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NEUROMODULATION (S TAYLOR, SECTION EDITOR)

Uncertainty and Promise: the Effects of Transcranial Direct Current Stimulation on Working Memory

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Abstract Working memory (WM) is an essential neuropsychological system that supports complex cognitive processes. Transcranial direct current stimulation (tDCS) uses electrical current to modulate brain activity and may serve as a tool for studying or even enhancing WM. Here, we review the recent research that has explored the effects of tDCS on WM in healthy young adults, older adults, and patient populations. We also discuss several recent meta-analyses that have examined the efficacy of tDCS as a WM intervention. While a majority of the papers reviewed suggest that tDCS can modulate WM, this effect is highly inconsistent. These seemingly conflicting results may be driven by differences in study design, tDCS protocol, or inter-individual differences. Future research should systematically vary stimulation parameters, combine tDCS with neuroimaging, and account for individual differences in order to accurately assess the value of tDCS as a way to study and enhance WM.

Keywords Transcranial direct current stimulation · tDCS · Neuromodulation · Brain stimulation · Working memory · Prefrontal cortex · Cognitive intervention · Cognitive enhancement

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Introduction

Working memory (WM) is a neuropsychological system that allows information to be manipulated and maintained temporarily in service of complex cognitive processes including goal-directed behavior, learning, and problem solving [1]. Dysfunction of WM is often observed in healthy older adults [2–4] and is a hallmark of several neurological disorders including schizophrenia [5], attention-deficit/hyperactivity disorder [6], and Parkinson's disease [7]. Because of its importance to cognition, a wide variety of interventions have been developed to prevent, cease, or even reverse WM decline, albeit with mixed results [8–10]. Despite some progress with current pharmacological, cognitive training, and behavioral interventions, there remains a pressing need for efficient interventions that can generate consistent and long-lasting benefits in WM.

One potential candidate is non-invasive brain stimulation, specifically transcranial direct current stimulation (tDCS). Because tDCS is relatively inexpensive, safe, and easy to administer, interest in tDCS as a cognitive enhancement tool has grown rapidly over the last decade. This interest spans basic scientific and clinical research; however, significant progress is needed in identifying optimal stimulation parameters and understanding the underlying neural mechanisms affected by tDCS [11]. Despite these and other challenges, the potential to modulate activity exogenously and facilitate cortical plasticity offers exciting opportunities to build upon neuroimaging observations, strengthen causal claims, and craft interventions for vulnerable and healthy populations. Here we provide an overview of tDCS followed by a focused review of the effects of tDCS on common WM task performance in healthy young adults, healthy older adults, and clinical populations. Additionally, we highlight a few seminal meta-analyses, discuss the current limitations of using tDCS to study cognitive

processes, and propose future directions for research employing tDCS to influence WM.

Transcranial Direct Current Stimulation

tDCS belongs to a family of non-invasive brain stimulation techniques that exploit electrical and magnetic principles to modulate neural activity exogenously (see [12•] for review). Although systematic investigations of its effects date back to the mid-1900s [13, 14], tDCS experienced a resurgence in interest in the early 2000s driven by advances in neuroimaging, transcranial magnetic stimulation (TMS), and safety standards [15]. In the past two decades, over 1000 papers have been published on the use of tDCS.

Administering tDCS

Traditionally, tDCS is administered by passing a weak constant electrical current through two electrodes housed in saline-soaked sponges. One sponge is fastened to the subject's scalp over a region of interest while the other (sometimes referred to as the reference) is placed over another cortical region or a non-cortical location such as the cheek or arm. The electricity generated by a battery-powered direct current stimulator flows from the anode electrode to the cathode electrode. Stimulation is generally applied for 10–30 min; however, the effects of tDCS have been shown to last as long as several hours [16], and multisession stimulation has been shown to result in improvements on cognitive tasks that are evident months after the intervention [17, 18]. Variations in current strength, electrode size, and stimulation duration modify the "dose" of stimulation and have been shown to modulate responsiveness to tDCS [19]. Importantly, increases in current density, which are determined by electrode size and current amplitude, increase the depth of the electrical field generated potentially resulting in a non-linear relationship between stimulation and its effects [19]. In a seminal study, Nitche and Paulus [20] showed that applying a weak positive or negative electrical current over the motor cortex increased or diminished cortical excitability, respectively, as measured by motor-evoked potentials. Thus, anodal stimulation is generally thought to increase neural excitability while cathodal stimulation is thought to inhibit neuronal activity. However, as discussed below, inconsistent results supporting this assumption have led to a call to eschew this simplistic understanding of polarity effects (see [21]).

One advantage of tDCS is the easy application of a placebo, or sham, condition built into many stimulators. Naïve subjects in parallel studies are effectively blinded to condition (i.e., unaware of whether or not they are being activated stimulated) [22] while some subjects in cross-over design studies have been shown to correctly identify conditions, albeit somewhat unreliably [23]. tDCS is also relatively safe. Documented side effects are minor, benign, and fleeting. tDCS has been used safely in studies of children and adolescents with few, minor adverse events reported [24]. Currently, the most commonly reported side effects include itching or tingling sensations at the electrode site, mild headache, burning sensation, and discomfort. However, there is a selective reporting bias such that nearly half of the studies examined in one review did not report the presence or absence of adverse events [25, see also Tables 1 and 2].

Proposed Mechanisms of tDCS

Despite the limited understanding of the underlying mechanisms of tDCS, the potential to modulate activation exogenously and increase neuroplasticity has far-reaching implications for cognition and behavior. Unlike TMS, which uses strong magnetic fields to disrupt brain activity directly, tDCS uses weak electrical fields that slightly modify the neural membrane potential making neurons more or less likely to fire [12•]. Current modeling indicates that conventional tDCS is less focal than TMS, and can affect cortical regions distant from the electrode [73]. Importantly, tDCS seems to work via two mechanisms: one that acts during stimulation and the other that acts following stimulation [74]. Consequently, attention should be paid to whether a study employs an *online* protocol, in which task performance is measured while receiving stimulation, an *offline* protocol, in which task performance is measured following stimulation, or some combination of the two.

During stimulation, tDCS is thought to act by modulating neuronal resting membrane potential in a polarity-specific manner. In this conceptualization, anodal stimulation depolarizes resting membrane potentials, thereby increasing firing rate, whereas cathodal stimulation hyperpolarizes resting membrane potentials, making them less likely to fire [75]. Following stimulation, the reverberating effects of tDCS are thought to rely on modulation of glutamatergic synapses which may, in turn, result in long-term potentiation (LTP) and long-term depression (LTD) acting in the previously stimulated regions [74]. tDCS-induced plasticity is modulated by acetylcholine, serotonin, and dopamine neurotransmitter systems and therefore may be governed, in part, by genetic polymorphisms [74, 76••, 77]. Beyond intracortical interneuron communication, tDCS has been shown to modulate cortico-cortico and cortico-subcortical functional connectivity [78, 79].

Recent Advances

Recently, modifications to the administration of tDCS aim to diversify its use as a neuromodulation tool and address shortcomings. These modifications have included high-definition

Table 1 Studies of tDCS on working memory in healthy young adults

	Mean age	Number of subjects	Anode	Cathode	Amp/ electrode	Duration	Online/ offline	Measure	Design	Findings	Side effects
Single-session											
Andrews et al., 2011 [26]	28	10	**F3**	rSO	1 mA; 35 cm^2	10 min	Offline	Digit span	Crossover	Anodal F3 + *N*-back improves digit span forward compared to prestim baseline; sham + *N*-back = tDCS alone	
Berryhill et al., 2010 [27]	25	11	**P4** lCheek	lCheek **P4**	1.5 mA; 35 cm^2	10 min	Offline	Sternberg	Crossover	Cathodal P4 worsens WM recognition accuracy compared to sham; sham = anodal P4	
Boehringer et al., 2012 [28]	25	40	rCheek	**rCerebellum**	2 mA; 25 cm^2	25 min	Offline	Digit span	Crossover	Cathodal R Cereb. worsens WM performance compared to sham	
Carvalho et al., 2015 [29•]	21	45	**F3** rSO	rSO **F3**	1 mA; 35 cm^2	20 min	Online	*N*-back	Crossover	20 min continuous anodal F3 improves WM accuracy compared to sham; 10-, 30-, and 60-m intervals in middle of stim remove effect	None
De Putter et al., 2015 [30]	23	66	**F3**	rSO	2 mA; 25 cm^2	25 min	Offline	RSpan	Parallel	Anodal F3 stimulation had no effect on WM performance	Itching, tingling, headache
Fregni et al., 2005 [31]	20	15	**F3** rSO	rSO **F3**	1 mA; 35 cm^2	10 min	Online	*N*-back	Crossover	Anodal F3 improves WM accuracy compared to sham; cathodal F3 approx. = sham	
Giglia et al., 2014 [32]	27	10	**F3** **F4**	rSO rSO	1 mA; 35 cm^2	10 min	Offline	Delayed spatial recognit.	Crossover	Anodal F4 improves WM accuracy but not RT compared to anodal F3 and sham	
Gladwin et al., 2012 [33]	22	14	**F3**	rSO	1 mA; 35 cm^2	10 min	Online	Sternberg	Crossover	Only in interference condition, anodal F3 improves RT but not accuracy	
Hoy et al., 2013 [34]	25	18	**F3**	rSO	1 mA; 35 cm^2 2 mA; 35 cm^2	20 min	Offline	*N*-back	Crossover	1-mA anodal F3 improved 2-back RT compared to 2 mA or sham with the largest improvements 40 m after stim; no effect on 3-back	
Jeon et al., 2012 [35]	37	32	**F3** **F4**	rSO lSO	1 mA; 35 cm^2	20 min	Offline	Digit span	Parallel	Anodal F3 improves digit span backward following stim and 2 weeks later	Skin redness, headache
Keeser et al., 2011 [36]	29	10	**F3**	rSO	2 mA; 35 cm^2	20 min	Offline	*N*-back	Crossover	Anodal F3 2 back WM accuracy and error rate compared to sham	None
Kim et al., 2014 [37•]	22	17	**F3**	rSO	1 mA; 35 cm^2	20 min	Offline	*N*-back	Crossover	Anodal F3 improved WM accuracy and/or RT and was associated with significantly larger current density at DLPFC for 9 participants	
Marshall et al., 2005 [38]	19-27 (range)	12	**F3**	**F4**	260 μA; 8 mm	15 min (15 s on/off)	Online	Sternberg	Crossover	Decreased RT with both anodal and cathodal	
Martin et al., 2014 [39]	23	19	**F3**	rArm	2 mA; 35 cm^2	30 min	Online/offline	*N*-back	Crossover	Online anodal F3 improved WM skill acquisition on day 2 of testing compared to offline	Skin redness, itching, tingling, burning
Meiron & Lavidor, 2013 [40]	25	41	**F3** **F4**	Cz Cz	2 mA; *A* 16 cm^2, *C* 35 cm^2	15 min	Online	*N*-back	Parallel	At high load, anodal F3 improves WM accuracy compared to sham in males	None
Mulquiney et al., 2011 [41]	29	10	**F3**	rSO	1 mA; 35 cm^2	10 min	Offline	*N*-back	Crossover	Anodal F3 improves 2 back RT but not accuracy compared to sham	
Mylius et al., 2012 [42]	24	24	**F3** **F4** rSO rSO	rSO lSO **F3** **F4**	2 mA; 35 cm^2	20 min	Online	*N*-back	Crossover	Anodal F3 or F4 and cathodal F3 or F4 have no effect on WM performance; cathodal F3 resulted in a reduction of outliers compared to sham	Headache
Nikolin et al., 2015 [43]	22	16	(HD) **F3** (HD) **CP5** (HD) **P9**	(HD) AF3, P5, FC, FC3 (HD) C5, TP7, CP3, P5 (HD) FP1, FP2, FC4	2 mA	20 min	Offline	*N*-back	Crossover	Anodal F3 improves WM speed but not accuracy compared to sham but not to other stimulation sites	Skin irritation, stinging, itching, erythema, headache

Table 1 (continued)

	Mean age	Number of subjects	Anode	Cathode	Amp/ electrode	Duration	Online/ offline	Measure	Design	Findings	Side effects
Ohn et al., 2008 [44]	27	15	**F3**	rSO	1 mA; 25 cm^2	30 min	Online/offline	*N*-back	Crossover	Anodal F3 improves WM accuracy after 30 min of stim; anodal F3 approx. = sham after 30 rest	None
Sandrini et al., 2012 [45]	25	27	**P3** **P4**	**P4** **P3**	1.5 mA; 35 cm^2	13 min	Offline	*N*-back	Parallel	Practice-dependent RT change was abolished in anodal P3 and cathodal P4 on 1-back, and anodal P4 and cathodal P3 on 2-back	
Sellers et al., 2015 [46]	Active (1): 26 Sham (1): 21 Active (2): 22 Sham (2): 21	41	**F3** **F4**	Cz Cz	2 mA; 35 cm^2	20 min	Offline	WAIS: WM subscales	Parallel	Anodal F3 and/or anodal F4 have no effect on WM performance	
Teo et al., 2011 [47]	27	12	**F3**	rSO	1 mA, 2 mA; 35 cm^2	20 min	Offline	Sternberg	Crossover	Anodal F3 at 2 mA improves 3 back RT but not accuracy; no effect on Sternberg	Skin tingling
Weigand et al., 2013 [48]	25	15	**F4** rSO	rSO **F4**	1 mA; 35 cm^2	15 min	Offline	*N*-back	Crossover	When followed by rTMS, anodal and cathodal F4 stimulation improve WM accuracy to fear-related stim and reduce WM accuracy to neutral stim compared to baseline	
Wu et al., 2014 [49]	26	20	**F4**	lCheek	1.5 mA; 25 cm^2	15 min	Offline	Corsi	Crossover	Anodal F4 improves WM span only in CBB + interference condition compared to sham	
Xu et al., 2015 [50]	27	31	(HD) **AF3**, **AF4**	(HD) OzPOz	2 mA,	20 min	Offline	*N*-back	Crossover	Anodal AF3 and AF4 has no effect on WM performance when compared to sham	
Zaehle et al., 2011 [51]	25	16	**F3** rMastoid	rMastoid **F3**	1 mA; 35 cm^2	15 min	Offline	*N*-back	Crossover	Anodal F3 improves selectivity but not RT compared to cathodal F3; anodal F3 results in amplified oscillatory power in theta and alpha bands	
Multisession											
Lally et al., 2013 [52]	23	21	**F3**	rCheek	1 mA; 35 cm^2	10 min × 1–2 days	Online	*N*-back	Parallel	Anodal F3 improves WM accuracy during online stimulation of first session only, compared to sham	
Martin et al., 2013 [53]	Active: 22 Sham: 23	52	**F3**	rDeltoid	2 mA; 35 cm^2	30 min × 10 days	Online/ Offline	Digit span, *N*-back	Parallel	Anodal F3 improves *N*-back accuracy during online stim compared to sham; no effect after accounting for baseline	Skin redness, itching, tingling, headache, fatigue, dizziness,
Motohashi et al., 2013 [54]	22	11	**F3**	rSO	1 mA; 35 cm^2	20 min × 4 days	Offline	*N*-back	Crossover	No effect of stimulation on WM performance	Skin itching, tingling
Richmond et al., 2014 [55]	21	58	**F3**	**F4**	1.5 mA; 35 cm^2	15 min × 10 days	Offline	Adaptive WM training	Parallel	Anodal F3 and cathodal F4 improves verbal WM accuracy compared to sham	Absent or mild misc.

Boldface denotes target electrode. Side effects: blank denotes no/unclear reporting of side effects

r right, *l* left, *SO* supraorbital gyrus, *DLPFC* dorsolateral prefrontal cortex

Table 2 Studies of tDCS on working memory in older adults and clinical populations

Authors	Popul.	Mean age	Number of subjects	Anode	Cathode	Amp/ electrode	Duration	Online/ offline	Measure	Design	Findings	Side effects
Berryhill & Jones, 2012 [56]	OA	64	25	**F3** **F4**	rcheek lcheek	1.5 mA; 35 cm^2	10 min	Offline	*N*-back	Crossover	Anodal F3 and F4 improves WM performance in high Ed OA; anodal F4 worsened WM performance in low Ed OA	
Nilsson et al., 2015 [57]	OA	69	30	**F3**	rSO	1 mA, 2 mA; 35 cm^2	25 min	Online/ offline	*N*-back	Crossover	Anodal F3 has no effect on WM performance	
Seo et al., 2011 [58]	OA	70	24	**F3**	Arm	2 mA; 25 cm^2	30 min	Offline	*N*-back	Parallel	Anodal F3 improves verbal 2-back accuracy but not RT or visual 2-back	Skin redness, aching
Jones et al., 2015 [18]	OA	64	72	**F4** **P4**	lcheek lcheek	1.5 mA; 35 cm^2	10 min × 10 days	Offline	Digit span, *N*-back	Parallel	Compared to sham, anodal F4 and/or P4 has no effect on WM training gains immediately after training, but does improves 2-back and Ospan performance after 1 month	
Park et al., 2014 [17]	OA	79	40	**F3** **F4**	Arm Arm	2 mA; 25 cm^2	30 min × 10 days	Online/ offline	Digit span, *N*-back	Parallel	Compared to sham, anodal F3 improves WM performance immediately following stim; only accuracy gains remain 7 and 28 days later; improves DSF 7 days after stim	
Clinical populations												
Boggio et al., 2009 [59]	AD	79	10	**F3** **T7**	rSO rsO	2 mA; 35 cm^2	30 min	Online	Digit span	Crossover	No effect of stimulation on WM performance	None
Moreno et al., 2015 [60]	MDD	Active: 27 Sham: 33	40	**F3**	**F4**	2 mA; 25 cm^2	30 min	Offline	*N*-back	Parallel	Anodal F3 improves cold and hot working memory in depressed subjects	
Oliveira et al., 2013 [61]	MDD	38	28	**F3**	**F4**	2 mA; 25 cm^2	30 min	Online	*N*-back	Parallel	Anodal F3 and cathodal F4 improves WM accuracy compared to sham	None
Ferrucci et al., 2009 [62]	MDD	52	8	**DLPFC**	**RDLPFC**	2 mA; 32 cm^2	20 min × 10 days (2× day)	Offline	Sternberg	Open label	No effect of stimulation on WM performance	Headache
Fregni et al., 2006 [63]	MDD	46	18	**F3**	rSO	1 mA; 35 cm^2	20 min × 5 days	Offline	Digit span	Parallel	Anodal F3 improves WM accuracy compared to sham	None
Loo et al., 2010 [64]	MDD	Active: 49 Sham: 46	40	**F3**	rSO	1 mA; 35 cm^2	20 min × 5–10 days	Offline	Digit span	Parallel	10 sessions of anodal F3 improves DSB accuracy compared to baseline; sham = anodal F3	Skin redness, itching, headache, nausea, others
Loo et al., 2012 [65]	MDD	Active: 49 Sham: 48	60	**F3**	rSO	2 mA; 35	20 min × 15–30 days	Offline	Digit span	Parallel	Anodal F3 has no effect on WM performance after 15 and 30 sessions compared to baseline	Skin redness, itching, headache, nausea, others
Salehinejad et al., 2015 [66]	MDD	28	30	**F3**	**F4**	2 mA; 35 cm^2	20 min × 10 days	Offline	CANTAB WM	Parallel	Anodal F3 and cathodal F4 improves visual WM performance compared to sham	None
Boggio et al., 2006 [67]	PD	Active: 59 Sham: 61	9	**F3** **M1**	rSO rSO	1 mA, 2 mA; 35 cm^2	20 min	Online	*N*-back	Crossover	Anodal M1 or 1 mA = sham; anodal F3 at 2 mA improves WM accuracy but not speed	
Hoy et al., 2014 [68]	Schiz	42	18	**F3**	rSO	1 mA, 2 mA; 35 cm^2	20 min	Offline	*N*-back	Crossover	2 mA anodal F3 improved WM accuracy compared to 1 mA or sham 20 min after stimulation, no effect on RT	None
Smith et al., 2015 [69]	Schiz	Active: 47 Sham: 45	29	**F3**	rSO	2 mA; 25 cm^2	20 min × 5 days	Offline	MCCB WM composite	Parallel	Anodal F3 improves verbal but not visual WM compared to sham	
Jo et al., 2009 [70]	Stroke	48	10	**F3**	rSO	2 mA; 25 cm^2	30 min	Online	*N*-back	Crossover	Anodal F3 improves WM accuracy compared to prestim baseline	Skin redness, aching, burning

Table 2 (continued)

Authors	Popul.	Mean age	Number of subjects	Anode	Cathode	Amp/ electrode	Duration	Online/ offline	Measure	Design	Findings	Side effects
Ulam et al., 2015 [71]	TBI	Active: 31 Sham: 36	26	**F3**	rSO	1 mA; 25 cm^2	20 min × 10 days	Offline	Digit span	Parallel	Anodal F3 has no effect on WM performance when compared to sham	Absent or mild misc.
Liu et al., 2016 [72]	TLE	43	33	**F3**	rSO	2 mA; 35 cm^2	20 min × 5 days	Offline	Digit span, letter-number sequencing	Parallel	Anodal F3 has no effect on WM performance compared to sham	

Boldface denotes target electrode. Side effects: blank denotes no/unclear reporting of side effects

r right, *l* left, *SO* supraorbital gyrus, *DLPFC* dorsolateral prefrontal cortex

tDCS (HD tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). Improvements in focal stimulation have been achieved by using high-definition tDCS, which involves a number of smaller, gel-based electrodes (approx. 12 cm^2) applied strategically in a ring around an area of interest (see [80] for detailed treatment). Whereas much initial research focused on stimulating the motor cortex, HD tDCS reportedly facilitates visual perception [81] and verbal learning [43] when applied to occipital and fronto-temporal regions, respectively. While HD stimulation combined with neuroimaging is needed to determine the extent of current dispersion, HD tDCS may help identify casual roles for specific brain regions and may be a safer, inexpensive alternative to TMS.

tACS entails the application of symmetrical oscillatory stimulation which has been shown to modulate and entrain cortical oscillations as measured by frequency bands (see [82] for review). tACS of the left dorsolateral prefrontal cortex (lDLPFC) can entrain gamma oscillations resulting in greater WM improvements at higher loads than those found using traditional tDCS [83]. Like tDCS, tACS may work by modulating neural membrane potential. Thus far, these changes appear not to have plasticity-inducing effects, thereby limiting the potential utility of tACS as a tool for cognitive intervention [84].

Finally, tRNS is a form of tACS that employs currents at random frequencies (0.1–640 Hz) resulting in LTP-like changes [85]. Unlike tDCS, tRNS is not sensitive to current flow, is NMDA-receptor independent, and is easier to blind [85, 86]. When compared to tDCS, tRNS has been shown to result in larger improvements in visual learning [87] and larger suppression of tinnitus symptoms [88]. Despite these promising recent findings, tRNS research is in its infancy and more work is needed to determine the optimal circumstances for using tRNS.

tDCS and Working Memory

Studies examining the effects of tDCS on WM are summarized in Tables 1 and 2. It is widely accepted that the dorsolateral prefrontal cortex (DLPFC) plays a crucial role in WM function [89]. Accordingly, most studies place electrodes of interest over regions that correspond to DLPFC location (BA 9/46; International 10-20 system: F3 or F4). The present review is limited to studies that employed a well-established WM task or variant. These include digit span forward and backwards, in which participants repeat number strings of increasing length in forward or reversed order [90], Corsi Block forward and backwards, which uses block locations to examine visuospatial WM [90], letter-number sequencing, which requires participants to organize a random series of numbers and letters into ascending order [90], the Sternberg

task, in which participants hold a varying number of items in mind and then judge whether or not a probe is in the remembered list [91], and the *N*-back task, which requires participants to match a current item and one presented a specified number of trials before [89].

Single-Session tDCS and Working Memory

Most tDCS research has been conducted on young, healthy adults and the effects on WM performance have been mixed. Several studies find that anodal tDCS applied to F3 results in improved WM performance [26, 31, 35, 36, 44], others find improvements in response time but not accuracy [41, 43, 47; but see 32], while still others find no effect of stimulation on performance [30, 42, 46, 50]. The seemingly contradictory results may have various origins including differences in stimulation parameters and task difficulty across studies. For example, Martin et al. [39] examined the effect of offline versus online anodal stimulation of F3 on an *N*-back task with adaptive difficulty within individuals. Online stimulation applied during adaptive *N*-back training resulted in significantly larger WM gains on a test the following day compared to offline stimulation before training. In another study [34], 1-mA, but not 2-mA, stimulation resulted in response time improvements on a 2-back task, with the greatest improvements present 40 min following stimulation. In addition to stimulation differences, differences in task demand may influence the effectiveness of tDCS. Recently, Wu and colleagues [49] found that anodal tDCS over rDLPFC resulted in improvements to spatial WM only in the most demanding condition (backwards Corsi recall with motor interference). Similarly, anodal stimulation over lDLPFC appears most effective in high-demand tasks [33, 40].

In a recent comprehensive meta-analysis, Horvath and colleagues [92••] reported finding no reliable effect of single-session tDCS on any of a number of cognitive tasks, including WM tasks. These results, however, run contrary to meta-analyses conducted by Hill et al. [93••] and by Brunoni and Vanderhaselt [94•]. Hill and colleagues [93••] examined the effects of tDCS on WM performance, specifically. They found that offline anodal stimulation results in improvements in WM response times and trends towards increased accuracy in healthy adults. In another meta-analysis, Brunoni and Vanderhaselt [94•] specifically examined the effects of non-invasive brain stimulation of DLPFC on *N*-back performance. The authors reported results similar to Hill and colleagues [93••]: a significant improvement in WM response time, but not accuracy, following tDCS. Hill [93••] suggests that the discrepancies between their meta-analysis and Horvath's meta-analysis could be due to differences in power. Hill's meta-analysis included a larger number of WM studies compared to Horvath's which parsed 53 cognitive studies into smaller subsamples (2 to 6 studies each) based on stimulation parameters and cognitive task. Price and Hamilton [95] have criticized this approach, claiming that running separate analyses on subsamples may yield results that are insufficiently powered to allow for meaningful interpretation. Horvath noted that their null effects arose from data from healthy young adults after a single-session of tDCS and suggested that tDCS administered in other populations, or over multiple sessions, may yield different results.

Multiple-Session tDCS and Working Memory

As highlighted by Horvath [92••], tDCS effects may need to accumulate across multiple sessions to be observed consistently in cognitive tasks. To date, only a handful of studies have used multiple sessions of tDCS to influence WM performance in healthy, young adults. Anodal stimulation of lDLPFC across two [52] and four [54] sessions did not result in WM improvements on *N*-back tasks. Martin et al. [53] examined the effect of ten sessions of anodal tDCS to lDLPFC administered while performing a WM training task (adaptive dual *N*-back) on training-task performance as well as on WM measures completed before and after the intervention. Online tDCS resulted in more accurate WM performance during stimulation, but did not increase post-stimulation performance on either the WM training task or the untrained tasks. In a more recent study, however, Richmond and colleagues [55] found that compared to sham stimulation, ten sessions of anodal tDCS to lDLPFC during verbal WM training resulted in significant improvement on the trained task. Further, active stimulation resulted in significant improvements on untrained WM tasks compared to a no-contact control group. However, there were no differences between active and sham groups or between sham and no-contact control groups on the untrained tasks. Importantly, Richmond and colleagues [55] employed a montage in which the cathode was placed over another cortical region (rDLPFC), unlike Martin and colleagues [53], who placed the cathode in an extracephalic position (right deltoid) to avoid confounding potentially inhibitory effects. This raises the intriguing possibility that the excitatory effects of the anode depend on inhibitory effects of the cathode over other, perhaps competing regions to improve WM.

Clinical Populations

WM dysfunction is a symptom often associated with neurological and neuropsychiatric disorders. tDCS has been reported to successfully enhance motor and cognitive function in disorders such as Parkinson's disease, aphasia, and neglect (see [96•] for review). tDCS has been shown to improve WM performance in people recovering from stroke [70], people diagnosed with Parkinson's disease [67], and people with schizophrenia [68, 69]. However, tDCS has shown no effect

on WM performance in people suffering from traumatic brain injury [71], temporal lobe epilepsy [72], or Alzheimer's disease [59]. In a preliminary meta-analysis, Hill and colleagues [93••] examined the effects of tDCS on WM performance in neuropsychiatric patient cohorts, including depression, Parkinson's disease, and schizophrenia. Unlike healthy adults, who exhibited improvement from offline stimulation, neuropsychiatric patients only showed significant improvements in WM accuracy with online stimulation. The authors speculate that, because patient populations have abnormalities in the balance of excitation and inhibition, stimulation *during* task may be necessary to adequately modulate this balance. However, it is worth noting that this meta-analysis collapsed across multiple types of neuropsychiatric disorders; patient populations may differ in responsive to tDCS.

The most extensive work to date on tDCS in patient populations has been in depression. Similar to patterns observed in healthy individuals, the results are inconsistent. Several studies employing multiple lDLPFC anodal stimulation sessions reported no effect on WM performance in depressed individuals [62, 64, 65], whereas other multisession stimulation studies using similar stimulation parameters reported significant improvements [63, 66]. Moreover, studies by Moreno et al. [60] and Oliveira et al. [61] on depressed participants found WM improvements after just one session of lDLPFC anodal stimulation. The studies reporting tDCS effectiveness on WM in depressed individuals had notably younger participants (M_{age} = 26.5–46.4) than studies in which the intervention was ineffective (M_{age} = 45.6–52.4) suggesting that age may interact with depression to affect tDCS efficacy.

Older Adults

Research examining how tDCS affects cognition in healthy older adults (65+) is relatively sparse. This is surprising because tDCS is thought to promote cortical plasticity [74], and aging is characterized by a decline in plasticity [97] making tDCS a potential promising intervention for cognitive aging. However, a recent meta-analytic review conducted by Summers and colleagues [76••] collected 25 separate studies, published over the last 5 years, and found a robust enhancing effect of anodal tDCS on cognitive processes in the elderly. Specifically, anodal tDCS enhanced performance on memory/WM tasks with an observed effect size of 0.45. Additionally, stimulation applied before task and to cortical regions other than DLPFC showed the largest effects [76••]. Another review focused specifically on WM in older adults found similar results [98•] suggesting that tDCS may serve as an effective WM intervention in the elderly.

Many of these meta-analyses and reviews are limited by the paucity of research focused specifically on tDCS and WM in older adults. For example, the Summers et al. [76••] review combines both long-term memory and WM into a single moderator variable. Individual studies of tDCS and well-accepted WM tasks, like the *N*-back task, often provide mixed results. Nilsson and colleagues [57] examined the effect of 1- and 2-mA single-session anodal stimulation to lDLPFC on 3-back performance in older adults. Anodal stimulation did not affect WM accuracy or response time during or after stimulation, regardless of stimulation amplitude. In contrast, Seo et al. [58] found that older adults who received anodal stimulation to this region performed better on a verbal *N*-back task, when compared to participants who received sham. Berryhill and Jones [56] found anodal tDCS improves WM performance, but only in highly educated older adults, suggesting that perhaps differences in participant characteristics and demographics may contribute to the observed inconsistent tDCS effects in older adults. Studies employing multiple stimulation sessions in older adults have also yielded a complex pattern of results. Whereas one recent study indicated that ten sessions of anodal lDLPFC stimulation coupled with cognitive training resulted in greater WM improvements immediately following stimulation, compared to those who received sham stimulation [17], another study employing a similar design found no effect [18]. In both studies, however, older adults who received active anodal stimulation maintained WM improvement at follow-up (7 days–1 month), compared to older adults who received sham stimulation, suggesting a potential role for tDCS in long-term maintenance of training benefits.

Methodological Issues and Other Challenges

In a recent review, Trembley and colleagues [99•] found that studies of tDCS applied to DLPFC reported inconsistent changes in WM performance. Anodal stimulation to left DLPFC resulted in increases in WM performance in some research and declines in WM performance in others. They observed a similarly discrepant pattern across studies using cathodal stimulation to this region. Inconsistent outcomes across studies could stem from differences in study design, stimulation parameters, and participant inter- and intra-individual differences. Notable methodological differences include electrode montage, current density and duration, online/offline stimulation, number of stimulation sessions, sham/active comparison condition, parallel/crossover design, washout period, age range, WM task, task difficulty, and participant/experimenter blindness to the stimulation conditions. Many of these differences are evident in Tables 1 and 2. The next section outlines additional issues that should be considered when designing or interpreting the results of a tDCS study.

Assumptions of Polarity

Anodal stimulation is theoretically associated with excitation, whereas cathodal stimulation is linked to inhibition. However, according to recent evidence, these polarity-specific assumptions, based primarily on initial research in the motor cortex, are violated in both motor and non-motor regions [21]. While the effects of tDCS on the human motor cortex can be measured directly with a combination of TMS and observed motor-evoked potentials, to date assessing tDCS effects on non-motor cortex relies on the performance of tasks hypothesized to depend on the underlying brain regions. That is, assessment of tDCS effects on non-motor cortex are indirect and thus more subject to uncontrolled variability. In their meta-analytic review, Jacobson and colleagues [21] noted that the anodal/excitation cathodal/inhibition dichotomy is primarily observed in motor studies and rarely (probability = 0.16) observed in cognitive studies. This disparity is driven by the lack of observed cathodal/inhibition effect, rather than the anodal/excitatory effect, which is more robust. The authors suggest that difficulty finding the cathodal/inhibition effect may stem from the fact that higher-order cognitive tasks depend on complex, multinode networks that are more widely distributed. This makes it more challenging to determine the critical site or loci where stimulation will be most effective. Cognitive processes may also compensate for inhibition to certain cortical regions, which could contribute to inconsistent outcomes from cathodal stimulation.

State-Dependent Effects

tDCS does not directly depolarize neurons, but instead appears to modulate the neuronal membrane, thereby changing the likelihood of firing. Therefore, the effects of tDCS are influenced by the state of the cortical region to which stimulation is applied [99•]. Because responsiveness seems to be largely governed by baseline cortical excitability, "excitatory" anodal stimulation applied to a region that is highly active may cause a reversal of the anticipated effect, instead resulting in inhibition [100]. Consequently, the type of task and task difficulty become particularly important variables. Compounding the complexity of this issue, variability in time of day, strategy, and fatigue can also influence the state of a network [99•].

In studies that used offline stimulation, instructions to participants ranged from sitting quietly to completing complex tasks, which could in principle lead to different responsiveness to tDCS. Consistent with this possibility, Carvalho et al. [29•] found that two cathodal stimulation sessions separated by a break improved WM task performance when compared to cathodal stimulation followed by anodal stimulation or two sham stimulation sessions. The authors interpret these results to suggest that modulation of baseline activity affects the subsequent effects of tDCS on behavior. Regarding online stimulation, the same task may elicit different patterns of activity across participants. For example, compared to healthy young adults, older adults and schizophrenic patients show hyperactivation of rDLPFC when successfully completing moderately challenging WM tasks [101, 102]. For this reason, identical electrode montages may have different behavioral consequences across populations.

Individual Differences in Responsiveness

Two studies have documented large inter-individual differences in tDCS responsiveness with less than half of the participants demonstrating the anticipated response [103, 104]. Research employing a combination of neuroimaging and current modeling finds that individual differences in physiology and anatomy, including skull morphology, fiber orientation, fat tissue, and cerebrospinal fluid, may modify the locus and extent of cortex stimulated by the same montage [76••]. Using individual structural MRI data to model current density, Kim et al. [37•] found that the participants exhibiting WM improvements had significantly larger current density than those who did not show improvements. Furthermore, older adults' electric fields have been shown to be 30 % weaker, on average, compared to their younger counterparts [76••]. This has important implications for tDCS responsiveness in older adults or any other group with different electrical fields than healthy young adults. Other individual differences, including genetic polymorphisms (e.g., BDNF [105]; COMT [106]), hormone levels, and neurotransmitter levels, have been shown to interact with tDCS to influence research outcomes (see [107] for review). These results underscore the important role of individual differences in tDCS efficacy and highlight the need for more accurate, individualized current flow modeling.

Conclusion

Inconsistent results have led to questions of whether or not tDCS is an effective neuromodulation tool for manipulating or enhancing WM. Interpretations of current findings are limited by small sample sizes and sparse replications. Future research should aim not only to replicate previous research but to extend it by evaluating systematic variations in stimulation parameters, such as current density and montage. Study design factors need to be investigated, such as task difficulty, number of stimulation sessions, and on- vs. off-line stimulation. Furthermore, additional research is needed to improve our understanding of how underlying neurobiological mechanisms impact the outcome of tDCS. Multimodal studies combining tDCS with neuroimaging may elucidate how different montages modulate specific brain regions; these studies may be used to create more detailed individualized current flow

models. Stimulation of a particular region may cause diffuse changes in multiple regions, so researchers must be cautious when using tDCS to link regions to functions [76••]. To address this limitation, research should be conducted that compares active stimulation montages to one another, in addition to sham stimulation. Given the potential promise of stimulation-driven WM enhancement in older adults, we encourage more researchers to explore the long-term effects of tDCS on cognition. Also, thorough documentation and reporting of adverse effects and participant awareness/blindness to condition is prudent and critical to evaluating study outcomes. Finally, we note that the value and significance of the foundational studies discussed in this review are not weakened by the challenges highlighted above. As Richard Feynman once said, "We scientists have a way of dealing with such problems. We ignore them, temporarily" [108]. Researchers have already demonstrated the considerable promise that tDCS holds for improving WM. We suggest that time to address these challenges is upon us.

Compliance with Ethical Standards

Conflict of Interest Tiffany K. Jantz, Ben Katz, and Dr. Patricia A. Reuter-Lorenz declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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