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Transcranial random noise stimulation is more effective than transcranial direct current stimulation for enhancing working memory in healthy individuals: Behavioural and electrophysiological evidence

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) has been shown to improve working memory (WM) performance in healthy individuals, however effects tend to be modest and variable. Transcranial random noise stimulation (tRNS) can be delivered with a direct-current offset (DC-offset) to induce equal or even greater effects on cortical excitability than tDCS. To-date, no research has directly compared the effects of these techniques on WM performance or underlying neurophysiological activity.
Objective: To compare the effects of anodal tDCS, tRNS + DC-offset, or sham stimulation over the left dorsolateral prefrontal cortex (DLPFC) on WM performance and task-related EEG oscillatory activity in healthy adults.
Methods: Using a between-subjects design, 49 participants were allocated to receive either anodal tDCS (N = 16), high-frequency tRNS + DC-offset (N = 16), or sham stimulation (N = 17) to the left DLPFC. Changes in WM performance were assessed using the Sternberg WM task completed before and 5- and 25-min post-stimulation. Event-related synchronisation/desynchronisation (ERS/ERD) of oscillatory activity was analysed from EEG recorded during WM encoding and maintenance.
Results: tRNS induced more pronounced and consistent enhancements in WM accuracy when compared to both tDCS and sham stimulation. Improvements in WM performance following tRNS were accompanied by increased theta ERS and diminished gamma ERD during WM encoding, which were significantly greater than those observed following anodal tDCS or sham stimulation.
Conclusions: These findings demonstrate the potential of tRNS + DC-offset to modulate cognitive and electrophysiological measures of WM and raise the possibility that tRNS + DC-offset may be more effective and reliable than tDCS for enhancing WM performance in healthy individuals.

Introduction

There is significant interest in the use of non-invasive transcranial electrical stimulation (tES) techniques to modulate a wide range of cognitive functions in both healthy and clinical populations [1]. The working memory (WM) system is among the most

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common targets for neuromodulation as it is central to a range of higher-order cognitive functions and is frequently impaired in many neurological and psychiatric conditions [2,3]. Delivery of anodal transcranial direct current stimulation (tDCS) to the left dorsolateral prefrontal cortex (DLPFC), a brain region crucially involved in WM processing [4,5], has been shown to significantly improve WM performance in healthy individuals [6–8]. However, recent systematic reviews and meta-analyses have highlighted that the effects of tDCS on WM performance are typically modest and heterogenous between studies [9–12]. There is also evidence that effects of tDCS are highly variable between individuals with regard to modulation of cognitive performance [11,13] and underlying brain activity [14]. These findings highlight the need to improve understanding of how tDCS influences the neurophysiological activity underlying WM and suggests the need for further research examining whether other forms of tES may induce more consistent effects on cognitive performance.

One factor thought to limit the effectiveness of tDCS is the activation of homeostatic neural mechanisms which counter-regulate the persistent changes in neuronal membrane potentials induced by direct current stimulation [1,15]. While tDCS delivers a direct electrical current with a constant intensity and fixed polarity at each electrode, transcranial random noise stimulation (tRNS) is another form of tES which delivers an alternating current with a randomly fluctuating frequency and intensity. In contrast to tDCS, it has been proposed that tRNS may induce more pronounced and reliable neuromodulatory effects by delivering a randomly fluctuating electrical field which prevents activation of homeostatic mechanisms [15]. tRNS can also be delivered with a direct current offset (DC-offset) to produce a unidirectional current flow analogous to tDCS, thereby combining the characteristics of tDCS (i.e. net polarisation of neuronal membrane potentials) and tRNS (i.e. introducing noise into the neural system) [16]. While several studies have found that delivering tRNS without a DC-offset can produce similar or even greater neuromodulatory effects on cortical excitability than anodal tDCS [17–19], recent evidence suggests that tRNS + DC-offset can induce more pronounced enhancements [16]. This raises the possibility that tRNS + DC-offset may prove more effective as a means to enhance cognitive performance; however, we are not aware of any research examining the effects of tRNS + DC-offset on WM performance or WM-related neurophysiological activity in healthy individuals.

Neurophysiological measures derived from electroencephalography (EEG) can provide an objective and temporally-precise means to examine the neuromodulatory effects of tES. WM processing in healthy individuals is supported by reliable and robust modulations of neural oscillatory activity within the theta (4–8 Hz), upper alpha (10–12.5 Hz), and gamma (30–100 Hz) frequency ranges [20–22]. Several studies have observed that enhancements in WM performance following anodal tDCS were accompanied by modulation of task-related oscillatory activity, indicating that modulation of oscillatory activity may reflect a potential neurophysiological process underlying the cognitive-enhancing effects of stimulation [23–25]. Further, electrophysiological effects of tDCS have been observed in the absence of improvements in cognitive performance [14], indicating that neurophysiological measures derived from EEG may be more sensitive than cognitive measures alone.

The current study aimed to directly compare the neuromodulatory effects of anodal tDCS and tRNS + DC-offset on WM performance and WM-related oscillatory activity in healthy adults. We hypothesised that both tDCS and tRNS would induce greater enhancements in WM performance when compared to sham stimulation. We further hypothesised that tRNS + DC-offset would induce greater increases in WM performance than anodal tDCS. We also hypothesised that, when compared to anodal tDCS, tRNS + DC-offset would induce more consistent improvements in WM performance. Exploratory analyses were also performed to investigate effects of tES on oscillatory activity recorded during completion of the WM task. We did not construct specific hypotheses regarding the direction of changes in oscillatory activity due to the paucity of relevant previous research.

Methods

Participants

Forty-nine healthy adults were recruited into the study. Written informed consent was obtained from all participants prior to engaging in the study. The experimental protocol was approved by the Alfred Human Research Ethics Committee and Monash University Human Ethics Committee and was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12612001061820). All participants were aged between 18 and 65 years, fluent in English, had normal or corrected-to-normal vision, and were confirmed as right-handed using the Edinburgh Handedness Inventory [26]. Prior to inclusion, participants were screened for current psychopathology using the Mini International Neuropsychiatric Interview for the DSM-IV [27], and a safety-screen was completed to identify and exclude any participants with contraindicators to tES. No participants were taking psychoactive medication at the time of testing, and none reported recreational drug use in the previous month. Using a parallel-group study design, participants were allocated to receive either tDCS, tRNS + DC-offset, or sham stimulation. Stratified randomisation was used to allocate participants to each condition based on age, gender, and WM ability as assessed using the Working Memory Index from the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) [28]. The stimulation groups did not significantly differ in age, years of formal education, or WM ability (all $p > .10$) (see Table 1 for demographic and clinical characteristics of the participants). All clinical interviews and cognitive tasks were administered by a single researcher trained in standardised administration.

Design and procedure

Data was collected during a single experimental session conducted at the Monash Alfred Psychiatry Research Centre, Melbourne. Participants first completed a clinical interview to collect demographic data and assess WM ability, and were then allocated to receive either sham stimulation, tDCS, or tRNS. The Sternberg WM task with concurrent EEG recording was administered at BASELINE, as well as approximately 5-min (POST-1) and 25-min (POST-2) following the end of stimulation (see Fig. 1 for illustration of study procedure and protocol). While not reported in the current study, effects of tES were also assessed using combined transcranial magnetic stimulation and EEG (TMS-EEG), recorded at BASELINE, as well as approximately 15-min (POST-1) and 35-min (POST-2) following the end of stimulation. Details of TMS-EEG procedure are presented in supplementary materials. There was minor variation in the timing of EEG and TMS-EEG recording post-tES (~15–30 s difference between participants), which reflected the time required to remove the tES electrodes and re-attach the EEG recording electrodes.

Transcranial electric stimulation

tES was delivered while participants completed the Paced Auditory Serial Addition Task (PASAT) (described below), given evidence that engaging in concurrent cognitive activity whilst

Table 1
Participant demographic characteristics (mean ± SD).

	Sham	tDCS	tRNS	F-statistic	*p*-value
Sample (*n*)	17	16	16		
Gender (F/M)	12/5	11/5	10/6		
Age (years)	31.05 ± 13.06	30.43 ± 12.01	27.60 ± 8.60	0.42	.659
Years of education	14.35 ± 1.69	14.75 ± 1.84	15.00 ± 1.41	0.64	.532
WAIS-IV WMI	108.59 ± 13.37	108.50 ± 9.56	111.06 ± 11.75	0.25	.778

Degrees of freedom = 48 for all comparisons.

receiving tDCS can produce more pronounced after-effects [29]. Stimulation was delivered using an Eldith Stimulator Plus (NeuroConn, Germany) and a pair of rectangular 5 × 7 cm electrodes (35 cm^2) attached to the scalp using Ten20 conductive paste (Weaver and Co., Colorado, USA). For all stimulation conditions, the anodal electrode was placed over the left DLPFC (F3 using the 10–20 system of electrode placement) and the cathodal electrode was placed over the right supraorbital area. tDCS was delivered at 1 mA (current density = 0.029 mA/cm^2) for a duration of 22 min (60 s ramp-up, 60 s ramp-down). High-frequency tRNS (100–640 Hz) was delivered with an intensity of 1 mA and a DC-offset of 1 mA for a duration of 22 min (60 s ramp-up, 60 s ramp-down). A high-frequency range was chosen based on previous research that the neuromodulatory effects of tRNS are primarily driven by oscillations in the upper end of the frequency range (100–640 Hz) [15]. Delivering tRNS + DC-offset with these parameters ensures that each electrode maintains a consistent polarity and produces a unidirectional current flow analogous to tDCS [16], whereby the current passes from the positively-charged anode (over the left DLPFC, current intensity fluctuates between +0.5 mA and +1.5 mA) to the negatively-charged cathode (over the right supraorbital area, current intensity fluctuates between −0.5 mA and −1.5 mA). Importantly, the stimulation parameters chosen for tDCS and tRNS + DC-offset ensures that both techniques deliver an approximately equivalent net charge over the course of the stimulation session (mean charge of +1 mA at anode and −1 mA at cathode) and is therefore appropriate for directly comparing effects of tES techniques. Sham stimulation was delivered for 22-min and involved delivery of active tDCS for a total of 2.5 min (60s ramp-up, held constant for 30s, 60s ramp-down). This sham procedure elicits an initial itching sensation under the electrodes to aid blinding, but participants receive no current for the remaining stimulation period, and has been shown to result in successful participant blinding [30,31]. Immediately following the end of stimulation, participants completed a questionnaire to evaluate whether tES caused any discomfort or adverse effects. The integrity of stimulation blinding was also assessed at this time by asking participants to report whether they believed they had received active or sham stimulation.

Estimation of the induced cortical electrical fields for tDCS and tRNS + DC-offset was achieved using the ROAST toolbox in MATLAB, which utilises a finite-element model of tES current-flow based on an MRI-derived template head [32]. Models were based on 7 × 5 cm rectangular electrodes (with a 3 mm thickness and a 2 mm layer of gel) placed over electrode sites F3 (corresponding to the left DLPFC) and AF8 (corresponding to the right supraorbital region). Default toolbox settings were used for determining conductivities of biological matter (i.e. skin, bone, cerebrospinal fluid, white/grey matter). For both tDCS and tRNS + DC-offset, finite-element modelling indicated that the induced electric field was maximal in the area surrounding the electrodes, with positive currents largely confined to the left frontal cortex. Further details of electrical field models are presented in supplementary materials.

Working memory tasks

Paced Auditory Serial Addition Task (PASAT)

Participants completed three 5-min blocks of the PASAT whilst receiving tES. The PASAT is a challenging mental arithmetic task which has been shown to engage fronto-parietal regions involved in WM processing, including the DLPFC [33,34]. We used an adaptive version of the PASAT in which interstimulus interval between the presentation of numbers adjusted based on the participants performance, thereby ensuring that the task remained challenging but achievable for all participants [35,36]. Participants began the first block of the PASAT after the initial ramping-up period for tES had ended, and each block was separated by a 1-min break. Further details of task administration and structure are presented in supplementary materials.

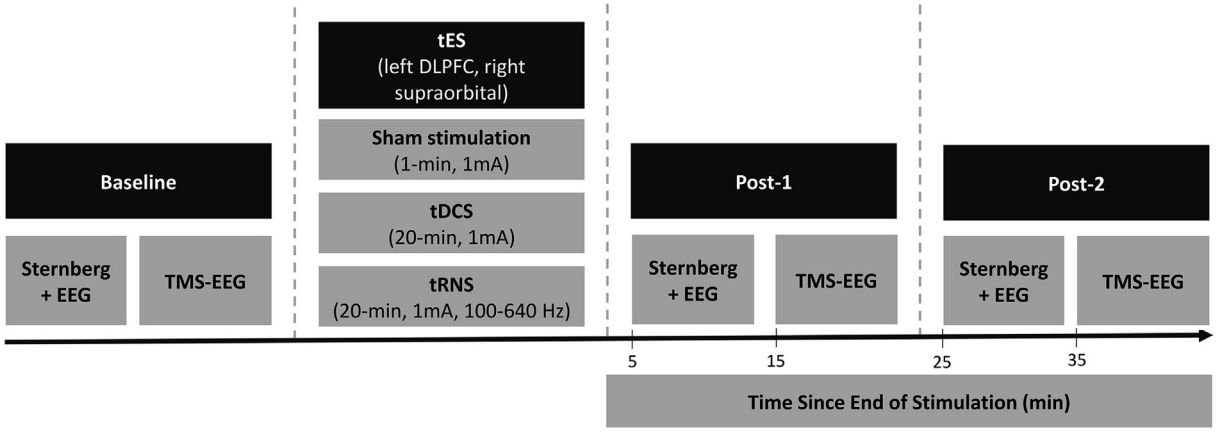

Fig. 1. Overview of experimental design and protocol.

Sternberg working memory task

Effects of tES on WM performance were assessed using a Sternberg WM task presented with Neuroscan Stim2 software (Compumedics, Melbourne, Australia). The task simultaneously presented eight letters to remember which were randomly selected from a set of 15 consonants. Following a retention period, participants were presented with a probe letter and responded as to whether it was present in the memory set. Sternberg task design and stimuli timing are presented in Fig. 2. Participants completed 52 trials of the Sternberg WM task with a short 30 s break in the middle, resulting in a total task duration of 10 min and 59 s. Additional task details are described in supplementary materials.

Electrophysiological recording and pre-processing

A detailed methodological description of EEG setup, recording, and pre-processing is provided in the supplementary materials. Briefly, 34 single Ag/AgCl scalp electrodes recorded EEG activity to Neuroscan Acquire software using a Synamps 2 amplifier (Compumedics, Melbourne Australia). Impedances were kept below 5 kΩ prior to recording. EEG was sampled at 1000 Hz with a bandpass of 0.1–100 Hz. EEG data was analysed offline in MATLAB (The Mathworks, Natick, MA) using EEGLAB for pre-processing (sccn.ucsd.edu/eeglab) [37] and fieldtrip for frequency analysis (http://www.ru.nl/donders/fieldtrip) [38].

Spectral analysis

EEG data was converted into the frequency domain using Morlet Wavelet Transform (3.5 oscillation cycles with steps of 1 Hz). Neural oscillatory power was calculated for each electrode within the theta (4–7 Hz), upper alpha (10–12.5 Hz), and gamma (35–45 Hz) frequency bands, with the frequency ranges chosen to correspond with previous research examining oscillatory activity during WM and the Sternberg task [39–44]. Modulation of oscillatory power was calculated as event-related synchronisation/desynchronisation (ERS/ERD%), which provides positive values when oscillatory power increases in the active test period compared to the reference period. The reference period used for baseline correction was defined as the middle 600 ms of the blank screen between the fixation cross and memory set. Average ERS/ERD% for each frequency band was calculated across the encoding (1800–5800 ms) and maintenance (5800–8800 ms) periods and then averaged over trials for each participant.

Statistical analysis

All statistical analyses were performed using either IBM SPSS Statistics, version 25 (IBM Corp, Armonk, NY) or MATLAB. Chi-square tests were used to assess the effectiveness of stimulation blinding between groups.

Cognitive data

Accuracy and response time on the Sternberg WM task were used as the primary WM outcome measures. One-way ANOVAs were used to confirm that stimulation conditions did not significantly differ in accuracy or response time at BASELINE (both $p > .05$). Effects of tES on accuracy and response time were first assessed separately using 3×3 mixed ANOVAs with CONDITION (sham, tDCS, and tRNS) as the between subjects factor and TIME (BASELINE, POST-1, and POST-2) as the within-subjects factor. Significant interaction effects were further explored via separate repeated measures ANOVAs for each stimulation condition to examine changes over TIME (BASELINE, POST-1, POST-2). Additionally, one-way ANOVAs were used to compare change-from-baseline (i.e., POST-1 - BASELINE, POST-2 - BASELINE) scores (Δ-scores) between stimulation conditions at each time-point (Δ-POST-1, Δ-POST-2). Analysis of Δ-scores allows for a direct comparison of whether changes in WM performance significantly differed between stimulation conditions, and is consistent with previous research examining tES-induced changes in WM performance [25,45]. Pairwise comparisons with Bonferroni correction were used to explore any significant main effects. Mauchly's test was used to evaluate the assumption of sphericity, with Greenhouse-Geisser corrections applied where appropriate. Finally, for WM performance variables which displayed significant changes over time, we examined the consistency of improvement induced by tDCS and tRNS by comparing the proportion of participants in each stimulation group who demonstrated improvements in accuracy which were greater than simple practice effects, defined as the mean change in performance displayed by the sham group from BASELINE to POST-1 or POST-2. A chi-square test was used to compare whether the proportion of participants displaying improvements greater than practice effects significantly differed between the tDCS and tRNS groups at POST-1 or POST-2.

EEG data

EEG data from 5 participants were excluded due to technical errors (2 participants) and excessive artefact in the EEG recording (3 participants), resulting in a total of 44 participants with valid EEG data (sham $n = 16$, tDCS $n = 14$, tRNS $n = 14$). Effects of tES on task-related oscillatory ERS/ERD% were examined via non-parametric cluster-based permutation analyses using the Fieldtrip toolbox [38]. This technique allows examination of global changes in oscillatory ERS/ERD% across all EEG electrodes whilst also controlling for multiple comparisons [46] and has been used in previous studies examining the effects of tES on WM-related oscillatory activity [40,45]. Clusters were defined as two or more neighbouring electrodes with a t-statistic < 0.05. Monte Carlo p-values (two-tailed) were then subsequently calculated using 2000 iterations. Effects of tES on oscillatory ERS/ERD% were first examined separately for each group using a repeated measures ANOVA design to compare changes in oscillatory ERS/ERD% over time from

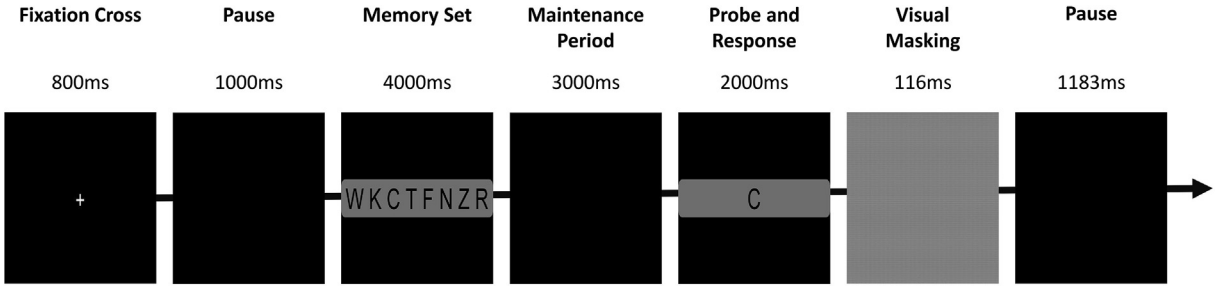

Fig. 2. Sequence and timing of stimuli for the Sternberg WM task.

BASELINE to POST-1 or POST-2. When any significant changes in oscillatory ERS/ERD% were observed over time, further comparisons were conducted using Δ-scores to compare whether the three stimulation conditions significantly differed in their effects on oscillatory ERS/ERD%, consistent with previous research examining effects of tES on WM-related oscillatory activity [25,45].

Results

Working memory performance

Accuracy

A significant time by stimulation condition interaction was observed for Sternberg task accuracy (F (4,92) = 3.855, p = .006, η_p^2 = 0.144). Post-hoc analyses revealed that accuracy significantly increased following tRNS (F (2,30) = 26.716, p < .001, η_p^2 = 0.640), with pairwise comparisons showing that accuracy significantly increased from BASELINE to POST-1 (mean difference = 11.06, p < .001), and from BASELINE to POST-2 (mean difference = 7.09, p = .002) (Fig. 3). No significant changes in accuracy were observed following either sham (F (2,32) = 2.965, p = .066, η_p^2 = 0.156) or tDCS (F (2,30) = 0.023, p = .977, η_p^2 = 0.002) (Fig. 3).

Direct comparison of stimulation conditions using accuracy Δ-scores revealed significant group differences at POST-1 (F (2,48) = 11.148, p < .001, η_p^2 = 0.326), with pairwise comparisons revealing that tRNS displayed significantly larger improvements in accuracy when compared to both sham (mean difference = 6.31, p = .036) and tDCS (mean difference = 11.54, p < .001), whereas no significant difference was observed between sham and tDCS (mean difference = 5.23, p = .106) (Fig. 4). As illustrated in Fig. 4, participants receiving tRNS displayed a more consistent pattern of improvement from BASELINE to POST-1, with 13 of the 16 participants in the tRNS group (81.25%) demonstrating improvements in accuracy that were larger than the mean improvement following sham (i.e. simple practice effects), whereas only 5 of the 16 participants in the tDCS group (31.25%) met this criterion. When compared to the tDCS group, a significantly higher proportion of individuals in the tRNS group displayed improvements in accuracy from BASELINE to POST-1 which were larger than simple practice effects (χ^2 (2, N = 49), = 8.20, p = .017).

Comparison of accuracy Δ-scores at POST-2 did not reveal significant differences between stimulation conditions (F (2,48) = 2.341, p = .108, η_p^2 = 0.092). Similar to the pattern of results observed at POST-1, participants receiving tRNS displayed a more consistent pattern of improvement from BASELINE to POST-2, with 11 of the 16 participants in the tRNS group (68.75%) demonstrating improvements in accuracy that were larger than the mean improvement following sham, whereas only 6 of the 16 participants in the tDCS group (37.50%) met this criterion. However, the proportion of participants who demonstrated improvements in accuracy which were greater than practice effects did not significantly differ between the tDCS and tRNS groups at POST-2 (χ^2 (2, N = 49), = 3.14, p = .208).

Response time

No significant time by stimulation condition interaction was observed for response time (F (3.53,81.25) = 1.589, p = .191, η_p^2 = 0.065) (Fig. 5). As the interaction term for response time was non-significant, no further analyses were performed for this variable.

Oscillatory ERS/ERD% during working memory processing

Exploratory analysis of oscillatory ERS/ERD% for the tRNS group revealed a significant increase in encoding period theta ERS from BASELINE to POST-1, which was present over left frontal regions (p = .008) (Fig. 6) and left parieto-occipital regions (p = .042). The tRNS group also displayed a significant reduction in encoding period gamma ERD over left frontal regions from BASELINE to POST-1 (p = .023) (Fig. 6). The tRNS group did not display any significant changes in theta, upper alpha, or gamma ERS/ERD% from BASELINE to POST-2 (all p > .05). As ERS/ERD% values are baseline corrected using a reference period (i.e. the middle 600 ms of the blank screen between the fixation cross and memory set), additional analyses were conducted to confirm that the significant changes in encoding period theta and gamma ERS/ERD% displayed by the tRNS group from BASELINE to POST-1 were not simply driven by changes in absolute power during the reference period used for baseline correction. Examination of changes in absolute oscillatory power for the tRNS group revealed that absolute theta and gamma

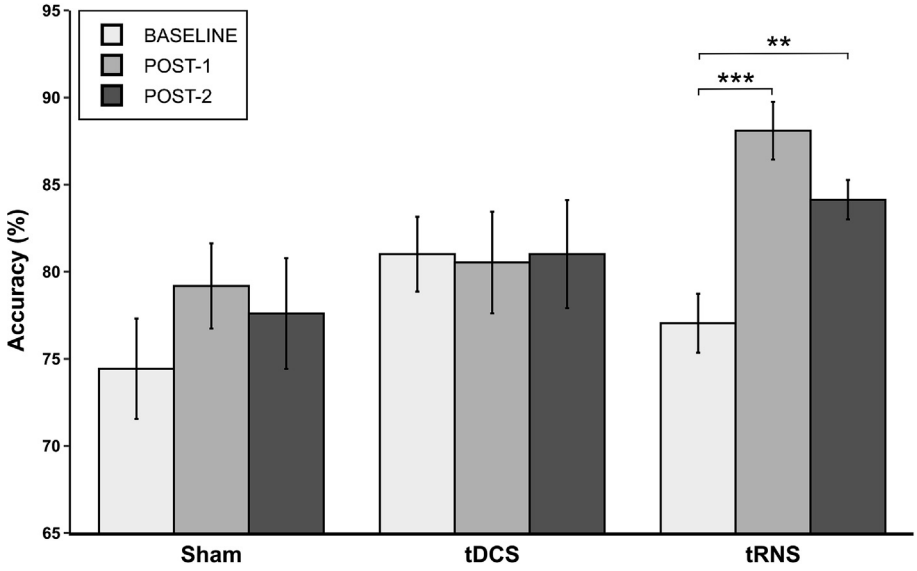

Fig. 3. Accuracy on the Sternberg WM task across the three time points (BASELINE, POST-1, POST-2). Error bars denote standard error of the mean. *p < .05. **p < .01. ***p < .001.

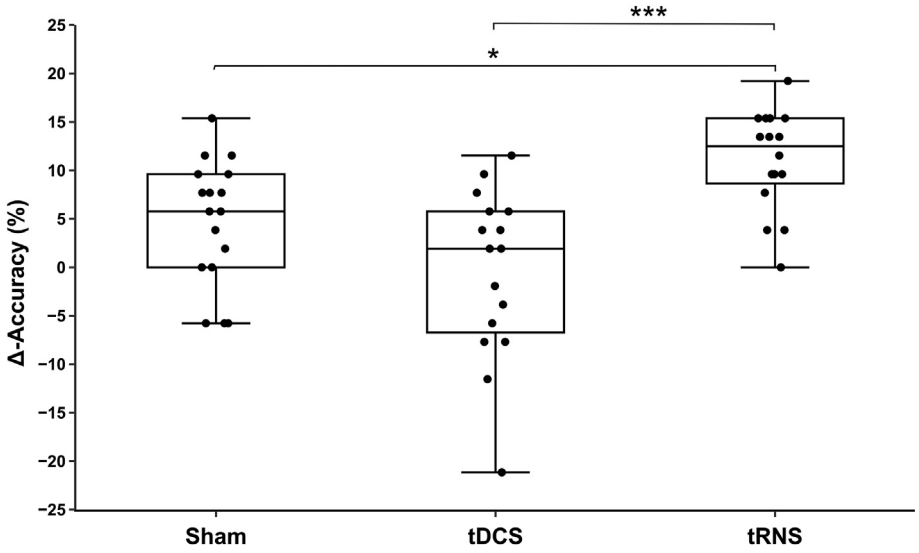

Fig. 4. Box-and-whisker plots with individual participant values overlaid (black circles) showing changes in Sternberg task accuracy from BASELINE to POST-1 (Δ-scores). Boxes extend from the 25th to 75th percentiles with the median represented by a horizontal line. Whiskers extend from the minimum to maximum values. *$p < .05$. **$p < .01$. ***$p < .001$.

power during the reference period did not significantly change from BASELINE to POST-1 (both $p > .05$). Consistent with the results observed for theta ERS/ERD%, the tRNS group displayed a significant increase in encoding period absolute theta power from BASELINE to POST-1, which was present bilaterally over frontal regions ($p = .003$). The tRNS group did not display any significant changes in encoding period absolute gamma power from BASELINE to POST-1 ($p > .05$). Further details regarding analyses of absolute oscillatory power are included in supplementary materials.

Exploratory analysis of oscillatory ERS/ERD% for the tDCS group did not reveal any significant changes in theta, upper alpha, or gamma ERS/ERD% from BASELINE to POST-1 (all $p > .05$). The tDCS group displayed a significant decrease in encoding period theta ERS over parieto-occipital regions from BASELINE to POST-2 ($p = .037$). No other changes in oscillatory ERS/ERD% were observed for the tDCS group from BASELINE to POST-2 (all $p > .05$).

Exploratory analysis of oscillatory activity for the sham group did not reveal any significant changes in encoding or maintenance period theta, upper alpha, or gamma ERS/ERD% from BASELINE to POST-1 or POST-2 (all $p > .05$).

Direct comparison of stimulation conditions using change-from-baseline-scores (Δ-scores) revealed that the tRNS group displayed significantly larger increases in theta ERS from BASELINE to POST-1 when compared to both sham (left frontal cluster: $p = .021$, parieto-occipital cluster: $p = .004$) and tDCS groups (left frontal cluster: $p = .003$; parieto-occipital cluster: $p = .005$) (Fig. 7). Further, the tRNS group displayed significantly less gamma ERD from BASELINE to POST-1 when compared to both the sham ($p = .021$) and tDCS groups ($p = .025$) (Fig. 8). Changes in theta ERS from BASELINE to POST-2 did not significantly differ between stimulation conditions (all $p > .05$). Exploratory correlations did not reveal any significant relationships between Δ-scores for accuracy and oscillatory ERS/ERD% (all $p > .05$).

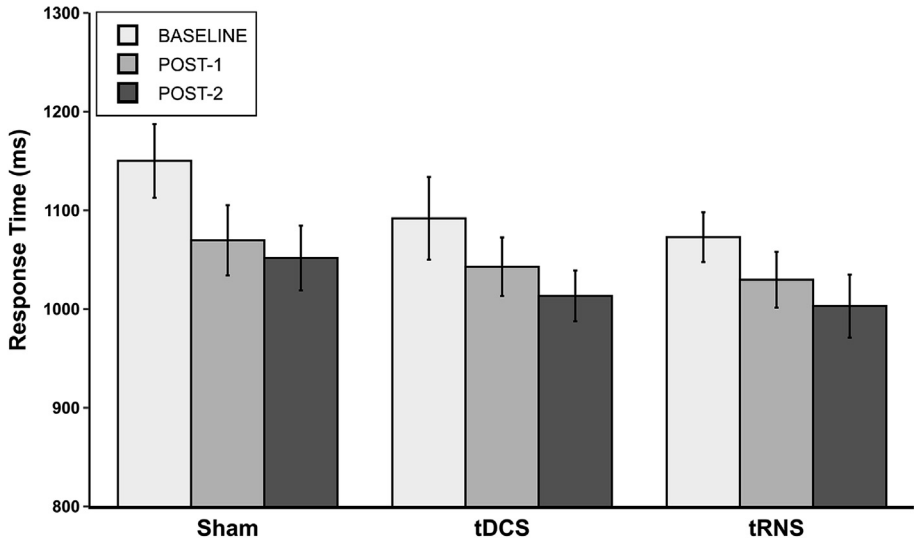

Fig. 5. Response time (ms) on the Sternberg WM task across the three time points (BASELINE, POST-1, POST-2). Error bars reflect the standard error of the mean.

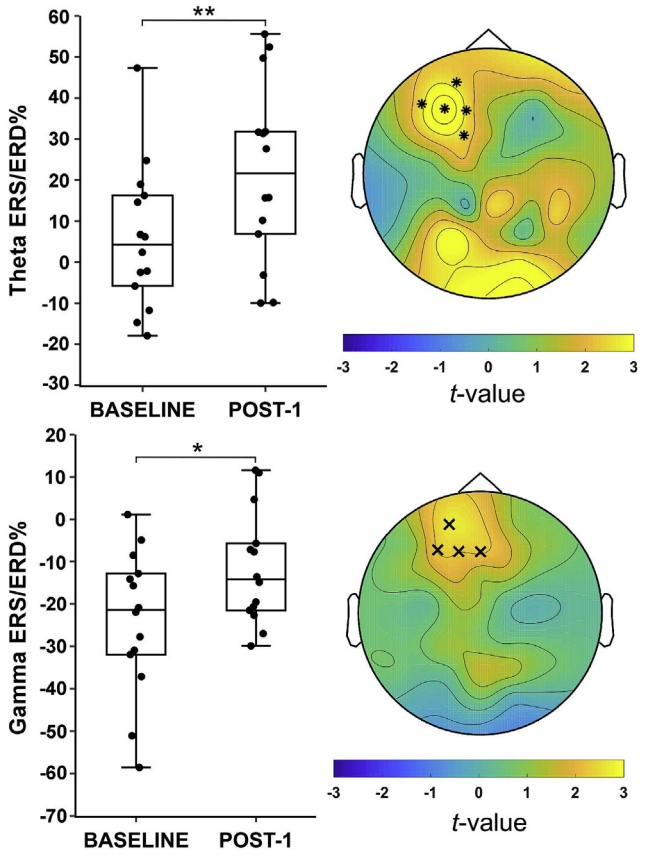

Fig. 6. Encoding period theta and gamma ERS/ERD% for BASELINE and POST-1 for the tRNS group. Box-and-whisker plot displays oscillatory ERS/ERD% at BASELINE and POST-1 (*$p < .05$, **$p < .01$), with positive values reflecting ERS and negative values reflecting ERD. Boxes extend from the 25th to 75th percentiles with the median represented by a horizontal line and individual participant data points overlaid (black circles). Whiskers extend from the minimum to maximum values. Topographical map displays differences in oscillatory ERS/ERD% (POST-1 - BASELINE), with EEG electrodes forming significant clusters marked by black crosses ($p < .05$) and stars ($p < .01$). Data displayed in the box-and-whisker plot reflects the average of electrodes marked in the topographical map.

tES tolerability and blinding integrity

The experimental protocol was well tolerated, and no significant adverse effects were reported. Fifteen of the 49 participants (30.61%) reported minor adverse effects whilst receiving tES, including: slight itching or discomfort under the electrode (15 participants), mild burning sensation (1 participant), or a mild headache (1 participants). The incidence of minor adverse effects did not significantly differ between the three stimulation conditions (all $p > .10$). Blinding of stimulation conditions was maintained as participants were unable to guess at better than chance level whether they had received active or sham stimulation (χ^2 (1, N = 49), = 2.451, $p = .294$).

Discussion

The aim of the present study was to directly compare the cognitive and neurophysiological effects of tDCS and tRNS as neuromodulatory tools for enhancing WM in healthy adults. When delivered using the current stimulation parameters, we found that tRNS + DC-offset over the left DLPFC significantly improved WM task accuracy, whereas no significant cognitive effects were observed following anodal tDCS or sham stimulation. Moreover, tRNS induced more consistent improvements in WM accuracy as compared to tDCS. Enhancements in WM performance immediately following tRNS were accompanied by increased theta ERS and diminished gamma ERD during WM encoding. In contrast, we did not observe any immediate effects of anodal tDCS on WM-related oscillatory ERS/ERD%; a decrease in encoding period theta ERS was observed 25-min post-stimulation, however these changes did not remain significant when compared to sham stimulation.

Cognitive effects of tES

To our knowledge, this reflects the first evidence showing tRNS to be more effective than anodal tDCS for enhancing WM performance in healthy adults. Results of the current study contrast with previous research by Mulquiney et al. [47], who found that tDCS but not tRNS over the left DLPFC significantly improved WM performance in healthy adults. There are several methodological factors which may have contributed to these conflicting findings. Firstly, the current study examined effects of tRNS + DC-offset, whereas Mulquiney et al. delivered tRNS without a DC-offset. Delivering tRNS without a DC-offset results in stimulation electrodes rapidly changing polarity with a randomly fluctuating frequency, whereas tRNS + DC-offset produces a consistent unidirectional current flow analogous to tDCS as the current intensity fluctuates entirely within the positive range at the anodal electrode (between +0.5 and + 1.5 mA using the current stimulation parameters) and entirely within the negative range at the cathodal electrode (−0.5 and −1.5 mA). tRNS + DC-offset has been shown to induce larger modulation of cortical excitability than tRNS without an offset [16], potentially because it combines the characteristics of tRNS (i.e. introducing noise into the neural system) with those of tDCS (i.e. consistent polarisation of neuronal membrane potentials). Given this, it is possible that the addition of a DC-offset may also increase the effectiveness of tRNS as a means to enhance cognitive performance in healthy adults. However, further research is needed to directly compare the neurophysiological and cognitive effects of delivering tRNS with and without a DC-offset. Secondly, the current study delivered tRNS for a duration of 20-min whereas Mulquiney et al. used a shorter duration of 10-min. Although delivery of tRNS for a duration of 10-min has been shown to induce enhancements in motor cortex excitability for up to an hour after stimulation [48], it is possible that longer stimulation durations are required to modulate excitability and cognitive performance in non-motor regions such as the prefrontal cortex.

Contrary to our predictions, we did not observe significant improvements in WM performance following anodal tDCS. Existing evidence for the facilitatory effects of anodal tDCS over the DLPFC on WM performance in healthy individuals is inconsistent, with several recent meta-analyses findings that effects of anodal tDCS on WM performance are typically modest and variable [9–11]. Moreover, effects of tDCS appear to be highly variable at the individual level, with one meta-analysis finding that only 16% of participants displayed the desired outcome in cognitive studies [13]. Consistent with this, we observed a high degree of variability in the effects of tDCS on WM performance, with only 31.25% of participants in the tDCS group displaying improvements in accuracy that were above-and-beyond what would be expected due to practice effects (i.e. greater than the average improvement shown by the sham group). In contrast, 81.25% of participants in the tRNS group demonstrated improvements in accuracy which were greater than practice effects. Taken together, our null findings are broadly consistent with previous research and suggest that a single session of anodal tDCS to the left DLPFC using the current stimulation parameters may not be sufficient to induce meaningful or consistent enhancements in WM performance in healthy adults. Furthermore, these findings indicate

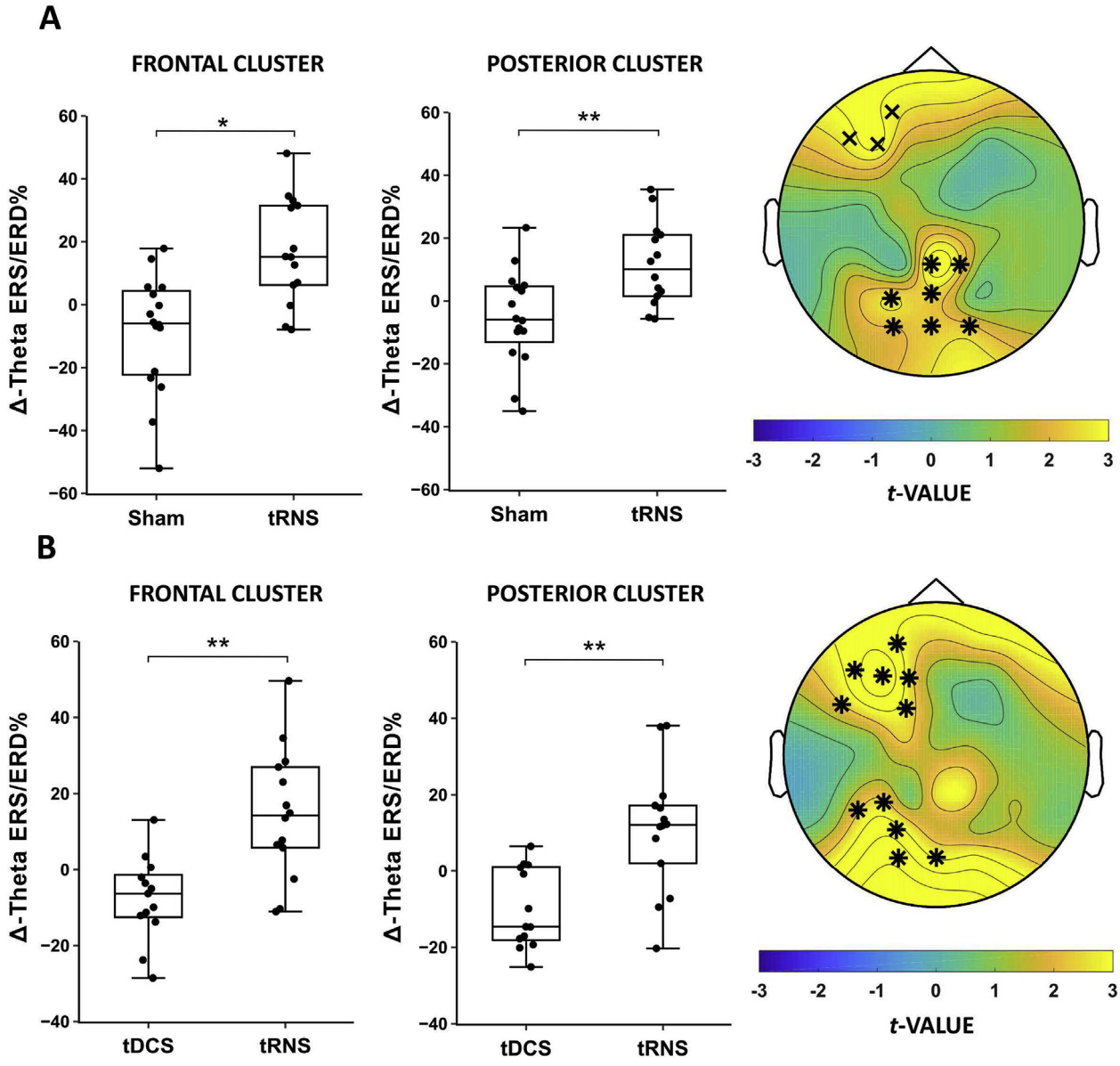

Fig. 7. Comparison of encoding period Δ-theta ERS/ERD% at POST-1 between the tRNS and sham conditions (A), and between the tRNS and tDCS conditions (B). Box-and-whisker plot displays Δ-theta ERS/ERD% (*$p < .05$, **$p < .01$), with individual participant data points overlaid (black circles). Boxes extend from the 25th to 75th percentiles with the median represented by a horizontal line. Whiskers extend from the minimum to maximum values. Topographical map displays differences in oscillatory ERS/ERD% when comparing tRNS to sham (A) and tRNS to tDCS (B), with EEG electrodes forming significant clusters marked by black crosses ($p < .05$) and stars ($p < .01$). Data displayed in the box-and-whisker plot reflects the average of electrodes marked in the topographical map.

that tRNS + DC-offset may reflect a more effective and reliable means to enhance WM performance in healthy adults.

Effects of tES on oscillatory ERS/ERD% during working memory processing

Enhancements in WM performance following tRNS were accompanied by changes in oscillatory ERS/ERD% during WM encoding. Immediately following tRNS, we observed increases in encoding period theta ERS over left frontal and parieto-occipital regions, and diminished gamma ERD over left frontal regions. Consistent with the pattern of cognitive improvements, alterations in oscillatory ERS/ERD% were maximal immediately following tRNS, but did not significantly differ when assessed at 25-min post-stimulation. Importantly, exploratory analyses of absolute oscillatory power for the tRNS group did not reveal any significant changes in absolute theta or gamma oscillatory power during the reference period used for calculation of ERS/ERD%. These findings indicate that significant changes in theta and gamma ERS/ERD% following tRNS were driven by alterations in oscillatory activity related to processes involved in WM encoding, rather than generalised effects on oscillatory power. Given evidence that higher WM performance is associated with a greater magnitude of theta and gamma power during WM encoding [42,43], the pattern of changes in oscillatory ERS/ERD% we observed following tRNS are consistent with increased efficiency of cognitive processing within fronto-parietal neurocircuitry which supports WM processing. Importantly, however, we did not observe any linear relationships between tRNS-induced enhancements of WM performance and changes in task-related theta and gamma ERS/ERD%, indicating that

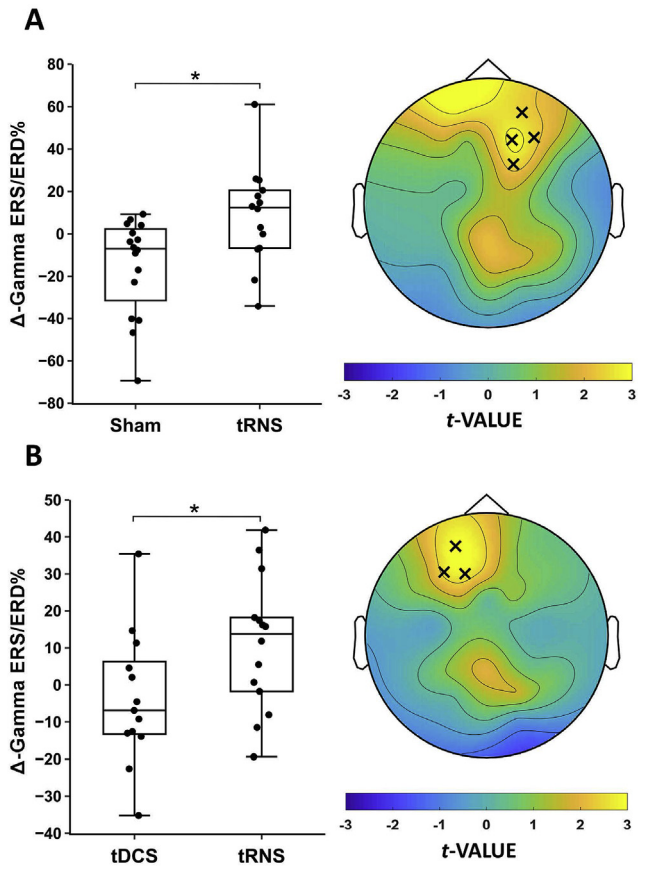

Fig. 8. Comparison of encoding period Δ-gamma ERS/ERD% at POST-1 between the tRNS and sham conditions (A), and between the tRNS and tDCS conditions (B). Box-and-whisker plot displays Δ-gamma ERS/ERD% (*$p < .05$, **$p < .01$), with individual participant data points overlaid (black circles). Boxes extend from the 25th to 75th percentiles with the median represented by a horizontal line. Whiskers extend from the minimum to maximum values. Topographical map displays differences in oscillatory ERS/ERD% when comparing tRNS to sham (A) and tRNS to tDCS (B), with EEG electrodes forming significant clusters marked by black crosses ($p < .05$) and stars ($p < .01$). Data displayed in the box-and-whisker plot reflects the average of electrodes marked in the topographical map.

modulation of task-related oscillatory ERS/ERD% does not appear to be a primary mechanism through which tRNS enhances WM performance. These findings conflict with previous literature linking increases in oscillatory power within these frequencies to improved WM performance [20–22] and suggests that the relationship between oscillations and WM performance is more complex than a directly causal relationship.

The precise neurophysiological mechanisms through which tRNS alters oscillatory activity remain poorly understood, and less is known about the mechanisms underlying tRNS + DC-offset [1]. One possible explanation relates to the stochastic resonance phenomenon, whereby the randomly fluctuating current delivered by tRNS introduces 'noise' into the neural system and thereby increases the synchronisation of neural firing via amplification of subthreshold oscillatory activity [1,15]. Within this context, effects of tRNS are state-dependent as the 'noise' introduced to the neural system primarily affects neurons which are close to the discharge threshold (i.e. task-dependent activity) [49]. As participants in the current study received tES whilst completing the PASAT, a cognitive task which has been shown to engage WM neurocircuitry [33,34], the 'noise' introduced by tRNS may have therefore amplified WM-related oscillatory activity in a manner consistent with the stochastic resonance phenomena. However, while this theoretical framework provides a potential explanation for the 'online' effects of tRNS on oscillatory activity, it remains unclear how tRNS-induced changes in oscillatory activity during stimulation are translated into long-term 'offline' effects which persist beyond the end of stimulation [50,51].

We did not observe any effects of anodal tDCS on WM-related oscillatory ERS/ERD% immediately following stimulation. Although a small decrease in parieto-occipital theta ERS was observed 25-min following tDCS, this change was not significant when compared to other stimulation conditions. Moreover, the absence of any changes in WM performance following tDCS limits our ability to interpret how these changes in oscillatory ERS/ERD% may relate to cognitive performance. There is limited research investigating the effects of anodal tDCS on WM-related oscillatory activity, however, our findings contrast with two previous studies which observed enhanced WM performance on a 2-back task and increased task-related theta activity following a single session of anodal tDCS to the left DLPFC [24,25]. One potential explanation for these conflicting findings relates to differences in the WM task used, as the *n*-back task requires simultaneous encoding, maintenance, and retrieval of information whereas the Sternberg WM task used in the current study temporally separates each phase of WM processing. Given this variation in cognitive demands, combined with evidence that the *n*-back and Sternberg tasks engage different neural regions [52], it remains possible that effects of tDCS on oscillatory ERS/ERD% were not observable when using the Sternberg task.

Given that recent research has raised concerns that commonly used sham tES protocols may induce active effects on neurophysiological and cognitive outcomes [14,53], it is relevant to note that we did not observe any significant changes in WM performance or oscillatory ERS/ERD% following sham stimulation. While the sham group demonstrated subtle and non-significant improvements in WM performance over time, these improvements are consistent with practice effects and were significantly weaker than those observed following tRNS. Given evidence that neurophysiological measures derived from EEG may be more sensitive than cognitive measures for assessing the effects of tES [14], the absence of changes in oscillatory ERS/ERD% following sham stimulation further increases confidence that the current sham protocol reflects an accurate control condition for comparing effects of tES methods.

Limitations and future directions

The current findings should be considered with a number of study limitations in mind. Firstly, we used a between-group design to prevent practice effects from repeated exposure to the WM task over multiple session, whereas evidence suggests that a within-groups design is most appropriate for minimising inter-individual response to tES [54]. However, we utilised stratified randomisation to ensure close balancing of groups on factors known to influence effects of tES, including age, gender, and WM ability, and therefore aimed to reduce the inter-individual variability introduced by the between-group design used in this study. Secondly, although the stimulation parameters used for tDCS and tRNS + DC-offset in the current study resulted in an equivalent net charge (i.e. dosage) over the stimulation session, the peak current intensity was higher in the tRNS + DC-offset (i.e. a maximum of 1.5 mA) than the tDCS condition (i.e. a maximum 1.0 mA). Given the role of current intensity in determining the voltage and distribution of the electrical field induced by tES (see Figs. S1 and S2 in supplementary materials for modelling of electrical field induced by tES at differing current intensities), variation in peak current intensity may have contributed to the divergent cognitive and electrophysiological effects of tDCS and tRNS + DC-offset. The current findings warrant

further research investigating which stimulation parameters (i.e. stimulation dosage, peak current intensity, duration) are primarily responsible for the cognitive and neurophysiological effects of tRNS + DC-offset. Thirdly, the current study limited analyses to the effects of tES on theta, upper alpha, and gamma ERS/ERD% as there is an extensive body of EEG research indicating their role in supporting WM encoding and maintenance in healthy individuals [20,21,55]. However, further investigation of the pattern of oscillatory effects of tES across every frequency band may be an informative analysis technique in future studies, particularly given emerging evidence implicating potential roles of delta and beta oscillations in cognitive processing [56–58]. Moreover, future research using EEG-derived measures of neural connectivity and cross-frequency coupling may provide more detailed information regarding the neurobiological effects of tES. Indeed, cross-frequency phase coupling of theta and gamma oscillations has been proposed as a potential neural substrate underlying the active maintenance of WM stimuli [55,59], and reflects a potentially useful neurophysiological measure for future research investigating the neurobiological changes underlying the cognitive effects of tES. Finally, while the current study examined effects of tES in healthy individuals, these findings highlight the potential utility of tRNS + DC-offset as a therapeutic tool for ameliorating cognitive deficits associated with various neurological or psychiatric conditions. Future research should aim to investigate the efficacy of tRNS + DC-offset in improving WM performance in psychiatric conditions which feature prominent WM deficits and aberrant WM-related oscillatory activity, such as depression or schizophrenia [44,60–62].

Concluding remarks

In conclusion, our findings show that a single session of tRNS + DC-offset over the left DLPFC can enhance WM performance and modulate task-related oscillatory ERS/ERD% in healthy adults. Delivery of tRNS + DC-offset induced more pronounced and consistent improvements in WM performance when compared to anodal tDCS, indicating that tRNS may overcome some of the factors contributing to high rates of inter-individual variability in the response to tDCS. These findings support the potential of tRNS as a neuromodulatory tool to alter behavioural and neurophysiological markers of WM in healthy adults. Future research is needed to investigate the therapeutic efficacy of tRNS + DC-offset for treatment of neurological and psychiatric conditions, particularly those which feature cognitive dysfunction.

CRediT authorship contribution statement

O.W. Murphy: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization. **K.E. Hoy:** Conceptualization, Methodology, Writing - review & editing, Supervision. **D. Wong:** Writing - review & editing, Supervision. **N.W. Bailey:** Methodology, Software, Writing - review & editing. **P.B. Fitzgerald:** Resources, Writing - review & editing, Funding acquisition. **R.A. Segrave:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.07.001.

References

[1] Fertonani A, Miniussi C. Transcranial electrical stimulation: what we know and do not know about mechanisms. Neuroscientist 2017;23:109–23.
[2] Rose EJ, Ebmeier KP. Pattern of impaired working memory during major depression. J Affect Disord 2006;90:149–61. https://doi.org/10.1016/j.jad.2005.11.003.
[3] Santarnecchi E, Brem A-K, Levenbaum E, Thompson T, Kadosh RC, Pascual-Leone A. Enhancing cognition using transcranial electrical stimulation. Curr Opin Behav Sci 2015;4:171–8.
[4] Barbey AK, Koenigs M, Grafman J. Dorsolateral prefrontal contributions to human working memory. Cortex 2013;49:1195–205.
[5] Petrides M. The role of the mid-dorsolateral prefrontal cortex in working memory. Exp Brain Res 2000;133:44–54.
[6] Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 2005;166:23–30. https://doi.org/10.1007/s00221-005-2334-6.
[7] Ohn SH, Park C-I, Yoo W-K, Ko M-H, Choi KP, Kim G-M, et al. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. Neuroreport 2008;19:43–7.
[8] Teo F, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Investigating the role of current strength in tDCS modulation of working memory performance in healthy controls. Front Psychiatr 2011;2:45. https://doi.org/10.3389/fpsyt.2011.00045.
[9] Brunoni AR, Vanderhasselt M-A. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cognit 2014;86:1–9. https://doi.org/10.1016/j.bandc.2014.01.008.
[10] Hill AT, Fitzgerald PB, Hoy KE. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. Brain Stimulat 2016;9:197–208. https://doi.org/10.1016/j.brs.2015.10.006.
[11] Mancuso LE, Ilieva IP, Hamilton RH, Farah MJ. Does transcranial direct current stimulation improve healthy working memory?: a meta-analytic review. J Cognit Neurosci 2016;28:1063–89.
[12] Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt M-A. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. Brain Stimulat 2016;9:501–17. https://doi.org/10.1016/j.brs.2016.04.006.
[13] Jacobson L, Koslowsky M, Lavidor M. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp Brain Res 2012;216:1–10.
[14] Nikolin S, Martin DM, Loo CK, Boonstra TW. Effects of TDCS dosage on working memory in healthy participants. Brain Stimulat 2018;11:518–27.
[15] Fertonani A, Pirulli C, Miniussi C. Random noise stimulation improves neuroplasticity in perceptual learning. J Neurosci 2011;31:15416–23.
[16] Ho K-A, Taylor JL, Loo CK. Comparison of the effects of transcranial random noise stimulation and transcranial direct current stimulation on motor cortical excitability. J ECT 2015;31:67–72.
[17] Inukai Y, Saito K, Sasaki R, Tsuiki S, Miyaguchi S, Kojima S, et al. Comparison of three non-invasive transcranial electrical stimulation methods for increasing cortical excitability. Front Hum Neurosci 2016;10:668.
[18] Laczó B, Antal A, Rothkegel H, Paulus W. Increasing human leg motor cortex excitability by transcranial high frequency random noise stimulation. Restor Neurol Neurosci 2014;32:403–10.
[19] Moliadze V, Fritzsche G, Antal A. Comparing the efficacy of excitatory transcranial stimulation methods measuring motor evoked potentials. Neural Plast 2014;2014:1–6. https://doi.org/10.1155/2014/837141.
[20] Jensen O, Gelfand J, Kounios J, Lisman JE. Oscillations in the alpha band (9–12 Hz) increase with memory load during retention in a short-term memory task. Cerebr Cortex 2002;12:877–82.

[21] Jensen O, Tesche CD. Frontal theta activity in humans increases with memory load in a working memory task. Eur J Neurosci 2002;15:1395–9.
[22] Roux F, Wibral M, Mohr HM, Singer W, Uhlhaas PJ. Gamma-band activity in human prefrontal cortex codes for the number of relevant items maintained in working memory. J Neurosci 2012;32:12411–20.
[23] Choe J, Coffman BA, Bergstedt DT, Ziegler MD, Phillips ME. Transcranial direct current stimulation modulates neuronal activity and learning in pilot training. Front Hum Neurosci 2016;10:34. https://doi.org/10.3389/fnhum.2016.00034.
[24] Hoy KE, Emonson MR, Arnold SL, Thomson RH, Daskalakis ZJ, Fitzgerald PB. Testing the limits: investigating the effect of tDCS dose on working memory enhancement in healthy controls. Neuropsychologia 2013;51:1777–84.
[25] Zaehle T, Sandmann P, Thorne JD, Jäncke L, Herrmann CS. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. BMC Neurosci 2011;12:2.
[26] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97–113.
[27] Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IVand ICD-10. J Clin Psychiatr 1998;59:2233.
[28] Wechsler D. Wechsler adult intelligence scale–fourth edition (WAIS–IV). San Antonio, TX: The Psychological Corporation; 2008.
[29] Andrews SC, Hoy KE, Enticott PG, Daskalakis ZJ, Fitzgerald PB. Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain Stimulat 2011;4:84–9.
[30] Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, et al. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol 2008;11:249–54.
[31] Ferrucci R, Bortolomasi M, Brunoni AR, Vergares M, Tadini L, Giacopuzzi M, et al. Comparative benefits of transcranial direct current stimulation (tDCS) treatment in patients with mild/moderate vs. severe depression. Clin Neuropsychiatry 2009;6:246–51.
[32] Huang Y, Datta A, Bikson M, Parra LC. Realistic volumetric-approach to simulate transcranial electric stimulation—ROAST—a fully automated open-source pipeline. J Neural Eng 2019;16:056006.
[33] Lazeron RH, Rombouts SA, de Sonneville L, Barkhof F, Scheltens P. A paced visual serial addition test for fMRI. J Neurol Sci 2003;213:29–34.
[34] Lockwood AH, Linn RT, Szymanski H, Coad ML, Wack DS. Mapping the neural systems that mediate the paced auditory serial addition task (PASAT). J Int Neuropsychol Soc 2004;10:26–34.
[35] Gronwall DMA. Paced auditory serial-addition task: a measure of recovery from concussion. Percept Mot Skills 1977;44:367–73.
[36] Siegle GJ, Ghinassi F, Thase ME. Neurobehavioral therapies in the 21st century: summary of an emerging field and an extended example of cognitive control training for depression. Cognit Ther Res 2007;31:235–62.
[37] Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004;134:9–21.
[38] Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011;2011:1.
[39] Bailey NW, Segrave RA, Hoy KE, Maller JJ, Fitzgerald PB. Impaired upper alpha synchronisation during working memory retention in depression and depression following traumatic brain injury. Biol Psychol 2014;99:115–24. https://doi.org/10.1016/j.biopsycho.2014.03.008.
[40] Hill AT, Rogasch NC, Fitzgerald PB, Hoy KE. Effects of prefrontal bipolar and high-definition transcranial direct current stimulation on cortical reactivity and working memory in healthy adults. Neuroimage 2017;152:142–57. https://doi.org/10.1016/j.neuroimage.2017.03.001.
[41] Howard MW. Gamma oscillations correlate with working memory load in humans. Cerebr Cortex 2003;13:1369–74. https://doi.org/10.1093/cercor/bhg084.
[42] Hsieh L-T, Ekstrom AD, Ranganath C. Neural oscillations associated with item and temporal order maintenance in working memory. J Neurosci 2011;31:10803–10.
[43] Roberts BM, Hsieh L-T, Ranganath C. Oscillatory activity during maintenance of spatial and temporal information in working memory. Neuropsychologia 2013;51:349–57.
[44] Segrave RA, Thomson RH, Cooper NR, Croft RJ, Sheppard DM, Fitzgerald PB. Upper alpha activity during working memory processing reflects abnormal inhibition in major depression. J Affect Disord 2010;127:191–8. https://doi.org/10.1016/j.jad.2010.05.022.
[45] Hill AT, Rogasch NC, Fitzgerald PB, Hoy KE. Effects of single versus dual-site High-Definition transcranial direct current stimulation (HD-tDCS) on cortical reactivity and working memory performance in healthy subjects. Brain Stimulat 2018.
[46] Maris E, Oostenveld R. Nonparametric statistical testing of EEG-and MEG-data. J Neurosci Methods 2007;164:177–90.
[47] Mulquiney PG, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Improving working memory: exploring the effect of transcranial random noise stimulation and transcranial direct current stimulation on the dorsolateral prefrontal cortex. Clin Neurophysiol 2011;122:2384–9. https://doi.org/10.1016/j.clinph.2011.05.009.
[48] Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci 2008;28:14147–55.
[49] Miniussi C, Harris JA, Ruzzoli M. Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci Biobehav Rev 2013;37:1702–12.
[50] Antal A, Herrmann CS. Transcranial alternating current and random noise stimulation: possible mechanisms. Neural Plast 2016;2016.
[51] Snowball A, Tachtsidis I, Popescu T, Thompson J, Delazer M, Zamarian L, et al. Long-term enhancement of brain function and cognition using cognitive training and brain stimulation. Curr Biol 2013;23:987–92. https://doi.org/10.1016/j.cub.2013.04.045.
[52] Veltman DJ, Rombouts SA, Dolan RJ. Maintenance versus manipulation in verbal working memory revisited: an fMRI study. Neuroimage 2003;18:247–56.
[53] Fonteneau C, Mondino M, Arns M, Baeken C, Bikson M, Brunoni AR, et al. Sham tDCS: a hidden source of variability? Reflections for further blinded, controlled trials. Brain Stimulat 2019. https://doi.org/10.1016/j.brs.2018.12.977.
[54] López-Alonso V, Cheeran B, Río-Rodríguez D, Fernández-del-Olmo M. Inter-individual variability in response to non-invasive brain stimulation paradigms. Brain Stimulat 2014;7:372–80. https://doi.org/10.1016/j.brs.2014.02.004.
[55] Roux F, Uhlhaas PJ. Working memory and neural oscillations: alpha–gamma versus theta–gamma codes for distinct WM information? Trends Cognit Sci 2014;18:16–25.
[56] Başar E, Düzgün A. Links of consciousness, perception, and memory by means of delta oscillations of brain. Front Psychol 2016;7:275.
[57] Lundqvist M, Rose J, Herman P, Brincat SL, Buschman TJ, Miller EK. Gamma and beta bursts underlie working memory. Neuron 2016;90:152–64.
[58] Chen Y, Huang X. Modulation of alpha and beta oscillations during an n-back task with varying temporal memory load. Front Psychol 2016;6:2031.
[59] Sauseng P, Klimesch W, Heise KF, Gruber WR, Holz E, Karim AA, et al. Brain oscillatory substrates of visual short-term memory capacity. Curr Biol 2009;19:1846–52.
[60] Cotrena C, Branco LD, Kochhann R, Shansis FM, Fonseca RP. Quality of life, functioning and cognition in bipolar disorder and major depression: a latent profile analysis. Psychiatr Res 2016;241:289–96.
[61] Lee J, Park S. Working memory impairments in schizophrenia: a meta-analysis. J Abnorm Psychol 2005;114:599.
[62] Murphy OW, Hoy KE, Wong D, Bailey NW, Fitzgerald PB, Segrave RA. Individuals with depression display abnormal modulation of neural oscillatory activity during working memory encoding and maintenance. Biol Psychol 2019;148:107766.