.299	2.103	0.035
Hoy, 2015	0.431	0.246	0.061	-0.052	0.914	1.750	0.080
Borghini, 2018	0.749	0.226	0.051	0.305	1.193	3.310	0.001
Borghini, 2018a	0.749	0.226	0.051	0.305	1.193	3.310	0.001
Jones, 2019	0.378	0.168	0.028	0.049	0.707	2.251	0.024
Jones 2019a	-0.232	0.164	0.027	-0.554	0.090	-1.411	0.158
Bender, 2019	0.754	0.303	0.092	0.160	1.347	2.489	0.013
Bender, 2019a	0.714	0.299	0.090	0.127	1.300	2.384	0.017
Reinhart, 2019	0.577	0.167	0.028	0.250	0.903	3.461	0.001
Reinhart, 2019a	-0.099	0.155	0.024	-0.402	0.204	-0.639	0.523
Reinhart, 2019b	0.586	0.205	0.042	0.185	0.987	2.865	0.004
Reinhart, 2019c	-0.242	0.192	0.037	-0.617	0.134	-1.260	0.208
Biel, 2021	0.046	0.417	0.174	-0.773	0.864	0.109	0.913
Biel, 2021a	0.218	0.419	0.175	-0.602	1.039	0.521	0.602
Biel, 2021b	0.693	0.430	0.185	-0.149	1.535	1.612	0.107
Biel, 2021c	0.295	0.420	0.176	-0.528	1.118	0.703	0.482
Biel, 2021d	0.544	0.416	0.173	-0.270	1.359	1.309	0.190
Biel, 2021e	0.742	0.422	0.178	-0.085	1.569	1.758	0.079
Thompson, 2021	0.337	0.144	0.021	0.054	0.619	2.338	0.019
Omnibus effect→	0.514	0.084	0.007	0.349	0.680	6.105	0.000

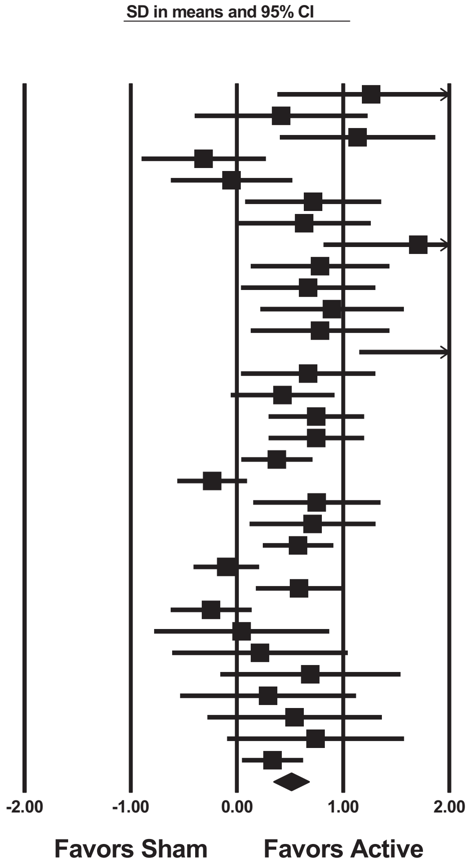

Figure 2. Overall meta-analysis effect size (Cohen's d omnibus effect = 0.514) of all included tACS studies. Corresponding forest plot shows the effects of favoring active stimulation (> 0) vs favoring sham stimulation (< 0).

the most benefit (d = 0.742), followed by frontal (d = 0.479), frontoparietal (d = 0.255), and frontotemporal stimulation (d = 0.202) (Q-stat = 9.082*; df* = *3; p* = 0.03).

Nonsignificant Moderator Variables

Nonsignificant moderator variables included 1) study design type (within-subject, *k* = 24; between-subject, *k* = 8) (Q-stat = 0.001, *df* = 1; *p* = 0.973); 2) online (*k* = 17) vs offline (*k* = 15) performance (Q-stat = 0.782; *df* = 1; *p* = 0.38); 3) waveform phase–in-phase (*k* = 28) vs antiphase (*k* = 2) (Q-stat = 1.559; df = 1; p = 0.212); 4) frequency (Hz) range 4 to 40 Hz (Q-stat = 2.848; d = 6; *p* = 0.83); 5) personalized (Hz) (*k* = 16) vs standard frequency (*k* = 16) (Q-stat = 0.470; *df* = 1; *p* = 0.50); 6) electrode type (conventional vs HD-tACS) (Q-stat = 1.104; *df* = 1; *p* = 0.30); and 7) stimulation hemisphere (bilateral vs left vs right; *k* = 5, 17, 10) (Q-stat = 0.133; *df* = 2; *p* = 0.071).

Meta-Regression for Continuous Variables

No significant differences were observed for stimulation duration (12-, 15-, 20-, 25-minutes) (*z* = −1.33; *p* = 0.19). Participant demographics did not reveal significant moderation of effect size by age (*z* = −1.10; *p* = 0.27) (mean age = 30.56 years; range = 20.5–69.6) or education (*z* = −1.22; *p* = 0.22; mean education = 16.7 years). In addition, young (k = 26) vs older adults (k = 6) was not a significant moderating variable (*p* = 0.364). Meta-regression revealed a significant moderation of effect size by percentage of female vs male participants (*z* = 1.95; *p* = 0.05), suggesting that studies with a higher number of female participants may benefit more from active tACS than from sham.

Publication Bias

Evaluation of publication bias revealed significant Begg (one-tailed *p* = 0.0003) and Egger (one-tailed *p* = 0.00018) tests, indicating the possibility of bias within this sample of literature.[62] Trim-and-fill analyses identified five putative outlier effects. If excluded, they only minimally reduced the omnibus effect size (d = 0.34).[56,63,64] Finally, the calculation of the classic fail-safe *N* indicated that 573 negative or "null" results would be needed to negate the present findings. Figure 3 displays the funnel plot for all included studies.

DISCUSSION

This systematic meta-analysis explored the efficacy of tACS in the enhancement of WM performance in healthy adults. Results revealed a significant, heterogeneous positive effect of active tACS in improving WM performance over sham. A previous meta-analysis assessed tACS on visual cognition[41] but assessed

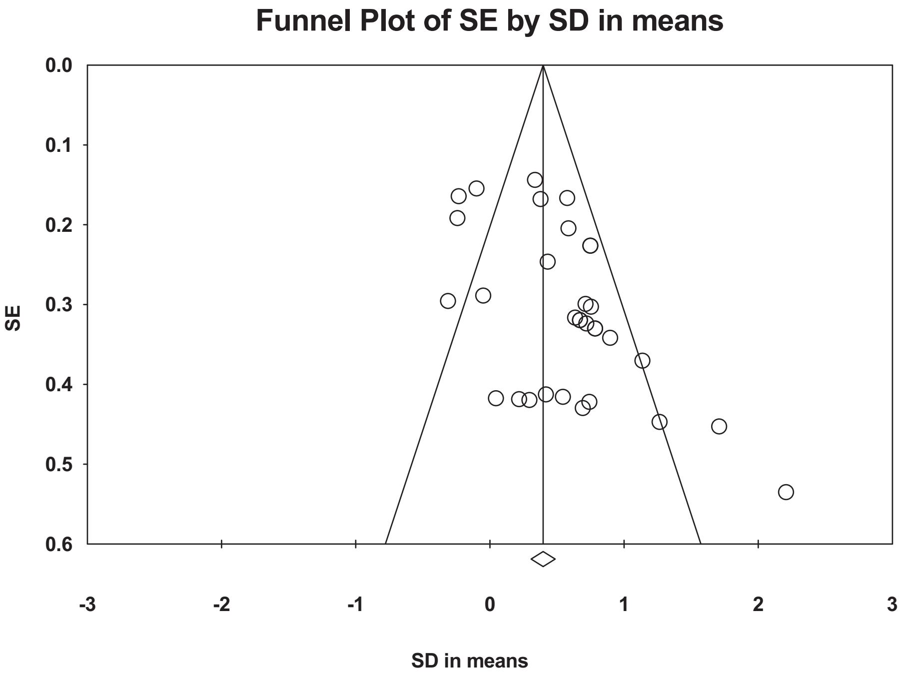

Figure 3. Funnel plot displays tACS effects for the assessment of publication bias.

different cognitive domains with no pooled effect size.[22] This meta-analysis extends the literature by assessing the effectiveness of tACS on WM behavioral performance and factors that might modulate stimulation effects, which, to our knowledge, has not been the primary focus of previous meta-analyses. In subanalyses, we explored potential moderator variables that could affect tACS response, including task-dependent effects, variations in stimulation parameters, and participant demographics. Collectively, these data suggest that active tACS may enhance WM performance in healthy individuals over sham.

As we predicted, a task-dependent effect of tACS was identified on the N-Back task, suggesting cognitive load may be important for stimulation response. The load effect was specific to 2-Back over 1-Back condition (which targets attention but lacks the manipulation aspects of WM), whereas the 3-Back condition was not significant. This indicates that capacity of tACS-induced enhancement may depend on the nature of the task, with limits that might relate to WM network ceiling effects, given the nonsignificant 3-Back condition. Previous research has shown that task-dependent effects of tES cognitive enhancements relate to the nature and cognitive load of the task being performed during stimulation;[6,31,65,66] this finding is also corroborated with state-dependent effects of tACS (ie, physiological state and fluctuations in neural activity) that have been suggested to occur in the motor system.[25] These results also align with functional neuroimaging evidence indicating that neural activation of WM-related brain regions correlates with the cognitive demands of a task.[67,68]

Verbal and nonverbal WM tasks are supported by different neural processes,[69] which could be differentially affected by tACS. Thus, we examined differences in task domain as potential moderating factors across three levels (verbal, spatial, and object stimuli). We identified significantly larger improvements in verbal than in spatial and object recognition tasks. Previous neuroimaging studies point to hemispheric lateralization between verbal vs spatial WM in left hemisphere (LH) vs right hemisphere (RH), respectively.[70] Because site specific effects may alter the impact of tACS for different WM subdomains, our results should be interpreted cautiously; very few studies in our analysis compared performance on the same behavioral task paired with stimulation at different sites.

Given the bihemispheric network of brain regions that are known to subserve WM, we examined hemisphere and stimulation region as moderator variables. Stimulation region was a significant moderator for active tACS—parietal lobe had the strongest effect on WM behavior, followed by frontal, frontoparietal, and frontotemporal. Hemisphere of stimulation (LH, RH, bilateral) did not significantly moderate tACS effects. The parietal region is understood to be an essential node in the WM network,[71] with involvement in short-term storage and retrieval of phonologically coded verbal information.[72] Patients with superior parietal lesions exhibit deficits when WM tasks require manipulation of information and show normal performance on rehearsal/retrieval processes, which indicates the critical nature of the parietal lobe during manipulation of WM information.[71] Our results suggest that parietal tACS is associated with improvement in several WM functions. This indicates that stimulation to other brain regions may be less effective. These findings underscore the importance of determining appropriate and optimal targets for WM task enhancement through tACS.

Across all effects, accuracy and reaction time were influenced by active stimulation over sham; accuracy significantly improved, whereas reaction time, a proxy for processing speed, slowed in response to stimulation. This is broadly consistent with previous research exploring tACS for cognitive remediation in healthy older adults, in which accuracy, but not reaction time, has been shown to be enhanced by active stimulation.[32] This is also consistent with previous studies using tDCS.[6,73] However, the finding could represent a speed-accuracy tradeoff whereby, owing to the WM benefits induced by stimulation, individuals are able to respond with fewer errors but at the cost of responding more slowly.[74]

Stimulation parameters including number of sessions and frequency (Hz) (standardized vs personalized [Hz]), are important factors that can affect tACS response. Consistently with previous studies,[75–77] we found that number of sessions (four vs two vs one) significantly moderated response to stimulation; a higher number of sessions was associated with more robust effects. This finding may relate to underlying mechanisms of neuroplasticity; studies of tES have shown that repeated sessions of stimulation may produce stable long-term changes in neuroplasticity through mechanisms like long-term potentiation.[76–78] Stimulation frequency, including standardized vs personalized Hz, did not significantly moderate tACS effects. It has been suggested that personalized frequency may confer greater benefits in behavior than does a standard frequency across participants.[32] However, our results suggest no significant difference between EEG-informed tACS vs standardized frequency across healthy participants. This may not necessarily mean that personalized tACS is less effective; across studies, different approaches are used to determine endogenous peak frequency (eg, EEG-triggered transcranial magnetic stimulation, closed-loop NIBS during task/rest).[22,27,32,79–82] Different methods may impart variability in personalization of tACS. More insight is needed to reduce the potential variability of EEG-informed tACS effects across studies. In addition, participant demographics may be a confounding factor; most studies included relatively young adults with high performance rates and ceiling effects compared with older adults with normal age-related decline.

Other parameters important to tACS response include duration of stimulation, online or offline task performance, in-phase vs antiphase waveforms, and conventional vs HD-tACS. Duration of stimulation (12-,15-, 20-, 25-minutes) was not associated with significant differences in tACS effects. This may indicate that the maximum benefit from tACS can be achieved in a short stimulation session in healthy young adults. Variables such as online (during) or offline (after stimulation) performance, in-phase vs antiphase, and conventional vs HD-tACS were also not significant moderators of response to tACS.

Demographic features such as age, sex, and education have the potential to influence response to stimulation and were examined as covariates using meta-regression. Mean age and education were nonsignificant factors with respect to stimulation effects. The age range across all effects was 20.5 to 69.6 years. We categorized subjects as young vs older adults (26 vs 6 effects, respectively) to examine potential age-related differences in tACS response but observed none. Sex was a significant covariate in response to stimulation; a higher percentage of female participants in studies was associated with greater WM performance. However, this finding could be driven largely by the higher number of women in this particular sample, and not an actual biological difference in response to tACS.

This study had several limitations. Although our criteria were broad, the final number of studies that met inclusion was low, and stimulation protocols varied. We acknowledge that methodologic heterogeneity across tACS protocols limits the ability to identify the most beneficial strategy. To be comprehensive, we performed several moderator analyses in which only a small number of effects could be compared. One area in which we think more data are needed is the determination of whether stimulation at personalized tACS frequencies vs standardized frequency influences stimulation effects in samples of young healthy adults. Specific regions of the WM network that are preferentially involved in particular aspects of WM may be differentially influenced by tACS (ie, variability of functional connectivity between regions within the WM network could affect response to stimulation). Future research combining tACS with neuroimaging techniques (eg, EEG, functional magnetic resonance imaging [MRI]; structural MRI) may provide greater insights into brain processing during WM performance and aid in the optimization of targeted stimulation sites for tACS WM enhancement.

CONCLUSIONS

In summary, we identified a significant, heterogeneous effect of tACS on the enhancement of WM performance and several factors that may affect response to stimulation. Future research in this area will need to address substantive gaps in the existing data by conducting studies with larger subject samples, increasing the focus on important parameter settings and protocol optimization, and further examining structure-function relationships mediating the effects of stimulation on specific WM abilities. Future studies that explore cross-frequency coupling during tACS and WM performance may provide greater guidance toward protocol optimization. Nonetheless, this meta-analysis provides support for the use of tACS as a tool to interrogate and improve WM and foundational evidence to support the exploration of tACS as a potential intervention for clinical populations with WM deficits.

Authorship Statements

Nicole R. Nissim was responsible for the project, literature search, data analyses, figures, and tables and prepared the original draft of the manuscript. Darrian C. McAfee, Shanna Edwards, Amara Prato, and Jennifer X. Lin aided in screening articles and compiling data. Jennifer X. Lin and Zhiye Lu aided in the manuscript draft and tables. H. Branch Coslett and Roy H. Hamilton were responsible for intellectual contribution to screening and extracted data, contributed to analyses, and aided in manuscript edits. All authors reviewed and approved the final manuscript.

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COMMENTS

This meta-analysis, which demonstrated that tACS is a useful and applicable technique that can increase WM capacity in healthy individuals, is another important step towards finding an effective tool for improving WM. The different experimental designs, stimulation parameters, WM tasks, variables, and outcomes were logically sorted and put into context. A very meritorious and necessary work.

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The meta-analysis by Nissim and colleagues systematizes and summarizes research to address the efficacy of tACS on WM in healthy individuals. The paper provides a good snapshot of the current state of the evidence and highlights the important factors that might be relevant when designing studies or analyzing results, including cognitive load/task difficulty, task domain/material, stimulation target/electrode positioning. The paper also draws attention to recent efforts to personalize tACS parameters and implementing an EEG-informed approach to adjusting the stimulation parameters. These efforts might be a way forward to increase the efficacy of tACS to modulate network-dependent functions. Despite the value of the presented results, it should be noted that only the studies with pre-post tACS assessment of WM were included in the analysis. Therefore, the conclusions are limited to specific experimental design in either between- or within-subject experiments. This, in my view, opens up an important question (which surpasses the scope of Nissim et al paper) of the nature of the cognitive function and the psychometric properties of the measures we use in brain stimulation experiments. Namely, the underlying assumption behind adopting the same session pre-post design is that the outcome measure reflects individual's state, thus exhibits great deal of day-to-day within-person variability (ie, has low test-retest reliability). This assumption is rarely corroborated with data in any given experiment and does not consider the retest effect as a potential confound (Scharfen J, Jansen K, Holling H. Retest effects in working memory capacity tests: a meta-analysis. *Psychon Bull Rev*. 2018;25:2175–2199. https://doi.org/10.3758/s13423-018-1461-6). Furthermore, other relevant task properties (eg, homogeneity, discriminative power, etc) tend to be overlooked or at least not systematically reported when assessing brain stimulation effects of cognition. Therefore, it is important to open a discussion on psychometrically informed experimental designs and increasing the precision and the validity of the outcome measures, as this might be one of the hidden sources of variability of the reported effects.

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