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RESEARCH ARTICLE

New information on the effects of transcranial direct current stimulation on n-back task performance

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Abstract

The n-back task is prototypical tool widely used to evaluate working memory (WM) abilities in healthy and clinical populations. Previous studies finding beneficial effects of transcranial direct current stimulation (tDCS) over the dorsal lateral prefrontal cortex (DLPFC) on n-back task performance were limited by the number of n-back "memory loads" utilized and the assessment of performance only immediately following stimulation. Our aims were to investigate both the immediate and lasting effects of six sessions of bilateral tDCS over the DLPFC on n-back performance. We used a 1-, 2-, 3-, and 4-back shaped WM task at three time points: pre-stimulation (T1), immediately following a final (6th) stimulation (T2), and 1 month following the final stimulation (T3). Twenty-five right-handed participants were randomly assigned to active or sham stimulation. Performance was evaluated by percentage hits, false alarms, and reaction times (RTs) for correct responses. Results showed lack of improvement in all outcome measures for both groups at T2. Except for general faster RT in the active group, no lasting effect on percentage hits and false alarms was found for all memory loads among both groups at T3. However, lenient analysis indicated improvement in RT for the 1-back memory load among the active group from T1 to T3. These results question the previously found effectiveness of tDCS over the DLPFC in improving short-term n-back performance and cast doubt on its long-term effectiveness.

Keywords Bilateral stimulation · n-Back task · tDCS · Lasting effect · Working memory

Introduction

The n-back task is a prototypical tool to assess working memory (WM) function (Veltman et al. 2003). It involves key processes of working memory such as monitoring, updating, and manipulation of information (Owen et al. 2005; Rodriguez-Jimenez et al. 2009). For the n-back task, the participant is presented with a stimulus in a series of numbers, letters, or shapes, and is asked to respond if the current stimulus is exactly the same as the stimulus presented *n* steps before, or to respond with one button when the stimulus matches the stimulus presented *n* steps before and another button when it does not, corresponding with the instructions (e.g., Zaehle et al. 2011). fMRI studies consistently report a common pattern of bilateral frontoparietal activation, particularly in the dorsolateral prefrontal cortex (DLPFC), during the processing of different n-back tasks (for review, see Owen et al. 2005).

Recently, transcranial direct current stimulation (tDCS) emerged as a noninvasive tool that may be used to improve cognitive abilities in healthy and clinical populations (e.g., Fregni et al. 2005; Jeon and Han 2012; Kim et al. 2014; Oliveira et al. 2013). tDCS induces short-term changes in cortical excitability by applying weak electrical currents over target brain regions (Nitsche and Paulus 2000). Anodal and cathodal stimulation can induce enhancement or reduction in neuronal activity, respectively, in the motor cortex; whether this directionality holds true for other brain regions is not yet definitively known.

Accumulating evidence points to the beneficial effects of tDCS on n-back performance. For instance, Fregni et al. (2005) investigated the effect of a single unilateral stimulation on 3-back letter task performance. They found improvement in accuracy rate only when the anode was placed over the left DLPFC, compared to sham

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stimulation; neither cathodal tDCS over the left DLPFC nor anodal stimulation over the primary motor cortex resulted in improvement. No significant effects of stimulation on reaction times were observed. Using single unilateral anodal tDCS (20 min, 2 mA) over the left DLPFC, Keeser et al. (2011) found improvement in subject accuracy as well, but also found improvement in reaction times (RTs) on 0-, 1-, and 2-back number tasks in an active stimulation group, compared with a sham group. The benefits of a single unilateral stimulation over the DLPFC have been further supported by studies using different levels of working memory load ($n = 0, 1, 2, 3$), different stimulation intensity (1 mA—2 mA) and different durations of stimulation (10–30 min) in healthy participants (Fregni et al. 2005; Keeser et al. 2011; Mulquiney et al. 2011; Zaehle et al. 2011). The effectiveness of tDCS on reaction times (but not percentage of accurate responses) was further supported by both a meta-analysis of n-back task studies (Brunoni and Vanderhasselt 2014) and a recent meta-analysis of studies involving various WM tasks (Hill et al. 2016).

Other research, however, challenges the finding that a single session of tDCS can modulate WM performance. Slower reaction time, in fact, was observed after applying a single session of bilateral anodal or cathodal stimulation over the DLPFC, compared to sham stimulation, using the Sternberg task (Marshall et al. 2005). In addition, no performance improvement was observed in a 3-back shape task among an active group, compared with a group receiving sham stimulation, following unilateral anodal stimulation over the left DLPFC in a study of older healthy adults (Nilsson et al. 2015). Similarly, no improvement was reported in a study testing the effects of one session of 20 min anodal stimulation over the cerebellum while participants performed 2-, 3-, and 4-back letter tasks (van Wessel et al. 2016). A recent study using a bilateral montage over the DLPFC with different current intensities and the 3-back letter task also reported no significant effects on WM performance (Nikolin et al. 2018; see also; Hill et al. 2017). These findings are consistent with a recent quantitative review of the effects of a single tDCS session on different cognitive task performance (Horvath et al. 2015). The results of the review did not support the assertion that a single session of tDCS produces a reliable effect on cognition in healthy adults. It has been suggested that the null results may be associated with the initial cortical activation state of the targeted neural region, such that cognitive or behavioral priming may have an impact on the stimulation results. Thus, different state-dependent effects among the studies included in the review may have resulted in the null findings. Taken together, results from studies testing the effects of a single tDCS session on n-back task performance in healthy participants have thus far been inconclusive.

Only a few studies have reported the long-term effects of consecutive tDCS sessions (Jones et al. 2015; Ruf et al. 2017) on n-back performance. Jones et al. (2015) investigated the long-term effects of unilateral tDCS-linked WM training in healthy aging participants using ten sessions of 1.5 mA for 10 min each. Participants were asked to complete cognitive tasks including a 2-back spatial task at three time points: before stimulation, after the tenth stimulation, and 1 month following the last stimulation. Results showed improvement for both active and sham groups, yet only in the active group was the improvement maintained 1 month after the last stimulation. Ruf et al. (2017) examined the effects of anodal tDCS (1 mA) to the left and right DLPFC on the efficacy of WM training. Stimulations were coupled with spatial and verbal WM training over three stimulation sessions. Multiple working memory loads were used. The study included three conditions: task-congruent (i.e., spatial WM task coupled with right stimulation, verbal WM task coupled with left stimulation), task-incongruent (spatial WM-left, verbal WM-right) and sham stimulation. The main finding was a steeper learning curve observed when WM training was combined with task-congruent tDCS relative to sham stimulation and task-incongruent tDCS. Furthermore, the observed beneficial effects lasted 9 months. Despite these preliminary positive outcomes, the number of studies researching this topic is quite sparse. In sum, the majority of n-back studies in the literature used only one session of stimulation (Fregni et al. 2005; Horvath et al. 2015; Hoy et al. 2014; Keeser et al. 2011; Muquiney et al. 2011; Nilsson et al. 2015; Zaehle et al. 2011), a unilateral montage (Fregni et al. 2005; Hoy et al. 2014; Jones et al. 2015; Keeser et al. 2011; Muquiney et al. 2011; Zaehle et al. 2011), and a single memory load (Fregni et al. 2005; Hoy et al. 2014; Lally et al. 2013; Nilsson et al. 2015; Teo et al. 2011; Zaehle et al. 2011). Given the limited number of studies testing the long-term effects of tDCS in healthy participants on n-back task performance (Jones et al. 2015; Ruf et al. 2017, coupled with cognitive training), the field would benefit from studies investigating a longer time course, bilateral montage, and various memory loads.

The aim of the present study was to examine the effects of bilateral tDCS over the DLPFC using four memory loads (1, 2, 3, 4) for the n-back task. Furthermore, we aimed to test both the immediate effect of tDCS on n-back performance after six sessions of stimulations, and the lasting effect (1 month following the sixth tDCS session). In accordance with neuroimaging studies showing the engagement of the DLPFC during the n-back task, we hypothesized that six sessions of stimulation would improve n-back task performance immediately following the last stimulation. Specifically, we expected faster reaction times in the active group, in comparison with the sham group (Brunoni and Vanderhasselt 2014). Based on the previous findings pointing to

long-term positive effects of consecutive tDCS brain stimulations (Jones et al. 2015), we also hypothesized that the improvement in n-back performance would still be present at the follow-up visit, 1 month after the sixth stimulation, only among the active group.

Methods

Participants

Twenty-five right-handed native Hebrew speakers participated in the study. Sixteen (eight females) participated in the active group and nine (three females) in the control (sham) group. All participants were blind to the type of tDCS delivered. No gender difference was found, χ^2 (1) = 0.65, p = .42. All participants had 12 years of education. The two groups were matched according to both semantic and phonemic fluency tests that assess language-based executive functioning (Kave et al. 2010). In the phonemic fluency test, the participant had 60 s to name as many words as possible that start with a specific Hebrew letter (b, g, sh). In the semantic fluency test, the participant was asked to name as many words as possible that belong to a specific category (animals, vehicles, fruits, and vegetables). *t* tests for independent samples indicated no significant differences between the active tDCS group and the sham group in performance on the semantic fluency and phonemic tests. The results are summarized in Table 1.

Task and stimuli

Participants were asked to perform 1-, 2-, 3-, and 4-back shape working memory (WM) tasks. They were provided a sequence of eight yellow shapes presented on a black background in the center of a screen. The shapes included circles, squares, hourglasses, triangles, stars, and pentagons. Each shape was presented for 500 ms with an interstimulus interval of 2500 ms, parameters used in a previous study in the literature (Jaeggi et al. 2010). Participants were instructed to respond (by pressing the "b" key) with their right (dominant) hand as quickly and accurately as possible only when the currently presented shape matched the shape that was presented one, two, three, or four trials before. The participants first completed the 1-back task, then the 2-back, 3-back, and finally the 4-back tasks. Each level contained three blocks, with a rest between the blocks if needed. A brief practice sequence of six trials was given prior each level. The practice session was conducted with feedback given by the experimenter. The experimenter then asked each participant whether the instructions were understood and whether an additional practice session was needed; the participants affirmed understanding and none requested more than one practice session. A total of 18 correct responses (hits) and 46 possible false alarms were possible for every level. Thus, the test sequence consisted of a total of 256 shapes with 72 (18 × 4) matching shapes (targets). For each participant, the percentage of hits, false alarms, and reaction times for correct responses in each level was calculated. The n-back task was generated using the Superlab pro v4.5 software (Cedrus Corporation, 1991).

tDCS protocol

tDCS was administered using a battery-driven, constant current stimulator (neuroConn DC stimulator plus, Incl GmbH) and a pair of conductive rubber electrodes (5 cm × 7 cm, 35 cm^2) covered in normal saline-soaked, synthetic sponges and restrained by a headband (Loo et al. 2011). Each side of the sponges was soaked with about 6 mL of saline solution (a total of 12 mL per sponge) of 0.09% NaCl concentration. A syringe was used to add more solution if needed. Fluid leaking was avoided by placing a towel across the participant. Bilateral montage was conducted to increase the activation of left DLPFC function, and decrease activation of the right DLPFC (Calautti et al. 2007; Kasahara et al. 2013). To stimulate the DLPFC, the anode electrode was placed over F3 (i.e., left DLPFC) and the cathode electrode over F4 (i.e., right DLPFC), according to the 10–20 international system for EEG electrode placement using universal electrode caps for standardized head sizes (see Seibt et al. 2015) with the longer side of the electrode positioned vertically. Each stimulation was applied for 20 min at 2-mA intensity. For the sham group, the stimulation ceased after 30 s.

Procedure

The study plan was approved by the Ethics Committee of the School of Education at Bar Ilan University. Informed

Table 1 Age and fluency scores

	Sham (n = 9)		Active (n = 16)		t (22)	p
	Mean	SD	Mean	SD		
Age	29.62	5.15	31.44	6.95	− 0.75	0.46
Semantic fluency test	64.37	13.49	65.22	7.53	− 0.17	0.86
Phonemic fluency test	42.69	7.84	41.89	11.58	− 0.21	0.84

consent was obtained from all individual participants included in the study.

The study involved seven visits with participants over the course of 6 weeks (see Fig. 1). At the first meeting, participants completed the phonemic and semantic fluency tests, followed by the baseline n-back task (T1). Immediately after performing the baseline task, the first stimulation session began. Each participant completed a total of six sessions of 20 min stimulation over 2 weeks, receiving three stimulations per week. During the stimulation, participants were quietly resting. At the end of the sixth stimulation, the participants repeated the n-back task (T2). One month following the last stimulation, each participant completed the n-back task for the third and last time (T3). All four working memory levels ($n=1$–4) of the n-back task were used at each time point (T1, T2, and T3).

The stimulation sessions were performed every other day of the week (excluding Saturday) over the course of 2 weeks, with equal gaps between sessions across participants. The rationale to use this method of stimulation is based on previous findings that showed lasting effects: improved cognitive inhibition that continued for 1 month after the sixth (last) stimulation (Metzuyanim-Gorelick and Mashal 2016) and improved naming ability in chronic aphasia patients 3 months following the last stimulation session (Lifshitz Ben Basat et al. 2016; see also DaSilva et al. 2012).

No side effects were observed throughout the experiment. All participants tolerated the simulation well, and did not report any sensation of pain or uncomfortable feelings during the stimulation sessions.

Data analysis

The number of correct responses (hits), false alarms, and mean reaction times of hits were calculated. Data analyses were performed with SPSS 23 using a three-way repeated measures analysis of variance (ANOVA) with two within-subject factors: memory load (four levels: $n=1$, $n=2$, $n=3$, and $n=4$) and time point (three time points: T1, T2, or T3) and group as a between-subject factor (active, sham). Post hoc analyses were conducted using Bonferroni correction. The analyses were performed on each of the three outcome measures (hits, false alarms, and reaction times) separately. The threshold of significance was set at 5% ($\alpha=0.05$).

Results

First, we examined if there were significant differences between the two groups at T1 (baseline) for the three outcome measures in each of the four load levels. Table 2 shows no group differences in hits, false alarms, or reaction times at baseline.

Next, we performed a three-way repeated measures ANOVA with stimulation group as a between-subject factor (active, sham), and time (T1, T2, T3) and memory load

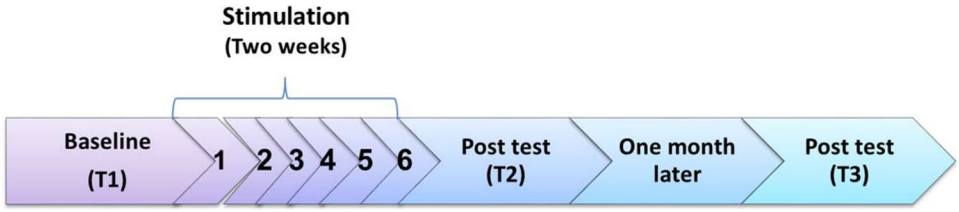

Fig. 1 Experimental design. For each time point, the participants completed all four levels of the *n*-back test

Table 2 Summary of the three outcome measures for the n-back task at T1

Measure	Load	Sham ($n=9$)		Active ($n=16$)		t (23)	p
		Mean	SD	Mean	SD		
Hit	1	95.5	8.38	95.56	7.38	− 0.02	0.99
	2	82.29	20.1	87.65	14.64	− 0.70	0.49
	3	68.03	18.06	67.28	14.81	0.11	0.92
	4	52.8	18.49	58.64	26.22	− 0.65	0.52
False alarm	1	1.11	1.72	0.75	1.13	0.56	0.78
	2	5.23	6.21	5.29	6.92	− 0.02	0.98
	3	14.65	7.45	17.99	13.26	− 0.81	0.43
	4	15.46	11.24	19.31	11.75	− 0.81	0.43
Reaction times	1	563.25	128.51	609.26	138.06	− 0.84	0.41
	2	762.5	215.7	790.68	154.79	− 0.34	0.73
	3	807.86	186.07	964.54	252.55	− 1.78	0.09
	4	876.58	267.89	1044.17	354.13	− 1.34	0.19

($n = 1, 2, 3, 4$) as within-subject factors for each of the three outcome measures (hits, false alarms, and reaction times) separately.

Hit scores

The main effects of stimulation group (active/sham), $F(1, 23) = 0.00$, $p = .99$, $\eta_p^2 = 0.00$, and time point, $F(2, 46) = 0.81$, $p = .45$, $\eta_p^2 = 0.03$, were not significant. The main effect of memory load was significant, $F(3, 69) = 94.14$, $p < .001$, $\eta_p^2 = 0.80$. A Bonferroni-adjusted t test indicated that increased memory load reduced the number of hits. As expected, the number of hits at n = 1 was significantly higher than $n = 2$ ($p < .05$), $n = 3$, and $n = 4$ ($ps < 0.001$), and the number of hits at $n = 2$ was significantly higher than $n = 3$ and $n = 4$ ($ps < 0.001$). Last, the performance at $n = 3$ was significantly higher than $n = 4$ ($p < .001$).

The two-way interactions of stimulation Group x Time Point, $F(2, 46) = 2.39$, $p = .10$, $\eta_p^2 = 0.09$, Stimulation Group x Memory Load, $F(3, 69) = 0.15$, $p = .93$, $\eta_p^2 = 0.01$, and Time Point x Memory Load, $F(6, 138) = 1.32$, $p = .25$, $\eta_p^2 = 0.05$, were not significant. Finally, the three-way interaction of Stimulation Group x Time Point x Memory Load was also not significant, $F(6, 138) = 0.71$, $p = .64$, $\eta_p^2 = 0.03$ (see Table 3).

Hit scores at each memory load separately

Despite the insignificant interaction of the stimulation group with memory load, and based on previous findings reporting improvement in RTs, accuracy, and error rates in 0-, 1-, and 2-back performance (e.g., Keeser et al. 2011), we sought to test whether any effects of type of stimulation were hidden within each memory load. Thus, to further examine possible tDCS effects on the number of hits, we performed repeated measures ANOVAs with time point (T1, T2, T3) as a within-subject factor and stimulation group (active, sham) as a between-subject factor, separately for each memory load.

The main effects of time point at each memory load [$n = 1$: $F(2, 46) = 1.51$, $p = .23$, $\eta_p^2 = 0.06$; $n = 2$: $F(2, 46) = 2.11$, $p = .13$, $\eta_p^2 = 0.08$; $n = 3$: $F(2, 46) = 0.45$, $p = .64$, $\eta_p^2 = 0.02$, and $n = 4$: $F(2, 46) = 0.96$, $p = .39$, $\eta_p^2 = 0.04$] were not significant. Importantly, the main effects of stimulation group were not significant at any memory load [$n = 1$: $F(1, 23) = 1.10$, $p = .30$, $\eta_p^2 = 0.05$; $n = 2$: $F(1, 23) = 0.00$, $p = .98$, $\eta_p^2 = 0.00$; $n = 3$: $F(1, 23) = 0.07$, $p = .79$, $\eta_p^2 = 0.00$; $n = 4$: $F(1, 23) = 0.00$, $p = .99$, $\eta_p^2 = 0.00$]. Furthermore, stimulation group did not interact with any time point [$n = 1$: $F(2, 46) = 1.49$, $p = .24$, $\eta_p^2 = 0.06$; $n = 2$: $F(2, 46) = 1.14$, $p = .33$, $\eta_p^2 = 0.05$; $n = 3$: $F(2, 46) = 1.08$, $p = .35$, $\eta_p^2 = 0.04$; $n = 4$: $F(2, 46) = 1.18$, $p = .32$, $\eta_p^2 = 0.05$].

Table 3 Hit scores by memory load, time and group

Time	Load	Sham ($n = 9$)		Active ($n = 16$)	
		Mean	SD	Mean	SD
T1 hits	1	95.5	8.38	95.56	7.38
	2	82.29	20.1	87.65	14.64
	3	68.03	18.06	67.28	14.81
	4	52.8	18.49	58.64	26.22
T2 hits	1	98.56	4.41	98.00	3.00
	2	88.87	16.85	87.56	15.66
	3	63.57	18.82	70.37	22.22
	4	57.67	16.74	58.02	28.61
T3 hits	1	98.88	2.42	93.78	9.44
	2	93.05	10.04	89.51	18.52
	3	65.27	18.65	64.66	15.76
	4	55.55	20.89	49.38	8.54

False alarm scores

The main effects of stimulation group, $F(1, 23) = 0.20$, $p = .66$, $\eta_p^2 = 0.01$, and time point, $F(2, 46) = 2.69$, $p = .08$, $\eta_p^2 = 0.10$, were not significant. Similarly to the hits, the main effect of memory load was significant, $F(3, 69) = 49.82$, $p < .001$, $\eta_p^2 = 0.68$. A Bonferroni-adjusted t test indicated that increased memory load increases the number of false alarms. In particular, less false alarms were performed on $n = 1$ than on n = 2 ($p < .05$), $n = 3$, and $n = 4$ ($p < .001$), and significantly less false alarms were performed on $n = 2$ than on $n = 3$ and $n = 4$ ($p < .001$). No significant difference was observed between $n = 3$ and $n = 4$ ($p = .11$).

The two-way interactions of Stimulation Group x Time Point, $F(2, 46) = 1.18$, $p = .32$, $\eta_p^2 = 0.05$, Stimulation Group x Memory Load, $F(3, 69) = 0.77$, $p = .52$, $\eta_p^2 = 0.03$, and Time Point x Memory Load, $F(6, 138) = 1.54$, $p = .17$, $\eta_p^2 = 0.06$, were all non-significant. The three-way interaction of Stimulation Group × Time Point × Memory Load was also non-significant, $F(6, 138) = 0.48$, $p = .82$, $\eta_p^2 = 0.02$ (see Table 4).

False alarm scores at each memory load

To further examine possible tDCS effects on the number of false alarms within a specific memory load, we performed repeated measures ANOVAs with time point (T1, T2, T3) as a within-subject factor and stimulation group (active, sham) as a between-subject factor separately for each memory load. Similarly to the hit analyses, the main effects of time point [$n = 1$: $F(2, 46) = 0.20$, $p = .82$, $\eta_p^2 = 0.01$; $n = 2$: $F(2, 46) = 1.90$, $p = .16$, $\eta_p^2 = 0.08$, and $n = 4$: $F(2, 46) = 0.26$, $p = .77$, $\eta_p^2 = 0.01$] were not significant. However, the main effect of time point at $n = 3$ was significant, $F(2, 46) = 6.56$, $p < .01$, $\eta_p^2 = 0.22$, suggesting that participants made fewer false alarms at T2 and T3 than on T1 ($ps < 0.05$).

Table 4 False alarm scores at all memory loads by group

Time	Load	Sham ($n=9$)		Active ($n=16$)	
		Mean	SD	Mean	SD
T1 false alarm	1	1.11	1.72	0.75	1.13
	2	5.23	6.21	5.29	6.92
	3	14.65	7.45	17.99	13.26
	4	15.46	11.24	19.31	11.75
T2 false alarm	1	1.60	2.54	0.53	1.59
	2	4.43	5.21	2.12	1.86
	3	12.64	7.66	9.79	5.51
	4	14.45	12.09	17.19	10.09
T3 false alarm	1	0.45	0.96	1.06	1.73
	2	3.59	4.49	3.17	5.05
	3	9.97	6.91	13.23	8.26
	4	15.77	10.89	19.05	15.70

Table 5 Reaction times at all memory loads by group

Time	Load	Sham ($n=9$)		Active ($n=16$)	
		Mean	SD	Mean	SD
T1 reaction times	1	563.25	128.51	609.26	138.06
	2	762.50	215.70	790.68	154.79
	3	807.86	186.07	964.54	252.55
	4	876.58	267.89	1044.17	354.13
T2 reaction times	1	553.89	135.02	665.03	127.10
	2	705.88	146.67	869.60	241.03
	3	821.41	215.72	1152.43	516.89
	4	975.51	257.55	1060.78	301.67
T3 reaction times	1	522.00	136.26	680.73	157.74
	2	731.90	207.25	955.57	219.19
	3	775.10	196.73	1099.69	398.69
	4	855.07	290.68	1191.36	440.19

The main effects of stimulation group were not significant at any memory load [$n=1$: $F(1, 23)=0.40$, $p=.53$, $\eta_p^2=0.02$; $n=2$: $F(1, 23)=0.26$, $p=.61$, $\eta_p^2=0.01$; n = 3: $F(1, 23)=0.19$, $p=.67$, $\eta_p^2=0.01$; $n=4$: $F(1, 23)=0.67$, $p=.42$, $\eta_p^2=0.03$]. Furthermore, none of the Stimulation Group x Time Point interactions were significant [$n=1$: $F(2, 46)=1.41$, $p=.25$, $\eta_p^2=0.06$; $n=2$: $F(2, 46)=0.61$, $p=.55$, $\eta_p^2=0.03$; $n=3$: $F(2, 46)=2.56$, $p=.09$, $\eta_p^2=0.10$; $n=4$: $F(2, 46)=0.02$, $p=.98$, $\eta_p^2=0.00$].

Reaction times of correct responses

The main effect of stimulation group on the reaction times of correct responses was significant, $F(1, 23)=7.26$, $p<.05$, $\eta_p^2=0.24$, indicating faster reaction times in the active (Mean = 745.91 ms, SD = 134.79) compared to the sham group (Mean = 923.65 ms, SD = 194.96) regardless of the time point and memory load. As expected, the main effect of memory load on reaction times for correct responses was significant, $F(3, 69)=32.93$, $p<.001$, $\eta_p^2=0.59$. A Bonferroni-adjusted t test indicated that reaction times for $n=1$ were significantly faster than $n=2$, $n=3$, and $n=4$ ($ps<0.001$), and the reaction times for $n=2$ were significantly faster than $n=3$ ($p<.05$) and $n=4$ ($p<.01$), with no significant difference in reaction times between $n=3$ and $n=4$ ($p=.84$). The main effect of time point was non-significant, $F(2, 46)=2.04$, $p=.14$, $\eta_p^2=0.08$.

The two-way interaction of Stimulation Group x Time Point, $F(2, 46)=4.21$, $p<.05$, $\eta_p^2=0.15$, was significant. A one-way repeated measures ANOVA for each type of stimulation group separately revealed no significant difference between the three time points in the active group, $F(2, 30)=0.81$, $p=.45$, $\eta_p^2=0.05$. However, a significant difference was observed in the sham group, $F(2, 16)=5.45$, $p<.05$, $\eta_p^2=0.40$, with slower reaction times at T3 compared to T1 ($p<0.05$), but not between T1 and T2 ($p=0.08$). The two-way interactions of Stimulation Group x Memory Load, $F(3, 69)=1.37$, $p=0.26$, $\eta_p^2=0.06$, and Time Point x Memory Load, $F(6, 138)=0.67$, $p=0.67$, $\eta_p^2=0.03$, were not significant.

Finally, the three-way interaction of Stimulation Group × Time Point × Memory Load was not significant, $F(6, 138)=1.10$, $p=.36$, $\eta_p^2=0.05$ (see Table 5).

Reaction times at each memory load

To further examine possible tDCS effects on reaction times, we performed repeated measures ANOVAs with time point (T1, T2, T3) as a within-subject factor and stimulation group (active, sham) as a between-subject factor for each memory load, separately. Similar to the hit analyses, the main effects of time point [$n=1$: $F(2, 46)=1.19$, $p=.31$, $\eta_p^2=0.05$; $n=2$: $F(2, 46)=2.41$, $p=.10$, $\eta_p^2=0.09$; $n=3$: $F(2, 46)=1.38$, $p=.26$, $\eta_p^2=0.06$, and $n=4$: $F(2, 46)=0.58$, $p=.56$, $\eta_p^2=0.02$] were not significant. The main effects of stimulation group [$n=1$: $F(1, 23)=3.81$, $p=.06$, $\eta_p^2=0.14$; $n=2$: $F(1, 23)=3.57$, $p=.07$, $\eta_p^2=0.13$, and $n=4$: $F(1, 23)=3.47$, $p=.07$, $\eta_p^2=0.13$] were not significant as well. However, a significant main effect of stimulation group was found at $n=3$, $F(1, 23)=7.72$, $p<.05$, $\eta_p^2=0.25$, indicating faster RTs in the active, compared with the sham, group. Stimulation group did not interact with time point at $n=3$, $F(2, 46)=1.33$, $p=.27$, $\eta_p^2=0.05$, and $n=4$, $F(2, 46)=1.97$, $p=.15$, $\eta_p^2=0.08$.

Nevertheless, significant interactions were found at $n=1$, $F(2, 46)=6.88$, $p<.01$, $\eta_p^2=0.23$, and at $n=2$, $F(2, 46)=4.67$, $p<.05$, $\eta_p^2=0.17$. A Bonferroni-adjusted t test at $n=1$ revealed that, whereas the active group exhibited faster reaction times at T3 compared to T1 ($p<.05$), the sham group responded slower at T3 compared to T1 ($p<.01$). No

significant differences in both groups were found between T1 and T2 measurements ($p = .99$ for the active group, and $p = .18$ for the sham group). A Bonferroni-adjusted t test at $n = 2$ revealed that, whereas the sham group exhibited slower reaction times at T3 compared to T1 ($p < 0.05$), with no difference between T1 and T2 measurements ($p = 0.37$), no significant differences between the three time points were found in the active group ($p = 0.36$).

Discussion

The present study investigated the short-term and the long-term effects of tDCS applied over the left DLPFC on working memory using four different levels of memory loads in healthy participants. The main finding was faster reaction times in the active group, compared with the sham group, as evinced by the main effect of stimulation group regardless of time point and memory load. This non-specific finding was driven by the faster RTs of the active group, compared with the sham group, for $n = 3$, as the separate analysis for each memory load revealed.

Our results did not find significant differences in accuracy scores (hits) and number of false alarms between the active and the sham groups either immediately after the last stimulation (T2) or 1 month later (T3), compared with baseline (T1), for all memory loads. No main effects for hits were found even when lenient statistical analyses were conducted for each memory load, separately, to reveal hidden effects. These null findings pertaining to the current parameters (four n-back tasks with shapes, bilateral stimulation over the DLPFC, 2 mA, 5 × 7 cm electrodes), are consistent with the conclusion that tDCS has no effect on the outcomes of any working memory tasks among healthy participants (Horvath et al. 2015). This conclusion is mitigated by recent meta-analyses (Hill et al. 2016; Mancuso et al. 2016); Hill et al. point to mixed effects of anodal tDCS on WM performance (either modest effect sizes or non-significant effects) while Mancuso et al. (2016) suggest that anodal DLPFC stimulation coupled with training may enhance WM performance. Recent promising results also indicate that tDCS is a beneficial tool, even for up to 9 months, if applied over the right DLPFC during a spatial training task and over the left DLPFC during verbal WM training task (Ruf et al. 2017). Thus, although drawing conclusions regarding the overall efficacy of tDCS for enhancing WM in healthy populations is difficult at present, future studies that test the effect of WM training combined with tDCS, higher current densities, longer stimulation durations, and different techniques (e.g., high-definition tDCS) are needed to establish the effectiveness of tDCS at modulating WM performance.

Our results do not support other findings that show improvement after applying tDCS (e.g., Hoy et al. 2014; Lally et al. 2013; Teo et al. 2011; Zaehle et al. 2011). A possible explanation for this apparent discrepancy in findings may be linked to task demands across studies. Whereas most of these studies tested only one level of memory load: either 3-back (Lally et al. 2013; Teo et al. 2011) or 2-back (Hoy et al. 2014; Zaehle et al. 2011), in the present study we tested four memory levels. The use of four levels in a row within one tDCS session, unlike the other studies, may have had a negative effect on performance due to the potential for increased weariness of the participants. It was noteworthy that follow-up analyses found slower RTs in the sham group at T3, compared to T1, for both $n = 1$ and $n = 2$. This is in contrast to the active group, who performed faster at T3, compared to T1, for $n = 1$ (with no difference in RTs for $n = 2$). The slower RTs in the sham group may have stemmed from increased weariness and/or lack of motivation in performing the task that the presence of active stimulation ameliorated for the active group. The suggestion that active stimulation may prevent weariness or improve motivation in task performance (at least for the easiest memory load) is novel and worthy of future exploration.

Indeed, it has been suggested that the left DLPFC serves as a key region for the integration of cognitive and motivational information (Savine and Braver 2010). In support of this notion, it was found that anodal tDCS over the left DLPFC enhanced solution recognition for difficult problems, and this effect was modulated by motivation-related personality traits (Metuki et al. 2012). Hence, motivation is a possible moderator of stimulation effect that may explain the improvement in RTs observed for the active group, but not the sham group, in the present study. Motivation traits were not controlled in the current study and, therefore, future studies should consider individual differences in trait motivation as a possible moderator when stimulating the DLPFC. In summary, the use of multiple increasing memory loads in one session and the possible effects of trait motivation may have contributed to the current study findings which appear to be in contradiction with previous findings.

Our results provide only weak support for the conclusions of a recent meta-analysis (Brunoni and Vanderhasselt 2014) pointing to faster (not more accurate) responses following tDCS over the DLPFC. Our results do show faster reaction times in the active, compared with the sham, group. However, this finding was not obtained for a specific memory load, indicating that regardless of the memory load and time point, active stimulation induced faster RTs than sham stimulation. The contrast between the non-specific stimulation effects demonstrated in our study and the meta-analysis finding may be linked to the criteria for including studies in the meta-analysis. Studies involving different stimulation sites were analyzed together (e.g. anodal to the left DLPFC, anodal to the right DLPFC), which may contribute to the discrepancy between the

current and the previous findings. Alternatively, it has been suggested that if a relatively small number of null results were to be added to the Brunoni and Vanderhasselt (2014) meta-analysis, such as the current study findings, the observed improvement of tDCS on response times could have been reduced to non-significance (Mancuso et al. 2016).

Another potential explanation for the non-specific RT improvements obtained in our study's active group may be related to the responding hand. Participants were instructed to respond to stimuli using their right (dominant) hand. In other words, participants responded with their contralateral hand to the target region (as anodal tDCS was applied over the left DLPFC). A recent tDCS study (Trumbo et al. 2016) that targeted the DLPFC instructed participants to respond with the ipsilateral hand of the anode electrode to reduce the potential for spread of cortical excitability to the motor cortex in the stimulated hemisphere. This potential spread of activation, combined with the proximity of the electrode to M1 in our study, may have reduced RTs, providing a possible explanation for our non-specific findings of faster RTs in the active group. This explanation may also shed light on the findings of a meta-analysis indicating that tDCS over the DLPFC reliably improves RTs but not accuracy rates for n-back tasks (Brunoni and Vanderhasselt 2014). However, although this potential explanation is reasonable, our post hoc analyses indicated that for n = 2 no improvement in RTs was observed in the active group compared with sham group, although this improvement was observed for the 3-back task. Therefore, it is important to further test this potential "hand use" confound by conducting future studies using the ipsilateral hand.

Another potential explanation for the discrepancy between our findings and previous studies reporting improvement in n-back task performance (Keeser et al. 2011; Muquiney et al. 2011; Zaehle et al. 2011) may be related to neural excitability. A recent theoretical framework suggests that the initial activity state of a targeted brain region (hence, target neurons) can modulate the efficacy of brain stimulation (Silvanto and Cattaneo 2017). Accordingly, adaptation of neurons induces a change in their operating range such that a stronger stimulus is needed to induce a certain level of neural firing. This implies that a higher stimulation intensity is needed to induce firing in adapted neurons. This explanation may be relevant to the current study. Performing four memory load levels in a row may have caused adaptation in the target neurons in the DLPFC and, as a result, a higher intensity of stimulation would have been necessary to produce task performance improvement. This theoretical framework (Silvanto and Cattaneo 2017), although based on a study that tested motion perception (not higher cognitive tasks as in the current study), may imply that using a specific memory load (instead of all four levels) is preferred.

It appears that our null findings are consistent with a recent study that used the same stimuli as the present study and reported no improvement after tDCS over the left DLPFC (Nilsson et al. 2015, see also Marshall et al. 2005). In the present study, we used shapes as stimuli, whereas most of the previous studies used letters or numbers (Fregni et al. 2005; Hoy et al. 2014; Teo et al. 2011; Zaehle et al. 2011). Because working memory is assumed to involve several subsystems, with sustained neuronal activity taking place for up to several tens of seconds in the prefrontal cortex as well as the parietal cortex (Passingham and Sakai 2004), future studies should test the potential effect of parietal stimulation using the n-back shape task.

As expected, we found significant main effects of memory load for all outcome measures. Thus, as the memory load decreases, false alarms, reaction times, and hit scores improve, attesting to the nature of the task. Moreover, although no significant interaction was found, when we analyzed the results for each memory load separately, improvement in RTs from T1 to T3 was observed for $n = 1$ in the active group. This result may suggest that tDCS can positively affect performance but only at a low memory load, as seen by Keeser et al. (2011) and Muquiney et al. (2011). Additionally, this improvement in RTs in the 1-back task may suggest that the participants' performance was not at its ceiling (at least not for processing speed) and, therefore, we may exclude the possibility that the lack of behavioral effects of stimulation was due to a ceiling effect for the lower load ($n = 1$).

Notwithstanding our novel findings, there are several study limitations that must be mentioned. First, most of the previous studies used unilateral montage, not the bilateral montage used in the current study; additional comparison between unilateral montage and bilateral montage, including the reverse montage (cathodal to left DLPFC vs. anodal to right DLPFC), is necessary to clarify the effectiveness of each montage. Second, to isolate performance changes elicited using tDCS, further variables should be controlled, such as anatomical brain differences (Kim et al. 2014), the effect of weariness, and individual differences in trait motivation. Third, the relatively small group sizes in our study may be responsible for the lack of significant findings; therefore, future studies should examine the effect of tDCS on WM performance with a larger sample. Moreover, the number of participants was not balanced between the two groups; despite the non-significant group differences at baseline, utilizing a sham group with a larger number of participants would better allow further exploration of the current study's unexpected finding of increased RTs at T3, compared to both T2 and to T1. Fourth, one disadvantage in using 5×7 cm electrodes is their lack of spatial focality, and there is evidence from computational modelling studies that electric fields induced by tDCS are

not always maximal directly under the anode (Miranda et al. 2013). Thus, it is not clear whether the bilateral montage used in the present study was accurately stimulating the DLPFC. Future studies that include computational modelling data of the current distribution across the cortex would be useful, to assess how focused the stimulation is when targeting the DLPFC. Fifth, the present study was designed to be single-blind, but participant blinding was not verified and no sensation data were collected; future studies would be enhanced by verifying that the blinding procedures are effective, particularly in multiple-session stimulation studies. Finally, in the current study, stimulation sessions were administrated every other day (6 sessions spanning 2 weeks). Further investigation is required to determine the optimal frequency of stimulation sessions necessary to induce long-term improvement. It is possible that daily stimulation sessions might elicit more effective results by inducing lasting plastic changes that promote synaptic strengthening (DaSilva et al. 2012).

In sum, the present study aimed to explore the potential impact of multiple variables in tDCS-induced n-back performance change, using four memory loads, bilateral montage, a long duration of stimulation (20 min in 2-mA dose) over the DLPFC, six stimulation sessions, and n-back testing across three time points. Taken together, the current findings largely do not support our hypotheses, namely that six sessions of stimulation would improve task performance immediately following the last stimulation, and that the improvement would be maintained in the active group a month following the last stimulation. The only finding was a general effect of faster responses in the active group over the sham group (regardless of memory load and time point). Further data are required to understand the possible effects of tDCS on cognitive abilities, and how these effects interact with potential interfering variables such as brain state, motivation, and participant fatigue. A future study should test whether pairing stimulations with cognitive training may be more efficient. To that end, further research, including the reporting of null findings when applicable, may shed light on the strengths and weaknesses of this technique.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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