

Direct-Current Stimulation Does Little to Improve the Outcome of Working Memory Training in Older Adults

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Abstract

The promise of transcranial direct-current stimulation (tDCS) as a modulator of cognition has appealed to researchers, media, and the general public. Researchers have suggested that tDCS may increase effects of cognitive training. In this study of 123 older adults, we examined the interactive effects of 20 sessions of anodal tDCS over the left prefrontal cortex (vs. sham tDCS) and simultaneous working memory training (vs. control training) on change in cognitive abilities. Stimulation did not modulate gains from pre- to posttest on latent factors of either trained or untrained tasks in a statistically significant manner. A supporting meta-analysis ($n = 266$), including younger as well as older individuals, showed that, when combined with training, tDCS was not much more effective than sham tDCS at changing working memory performance ($g = 0.07$, 95% confidence interval, or CI = $[-0.21, 0.34]$) and global cognition performance ($g = -0.01$, 95% CI = $[-0.29, 0.26]$) assessed in the absence of stimulation. These results question the general usefulness of current tDCS protocols for enhancing the effects of cognitive training on cognitive ability.

Keywords

tDCS, brain stimulation, working memory training, cognitive training, transfer

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Working memory (WM), a central component of general cognition, has a close relationship to fluid intelligence (Conway & Kovacs, 2013). This close relationship suggests that broad cognitive improvement may be possible through WM training. The controversial promise of long-term generalized cognitive enhancement from relatively limited practice on a narrow set of tasks has inspired a wealth of research and numerous commercial brain-training tools that promise fundamental improvements. The empirical evidence amassed to date shows improvements in WM tasks that are similar to the trained tasks. However, evidence on the transfer of improvements to untrained tasks and broad cognitive abilities is more limited, and the credibility and size of these effects remain debatable (Au, Buschkuhl, Duncan, & Jaeggi, 2016; Au et al., 2015; Dougherty, Hamovitz, & Tidwell, 2016; Karbach & Verhaeghen, 2014; Melby-Lervåg, Redick, & Hulme, 2016; Simons et al., 2016).

An absence of transfer could simply reflect the lack of a causal within-persons relationship between WM and

fluid intelligence or a failure of the training to engage the processes that the constructs share (Harrison et al., 2013). An alternative view is that an intrinsic limitation of the adult brain's capacity for change prevents transfer from occurring (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010). Such a limitation could be restricting training gains to task-specific knowledge and strategies, and preventing modulation of task-general processing capacity relevant to broader cognition. This intrinsic limitation could be expected to vary between individuals and be stronger in older age (Kühn & Lindenberger, 2016). The primary question posed in the present work was whether the potential for plastic change can be increased to allow for larger transfer of improvements from WM training to broad cognitive abilities in older age.

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Transcranial direct-current stimulation (tDCS) is a non-invasive brain stimulation technique with potential effects on brain plasticity (Dayan, Censor, Buch, Sandrini, & Cohen, 2013). Although the weak direct current that is passed through the brain via electrodes on the scalp is not sufficient to induce an action potential, some researchers claim that it modulates resting membrane potential and thereby increases spontaneous neuronal activity underneath the anodal electrode and decreases it under the cathodal electrode (Creutzfeldt, Fromm, & Kapp, 1962; Nitsche et al., 2003). Some effects of tDCS have been shown to persist for up to 90 min after the end of the stimulation (Nitsche & Paulus, 2001). Pharmacological manipulations have implicated neuroplastic mechanisms that may relate to long-term potentiation in these long-lasting effects (Nitsche et al., 2003). Other studies have suggested that neurotrophic factors increase (Fritsch et al., 2010) and γ -aminobutyric acid decreases (Stagg et al., 2009) during anodal stimulation.

The potential of tDCS as a tool for modulating cognitive, motor, and behavioral functions has resulted in a quick accumulation of research, broad media coverage, and more than 20 patents for commercial applications (Dubljevic, Saigle, & Racine, 2014; Martins, Fregni, Simis, & Almeida, 2017). Early work showed mixed results, but the authors of recent meta-analyses of studies on healthy populations conclude that anodal tDCS may have concurrent effects on some aspects of cognitive performance (e.g., Hill, Fitzgerald, & Hoy, 2016; Mancuso, Ilieva, Hamilton, & Farah, 2016; Summers, Kang, & Cauraugh, 2016). Numerous researchers have taken promising past results together with the potentially plasticity-enhancing effects of anodal tDCS to suggest that combining stimulation with cognitive training may be a particularly useful application of the technique (e.g., Mancuso et al., 2016; Martins et al., 2017). In the present empirical work, the primary objective was to investigate whether simultaneous anodal tDCS and WM training in older adults improves the key outcomes of training: transfer of improvements to broad cognitive abilities, measured when participants are not receiving tDCS (i.e., off-line; that is, sufficiently long after stimulation to exclude direct physiological effects of stimulation).

We used a full factorial design to test the interaction effect of tDCS and WM training on the transfer of training gains to untrained tasks and domains. The manipulation of stimulation (anodal tDCS vs. sham tDCS) was therefore fully crossed with the manipulation of training (WM vs. control) over 20 intervention sessions in a between-subjects design. The target of stimulation, the left dorsolateral prefrontal cortex (dlPFC), was selected because of its central role in WM (D'Esposito, Postle, & Rypma, 2000). The empirical investigation was supplemented with a meta-analysis of previous studies that also investigated effects

of anodal tDCS on changes in WM performance and general cognition performance from immediately before to immediately after training (both measured off-line). Although the empirical work focused on an older age group, the meta-analysis also included younger adult samples. Because previous studies have contrasted the effects of anodal tDCS and sham tDCS only under the same active training conditions, the meta-analysis did not allow for the estimation of the interaction effect but offered a cumulative scientific approach, increased statistical power, and explicit contextualization of the results.

Method

Participants

We recruited healthy participants between 65 and 75 years of age with no contraindications for tDCS. Participants were recruited through local newspaper advertisements (see Table S1 in the Supplemental Material available online for full inclusion and exclusion criteria). One hundred forty two participants met the eligibility requirements and began the study after providing informed consent. The study was approved by the regional ethical review board in Stockholm (Case No. 2014/2188-31/1) and conducted in accordance with the Declaration of Helsinki. Participants were randomly allocated to four experimental groups, using age, sex, and pretest score on Raven's Progressive Matrices (Raven, 1960) as stratifiers. Two participants were excluded shortly after entry into the study because they no longer met the study criteria. Seventeen participants dropped out during the study because they could not make the time commitment ($n = 5$), had incidental magnetic-resonance findings ($n = 4$), experienced mild adverse events (mainly skin irritation; $n = 4$), or developed an unrelated illness ($n = 3$), and 1 dropped out for unknown reasons. The dropout rate was similar in the four experimental groups. Consequently, 123 participants completed the study and were included in analyses (Table 1).

Calculating power for the planned structural equation modeling is complicated, and we therefore roughly determined the targeted sample size for detecting an interaction of within- and between-subjects variables with a traditional analysis of variance. Our calculations indicated that a sample size of 120 would provide a power of .86 (assuming an alpha level of .05) to detect the hypothesized interaction if the true effect were 0.4 standard deviations. That sample would also provide power of .90 to detect a main effect of stimulation on change in scores given a true main effect of 0.3 standard deviations (Mancuso et al., 2016). We deemed these power estimates satisfactory. To further increase statistical power, we supplemented the empirical study with a meta-analysis.

Table 1. Demographic Information for the Four Experimental Groups

Variable	tDCS + WM task (<i>n</i> = 32)	tDCS + control task (<i>n</i> = 30)	Sham tDCS + WM task (<i>n</i> = 33)	Sham tDCS + control task (<i>n</i> = 28)
Age (years)	<i>M</i> = 69.31, <i>SD</i> = 2.73	<i>M</i> = 69.87, <i>SD</i> = 2.91	<i>M</i> = 69.64, <i>SD</i> = 2.97	<i>M</i> = 69.82, <i>SD</i> = 2.62
Sex	16 female, 16 male	17 female, 13 male	22 female, 11 male	16 female, 12 male
Education (years)	<i>M</i> = 15.05, <i>SD</i> = 3.19	<i>M</i> = 14.29, <i>SD</i> = 2.29	<i>M</i> = 14.68, <i>SD</i> = 2.86	<i>M</i> = 15.84, <i>SD</i> = 4.09
Physical activity (score) ^a	<i>M</i> = 2.13, <i>SD</i> = 0.71	<i>M</i> = 2.21, <i>SD</i> = 0.78	<i>M</i> = 2.30, <i>SD</i> = 0.64	<i>M</i> = 2.29, <i>SD</i> = 0.66
Reasoning ability (score) ^b	<i>M</i> = 7.06, <i>SD</i> = 2.72	<i>M</i> = 6.97, <i>SD</i> = 3.02	<i>M</i> = 6.88, <i>SD</i> = 2.36	<i>M</i> = 6.93, <i>SD</i> = 2.26
Number of dropouts ^c	4	5	4	4

Note: tDCS = transcranial direct-current stimulation, WM = working memory. ^aThe amount of physical activity per week was reported on a 3-point scale (1 = < 150 min, 2 = > 150 min, 3 = > 200 min). ^bReasoning ability was indexed using Raven's Progressive Matrices (Raven, 1960; maximum score = 18). ^cThe number of dropouts is not included in the final per-cell sample size.

Experimental design and procedure

The study employed a 2 (cognitive training: WM vs. control) × 2 (stimulation: tDCS vs. sham tDCS) × 2 (time: pretest vs. posttest) mixed factorial design. An average of 19 sessions of adaptive WM training (*M* = 19.29, *SD* = 1.01) or control training (*M* = 19.07, *SD* = 1.32) were completed over 4 weeks. In these sessions, tDCS or sham tDCS was administered while participants were engaged in cognitive training.

We evaluated the effects of the intervention on change in several cognitive abilities that were statistically represented as latent (i.e., unobserved) variables (or factors) of multiple cognitive tasks (Noack, Lövdén, & Schmiedek, 2014; Shipstead, Redick, & Engle, 2012). The cognitive test battery was administered before and after the intervention period and included both tests that were trained in the WM training (i.e., those that captured updating and switching ability) and tests that were not (see Tables S2 and S3 in the Supplemental Material for an overview and detailed descriptions of the tests, respectively). The tasks formed latent factors of trained updating and switching with trained stimuli (indexed by the exact tasks used during WM training but with an identical difficulty level for all individuals at pretest and posttest), trained updating and switching with untrained stimuli, updating and switching with untrained task paradigms, verbal and spatial reasoning, episodic memory, and perceptual matching. The test battery was identical at pretest and posttest and was completed over four sessions, each lasting for 150 to 180 min including breaks. Pretesting took place 2 weeks before the intervention started, and posttesting was completed in the week after completion of the intervention.

Cognitive training. In keeping with current recommendations in the field of WM training, we employed

training that was adaptive in nature, targeted theoretically motivated constructs, and promoted process-based improvements over strategy-based improvements by including several training tasks and stimuli sets. The WM training focused on two areas: (a) the ability to continuously maintain and update mental representations (*updating*) and (b) the ability to flexibly switch between different rules and tasks (*switching*). Switching was trained with task-switching and rule-switching tasks, and updating was trained with *n*-back and running-span tasks (see Table S4 in the Supplemental Material for detailed task descriptions). To promote improvements in processing efficiency over strategy-based improvements further, we programmed each of the four WM tasks to alternate between four different stimuli sets.

The design also included an active control group that received training of equivalent scope but with a different target domain. The control training focused on perceptual speed using four versions of the same perceptual-matching test. Participants were blind to the hypotheses about the two training protocols. In both training programs, participants spent approximately 10 min on each of the four training tests, the order of which varied among training sessions. This resulted in 40 min of active training per session. Each training task consisted of a set of runs, which allowed performance to be regularly evaluated against a predetermined criterion and the difficulty level to be increased as participants' performance improved to meet the criterion (see Table S5 in the Supplemental Material for details on difficulty levels). To ensure a maximal training load, we always trained participants at the highest level reached. The average level reached by the end of the intervention, averaged over the four respective tasks, was equivalent for the two training protocols (WM: *M* = 10.877, *SD* = 4.218; control: *M* = 11.289, *SD* = 1.923), $t(121) = 0.682, p = .496$.

To increase motivation, we presented participants' performance relative to the predetermined criterion after each run, and a figural progress indicator informed participants of their current level. Every fifth training session, participants were given a printout of their progress to date. Motivation levels were assessed daily on a 5-point Likert scale ("How motivated do you feel to solve the tasks today?" 1 = *not motivated at all*, 5 = *very motivated*). Levels of motivation were generally high across the intervention period, with no significant difference between training groups (WM: $Mdn = 4.474$, control: $Mdn = 4.416$, Mann-Whitney $U = 1,851$, $p = .862$).

Brain stimulation. Direct current was delivered using the DC-STIMULATOR PLUS (neuroConn, Ilmenau, Germany) and was transferred by two saline-soaked surface electrodes placed on the scalp. The anode (7×5 cm) was positioned horizontally to target the left dlPFC, which corresponds to F3 in the 10-20 international system for electrode placement. The anode was shifted slightly laterally, toward F5, and slightly posteriorly, such that its superior-anterior quarter section and not the center was positioned over F3. The lateral shift was intended to maximize peak current density underneath F3, and the posterior shift minimized the risk of shunting by ensuring the recommended minimum interelectrode distance of 8 cm for all participants (Faria, Hallett, & Miranda, 2011; Seibt, Brunoni, Huang, & Bikson, 2015). The cathode (7×5 cm) was positioned over the contralateral supraorbital area. Electrode placements were based on measurements using the 10/20 BraiNet placement cap (Jordan NeuroScience, Redlands, CA). Before fixing the electrodes with rubber straps, the scalp was prepared by parting any hair, cleaning the skin with disinfectant and saline solution, and subsequently ensuring that the scalp was completely dry except for the electrode areas. Impedance was confirmed to be below 20 k Ω before stimulation was initiated.

For active tDCS, a constant current of 2 mA was delivered for 25 min, with an additional 8-s ramp-up and 5-s ramp-down period. For sham tDCS, the same procedure and stimulation intensity was used, but the stimulation lasted for 30 s only. The procedure for the active tDCS and sham tDCS was otherwise identical, and both participants and experimenters were blind to stimulation assignment. To avoid distraction caused by starting the stimulation, we initiated the training program 5 min after the stimulation, which left 20 min of the stimulation to directly coincide with the training. These 20 min covered two out of the four tasks. The order of tasks varied from session to session. An assessment after the last intervention session revealed that participants were blind to stimulation condition (52% incorrect guesses, 48% correct guesses; $p = .72$ by binomial test).

Side effects of tDCS were evaluated four times, once per week, during the intervention period with ratings on

a 5-point Likert scale (0 = *I did not experience the side effect at all*, 5 = *The side effect was so severe that I considered terminating or had to terminate the stimulation*). On each evaluation occasion, ratings were made before, during, and after the training in that session. Five direct side effects of tDCS were evaluated: itching, pain, burning, heating, and pinching underneath the electrodes. Ratings for the different time periods, averaged over the four evaluation occasions, were generally very low; the maximum average was 1.265 ($SD = 1.200$) for burning underneath the electrodes for the stimulation period before the training started. Collapsing the scores across time periods, we found no difference between the direct-side-effects ratings of participants who received tDCS and those who received sham tDCS (all $ps > .136$ by Mann-Whitney U test).

Data analysis

Latent-change-score modeling (McArdle & Nesselrode, 1994) was adopted to test the effect of training, stimulation, and the interaction of training and stimulation on change in cognitive performance from pretest to posttest (Fig. 1). Ability factors that represented the shared variance among multiple tests measuring the construct were formed from the pretest and posttest data, and a latent change score, which represented the difference between pretest and posttest performance, was estimated. This allowed for change to be estimated as a latent variable, attenuating reliability problems of change scores and allowing for task-specific variance to be reduced in favor of task-general (ability) variance. The pretest and change factors were regressed on the predictors (stimulation, training, Stimulation \times Training) as shown in Figure 1. Active tDCS was coded as 1, and sham tDCS was coded as -1 . WM training was coded as 1, and control training was coded as -1 . We estimated a separate model for each of the considered cognitive abilities. See Table S6 in the Supplemental Material for means and standard deviations for each separate task as a function of group.

Before estimation, we screened all variables for univariate outliers using the outlier-labeling rule, which identified outliers as observations outside the interquartile range of the measure multiplied by a factor of 2.2. Detected outliers were deleted using pairwise deletion (see Table S6 in the Supplemental Material for effective sample size for all variables). The resulting scattered missing values were accommodated under the missing-at-random assumption using full-information maximum-likelihood estimation in Amos software (Version 23.0; Arbuckle, 2014).

Measurement invariance over time is important for the interpretability of results, as it ensures that the same latent variables are represented on each measurement occasion (Meredith & Teresi, 2006). Weak, strong, and

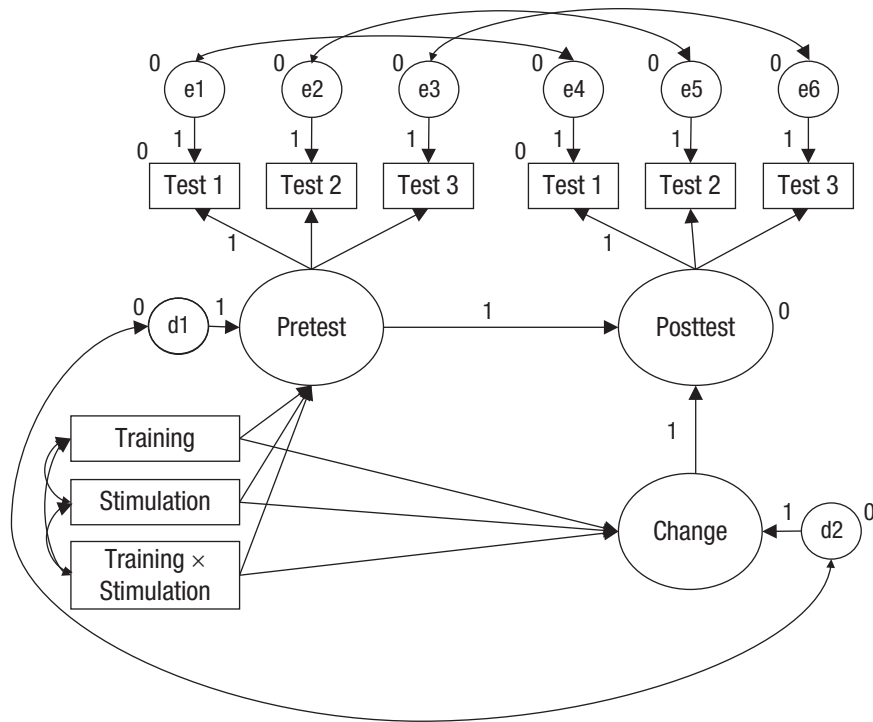


Fig. 1. Graphical representation of the latent-change-score model used to assess effects of training, stimulation, and their interaction on cognitive performance. Observed variables are represented by squares, latent variables by ellipses, and residuals by circles. The residual of the observed variables (error terms) are represented by e1 through e6, and d1 and d2 represent the residual of the latent variables for pretest and change (disturbance terms). Regression weights are represented by single-headed arrows and covariances by double-headed arrows. Regression weights marked with a 1 were restricted to 1. For variables marked with 0s, intercepts were restricted to equal 0. All other regression weights, covariances, and intercepts were estimated.

strict levels of measurement invariance were assessed by sequentially constraining the factor loadings, the intercepts of the observed variables, and the residuals of the observed variables to be equal at pretest and posttest. Results are reported for the highest level of measurement invariance admissible, and models were screened for Heywood cases. Updating with untrained stimuli, updating with untrained tasks, trained updating, switching with untrained tasks, and sustained attention all met the criteria for strict invariance, that is, there were no significant differences between the weak and the free models (all χ^2 s ≤ 2.196 , $ps \geq .138$), between the strong and the weak models (all χ^2 s ≤ 1.209 , $ps \geq .272$), or between the strict and the strong models (all χ^2 s ≤ 3.386 , $ps \geq .184$) for any of these ability factors.

For updating with untrained tasks, the free- and weak-invariance models failed to converge, which means that some caution must be used in the interpretation of this variable at the strict level of invariance. For trained updating, the residual variance was estimated to be zero for two of the observed variables and results are therefore reported for a model in which the covariance between

these residuals was fixed to zero. Switching with untrained tasks was not considered further because of substantial negative residual variance in the observed variables in the strict-, strong-, and weak-invariance models (all estimates ≤ -10.209). Similarly, sustained attention was not considered because of zero or negative estimates of residual change in all invariance models, with and without the predictors included in the model (all estimates ≤ 0). Verbal reasoning and episodic memory met the criteria for strong invariance, that is, there were no significant differences between the weak and the free models (all χ^2 s ≤ 4.597 , $ps \geq .059$) or between the strong and the weak models (all χ^2 s ≤ 1.76 , $ps \geq .185$). For episodic memory, the weak-invariance model was nevertheless selected because of negative residual-variance estimates for the observed variables in the strong-invariance model that were not present in the weak-invariance model. Spatial reasoning, trained switching, and perceptual-matching speed met the criteria for weak invariance, that is, there were no significant differences between the weak and the free models (all χ^2 s ≤ 1.537 , $ps \geq .272$). Switching with untrained stimuli did not meet the criteria for weak invari-

ance and was therefore not considered ($\chi^2 = 4.71$, $p = .030$). Thus, for evaluating the effects of training, stimulation, and their interaction, we considered the ability factors of trained updating, trained switching, updating with untrained stimuli, updating with untrained tasks, spatial reasoning, verbal reasoning, episodic memory, and perceptual speed. All these models had good fit (root-mean-square error of approximation $< .06$; comparative fit index $> .95$; see Table S7 in the Supplemental Material), and the loadings of the tasks on the latent factors were generally high (all standardized loadings $> .48$) and significant.

Statistical significance of the training, stimulation, and Training \times Stimulation effects was assessed using chi-square difference tests to compare a model in which the relevant effect was restricted to zero with a model in which the effect was estimated freely. To deal with multiple comparisons, we report statistical significance relative to a Bonferroni-corrected alpha level of .00625, given from eight final models. For the sake of completeness, effects below the traditional alpha level of .05 are mentioned in Results. Standardized regression coefficients (β s), which can be interpreted as correlations, are reported as effect sizes.

Meta-analysis

The meta-analysis was designed in accordance with the statement for systematic reviews developed by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (www.prisma-statement.org; see Fig. S8 in the Supplemental Material for the literature search flow). The online databases Web of Science and PubMed were searched on April 21, 2016, using each of two keywords, “transcranial direct current stimulation” and “tDCS,” combined with each of the following: “training,” “memory,” “cognit*,” “practice,” “longitudinal,” and “learning.” The reference sections, relevant reviews, and reports were also searched for eligible studies.

Empirical investigations in any report format published in English were eligible. Eligible samples were those containing healthy adults 18 years old or older. Research on nonhuman subjects and clinical conditions, qualitative studies, and nonempirical publications were excluded. Randomized sham-controlled studies using anodal tDCS in combination with cognitive training over a minimum of two sessions and testing without stimulation before and after the sessions were included. Since learning is a continuous process with unknown carryover and interaction effects with stimulation, studies employing within-subjects designs were excluded.

Eligible outcome measures had to assess cognitive performance within 2 weeks after the training period without tDCS. We focused on obtaining one average measure of WM performance (summarizing performance

on all tasks measuring WM performance) and one measure of global cognition (summarizing performance on all cognitive measures reported) per study. Since the types and number of outcomes measures varied across tasks and reports, a priori criteria were used to select dependent variables: Accuracy measures were favored over reaction time measures unless performance was near or at ceiling, which was defined as the maximum mean at posttest being within 1 standard deviation of the maximum of the measurement scale. For studies that reported multiple accuracy-based measures, measures such as d' , which combine hit rates with false alarm rates, were preferred. See Table S9 in the Supplemental Material for a complete list of the selected outcome measures for the analysis on WM and global cognition. To arrive at a single effect size per study, we averaged effect sizes from multiple task conditions before averaging effect sizes across tasks. When studies included multiple groups that received anodal stimulation of different brain regions, we selected the group with stimulation sites most similar to those used in our empirical study (e.g., left rather than right dlPFC and dlPFC rather than parietal stimulation) for primary analysis. Secondary analysis was conducted on results collapsed across all available groups that received anodal stimulation.

The analyses were conducted using the *metafor* package (Viechtbauer, 2010) in the R 3.3.0 environment (R Core Team, 2016). As described and recommended by Becker (1988), the difference in standardized mean change from pretest to posttest for the tDCS group and the sham-tDCS group was calculated for all selected outcome measures using raw-score standardization:

$g = g_{\text{tDCS}} - g_{\text{sham}}$, where

$$g_{\text{tDCS}} = \left(c(n_{\text{tDCS}} - 1) \frac{\bar{x}_{\text{post_tDCS}} - \bar{x}_{\text{pre_tDCS}}}{SD_{\text{pre_tDCS}}} \right) \text{ and}$$

$$g_{\text{sham}} = \left(c(n_{\text{sham}} - 1) \frac{\bar{x}_{\text{post_sham}} - \bar{x}_{\text{pre_sham}}}{SD_{\text{pre_sham}}} \right).$$

In these equations, $\bar{x}_{\text{post_tDCS}}$ and $\bar{x}_{\text{pre_tDCS}}$ are the means at posttest and pretest, respectively, for the tDCS group, $SD_{\text{pre_tDCS}}$ is the standard deviation of the pretest scores, $c(n - 1)$ is a bias-correction factor (see Equation 5 in Morris, 2000), n_{tDCS} is the sample size of the tDCS group, and $\bar{x}_{\text{post_sham}}$, $\bar{x}_{\text{pre_sham}}$, $SD_{\text{pre_sham}}$, and n_{sham} are the analogous values for the sham-tDCS group. The signs for g_{tDCS} and g_{sham} were assigned so that a high value represented an improvement in performance in all outcome measures. A more positive value for g therefore

indicated greater gains from pretest to posttest in the tDCS group. All of the analyses were repeated with an alternative effect size standardized on the basis of the pooled pretest standard deviation (d_{ppc2} in Morris, 2008). This analysis resulted in similar conclusions (see Table S10 in the Supplemental Material).

Sampling variance was estimated with Equation 13 in Becker (1988). Since all necessary pretest-posttest correlations could not be obtained from the individual studies, a correlation of .5 was assumed. Analyses were performed with correlation coefficients of .2 and .9 to assess the dependence on this assumption. Since the decision regarding statistical significance did not change, results were reported for $r = .5$ only. The standard inverse-variance method for random-effects models was used to weight the effect sizes when estimating the final outcome. Heterogeneity was evaluated with an extension of

the Cochran Q test, τ^2 and I^2 , in order to assess significance, between-studies variance, and the ratio of true heterogeneity to total variation in the observed effects. Publication bias was tested in a mixed-effects meta-regression model for funnel-plot asymmetry using standard error as a predictor.

Results

Empirical investigation

The results revealed a statistically significant main effect of training (WM vs. control) on change in cognitive performance from pretest to posttest for the latent cognitive factors of trained updating, trained switching, updating with untrained stimuli, and perceptual-matching speed (all β s > 0.52, p s < .001; see Table 2 for all individual

Table 2. Results From the Latent-Change-Score Models: Effects of Stimulation, Training, and Their Interaction on Cognitive Performance at Pretest and on Cognitive Change

Ability factor and measure	Overall mean	Predictor					
		Stimulation		Training		Training \times Stimulation	
		<i>b</i>	β	<i>b</i>	β	<i>b</i>	β
Updating with trained stimuli ^a							
Pretest performance	1.274* (0.012)	-0.002 (0.010)	-0.017	0.007 (0.010)	0.068	-0.017 (0.104)	-0.161
Change from pretest to posttest	0.074* (0.008)	-0.011 (0.007)	-0.169	0.034* (0.007)	0.526	0.008 (0.243)	0.1130
Switching with trained stimuli ^b							
Pretest performance	30.613* (0.737)	0.093 (0.565)	0.016	0.433 (0.568)	0.073	-0.264 (0.565)	-0.044
Change from pretest to posttest	15.011* (0.532)	-0.487 (0.370)	-0.068	6.486* (0.502)	0.904	0.317 (0.370)	0.044
Updating with untrained stimuli ^a							
Pretest performance	1.292* (0.013)	0.004 (0.001)	0.040	0.009 (0.001)	0.084	-0.005 (0.001)	-0.050
Change from pretest to posttest	0.107* (0.009)	-0.015 (0.008)	-0.198	0.059* (0.008)	0.761	-0.007 (0.008)	-0.096
Updating with untrained task ^a							
Pretest performance	1.105* (0.047)	-0.005 (0.036)	-0.015	0.030 (0.036)	0.097	-0.005 (0.036)	-0.015
Change from pretest to posttest	0.159* (0.032)	0.007 (0.020)	0.129	0.004 (0.020)	0.078	-0.012 (0.020)	-0.223
Spatial reasoning ^b							
Pretest performance	6.961* (0.232)	-0.091 (0.194)	-0.046	0.019 (0.194)	0.010	0.091 (0.194)	0.046
Change from pretest to posttest	0.916* (0.916)	-0.018 (0.103)	-0.050	0.113 (0.103)	0.322	-0.200 (0.103)	-0.570
Verbal reasoning ^c							
Pretest performance	5.223* (0.199)	-0.002 (0.173)	-0.001	0.196 (0.174)	0.117	0.093 (0.173)	0.056
Change from pretest to posttest	0.589* (0.097)	0.057 (0.083)	0.154	-0.165 (0.084)	-0.448	-0.016 (0.083)	-0.045
Episodic memory ^b							
Pretest performance	16.842* (0.419)	0.079 (0.270)	0.038	-0.012 (0.265)	-0.006	-0.495 (0.337)	-0.235
Change from pretest to posttest	0.011 (0.349)	0.097 (0.238)	0.072	0.023 (0.234)	0.017	0.524 (0.304)	0.390
Perceptual speed ^b							
Pretest performance	19.439* (0.556)	-0.252 (0.406)	-0.064	0.324 (0.406)	0.082	0.119 (0.405)	0.030
Change from pretest to posttest	9.531* (0.486)	-0.032 (0.317)	-0.006	-4.484* (0.482)	-0.864	-0.149 (0.317)	-0.029

Note: Standard errors are given in parentheses. Asterisks indicate significant results ($p < .00625$, Bonferroni corrected, derived from chi-square difference tests contrasting a model with the relevant effect restricted to zero with a model with the effect freely estimated). Active transcranial direct-current stimulation (tDCS) was coded as 1, and sham tDCS was coded as -1. Working memory training was coded as 1, and control training was coded as -1.

^aResults for this variable are reported at the strict level of measurement invariance. ^bResults for this variable are reported at the weak level of measurement invariance. ^cResults for this variable are reported at the strong level of measurement invariance.

effects). Participants who received WM training improved more in the tasks that they had trained on (trained updating and switching) and in similar tasks with new stimuli (updating with untrained stimuli). Participants who received control training improved more in tasks that they had trained on (perceptual-matching speed).

Notably, the effect of the critical interaction between training (WM vs. control) and stimulation (tDCS vs. sham tDCS) on change in cognitive performance from pretest to posttest was not statistically significant for any of the latent cognitive factors considered, trained or untrained (see Table 2). Thus, the results provided no evidence of the hypothesized greater cognitive improvement from pretest to posttest (i.e., performance measured without stimulation) following tDCS in combination with WM training relative to either intervention alone. Furthermore, no main effect of stimulation was detected for any of the latent cognitive abilities, so the experiment provided no evidence of a beneficial effect of multiple sessions of tDCS across training types. Figure 2 illustrates the main outcome of the analyses. Figure 2a depicts the scores for the factor of the trained switching tasks, demonstrating an example of an effect of training but no interaction between training and stimulation for trained tasks. Figure 2b depicts the scores for the factor of the spatial-reasoning tasks, demonstrating that there was no effect of training or interaction between training and stimulation for untrained tasks.

Using an uncorrected alpha level of .05, we also found a statistically significant effect of training for verbal reasoning in an unexpected direction: greater improvements after control than after WM training ($\beta = -0.448, p = .049$). Similarly, the interaction of training and stimulation on episodic memory was significant at the uncorrected alpha level ($\beta = 0.390, p = .034$), which seemingly reflected improvements in the control group with sham tDCS and the WM group with tDCS, no change in the control group with tDCS, and a worsening of performance in the WM group with sham tDCS. We note that these effects were not predicted and would not persist under our alpha level corrected for multiple comparisons ($\alpha = .00625$). We consequently refrain from further interpretation of these effects.

There were also no statistical differences between the stimulation groups in the progress through the levels of difficulty in the four training tasks during training and stimulation (see Table S11 in the Supplemental Material). These data should be carefully interpreted, however, because the training tasks were designed primarily for training purposes and not for reliably assessing performance and learning curves. For example, the difficulty manipulation was of a different magnitude and quality

between different levels, and the data for the two training paradigms were not comparable.

Meta-analysis

We followed up the empirical investigation with a meta-analysis. Six previous studies met inclusion criteria for the meta-analysis. All of them contrasted the effects of anodal tDCS over the dlPFC with sham tDCS under the same cognitive-training conditions (see Table S12 in the Supplemental Material for a detailed description and reference list). When we added the results of the WM training arm of the present empirical investigation, a total of seven independent studies were available for analysis, six of which implemented training protocols that targeted WM. Two separate analyses were conducted, one for WM and one for global cognition as the outcome (all cognitive measures, including WM). Total sample size was 131 in the tDCS category and 135 in the sham-tDCS category.

There was no evidence of greater change in WM performance from pretest to posttest when cognitive training was combined with tDCS than when it was combined with sham tDCS ($g = 0.07, SEM = 0.14, 95\%$ confidence interval, or $CI = [-0.21, 0.34], p = .64$; Fig. 3a). The analysis revealed no statistically significant heterogeneity— $Q(7) = 2.53, p = .87; I^2 = 0.00\%; \tau^2 < 0.01, SE = 0.08$ —and no evidence of publication bias ($z = -0.39, p = 0.69$). Similarly, there were no statistically significant effects on global cognition performance ($g = -0.01, SEM = 0.14, 95\% CI = [-0.29, 0.26], p = .92$; Fig. 3b), and there was no evidence of heterogeneity— $Q(7) = 1.93, p = .93; I^2 = 0.00\%; \tau^2 < 0.01, SE = 0.07$ —or publication bias ($z = -0.15, p = 0.88$). Furthermore, when we restricted the analysis to the five studies that tested young participants, there was no statistically significant difference between the effect of tDCS and sham tDCS on WM performance ($g = 0.12, SEM = 0.17, 95\% CI = [-0.22, 0.46], p = .49$) or global cognition performance ($g = 0.03, SEM = 0.17, 95\% CI = [-0.30, 0.36], p = .86$). There was also no evidence of heterogeneity for WM performance— $Q(4) = 1.32, p = .86; I^2 = 0.00\%; \tau^2 < 0.01, SE = 0.10$ —or global cognition performance— $Q(4) = 1.47, p = .83; I^2 = 0.00\%; \tau^2 = < 0.01, SE = 0.10$.

Collapsing across available groups receiving anodal stimulation (two studies included multiple groups: Au, Katz, et al., 2016; Jones, Stephens, Alam, Bikson, & Berryhill, 2015), rather than selecting one group per study with most similar tDCS parameters to our empirical study did not change this picture much (WM performance: $g = -0.05, 95\% CI = [-0.31, 0.21]$; global cognition performance: $g = -0.05, 95\% CI = [-0.30, 0.20]$). Results were also not substantially different when restricting studies to those employing traditional WM training (i.e., excluding

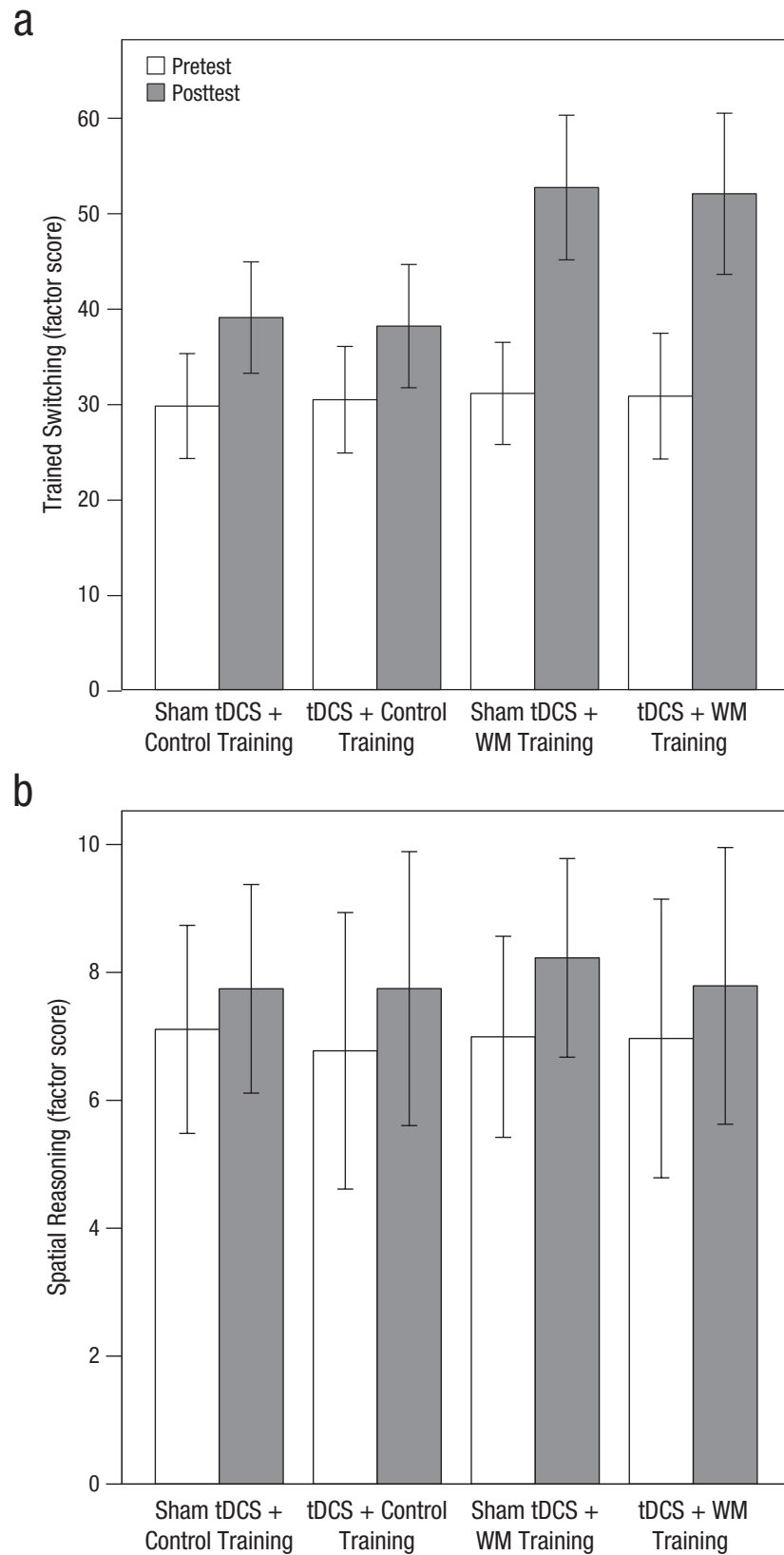


Fig. 2. Results of the empirical study: mean factor score extracted from the latent-change-score models for (a) trained switching (tasks practiced during working memory training) and (b) spatial reasoning (untrained tasks in the domain of spatial reasoning), separately for each of the four groups at pretest and posttest. Error bars represent ± 1 *SD*. tDCS = transcranial direct-current stimulation, WM = working memory.

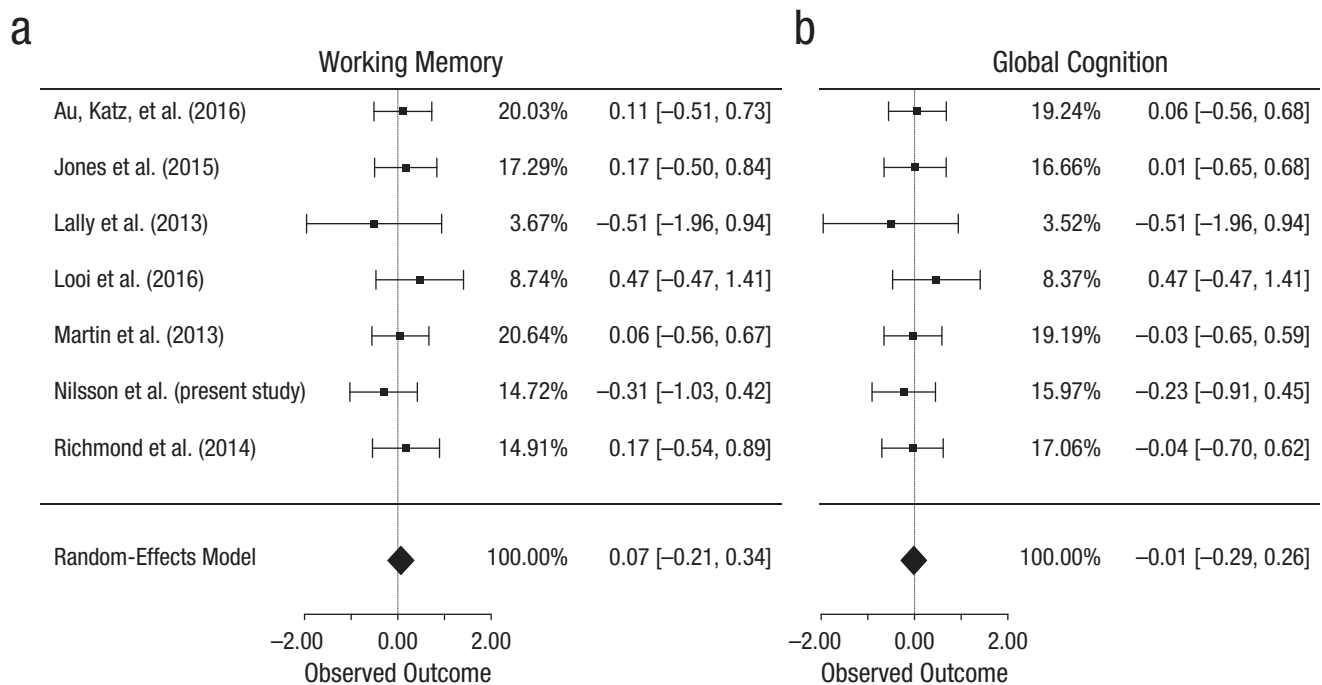


Fig. 3. Results of the meta-analysis: forest plot showing the observed effect sizes (with corresponding 95% confidence intervals) for (a) working memory performance and (b) global cognition performance in each included study. The percentages are inverse-variance weights. The diamond shows the summary estimate based on the random-effects model; its outer edges indicate the 95%-confidence-interval limits.

Looi et al., 2016; WM performance: $g = 0.03$, 95% CI = [-0.26, 0.32]; global cognition performance: $g = -0.06$, 95% CI = [-0.34, 0.22]).

Discussion

The empirical study reported here allowed us to dissect the effect of stimulation (tDCS, sham tDCS), the effect of cognitive training (WM, control), and, critically, their interactive effect on change in cognitive performance (assessed without stimulation) in older individuals. The cognitive test battery included more than one measure per construct of interest, which enabled us to model cognitive change at the ability level (i.e., as a latent factor) and therefore to reduce task-specific influences in favor of task-general effects (Noack et al., 2014; Shipstead et al., 2012). The analyses provided no statistical evidence that stimulation and cognitive training interacted to affect any of the cognitive domains we considered. The stimulation thus failed to modulate either training gains (assessed when stimulation was absent at pretest and posttest) or the transfer of gains to untrained tasks or domains after WM training. Moreover, tDCS did not provide an advantage over sham tDCS in either type of training conducted in this study (WM or control), which calls into question the overall usefulness of dlPFC tDCS in combination with cognitive engagement in older adults for causing improvement in cognitive performance that outlasts the stimulation itself.

When we aggregated the results of the empirical investigation with the results of previous studies ($N = 266$; tDCS: $n = 131$, sham: $n = 135$), tDCS combined with cognitive training did not improve, in a statistically significant way, either WM or global cognition performance (assessed off-line) more than sham tDCS combined with cognitive training did. It should be noted, though, that because of the small number of studies available, the meta-analysis had limited power to detect effects, evidence of heterogeneity, and publication bias. However, effect-size estimates, and their confidence intervals, for differential change in WM performance ($g = 0.07$, 95% CI = [-0.21, 0.34]) and global cognition performance ($g = -0.01$, 95% CI = [-0.29, 0.26]) suggest that a positive and general effect of current tDCS protocols on off-line cognitive performance measured immediately after cognitive training is not very likely or is at least likely to be small.

The lack of an effect in the meta-analysis appears inconsistent with the results of a recent meta-analysis of 10 studies, which provided support for the hypothesis that left dlPFC stimulation coupled with WM training over several sessions has a small but significant effect on subsequent WM performance ($g = 0.29$, 95% CI = [0.06, 0.52]; Mancuso et al., 2016). The authors, however, noted that even a few additional studies with nonsignificant findings would have rendered their finding nonsignificant. Here, we added the current empirical study and a few recently published studies (Au, Katz, et al., 2016; Jones et al., 2015; Looi et al., 2016), which may explain

the inconsistency. Other than the inclusion of studies published after the analysis by Mancuso and colleagues, other discrepancies in study-inclusion criteria likely contribute to the inconsistency. Because of the importance of repeated practice for training gains, we included only studies that had a minimum of two tDCS sessions combined with cognitive training. Furthermore, the analysis was restricted to studies with between-subjects designs. The method used to calculate effect sizes may also have contributed to the inconsistency. Here, effect sizes reflected differential change in performance from pretest to posttest in the tDCS group relative to the sham-tDCS group (Becker, 1988; Morris, 2000).

Although we found little support for the hypothesis that WM training combined with tDCS is superior to WM training combined with sham tDCS, the empirical study did demonstrate that cognitive training resulted in improvements in trained tasks across stimulation protocols. Relative to participants who received the control training, participants who were trained on switching and updating during the intervention period demonstrated greater gains in these tasks, for trained and untrained stimuli sets alike. Similarly, participants in the control training group demonstrated greater gains than participants in the WM training group in the perceptual-matching tasks that constituted the control training. However, we found no statistical evidence that gains from WM training generalized to broad cognitive abilities, as evidenced by the lack of an effect of training on the factors of untrained tasks. Available meta-analyses on cognitive training have also found smaller effects on transfer tasks than on trained tasks, and the evidence on transfer effects is heavily debated (Au, Buschkuehl, et al., 2016; Au et al., 2015; Karbach & Verhaeghen, 2014; Melby-Lervåg & Hulme, 2015; Melby-Lervåg et al., 2016; Shipstead et al., 2012; Simons et al., 2016). In the present empirical study, statistically differential gains from WM training relative to control training did not even extend to untrained tasks that nevertheless tapped the trained abilities. This suggests that the training gains in this study were mostly restricted to task-specific knowledge and strategies, and that there were limited effects on processing efficiency (Lövdén et al., 2010).

The reported results should not be generalized beyond the specific conditions and designs of the considered studies. For example, we did not address effects of anodal tDCS on performance and learning rate during stimulation. Furthermore, although our empirical study showed no statistically significant effects on trained tasks (assessed before and after training without concurrent stimulation), the meta-analytic outcomes mixed transfer and training tasks and were therefore not informative of effects on trained tasks per se. We also note that several of the

studies included in the meta-analysis found beneficial effects of anodal tDCS combined with cognitive training on select cognitive tasks and time points (e.g., at maintenance assessments). Here, we focused on what is arguably the primary outcome of WM training: improvements to broad cognitive abilities and global cognitive performance immediately after the intervention. Future confirmatory work should address whether effects are limited to certain cognitive abilities or tasks and whether they materialize at time points other than immediately after the intervention period.

A major challenge in the interpretation of the results reported here and in the tDCS field in general is an incomplete knowledge of the mechanism that may underlie effects of tDCS and how tDCS can be optimized to modulate behavior and cognition (Fertonani & Miniussi, 2017). At a basic level, it is possible that the amount of current entering the target region was insufficient to produce the intended effects in our empirical study. Although we were careful to follow current recommendations on how to apply tDCS to optimally target the dlPFC, we cannot exclude the possibility that shunting or electrode drift prevented a sufficient dose of current from entering the target region (Miranda, Lomarev, & Hallett, 2006). It is also possible that other parameters, such as intensity or duration, may have been suboptimal. For example, in our empirical study, ethical considerations limited the stimulation period to 20 min, which left another 20 min of training without concurrent stimulation. Although there has been evidence to suggest that effects can outlast the stimulation period itself (Nitsche & Paulus, 2001), the impact of this procedure compared with continuous stimulation during training is unknown.

Interindividual differences are another important consideration (e.g., Wiethoff, Hamada, & Rothwell, 2014). Gross anatomical features and microarchitectural features influence tDCS current distribution and vary between individuals (Kim et al., 2014). It is particularly relevant to the present empirical study, which investigated effects in an older sample, that tDCS response may differ in older and younger adults (Heise et al., 2014). Although we arrived at unchanged statistical decisions when the meta-analysis was restricted to studies with younger adults, and we must conclude that any true effect in younger adults is also likely to be small, the point estimates were slightly larger in this subanalysis (WM performance: $g = 0.12$, 95% CI = $[-0.22, 0.46]$; global cognition performance: $g = 0.03$, 95% CI = $[-0.30, 0.36]$). We therefore underscore that the true influence of age on tDCS effects remains unknown and that the results of our empirical study should not be generalized beyond the target population of older adults.

The contribution of the present work to the field of tDCS is both timely and needed. The idea of the

technique as a safe and effective modulator of cognitive function has been as seductive to the research community as it has been to the media (Dubljevic et al., 2014; Fertonani & Miniussi, 2017). A growing number of people in the general public, presumably inspired by such uninhibited optimism, are now using tDCS to perform better at work or in online gaming, and online communities offer advice on the purchase, fabrication, and use of tDCS devices (Batuman, 2015). Unsurprisingly, commercial exploitation is rapidly being developed to meet this new public demand for cognitive enhancement via tDCS, often without a single human trial to support the sellers' or manufacturers' claims (Malavera, Vasquez, & Fregni, 2015). Although tDCS may be beneficial in some contexts, we conclude that current frontal anodal tDCS protocols do little to improve the primary outcomes of WM training. These results lead us to call for a more cautious appraisal of the potential applications of tDCS.

Action Editor

John Jonides served as action editor for this article.

Author Contributions

M. Lövdén developed the study concept. J. Nilsson and A. V. Lebedev designed the study. Data collection and search and coding of data for the meta-analysis were performed by A. Rydström. J. Nilsson and A. V. Lebedev analyzed the data under the supervision of M. Lövdén. J. Nilsson and M. Lövdén drafted the manuscript, and the other authors provided critical revisions. All authors approved the final version of the manuscript for submission.

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Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Supplemental Material

Additional supporting information can be found at <http://journals.sagepub.com/doi/suppl/10.1177/0956797617698139>

Open Practices

Swedish data-protection laws prohibit us from putting the data in the public domain, but data can be requested from the authors and subsequently transferred for well-defined analysis projects that are in line with the one covered by the original ethical approval. This requires a data-use agreement, which effectively transfers the confidentiality obligations of the institution at which the original research was conducted (Karolinska Institutet) to the recipient of the data.

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