The effect of prefrontal transcranial direct current stimulation (tDCS) on attention network function in healthy volunteers.

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Abstract

Objectives: The effect of acute transcranial direct current stimulation (tDCS) on cortical attention networks remains unclear. We examined the effect of 20 minutes of 2mA prefrontal dorsolateral prefrontal cortex (DLPFC) tDCS (bipolar balanced montage) on the efficiency of alerting, orienting and executive attention networks measured by the attention network test (ANT).

Materials and Methods: A between-subjects stratified randomised design compared active tDCS vs. sham tDCS on attention network function in healthy young adults.

Results: Executive attention was greater following active vs. sham stimulation (d= 0.76) in the absence of effects on alerting, orienting or global RT or error rates. Group differences were not moderated by state-mood.

Conclusion(s): 20 minutes of active 2mA tDCS over left DLPFC is associated with greater executive attention in healthy humans.

Introduction

The functional neuro-architecture of the attention system features three separable

networks: alerting, orienting and executive attention/control [1]. The alerting system is

spatially broad and facilitates distributed processing of temporally anticipated but not

spatially localized events, and is associated with increased activity in thalamic, anterior

and posterior cortical sites networks. Orienting enables the selection/allocation of

resources towards the spatial location of anticipated/salient stimuli and activates parietal

cortex and frontal eye-fields. Executive control coordinates voluntary (over

involuntary/automatic) responses and activates lateral and medial prefrontal cortex (PFC)

and anterior cingulate cortices [2-3].

The prefrontal cortex (PFC) has long been considered to play a key role in the executive

control of attention. Early animal behavioural studies [e.g. 4-5] describe the effects of

frontal damage as "a disruption of goal-directed behaviours" and recent clinical

neuropsychological studies in humans with PFC lesions reveal selective deficits in

executive attention [6-10]. Neuroimaging studies reveal positive correlations between

neuronal activity in subregions of PFC and executive control (for review, see [11]). Taken

together, extant evidence implicates PFC in executive attention control [12].

tDCS is a non-invasive brain stimulation method, which alters cortical tissue 'excitability'

through applying a weak (0.5-2mA) constant direct current via scalp electrodes to the

cortical region of interest (13). In contrast to other neurostimulation modalities, tDCS

does not directly trigger action potentials in neuronal cells, but instead changes overall

tissue excitability [14]. Transcranial magnetic stimulation (TMS) of cortical attention

networks selectively modulates corresponding behavioural performance measures [15].

However, recent meta-analysis [16] suggests the effects of acute transcranial direct

current stimulation (tDCS) remains unclear [16] and highlights the need for future studies to i) include performance measures that can dissociate the selective effects of tDCS across attention networks and ii) examine state-dependent variables that might moderate the effects of tDCS on cognition (see [17]). Stimulation of posterior parietal cortex modulates orienting networks [18], but a corresponding effect of PFC tDCS on executive attention has not been demonstrated [18]. Other studies have examined the effects of tDCS on attention to emotional information and provide evidence that 20 minutes of active DLPFC tDCS with a bipolar balanced montage can reduce vigilance to threat [19], and that 17 minute 1mA monopolar stimulation of left PFC can enhance attention training procedures that direct attention away from threat stimuli [20].

We examined the effect of 20 minutes of 2mA prefrontal DLPFC tDCS on the efficiency of alerting, orienting and executive attention networks measured by the attention network test (ANT) [21] - a cued reaction time flanker task that requires participants to make a swift response to central targets (flanked by distracter stimuli) cued by temporal-onset (alerting) and/or spatial (orienting) visual stimuli. The Attention Network Test (ANT) is a well-established and widely used simple, computerised task that combines a flanker task and a cued-reaction time task. Participants make a speeded response to classify the direction of a central arrow, which is flanked by two pairs of arrows that either point in the same direction as the target arrow (congruent condition) or in the opposite direction (incongruent condition). The ANT has subsequently been used to characterise attentional deficits in alerting, orienting and executive attention in healthy individuals, and at-risk/clinical groups [e.g.22].

Consistent with animal, PFC lesion studies in humans [6-10; 23] and functional neuroimaging evidence we predicted that a 20-minute session of active prefrontal tDCS

would selectively improve executive attention control compared to sham tDCS. Following

recommendations from recent meta-analyses [e.g. 16] we used a robust physical and

mental health screening procedure to match groups, examined subjective and autonomic

state-dependent measures of mood/arousal at baseline and post-stimulation, and

examined retrospective expectancies about stimulation condition that might have

affected predicted training effects.

Method

Participants: Thirty healthy volunteers were recruited through online adverts and

randomized (by gender) to receive either 2mA active tDCS (n = 15; 10 females, 5 males;

mean age = 20.8 years, SD=1.8) or non-active sham stimulation (n = 15; 11 females, 4

males; mean age = 21.5 years, SD=2.9). Participants underwent a telephone health screen

prior to the testing session and a mental health screen on the day of the study session,

using a structured diagnostic interview (Mini International Neuropsychiatric Interview

MINI; [24]. A physical health checklist screened participants against current and lifetime

physical illness exclusion criteria. Eligible participants were required to be aged 18-55

years. All participants were right handed. Exclusion criteria included metal or electronic

implants, epilepsy, recent medication (past 8 weeks bar topical treatment, paracetamol,

oral, injectable, or skin patch contraception), pregnancy, elevated blood pressure

(>140/90 mm Hg), cardiovascular disease, lifetime history of psychiatric

illness/alcohol/drug dependence, current smoker, body mass index (BMI) <18 or

$\geqslant$28 kg/m2, and recent use of alcohol (confirmed by breath test). The research was

approved by the Ethics and Research Governance Committee, Department of Psychology,

University of Southampton and conducted in experimental laboratories with controlled

lighting and temperature in the Department of Psychology, Highfield Campus,

Southampton. All procedures complied with the Helsinki Declaration of 1975, as revised in 2008. Participants provided informed consent, were debriefed upon completion and compensated with either "study participation credits" (if university students) or with financial compensation at the rate of £6/hour.

Protocol (see Figure 1): Before and after stimulation we measured participant mood (positive and negative affect, PANAS, [25]), anxiety (modified GAD-7, [26]), subjective alertness (visual analogue), heart rate and blood pressure.

The intervention was a 20 minute double-blind 2mA stimulation with a bipolar-balanced montage (anode centred over left DLPFC[1], F3, cathode centred over right DLPFC, F4) or non-active sham tDCS (HDCkit, Magstim, UK). To increase the power of our study to detect predicted effects we utilised a comparatively high current intensity of 2mA with 4x4cm electrodes encased in saline soaked sponge pads to achieve a current density = $0.125mA/cm^2$ (akin to [19, 27] and larger than current densities reported in recent meta-analyses [16]). In the active condition the stimulator supplied the 2mA current for 20 minutes. In the sham condition 2mA stimulation was ramped up and delivered for the first 15 seconds only. The participant was instructed to remain seated, relaxed and refrain from any motor activity for the duration of the stimulation. Immediately after stimulation (active or sham) physiological and subjective measures were collected (peak effects). Participants then completed the ANT (commencing within 2 minutes of stimulation offset), which lasted approximately 20 minutes.

Attention Network Test (see Figure 2). A central fixation cross was presented for 400–1600 ms, followed by a cue for 100 ms (except on no-cue trials). 400 ms after cue offset (500ms in no-cue trials), target and flanker arrows were displayed until response. Centre

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[1] Though electrodes were centred over F3 and F4 to maximise stimulation of DLPFC we acknowledge that stimulation likely extended beyond these sites to broader PFC.

and double cues (appearing above and below fixation) signalled target onset. Spatial cues

(displayed *either* above *or* below fixation) signalled the onset *and* spatial location of

target arrows. Targets were flanked by a pair of distracter arrows that pointed in the

same (congruent) or opposite (incongruent) direction as the target. Participants

completed 8 practice trials and 128 randomized experimental trials (16 counterbalanced

trials/cue-type condition). Stimuli were presented using Inquisit 2.

See Figure 1 for study overview and Figure 2 for summary of trial events in the Attention
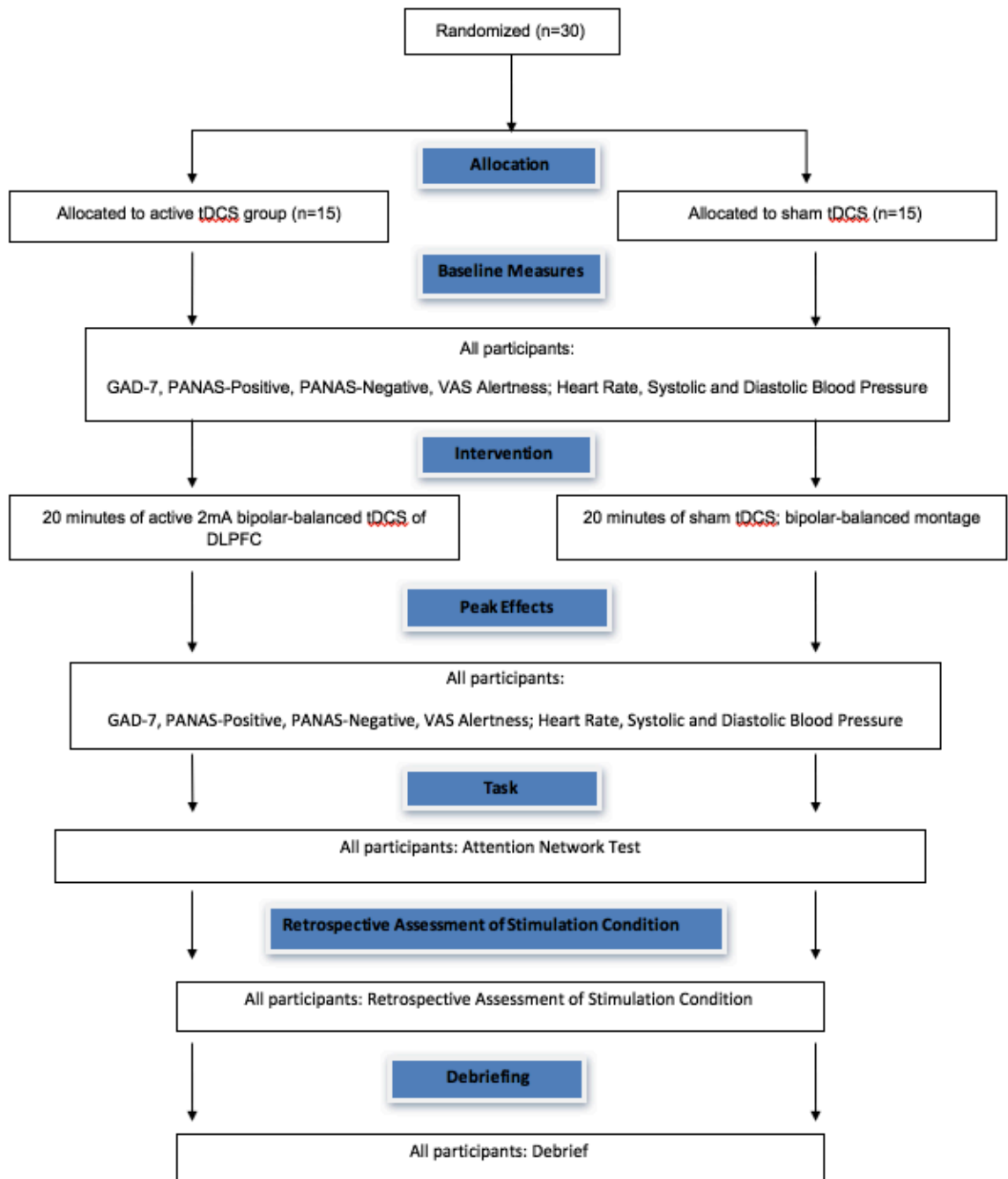
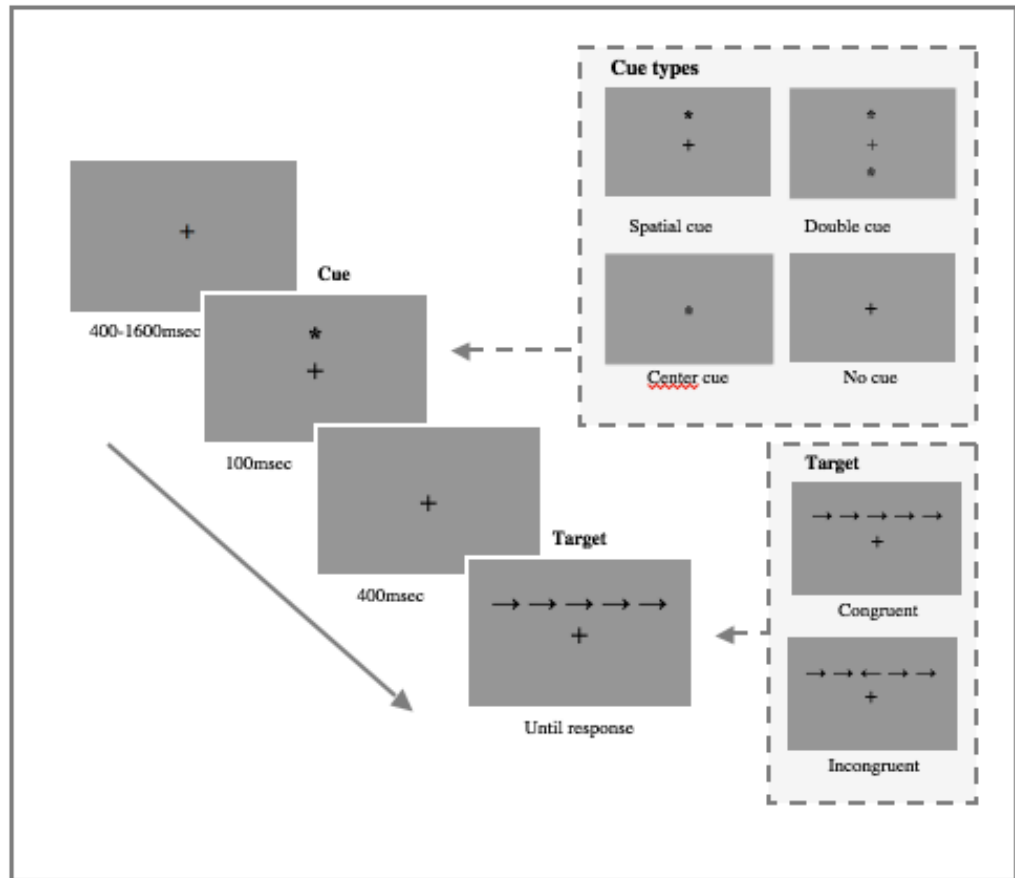Network Test.

Figure 1 Study overview.

Figure 2 Summary of trial events in the Attention Network Test.

Adapted from: Garner et al (2012)

Data Analysis

Incorrect responses (0.8%) and RTs greater than 1000ms (1.6%, identified as outliers using boxplots) were removed (with no difference between groups, F's <1). The alerting effect was calculated by subtracting the mean RT from double-cue trials from the mean RT on no-cue trials (RT(no-cue) – RT(double-cue)). The orienting effect was calculated by subtracting the mean RT on spatial-cue trials from the mean RT on centre cue trials (RT(center-cue) – RT(spatial-cue)). The executive control effect was calculated by subtracting the mean RT of all congruent trials, from the mean RT of incongruent trials (RT(incongruent) – RT(congruent)). Large positive alerting and orienting scores reflect

increased alerting and orienting network function respectively. Conversely low positive execute control scores reflect improved executive control (i.e. reduced effect of flanker distractors on incongruent vs. congruent trials).

Independent samples t-tests compared active and sham tDCS groups on baseline and post-stimulation anxiety, mood, heart rate and blood pressure. Separate 2(Group: active vs. sham) x 2 (Time: baseline vs. post-stimulation) mixed design analyses of variance (ANOVA)s tested for group differences in anxiety, mood, heart rate and blood pressure over time.

Reaction time data was entered into an omnibus 2(Group: active vs. sham) x 4(Cue-type: spatial, double, central, no cue) x 2(Congruence: congruent vs. incongruent) ANOVA. This omnibus analysis tests for group differences in global reaction time (i.e. main effect of Group) and interactions that would reflect a selective effect of group on task performance. Three separate independent samples t-tests compared active vs. sham tDCS groups on alerting, orienting and executive control attention network scores. All analyses were performed using SPSS software v23.

Results

Effects of 2mA anodal tDCS of the left DLPFC on mood and anxiety levels

Independent samples t-tests indicate that the active and sham tDCS groups did not significantly differ on measures of pre-existing (nor post-stimulation) anxiety (GAD-7), mood (PANAS), or alertness, nor in heart rate or blood pressure (F's $(1,28) < 3.41$, p's$>.08$, see Table 1). ANOVA suggested that anxiety (GAD-7), negative affect (PANAS-neg) and blood pressure were unaffected by Time, Group and their interaction ($Fs(1, 28) < 2.49$, $ps > .126$). ANOVA provided evidence that across participants positive affect, alertness and

heart rate decreased from baseline to post-stimulation (Fs(1,28) > 6.67, ps > .015), but there were no effects of Group (Fs(1,28) < 3.59, ps > .07), nor Group x Time interaction Fs(1,28) < 1.56, ps > .22. Taken together these results suggest that tDCS and sham groups were well matched at baseline, but that tDCS did not modulate anxiety, mood nor autonomic arousal compared to sham stimulation.

Consequently any observed differences in attention network function cannot be attributed to unanticipated group differences in mood or arousal at baseline nor post-stimulation.

ANT

The omnibus group(2) x cue-type(4) x congruence(2) ANOVA revealed a main effect of cue type (F(3,84)=22.85, p <.001) characterized by faster RTs on spatial cue trials (m = 498msec) compared to double (m = 524msec) and central (m = 522) cue trials, which in turn were faster than no-cue trials (m = 543), (p's < .01). There was also a main effect of congruency – characterised by quicker reaction times on congruent vs. incongruent trials (F(1,28)=336.94, p <.001). An interaction between congruency and tDCS group (F(1,28)=4.27, *p* <.05) was characterised by faster RTs on incongruent trials following active vs. sham tDCS compared to congruent trials. All other effects were non-significant (Fs < 1.18, ps > .32). Global RT and error rate were unaffected by stimulation condition, Fs < 1.

A series of three separate independent samples t-tests compared active vs. Sham tDCS groups on alerting, orienting and executive control attention network scores. Executive attention control network scores were lower (reflecting greater executive attention control) following active vs. sham stimulation t(28) = 2.06, *p* = .04, d = 0.76, see Figure 3.

Alerting and orienting attention network function were unaffected by stimulation

condition, see Table 2 and Figure 3. Group differences were not moderated by

baseline/change in mood, alertness, heart rate or blood pressure.

Supplementary analyses examined whether group differences in alerting and orienting

were moderated by 'target congruence' (i.e. whether group differences were observed on

easier congruent trials but not more challenging incongruent trials). Separate 2 (Group) x

2(congruence) ANOVAs on alerting and orienting scores did reveal significant effects of

congruency ($F_{(1,28)}=17.28$, $p <.001$; $F_{(1,28)}=11.71$, $p<.01$) on alerting and orienting

respectively, with better performance on congruent as compared to incongruent trials

(consistent with the main effect of Congruence revealed in the omnibus ANOVA). There

were no effects of tDCS group nor congruency x group interactions (F's <0.01, p's $>.95$)

and consequently there was no evidence that tDCS affected alerting and orienting

attention network function (on easier congruent, or more challenging incongruent trials).

Blinding

Participants could retrospectively identify their stimulation condition (Active 12/15

correct; Sham 12/15 correct). The effect of tDCS vs. sham on executive attention was

greater in participants who were aware of their stimulation condition ($d_{(aware, n = 24)} = 0.96$

vs. $d_{(all, n=36)} = 0.76$). The perceived stimulation group had a smaller effect on executive

control $t(28) = 1.82$, $p = .08$, $d = 0.69$ and no effect on other performance measures,

mood, alertness and heart rate/blood pressure t's < 1.

Table 1

Effects of active vs. sham tDCS on mood state, arousal and attention network function.

State measure	Time	Active tDCS n=15 10 females mean age = 20.8yrs (SD=1.8)		Sham tDCS n=15 11 females mean age = 21.5yrs (SD=2.9)		
		M	SD	M	SD	t(28)=
GAD7(Anxiety)	Baseline	15.95	15.06	18.02	11.77	0.42 (p=.68)
	Post-stim.	14.53	14.78	14.38	13.04	0.03 (p=.98)
PANAS-P (Positive Affect)	Baseline	23.73	6.23	27.80	6.21	1.79 (p=.08)
	Post-stim.	21.40	6.09	24.60	5.47	1.51 (p=.14)
PANAS-N (Negative Affect)	Baseline	12.13	2.30	12.13	2.56	0.01 (p>.99)
	Post-stim.	11.33	2.00	12.80	5.93	0.91 (p=.37)
Alertness	Baseline	94.73	20.08	106.60	27.42	1.35 (p=.19)
	Post-stim.	68.73	25.40	84.47	35.16	1.41 (p=.17)
HR (BPM)	Baseline	76.67	9.45	73.27	10.67	0.92 (p=.36)
	Post-stim.	68.67	11.56	69.67	9.44	0.26 (p=.80)
SBP	Baseline	118.87	13.86	115.60	12.27	0.66 (p=.52)
	Post-stim.	117.73	22.98	113.67	11.34	0.62 (p=.54)
DBP	Baseline	67.33	9.85	68.93	6.93	0.02 (p=.99)
	Post-stim.	71.93	23.38	66.47	8.55	0.85 (p=.40)

Table 2

Mean Reaction Times in each cue type x congruence condition in Active and Sham tDCS groups.

| | Active tDCS | | Sham tDCS | | |
| | n=15 | | n=15 | | |
	M	SD	M	SD	t(28) =
Central cue congruent	472.5	101	482.6	75.4	0.31, *p* = .76
Central cue incongruent	557.6	84.0	573.6	62.3	0.59, *p* = .59
Double cue congruent	461.3	71.8	471.8	67.0	0.37, *p* = .71
Double cue incongruent	559.0	92.0	603.1	60.0	1.56, *p* = .13
Spatial cue congruent	466.1	82.8	473.7	75.0	0.26, *p* = .79
Spatial cue incongruent	518.6	76.0	533.4	63.4	0.58, *p* = .57
No cue congruent	501.5	89.6	513.3	79.4	0.38, *p* = .71
No cue incongruent	558.2	91.9	597.4	75.5	1.28, *p* = .21
Error Rate	0.04	0.04	0.02	0.02	1.56 (*p*=.13)
Mean RT	462.10	62.57	501.94	48.56	0.88 (*p*=.43)
Attention Network Performance					
Alerting	19.71	23.98	17.90	31.86	0.18 (*p*=.86)
Orienting	22.67	25.66	24.52	27.44	0.19 (*p*=.85)
Executive Control	72.99	21.55	91.51	27.21	2.06 (*p*<.05)
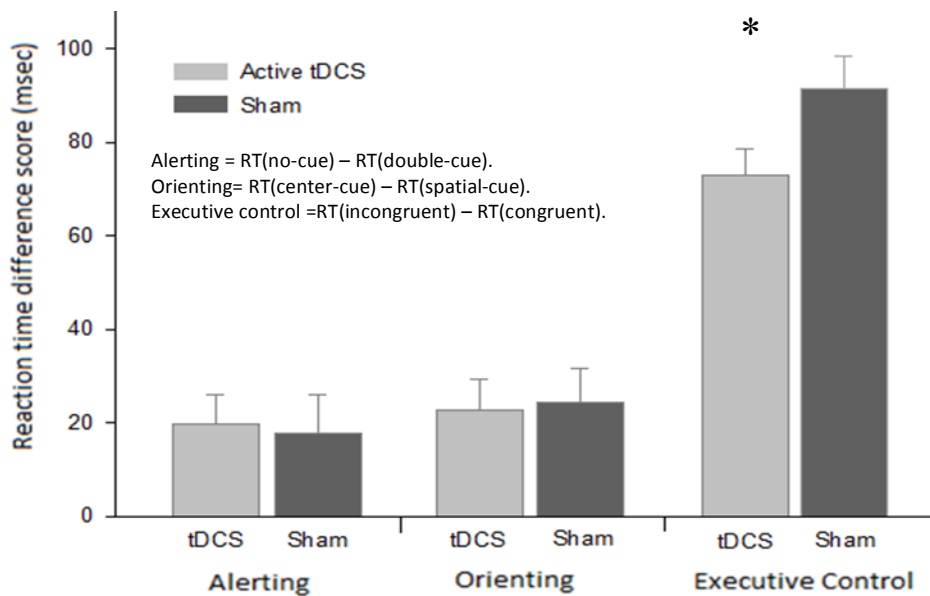
Figure 3 *Selective effect of tDCS vs. sham on executive control.*

Discussion

Executive attention on the ANT was superior following 20 minutes of 2mA anodal tDCS of left DLPFC using a balanced montage, when compared to sham stimulation. These findings support evidence from neuroimaging studies that implicate PFC in executive attention during the ANT (e.g. [2]). The effects of tDCS on executive control complement findings from other studies in healthy volunteers, including evidence that 10 minutes of anodal 1.5 mA tDCS over the pre- supplementary motor area improves inhibitory control in a stop-signal task (vs. cathodal tDCS and no stimulation control; [28]); that 10 minutes of 1 mA left anodal tDCS of DLPFC reduces distraction in a Sternberg memory task; and that anodal tDCS of the left DLPFC enhances computerised attentional bias training towards and away from target stimuli [20] and reduces eye fixation durations to threat [27]. Our findings also extend recent findings from studies that have specifically examined the effect of tDCS on ANT

performance. Roy et al [29] found tDCS of the right parietal cortex increased spatial re-orienting, while tDCS of the other cortical targets (left parietal and dorsolateral) did not modulate alerting nor executive attention control – perhaps reflecting ceiling effects in high functioning healthy participants. Consequently positive effects in our study (and [19,27]) might reflect the higher current intensity and density required to modify attention in healthy adults (2mA vs. 1.5mA in Roy et al [29]).

We did not observe any effects of tDCS on mood or anxiety, consistent with null effects observed in other acute administration tDCS studies (e.g. [30]). Large standard deviations (see table 1) might reflect large individual differences in mood and arousal that mask small effects of tDCS group. We selected short established measures of anxiety, mood and arousal and administered these immediately after stimulation in fixed order (and typically completed within 2 minutes before the ANT commenced). These instruments might lack sensitivity required to detect small changes in mood over time, however it is more likely the evidence to date, together with our own findings, suggest that acute tDCS administration may not achieve reliable changes in mood to the extent seen following repeated administration in clinical groups [e.g.31].We did not include an active control site or low current control condition to test for dose response, and participants were able (when asked) to retrospectively discriminate stimulation condition. The lack of an off-target active control condition (OAS) is a limitation particularly if unsuccessful blinding increases demand characteristics (e.g. increased motivation to perform well). In our study, though demand characteristics cannot be excluded, participants in the active condition did not display significant improvements in global reaction times or error rates in any of the trial types, nor any improvements in mood thus suggesting the effect of anodal tDCS on the executive control occurred independently of mood or motivation. Consequently we offer evidence

that 2mA DLPFC stimulation selectively modulates the executive attention subtest of the ANT. Future research should examine whether the effect of tDCS of DLPFC on executive attention is enhanced during concomitant stimulation (see [32]), repeated administration and higher current density, and whether these positive effects generalise across behavioural measures of executive attention, and varying cognitive loads. Previous studies have used the ANT to reveal deficits in executive attention in anxiety, depression and chronic pain e.g. fibromyalgia (e.g. [33]). Interestingly, recent evidence suggests 20 minutes of anodal tDCS (1mA) over left DLPFC (vs. sham) can selectively improve executive attention and orienting performance in patients with fibromyalgia [34] raising the possibility that our stimulation protocol might improve executive attention deficits in populations characterised by impaired executive attention on the ANT, including patients with mood and anxiety disorders.

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