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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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ABSTRACT

Background: Several 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 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). The 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, CENTRAL and Scopus from July 1998 to June 2014.
Results: In healthy cohorts, a-tDCS produced a trend towards improvement for offline WM accuracy ($p = 0.05$) and a small, but significant improvement in reaction time ($p = 0.04$); however, no significant effects were observed for online tasks (accuracy [$p = 0.29$], 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: This review provides some 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.

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.

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

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(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].

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 show 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 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), PsycINFO (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL) (Ovid) and SCOPUS from 1 July 1998 (i.e., first published evidence of the effects of a contemporary tDCS paradigm on cortical excitability by Priori et al. [56]) to 17 June 2014 (see Supplementary 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 screened (see Fig. 1 for a flow-chart depicting relevant stages of the literature search and selection process).

Selection criteria

Included studies were required to meet the selection criteria outlined in Table 1. Specifically, studies were included if: (1) they 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 were available for at least

Table 1
Inclusion and exclusion criteria.

	Inclusion	Exclusion
Participants	≥18 years of age	Non-human subjects
	Either healthy or suffering from a neuropsychiatric illness	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	Other type of WM assessment
	WM measured either 'online' or 'offline'	Distinction not made between 'online' and 'offline' WM assessment
Trial design	Randomised controlled trials	Review articles
	Controlled trials	Case reports
	Single or double-blind	
Publication type	Published in a peer-reviewed journal	Unpublished data, grey literature
	Written in English	Non-English language articles

DLPFC, dorsolateral prefrontal cortex; WM, working memory.