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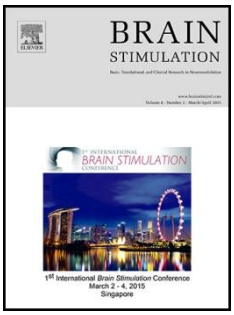

Title: Effects of Anodal Transcranial Direct Current Stimulation on Working Memory: a Systematic Review and Meta-Analysis of Findings From Healthy and Neuropsychiatric Populations

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Effects of Anodal Transcranial Direct Current Stimulation on Working Memory: A Systematic Review and Meta-Analysis of Findings from Healthy and Neuropsychiatric Populations

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Highlights

- We performed a meta-analysis investigating working memory (WM) enhancement with anodal tDCS (a-tDCS) in healthy and neuropsychiatric cohorts.
- We examined both online and offline effects of stimulation.
- We explored the role of current density and stimulation duration on WM performance.
- Our results demonstrate mixed effects of a-tDCS on WM performance.
- A-tDCS enhanced offline WM accuracy and reaction time in healthy populations and online WM accuracy in neuropsychiatric populations. No other significant results were obtained.
- We provide some limited evidence that higher current densities and longer stimulation durations might be more effective at modulating WM.

Abstract

Background: A number of studies have trialled anodal transcranial direct current stimulation (a-tDCS) for the enhancement of working memory (WM) in both healthy and neuropsychiatric populations. However, the efficacy of this technique for improving WM function in these cohorts remains to be clearly established.

Objective: This review provides a quantitative synthesis of the published literature investigating the effects of a-tDCS, compared to sham, on WM, as assessed using the n-back, Sternberg and digit-span tasks. We also separated results from tasks performed 'online' (during stimulation) and 'offline' (following stimulation). A secondary aim was to assess for any additional effects of current density and stimulation duration.

Methods: Comprehensive literature searches were performed using Medline, Embase, PsychInfo, the Cochrane Central Register for Controlled Trials (CENTRAL) and Scopus from July 1998 through to June 2014.

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Results: In healthy cohorts, a-tDCS led to small but significant improvements in offline WM accuracy (p = 0.04) and reaction time (p = 0.04), however no significant effects were observed for online tasks (accuracy [p = 0.20], reaction time [p = 0.42]). In the neuropsychiatric cohort, a-tDCS significantly improved accuracy for online (p = 0.003), but not offline (p = 0.87) tasks and no effect was seen for either online (p = 0.20) or offline (p = 0.49) reaction times. Secondary analyses controlling for current density and stimulation duration provided limited support for the role of these factors in influencing a-tDCS efficacy.

Conclusions: Overall, this review provides some limited evidence of a beneficial effect of a-tDCS on WM performance. However, the small effect sizes obtained, coupled with non-significant effects on several analyses require cautious interpretation and highlight the need for future research aimed at investigating more optimised stimulation approaches.

Keywords: Transcranial direct current stimulation (tDCS); cognition; working memory; dorsolateral prefrontal cortex; psychiatry

Introduction

Cognitive deficits, including working memory (WM) impairment, are core features of a number of neuropsychiatric disorders, contributing substantially to burden of disease and remaining largely refractory to conventional drug-based therapies [1-3]. Transcranial direct current stimulation (tDCS) is emerging as a safe and relatively inexpensive means of modulating both psychological and physiological processes through the non-invasive application of low-voltage currents to the brain [4]. Indeed, a number of studies have now reported beneficial effects of tDCS on memory function in neuropsychiatric populations [5-12] as well as in healthy individuals [13-24]. However, despite these promising findings, the level of efficacy with which this nascent technology can modulate cognition, as well as the optimal parameters required for achieving these outcomes, remain to be fully elucidated.

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Administration of tDCS typically involves applying two large (25-35 cm^2) saline-soaked sponge electrodes, consisting of an anode and a cathode, to the scalp. A weak constant current in the range of 1-2 mA is then passed through the electrodes for several minutes resulting in either facilitation or inhibition of spontaneous neuronal activity within the underlying cortex [25-27]. Specifically, anodal tDCS (a-tDCS) is able to enhance cortical excitability, while cathodal stimulation typically leads to a reduction in excitability [4, 26, 28, 29]. Importantly, the effects of tDCS have been shown to persist for over an hour beyond the period of stimulation [28, 30]. Such ongoing effects are likely the result of N-methyl-D-aspartate (NMDA) receptor mediated neuroplasticity-based mechanisms [31, 32] and are, to some extent, contingent on stimulation parameters including the current density (i.e., the ratio of injected current divided by the electrode surface area) and stimulation duration [27, 28, 33].

To date, the ability of a-tDCS to modulate WM has been explored in a number of studies, albeit with mixed results. WM provides the ability to hold and manipulate information over a short period of time, with WM capacity linked to a variety of higher order cognitive abilities including selective attention, reading comprehension, reasoning and complex decision making [34-38]. Moreover, dysfunctional WM has been reported in a range of neuropsychiatric conditions including depression [39], schizophrenia [40] and Parkinson's disease [41]. The dorsolateral prefrontal cortex (DLPFC; Brodmann area 9/46), with its robust neuroanatomical connections to numerous cortical and subcortical structures, is strongly implicated in WM [42-44] and consequently, the majority of research investigating the effects of a-tDCS on WM function has chosen the DLPFC as the target region for stimulation, which can be accurately stimulated by positioning the anode over either the F3 (left DLPFC) or F4 (right DLPFC) regions on the scalp in accordance with the international 10-20 system for electrode placement [45].

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Although a number of studies have demonstrated improvements in WM in both healthy and clinical cohorts, either during ('online'), or shortly after ('offline') a-tDCS delivery, heterogeneous outcomes between individual studies, coupled with differences in experimental methodology make accurate judgements regarding efficacy incredibly challenging. Small sample sizes, which are present in many such studies, are one potential limiting factor and pooling the results from these experiments in a meta-analysis can help curtail this problem. Furthermore, inter-study variability in stimulation parameters such as current density and stimulation duration, both of which are known moderators of tDCS dose [46, 47], also likely contributes to the disparity in results observed thus far. Available neurophysiological data from studies of the motor cortex shows some support for a dose-response relationship between cortico-spinal excitability and either current density or stimulation duration, whereby, within specific limits, larger current densities or longer stimulation durations lead to more pronounced excitability changes [26, 48, 49]. However, these results are certainly not without exception [33, 50, 51] and whether any such relationship can be extended to stimulation of other brain regions, or to cognitive/behavioural outcome measures, remains to be established, with inconsistent findings having been reported thus far [11, 16, 52, 53]. As such, carefully constructed quantitative reviews which employ rigorous and transparent inclusion/exclusion criteria and attempt to account for methodological variables which are known to influence the outcome measures are vital for gaining a better understanding of tDCS-related effects [54, 55].

The goals of the present systematic review and meta-analysis were twofold. Our primary aim was to evaluate the efficacy with which a-tDCS, compared to sham, could improve WM in both healthy and neuropsychiatric cohorts. In order to achieve this aim we analysed results from n-back, Sternberg and digit-span WM tasks, taking into account both online and

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offline effects, where possible. Additionally, as the optimal stimulation parameters required to enhance WM function remain unclear, our secondary aim was to investigate whether differences in two important a-tDCS parameters, namely current density and stimulation duration, might impact WM performance. We anticipated that such analyses could help to better identify important variables for consideration in future trials. We specifically hypothesised that, compared to sham, a-tDCS would lead to significant improvements in WM in both healthy and neuropsychiatric cohorts. Furthermore, we also anticipated that higher current densities and longer stimulation durations would produce more robust improvements in WM function.

Methods

Protocol registration

The protocol for this systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42014013464).

Literature search

An extensive literature search was conducted using the following databases: MEDLINE (PubMed), EMBASE (Ovid), PsychINFO (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL) (Ovid) and SCOPUS from July 1, 1998 (i.e., first published evidence of the effects of a contemporary tDCS paradigm on cortcical excitability by Priori et al. [56]) until 17 June 2014 (see Supplemental Material for detailed search strategy)**.** Once all relevant studies were retrieved, their title and abstract were screened against the inclusion/exclusion criteria (Table 1). In cases where the title and abstract alone provided insufficient information to determine whether the study could be included, the full-text version of the article was

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screened (see Figure 1 for a flow-chart depicting relevant stages of the literature search and selection process).

INSERT FIGURE 1 HERE

Selection Criteria

Included studies were required to meet the selection criteria outlined in Table 1**.** Specifically, studies were included if they: (1) were performed on either healthy volunteers, or individuals suffering from a neuropsychiatric illness, (2) participants were over the age of 18 years, (3) either 'online' or 'offline' data was available for at least one of the specified WM tasks, (4) studies were published in a peer-reviewed scientific journal, (5) sham stimulation was used as a comparator, (6) articles were written in English and (7) studies employed, at a minimum, a single-blind technique (i.e., participants blinded to the type of stimulation they received). Both parallel and crossover study designs were included and studies employing repeated stimulation sessions were also included provided that they met all other inclusion criteria. Furthermore, studies were limited to those which applied stimulation to the DLPFC. The DLPFC was included as the stimulation site for WM studies for two main reasons. Firstly, due to its direct involvement in this type of memory [57, 58] and secondly, to help maintain consistency between the different individual studies, the vast majority of which selected the DLPFC as the target for stimulation.

INSERT TABLE 1 HERE

Working Memory Tasks

N-Back and Sternberg Tasks

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The n-back and Sternberg tasks are frequently employed as indexes of WM function in tDCS research. The n-back task involves the presentation of a consecutive series of stimuli (letters or numbers) to the participant who is required to respond when a match is obtained between the present stimulus and that presented 'n' trials earlier (e.g., 2 trials earlier for the 2-back task). In the present review we included experiments utilising either 1-back, 2-back or 3-back tasks; 0-back tasks were excluded as they do not require the manipulation of information within WM [57]. The Sternberg task [59] involves the presentation of a memory set of several letters, which after a retention period of several seconds is followed by a probe stimulus containing a single letter. The participant is required to determine whether this probe stimulus also appeared in the previous memory set. In the current meta-analysis, WM performance on both tasks was segmented into data for accuracy and reaction time. Accuracy measures how well a participant can respond to a correct target stimulus, while reaction-time measures how quickly they are able to do so. In addition, we chose to separate tasks based on whether they were performed 'online' (i.e., during a-tDCS delivery), or 'offline' (i.e., after a-tDCS had been administered). This decision was made based on the different neurobiological processes know to occur during and directly after stimulation, whereby the online effects of a-tDCS have been attributed to resting membrane potential alterations, while the offline effects of a-tDCS appear to result from modulation of synaptic plasticity [60, 61].

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Digit-Span Task

Several published studies [8-10, 18] have utilised the digit-span task to assess WM. This task requires participants to repeat back a series of digits read-out by an examiner, either in the same order in which they were presented (digits forward), or in reverse order (digits backward) and is included as a subset for the assessment of WM in the Wechsler Adult

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Intelligence Scale [62]. In the current analysis, both digits-forward and digits-backward results were included as measures of WM accuracy.

Risk of bias

We utilised the risk of bias assessment tool provided as part of the RevMan software package [63]. Figure 2 depicts the methodological quality graph obtained indicating the authors' judgements regarding risk of bias for various aspects of each included study. In addition, funnel plots were generated to assess for any potential publication bias (Figure 3).

INSERT FIGURE 2 HERE

INSERT FIGURE 3 HERE

Data extraction

Means and standard deviations of the outcome measures of interest were collected, as were sample sizes for each included study. In cases where standard error values were reported, standard deviation values were calculated using the formula: SD = SE √n [64]. If studies contained data in a graphical rather than a numerical format, the Plot Digitizer software package [65] was used to extract the plotted values. This Java-based software allows plotted values to be accurately converted into a numerical format and has been previously employed in a number of other meta-analytical reviews [e.g., 48, 66, 67]. In instances where insufficient data was available, or where there was any ambiguity regarding the data presented, an attempt was made to contact the corresponding author(s) via email to obtain further information/clarification. Many of the studies included in the current review also

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reported results for more than one experimental condition. For example, several studies performed separate experiments investigating different stimulation intensities [e.g., 16, 53], post-stimulation time-points [e.g., 11, 16], or memory load [e.g., 15, 20]. In these instances, each experimental condition was treated as a unique dataset. Table 2 provides a summary of the characteristics of the studies included in this review.

INSERT TABLE 2 HERE

Meta-Analysis

All studies included in the analyses used continuous outcome measures. The RevMan software package, version 5.3 [63] was used to calculate effect size. The standard mean difference (SMD) was chosen to measure effect size as it allows for direct comparisons to be made between studies utilising different memory scales [64]. The particular formulation of the SMD implemented by the RevMan package is Hedge's adjusted *g*, which is similar to Cohen's *d*, but includes an adjustment for small sample bias [68]. Using the convention proposed by Cohen [69], effect sizes can be interpreted as either small (0.2), medium (0.5) or large (0.8).

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Tests of Heterogeneity and Selection of Statistical Model

We tested for heterogeneity using the chi-squared test [64]. Heterogeneity was also further quantified using the I^2 statistic, which can range from 0% to 100%, where 0% indicates no heterogeneity, values between 30 – 60% represent moderate heterogeneity, while values between 75 – 100% are indicative of high levels of heterogeneity [64]. Statistical heterogeneity was low for all included datasets. Nevertheless, although overall low heterogeneity was observed, a random-effects model was chosen for all statistical analyses.

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The random-effects model, as opposed to a fixed-effects model, is generally considered to be more appropriate for analysing data which has been accumulated from a series of independent studies and is able to better account for differences in effect sizes across studies [70].

Results

Study selection

Online database searches identified a total of 495 records matching the specific search terms. After removal of duplicate records, 302 studies remained. Screening of the title and abstract of these studies excluded a further 278 records which failed to meet inclusion criteria. Full-text versions of the remaining 24 articles were then screened for eligibility, which excluded a further eight studies. The remaining 16 studies met all inclusion criteria and were included in the current review. Overall, sample sizes were relatively small and considerable inter-study variability was present, with sample sizes ranging from 10 to 60 participants (median = 18). Crossover experimental designs were also favoured by the majority of studies, with only four [8-10, 12] utilising parallel designs. In addition, most studies employed single a-tDCS sessions, with three of the 16 studies [8-10] using repeated stimulation sessions. Both current density and duration of stimulation varied considerably between studies, with current densities ranging from 0.029 to 0.08 mA/cm^2 and stimulation durations ranging from 10 to 30 minutes. In terms of electrode placement, the left DLPFC was chosen as the target site for anodal stimulation in all but two experiments (i.e., Berryhill & Jones, experiment 2; Mylius et al., experiment 2) [17, 71], which chose the right DLPFC as the stimulation target; while the cathode was placed over the contralateral supraorbital region in all experiments except for Berryhill & Jones (experiments 1 and 2 - cathode placed over contralateral cheek) [17] and Oliveira et al. (cathode placed over F4) [12].

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Participants in included studies

A total of 352 participants were included from all combined trials, comprising of 170 healthy individuals and 182 individuals with a neuropsychiatric diagnosis. These numbers could be further partitioned into 146 with a diagnosis of depression, 18 with Parkinson's disease and 18 with schizophrenia.

Risk of Bias

A risk of bias graph summarising the authors' judgements about the likelihood of any systematic error being present in the included studies is presented in Figure 2. Overall, risk of bias was low, nevertheless all six domains of bias covered by the risk of bias assessment tool contained some level of unclear risk. This was most pronounced for the 'selection bias' and 'detection bias' domains. Specifically, although some blinding information was available from all of the studies (e.g., single, or double blind), detail was often lacking about blinding of outcome assessors. In addition, although many of the included studies stated that stimulation session orders were randomised (crossover designs) or that participants were randomly allocated to either active or sham stimulation groups (parallel designs), information pertaining to exactly how randomization was achieved was often lacking. Funnel plots exploring potential publication bias are presented in Figure 3. These plot the effect size (horizontal axis) against the standard error of the SMD (vertical axis). Typically, studies with larger sample sizes cluster closer to the top of the graph, with smaller studies scattered more widely at the bottom [72]. In the absence of bias, the plot should roughly resemble an inverted funnel, symmetrical around the mean effect size [73]. In the present review, no evidence of obvious asymmetry was seen in any of the funnel plots, suggesting an absence of publication bias.

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Change in reaction time on n-back/Sternberg tasks with a-tDCS compared to sham stimulation

Figure 4A provides a summary of the reaction time results for the healthy cohort. The combined results from online and offline studies demonstrate that a-tDCS, compared to sham, produced a small but significant reduction in reaction times on the WM tasks (SMD = -0.15, 95% CI = -0.29, -0.01, p = 0.03). These results failed to reach significance at the subgroup level for online WM tasks (SMD = -0.12, 95% CI = -0.42, 0.17, p = 0.42), however a small, but significant reduction in reaction time was observed for offline tasks (SMD = -0.16, 95% CI = -0.31, -0.00, p = 0.04). Figure 4B summarises the reaction time results for the clinical cohort. The combined results demonstrate no significant change in reaction time with a-tDCS (SMD = -0.14, 95% CI = -0.39, 0.11, p = 0.26), with subgroup analyses also showing no significant change in reaction time for either the online (SMD = -0.43, 95% CI = -1.10, 0.23, p = 0.20) or offline (SMD = -0.09, 95% CI = -0.36, 0.17, p = 0.49) tasks.

INSERT FIGURE 4 HERE

Change in accuracy on n-back/Sternberg/digit-span working memory tasks with a-tDCS compared to sham stimulation

Figure 5A provides a summary of the accuracy results for the healthy cohort. Overall, greater response accuracy was achieved by participants who received a-tDCS compared to sham stimulation (SMD = 0.16, 95% CI = 0.03, 0.29, p = 0.02). This finding did not reach significance for online assessments (SMD = 0.23, 95% CI = -0.12, 0.58, p = 0.20), however it remained significant at the subgroup level for tasks performed offline (SMD = 0.14, 95% CI = 0.00, 0.29, p = 0.04). The forest plot for the clinical cohort is shown in Figure 5B. In this group, no

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overall effect of a-tDCS on WM accuracy was observed (SMD = 0.11, 95% CI = -0.07, 0.29, p = 0.24), however, subgroup analyses revealed a significant and moderate improvement in accuracy for tasks performed online (SMD = 0.77, 95% CI = 0.26, 1.29, p = 0.003), while no significant change in accuracy was observed for offline tasks (SMD = 0.02, 95% CI = -0.17, 0.20, p = 0.87).

INSERT FIGURE 5 HERE

Effect of current density and stimulation duration

Current density and stimulation duration are both known to influence tDCS dose. As there was considerable variation between studies with regard to these two parameters, separate analyses were performed in an attempt to better elucidate any moderating effects on WM performance. In all analyses, we pooled results from healthy and neuropsychiatric cohorts in order to maintain suitable statistical power. Furthermore, when investigating the effect of current density on WM performance, data was pooled from online and offline experiments. However, only offline data were analysed for comparisons based on stimulation duration, as online task performance should not be affected by this parameter.

Separate forest plots were generated comparing a-tDCS to sham stimulation on accuracy and reaction time for WM experiments using either lower (≤0.029 mA/cm^2) or higher (>0.029 mA/cm^2) stimulation current densities as well as for offline experiments using shorter (≤10 minutes) compared to longer (>10 minutes) stimulation durations. The results of these subsequent analyses are summarised in Table 3 (See Supplemental Information

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Figures S1-S9 for accompanying forest plots and flow-diagram indicating how individual data-sets were dichotomised with regard to current density and stimulation duration). In all instances, the effect sizes for both reaction time and accuracy in the a-tDCS compared to sham conditions on WM tasks remained modest. However, there was some indication that higher current densities and longer stimulation durations have a greater impact on WM performance. Specifically, the pooled data demonstrate significantly improved WM accuracy scores compared to sham in the higher current density group ($p = 0.005$), but not in the lower current density group ($p = 0.48$). Similarly, compared to sham, reaction times were also significantly improved with longer stimulation durations ($p = 0.04$), but not with shorter stimulation durations ($p = 0.58$). Additionally, effect sizes were also larger for these significant analyses.

INSERT TABLE 3 HERE

Discussion

The present systematic review and meta-analysis aimed to provide a comprehensive assessment of the effects of a-tDCS, compared to sham, on WM in both healthy and neuropsychiatric populations, examining both online and offline task performance. Our secondary aim was to assess if a-tDCS efficacy was influenced by either current density or stimulation duration. Given the expanding use of a-tDCS, both as a means of modulating cognitive processes in healthy populations, as well as an emerging therapeutic device for the treatment of memory dysfunction in clinical cohorts, we felt that such a review was necessary to better delineate the effects achieved thus far with this technology.

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Overall, with respect to the primary aim of the study, we found only partial support for our hypothesis of an enhancing effect of a-tDCS on WM performance. Specifically, in healthy cohorts, both reaction times and response accuracy on the offline WM tasks were shown to be significantly improved with stimulation, while online response accuracy was improved in the neuropsychiatric cohort. No significant results were obtained for WM tasks performed online in the healthy cohort, whereas the neuropsychiatric cohort showed no significant improvement in offline WM performance. To date, two previous quantitative reviews have explored the effects of a-tDCS on WM. Brunoni and Vanderhasselt [74] pooled results from studies investigating the effects of either repetitive transcranial magnetic stimulation (rTMS) or a-tDCS applied over the DLPFC on n-back task performance in healthy and neuropsychiatric cohorts, ultimately finding an overall improvement in both reaction time and accuracy scores. However, meta-regression analyses performed by these authors indicated that WM accuracy was only improved in participants receiving rTMS and not a-tDCS. In comparison, our results indicate that a-tDCS applied to the DLPFC does appear to have some capacity for enhancing WM accuracy, with significant offline improvements seen in the healthy group and significant online improvements seen in the clinical group, despite our results demonstrating only very modest effect sizes. It is quite likely that this divergent finding is due to the broader inclusion criteria used in the present review, which combined results from a larger number of studies and did not restrict WM assessment to the n-back task alone.

In a more recent quantitative review, Horvath et al. [75] explored the effects of single-session tDCS on a wide range of cognitive processes in healthy adults. These authors ultimately reported a null effect of stimulation on all analysed cognitive outcome measures, including WM. These findings differ from our results with respect to the significant improvements we observed in offline accuracy and reaction time in healthy controls. It is

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possible that this discrepancy is due to a greater level of statistical power in the current study, which pooled data from a larger number of experiments. However there are also a number of reported statistical and methodological issues with Horvath et al. which limits the validity of directly comparing these two studies [76, 77].

Our finding of significant offline accuracy and reaction time effects in healthy cohorts and a significant online effect for accuracy in the neuropsychiatric cohort is interesting. Although the basis for these differences remains uncertain, the different neurobiological processes, which occur during, compared to following stimulation, might provide one potential explanation. Specifically, the online effects of a-tDCS appear to be solely dependent on membrane potential changes [60, 78], whereas offline effects are driven by changes in synaptic strength involving the modulation of GABAergic and glutamatergic activity [32, 60, 78]. While speculative, in patient populations, where there is abnormal excitation/inhibition (E/I) balance and impaired plasticity [30, 79, 80], the initial membrane potential changes might alter the cortical environment sufficiently to modulate this balance leading to subsequent detectable changes in behaviour. While in healthy controls, who presumably have more optimal homeostatic control of cortical excitability and inhibition [80], any online changes in neuronal firing rates may not be robust enough to lead to a demonstrable behavioural change. However, it is possible that the later occurring (i.e., offline) synaptically driven changes might more strongly influence behavioural responses in this group. Clearly, however, further research conducted in healthy and clinical cohorts is required to better contextualise these findings.

The secondary aim of this review was to investigate whether differences in current density and stimulation duration could affect the efficacy of a-tDCS mediated WM enhancement. Previous research applying a-tDCS over the motor cortex has found that increases to either

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of these parameters, within specific limits, can lead to subsequent increases in cortico-motor excitability [26, 28, 49]; however whether similar effects might also be observed for behavioural outcome measures and in other brain regions, remains uncertain. In the present review, we pooled results from experiments conducted in both healthy and neuropsychiatric populations based on: (1) anodal current density either greater than, or less than/equal to 0.029 mA/cm^2 (i.e., equivalent to 1mA applied using a 35 cm^2 electrode) and (2) stimulation durations either greater than, or less than/equal to 10 minutes. Although the SMD effect sizes failed to reach significance in the majority of analyses (see Table 3), accuracy scores were shown to be significantly improved in the higher current density group ($p = 0.005$), but not the lower current density group ($p = 0.48$); while longer ($p = 0.04$), but not shorter ($p = 0.58$) stimulation durations also led to significantly faster reaction times. In both of these instances, effect sizes were also larger for the higher current density and longer stimulation duration groups.

These results, therefore, provide some limited support for a potential dose-response relationship involving current density and duration of stimulation. Nevertheless, the precise implications of these findings remain unclear, as effect sizes remained modest and several analyses failed to reach significance. Interestingly, these findings are largely consistent with two recent meta-analyses exploring the effects of tDCS over motor regions. Specifically, Bastani and Jaberzadeh [48] found that, in healthy populations, a-tDCS applied using greater current densities and longer stimulation durations resulted in larger changes in cortico-spinal excitability as measured using TMS evoked potentials [48]; while Chhatbar et al. [81] also recently described a positive dose-response relationship involving current density in studies utilising tDCS for the treatment of post-stroke motor recovery. Our current results build on these interesting findings by providing some initial support for a dose-dependent effect of a-tDCS for WM enhancement, when applied over the DLPFC. However, it is

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important to note that the dose analysis combined patients with healthy controls and there is some evidence that tDCS dose-effects may differ between these two populations [11, 16]. Future studies, which attempt to further explore this potential association, are therefore warranted. Such studies would also benefit from the collection of both behavioural and neurophysiological data, which could provide important information regarding the neurophysiological mechanisms underlying any cognitive modulation. Functional imaging techniques such as EEG and fMRI, as well as the more recently developed combined TMS and EEG (TMS-EEG) provide powerful ways of exploring these brain-behaviour relationships [82-84].

Limitations

The current findings should be discussed in light of a number of important limitations. First, as we restricted our literature search to peer-reviewed English language articles, this would have excluded any unpublished articles, or articles published in the grey literature (i.e., literature that has not been published in peer-reviewed scientific journals). It is possible that this may have led to a degree of publication bias, however this was not reflected in our funnel plots, which were symmetrical and did not show any evidence of small study effects. Second, although several different neuropsychiatric populations were included in the current meta-analysis, including participants with depression, schizophrenia and Parkinson's disease, the efficacy of a-tDCS in enhancing WM function in other disorders remains to be established, which somewhat limits the generalizability of the results. Furthermore, it is possible that underlying neurobiological differences between participants with different neuropsychiatric diagnoses could have potentially affected the pooled results, as some disorders might respond better to a-tDCS than others. Sample sizes in many of the studies included in the current review were also modest and given that participants in a number of studies were receiving medication, there remains a possibility of medication-related

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interaction effects. Finally, in all the included studies, WM was assessed either during, or shortly after treatment with a-tDCS, therefore no comment can be made as to the duration of post-stimulation treatment effects.

Future Directions

The results from this review highlight the need for further well-powered randomised controlled trials to more thoroughly assess the efficacy of a-tDCS for improving WM function in both healthy and clinical populations. In particular, systematic evaluation of any moderating effects of current density and stimulation duration would be of particular interest, given our current findings. In addition, it would be useful to more comprehensively explore differences between online versus offline WM changes. There is also a growing need for research examining the effects of stimulation over multiple brain regions, either independently or simultaneously. Results from neuroimaging studies highlight a number of widely distributed cortical networks implicated in WM function, incorporating frontal, parietal and cerebellar brain regions [85-89]. Hence, research into the differential effects of stimulation over these locations might help further delineate the neural mechanisms underlying WM processes and might also help uncover additional therapeutic targets. Recently developed multichannel stimulation devices, which allow for stimulation over multiple cortical sites using small 'high definition' electrodes, provide a novel way of potentially achieving this aim [90]. Finally, if a-tDCS is to become an effective neuro-rehabilitative device, it is imperative that it induces behavioural changes that last well beyond the period of stimulation. Currently, little research has been conducted into the long-term effects of a-tDCS, however there is emerging evidence that repeated same-day stimulation sessions can substantially prolong changes in cortical excitability [91, 92]; however whether these changes also translate into lasting behavioural improvements remains to be established.

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Conclusions

Overall, this systematic review and meta-analysis indicates that a-tDCS has some limited capacity to enhance WM in both healthy and neuropsychiatric populations. Specifically, offline WM accuracy and reaction times were improved in the healthy cohort, while online accuracy scores were improved in the neuropsychiatric cohort. However, the modest effect sizes obtained, coupled with non-significant effects on a number of analyses make firm conclusions regarding the overall efficacy of a-tDCS for either enhancing WM in healthy populations, or treating its dysfunction in neuropsychiatric cohorts, difficult. Nevertheless, given the very limited options currently available for the amelioration cognitive dysfunction in neuropsychiatric disorders, there is clearly a need for further investigation of refined tDCS protocols targeted towards restoration of WM function. Our finding that higher current densities and longer stimulation durations might be more effective at modulating WM provides one potential avenue for future research and is also consistent with previous behavioural and neurophysiological analyses performed in motor brain regions [48, 81]. Future research is needed to more thoroughly explore and refine the optimal stimulation parameters required for a-tDCS-based cognitive enhancement, implementing well-powered experimental designs and using both healthy and clinical populations.

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Figure Legends

Figure 1: PRISMA flow chart depicting the flow of information through different phases of the review

Figure 2: Risk of bias graph indicating the review authors' judgements about each risk of bias item presented as percentages across all included studies

Figure 3: Funnel plots exploring publication bias: Accuracy in healthy (A) and clinical (B) cohorts and Reaction time in healthy (C) and clinical (D) cohorts. Circles denote WM tasks performed online, while triangles denote WM tasks performed offline. The horizontal axis represents the effect size (SMD), while the vertical axis indicates the standard error (SE) of

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the SMD. In all instances, the studies appear roughly symmetrical around the SMD, suggesting a lack of publication bias

Figure 4: Forest plot depicting the effect of a-tDCS compared to sham stimulation on reaction times for the working memory tasks in healthy (A) and neuropsychiatric (B) cohorts

Figure 5 Forest plot depicting the effect of a-tDCS compared to sham stimulation on accuracy for the working memory tasks in healthy (A) and neuropsychiatric (B) cohorts

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Table 1: Inclusion and Exclusion Criteria

	Inclusion	Exclusion

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Participants	≥ 18 years of age Either healthy or suffering from a neuropsychiatric illness	Non-human subjects Neuropsychiatric illness secondary to another illness
Intervention	tDCS, anode applied over either the left or right DLPFC	Anode applied over brain region other than DLPFC
Comparison	Sham stimulation	Any other control group
Outcomes	WM as measured by n-back, Sternberg, or digit-span tasks WM measured either 'online' or 'offline'	Other type of WM assessment Distinction not made between 'online' and 'offline' WM assessment
Trial Design	Randomised controlled trials Controlled trials Single or double-blind	Review articles Case reports
Publication Type	Published in a peer-reviewed journal Written in English	Unpublished data, grey literature Non-English language articles

DLPFC = dorsolateral prefrontal cortex; WM = working memory

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Table 2: Characteristics of included working memory studies

Study	Trial Design	Cohort	Experiment	Sample Size	Intervention	Anode Location	Cathode Location	Stimulation Duration (min)	Stimulation Strength (mA)	Anode Size (cm^2)	Current Density (mA/cm^2)	Online/Offline Memory Task	Memory Task
Andrews et al. (2011)	Crossover	HS	1	10	a-tDCS	F3	RSO	10	1	35	0.029	Offline	Digits Forward
			2	10	a-tDCS	F3	RSO	10	1	35	0.029	Offline	Digits Backward
			3	11	a-tDCS	F3	RSO	10	1	35	0.029	Offline	Digits-Forward
			4	11	a-tDCS	F3	RSO	10	1	35	0.029	Offline	Digits-Backward
Berryhill and Jones (2012)	Crossover	HS	1	25	a-tDCS	F3	CC	10	1.5	35	0.043	Offline	2-back
			2	25	a-tDCS	F4	CC	10	1.5	35	0.043	Offline	2-back
Boggio et al. (2006)	Crossover	PD	1	9	a-tDCS	F3	RSO	20	1	35	0.029	Online	3-back
			2	9	a-tDCS	F3	RSO	20	2	35	0.057	Online	3-back
Fregni et al. (2005)	Crossover	HS	-	15	a-tDCS	F3	RSO	10	1	35	0.029	Online	3-back
Fregni et al. (2006)	Parallel	Depression	1	18	a-tDCS	F3	RSO	20	1	35	0.029	Offline	Digits Forward
			2	18	a-tDCS	F3	RSO	20	1	35	0.029	Offline	Digits Backward

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Hoy et al. (2013)	Crossover	HS	1	17	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T0)	2-back
			2	17	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T0)	2-back
			3	17	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T0)	3-back
			4	17	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T0)	3-back
			5	17	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T20)	2-back
			6	17	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T20)	2-back
			7	17	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T20)	3-back
			8	17	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T20)	3-back
			9	17	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T40)	2-back
			10	17	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T40)	2-back
			11	17	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T40)	3-back
			12	17	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T40)	3-back
Hoy et al. (2014)	Crossover	SCZ	1	18	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T0)	2-back
			2	18	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T0)	2-back
			3	18	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T20)	2-back
			4	18	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T20)	2-back
			5	18	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T40)	2-back
			6	18	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T40)	2back
Jeon et al. (2012)	Parallel	HS	1	32	a-tDCS	F3	RSO	20	1	35	0.029	Offline	Digits Forward
			2	32	a-tDCS	F3	RSO	20	1	35	0.029	Offline	Digits

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												Backward
Keeser et al. (2011)	Crossover	HS	1	10	a-tDCS	F3	RSO	20	2	35	0.057	Offline	1-back
			2	10	a-tDCS	F3	RSO	20	2	35	0.057	Offline	2-back
Loo (2010)	Parallel	Depression	1	40	a-tDCS	F3	RSO†	20	1	35	0.029	Offline	Digits Forward
			2	40	a-tDCS	F3	RSO†	20	1	35	0.029	Offline	Digits Backward
Loo et al. (2012)	Parallel	Depression	1	60	a-tDCS	F3	RSO†	20	2	35	0.057	Offline	Digits Forward
			2	60	a-tDCS	F3	RSO†	20	2	35	0.057	Offline	Digits Backward
Mulquiney et al. (2011)	Crossover	HS	1	10	a-tDCS	F3	RSO	10	1	35	0.029	Offline	1-back
			2	10	a-tDCS	F3	RSO	10	1	35	0.029	Offline	2-back
			3	10	a-tDCS	F3	RSO	10	1	35	0.029	Online	Sternberg
Mylius et al. (2012)	Crossover	HS	1	12	a-tDCS	F3	RSO	20	2	35	0.057	Online	2-back
			2	12	a-tDCS	F4	LSO	20	2	35	0.057	Online	2-back
Ohn et al (2008)	Crossover	HS	1	15	a-tDCS	F3	RSO	30	1	25	0.04	Online	3-back
			2	15	a-tDCS	F3	RSO	30	1	25	0.04	Offline	3-back
Oliveira et al. (2013)	Parallel	Depression	-	28	tDCS	F3	F4	30	2	25	0.08	Online	2-back
Teo et al. (2011)	Crossover	HS	1	12	a-tDCS	F3	RSO	20	1	35	0.029	Online	3-back
			2	12	a-tDCS	F3	RSO	20	2	35	0.057	Online	3-back
			3	12	a-tDCS	F3	RSO	20	1	35	0.029	Offline	Sternberg

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	4	12	a-tDCS	F3	RSO	20	2	35	0.057	Offline	Sternberg

CC = contralateral cheek, HS = healthy sample, LSO = left supraorbital area, PD = Parkinson's disease, RSO = right supraorbital area (+ denotes lateral aspect), SCZ = schizophrenia, T0 = 0 minutes post-stimulation, T20 = 20 minutes post-stimulation, T40 = 40 minutes post-stimulation

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Table 3: Summary of the effects of a-tDCS compared to sham on working memory (reaction time and accuracy) controlling for current density and stimulation duration

Stimulation Parameter	Value	Outcome Measure	N of Experiments	SMD (95% CI)	P-Value
Current density	≤0.029 mA/cm^2	Reaction time	16	-0.17 (-0.35, 0.02)	0.07
Current Density	>0.029 mA/cm^2	Reaction time	20	-0.13 (-0.29, -0.02)	0.10
Current density	≤0.029 mA/cm^2	Accuracy	26	0.05 (-0.10, 0.20)	0.48
Current Density	>0.029 mA/cm^2	Accuracy	21	0.21 (0.06, 0.36)	0.005
Stimulation duration	≤10 minutes	Reaction time	4	-0.09 (-0.43, 0.24)	0.58
Stimulation duration	>10 minutes	Reaction time	23	-0.15 (-0.30, -0.01)	0.04
Stimulation duration	≤10 minutes	Accuracy	8	0.06 (-0.21, 0.32)	0.66
Stimulation duration	>10 minutes	Accuracy	31	0.10 (-0.02, 0.23)	0.10

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