

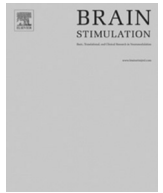
PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/168096>

Please be advised that this information was generated on 2019-03-26 and may be subject to change.



Reduced Affective Biasing of Instrumental Action With tDCS Over the Prefrontal Cortex



Verena Ly ^{a,b,*}, Til O. Bergmann ^{b,c,d,e}, Thomas E. Gladwin ^{a,b,f}, Inge Volman ^{a,b,g},
Niccolo Usberti ^b, Roshan Cools ^{b,h,1}, Karin Roelofs ^{a,b,1}

^a Behavioural Science Institute, Radboud University, 6525 HR Nijmegen, The Netherlands

^b Donders Institute for Brain, Cognition, and Behaviour, Centre for Cognitive Neuroimaging, Radboud University, 6525 EN Nijmegen, The Netherlands

^c Department of Psychology, Christian-Albrechts-University of Kiel, 24118 Kiel, Germany

^d Department of Neurology and Stroke, Hertie Institute for Clinical Brain Research, University of Tübingen, 72076 Tübingen, Germany

^e Institute for Medical Psychology and Behavioral Neurobiology, University of Tübingen, 72076 Tübingen, Germany

^f Research Centre – Military Mental Health, Ministry of Defense, 3584 CX Utrecht, The Netherlands

^g Institute of Neurology, University College London, London WC1N 3BG, United Kingdom

^h Department of Psychiatry, Radboud University Medical Center, 6525 GA Nijmegen, The Netherlands

ARTICLE INFO

Article history:

Received 11 October 2015

Accepted 2 February 2016

Available online 9 February 2016

Keywords:

Transcranial direct current stimulation (tDCS)

Affective biases

Instrumental action

Decision making

Emotion

Prefrontal cortex

ABSTRACT

Background: Instrumental action is well known to be vulnerable to affective value. Excessive transfer of affective value to instrumental action is thought to contribute to psychiatric disorders. The brain region most commonly implicated in overriding such affective biasing of instrumental action is the prefrontal cortex.

Objective: The aim of the present study was to *reduce* affective biasing of instrumental action using transcranial direct current stimulation (tDCS) in young healthy human volunteers.

Methods: In a double-blind, randomized between-group design, 120 participants received anodal, cathodal and sham tDCS while at the same time (online) performing a task that assessed affective biasing of instrumental action. We placed tDCS electrodes over the anterior part of the prefrontal cortex based on evidence from brain stimulation work demonstrating the role of this brain region in controlling affective biasing of instrumental action.

Results: We showed that prefrontal tDCS reduced affective biasing of instrumental action. Specifically, prefrontal tDCS reduced the degree to which aversive (versus appetitive) cues potentiated instrumental avoidance and suppressed instrumental approach. Contrary to our hypothesis, this effect was seen for cathodal tDCS rather than anodal tDCS.

Conclusion: The results demonstrate the potential utility of prefrontal tDCS as a tool for reducing affective biasing of instrumental behavior, thus opening avenues for interventional research on psychiatric disorders that implicate excessive transfer of affective value.

© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Affect is well known to influence instrumental action [1]. Contemporary literature on multiple behavioral control systems suggests that such affective biasing of instrumental action reflect interactions between a Pavlovian or 'affective' system and an instrumental system [2–7]. According to this literature, appetitive and aversive

values can transfer to and interact with an instrumental system, thus biasing our instrumental behavior. Although affective biasing of instrumental action are usually adaptive, they may also corrupt behavior, as illustrated by behavioral anomalies in psychiatric disorders [8,9]. The prefrontal cortex (PFC), a region compromised in a variety of psychiatric disorders [10–12], has been suggested to override affective biasing of instrumental action [13–16]. Causal evidence has been provided by Volman et al. [14], who have shown that inhibiting the anterior PFC using continuous theta burst transcranial magnetic stimulation *increases* affective biasing of rule-based behavior by affective faces. The obvious next step is to establish whether the PFC can be modified to *reduce* affective biasing of behavior, for example for therapeutic purposes.

* Corresponding author. Tel.: +31 6 21597484; fax: +31 24 3610989.

E-mail address: v.ly@donders.ru.nl (V. Ly).

¹ R. Cools and K. Roelofs contributed equally to this work.

The aim of the present study was to assess in a large sample of healthy subjects whether prefrontal transcranial direct current stimulation (tDCS) can be used to *reduce* affective biasing of instrumental action. This noninvasive brain stimulation technique modulates regional neural excitability by delivering a constant low current that shifts the neurons' resting membrane potential toward depolarization or hyperpolarization, depending on montage and polarity (anodal/cathodal) of the electrodes. Therefore, tDCS has the potential for bidirectional polarity dependent modulation such that anodal tDCS increases and cathodal tDCS decreases neural excitability [17]. In a double-blind, randomized between-group design, we assigned participants to one of three stimulation groups: anodal, cathodal, and sham (placebo). Affective biasing of instrumental action was quantified with a modified version of a validated affective decision making task [18]. This task requires participants to perform learned approach/avoidance actions in response to instrumental targets, while being primed by affective (angry/happy) faces. Using a similar task, we have previously demonstrated that instrumental action is biased by affective cues even in young healthy volunteers: angry (versus happy) face-stimuli facilitated instrumental avoidance while inhibiting instrumental approach actions [18].

We predicted bidirectional effects of prefrontal anodal and cathodal tDCS (versus sham) on this affective biasing effect, based on previous studies demonstrating a key role for the PFC in related affective biasing paradigms [14–16]. Thus, given the hypothesis that the PFC can override affective biasing, we anticipated that increasing PFC excitability with anodal tDCS would reduce affective biasing of instrumental action. Conversely, decreasing PFC excitability with cathodal tDCS was anticipated to increase affective biasing of instrumental action.

Materials and methods

Participants

A total of 121 students from the Radboud University were included. One replacement participant was included, due to an error running the experimental task (resulting in $n = 121$), to have a total of 120 complete datasets: 40 per stimulation group (anodal/cathodal/sham). Given the gender differences in the processing of affective faces [19], and to reduce between-subject variability, this study was restricted to women. All participants were healthy with normal or corrected-to-normal visual acuity. Exclusion criteria were regular use of medication (except for contraceptives), use of psychotropic drugs and conditions affecting posture and limb movements (preventing completion of the experimental paradigm, which involved posture/limb movements; see below). Participants were matched across stimulation groups on education level (all received higher level education) and age (in years) ($F_{(2, 117)} = 1.21, p = 0.301$; anodal: $M = 22.3, SD = 2.64$, cathodal: $M = 21.9, SD = 2.53$, sham: $M = 21.4, SD = 2.81$). All participants gave written informed consent and received payment or course credits as a reimbursement for participation. The study was performed in accordance with the Declaration of Helsinki and approved by the local ethical committee (2013/240).

General procedure

Upon arrival, participants were reminded of the experimental procedure. Subsequently, we positioned the tDCS electrodes on the participants' heads and they received instructions for the affective decision making task. Participants completed this task while at the same time (online) receiving anodal, cathodal or sham tDCS that targeted the PFC. Two separate experimenters enabled adherence to a double blind randomized procedure: one of the experim-

ers, blind to the stimulation condition, instructed the participants, whereas the other experimenter applied the stimulation.

Transcranial direct current stimulation

The bilateral prefrontal targets for tDCS were selected based on previous brain stimulation work [14]: two electrodes (each 2 by 3.5 cm, with a split cable, i.e., 14 cm² in total; resulting current density of 0.071 mA/cm² at 1 mA) were placed on the anterior PFC, at the Fp1 and Fp2 positions respectively according to the 10/20 EEG system. The spatial accuracy of the 10/20 system is considered sufficient given the limited spatial resolution of tDCS [20]. A large reference electrode (5 by 10 cm, i.e., 50 cm²) strongly minimizing the current density (0.02 mA/cm² at 1 mA), and thereby the effectiveness of stimulation at the reference site [21], was placed along the midline with its posterior short side above the inion (Fig. 1). This reference electrode location was chosen to maximize frontal-posterior current flow through the anterior PFC by minimizing lateral shunting along the skin [22] and at the same time preventing stimulation of the vestibular system implicated in body balance and equilibrium [23]. Prior to the placement of the electrodes we prepared the participants' scalp with alcohol and abrasive gel to increase conductance. We used conductive rubber electrodes in combination with Ten20 EEG conductive paste (Weaver and Company, Aurora, CO) to ensure optimal fixation and conductance throughout the experiment. tDCS was applied using a battery-driven DC-stimulator system (NeuroConn, Germany). For both tDCS conditions, 1 mA was delivered for 25 minutes with 30 s of each ramping-up and ramping-down. For 'anodal tDCS', the anterior PFC target electrodes were connected as anode and the ineffective reference electrode as cathode. The polarity was reversed for 'cathodal tDCS'. For the sham condition, the anodal configuration was used but was merely ramped-up to 1 mA and ramped-down to 0 mA within the first 60 s to mimic initial skin sensations without any effective stimulation [17]. This manipulation, together with our between-subjects design, ensured that the stimulation protocol remained blind to the participants. A three-choice questionnaire (stimulated, not stimulated, not sure) that was administered at the end of the experiment showed that participants were not aware of the stimulation condition received (chi-square test; $\chi^2_{(4)} = 1.42, p = 0.841$).

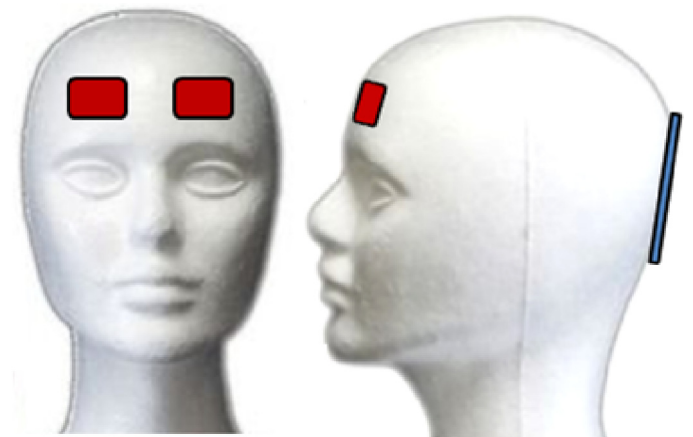


Figure 1. tDCS montage. The anterior PFC (Fp1 and Fp2) was targeted bilaterally with two small electrodes (each 2 by 3.5 cm; anode for 'anodal tDCS', and cathode for 'cathodal tDCS') connected via a split cable, and the reference electrode (cathode for 'anodal tDCS', and anode for 'cathodal tDCS') was placed along the midline with its posterior short side above the inion (5 by 10 cm).

Affective decision making task

The current paradigm was a modified version of a previously employed affective decision making task combined with a balance board [18] (Fig. 2). Analogous to classic Pavlovian-to-instrumental transfer tasks [5], the current version consisted of two separate phases. In the first phase, the instrumental learning phase, participants were required to learn the instrumental responses. The second phase consisted of a transfer phase in extinction (i.e., without reinforcement) with concurrent tDCS, where we assessed the primary effect of interest, affective biasing of instrumental action. The rationale for disentangling instrumental learning from the transfer phase in the current version is to isolate the effects of tDCS on the transfer of affective value to instrumental behavior from the potential influence of tDCS on instrumental learning. The exact procedure per phase is described below.

Instrumental learning phase

This phase consisted of a probabilistic learning task, where participants had to learn to choose between whole body go- and no go-responses by trial and error on the basis of monetary outcome (wins/losses of 0.20€). The task was framed in terms of a gems collecting task. It consisted of two types of blocks with different action-contexts: approach and avoidance action-contexts. The action-context determined the nature of the go-response in a block: approach or avoidance. In the approach action-context, participants had to choose between an (active) approach go-response versus a (passive) approach no go-response upon presentation of the instrumental target (colored shape, representing a gem). Similarly, in the avoidance action-context the choice was between an avoidance go-response versus an avoidance no go-response. Thus, in total, there were four types of instrumental response: approach-go, approach-no go, avoidance-go, avoidance-no go.

On each trial, the instrumental target appeared either on the left or right side of the screen, upon which the participant had to make a go- or no go-response. For the go-responses (approach-go/avoidance-go), participants were instructed to make sideway (not forward/backward) steps toward (approach-go) or away from (avoid-go) the side where the gem was presented to approach or avoid the gem respectively (Fig. 1B [right]). Participants were instructed to remain stationary in the center of the board for a no go-response (approach-no go/avoid-no go).

Go- and no go-responses were equally rewarded by designating the go-response as the optimal response to half of the instrumental targets. In the approach action-context, good gems (targets 1–3) were to be approached, whereas bad gems (targets 4–6) were not. Similarly, bad gems in the avoidance action-context (targets 7–9) were to be avoided, whereas good gems (targets 10–12) were not. As such, the value of the four types of instrumental responses was matched. Participants were informed that correct choices were reinforced probabilistically, but not about the nature of the probabilistic associations ($p(\text{win}|\text{correct}) = 0.70$).

If a go-response had not been made within 2500 ms, a no go-response was recorded. Response feedback in terms of a square turning orange for a go-response; remaining white for a no go-response was provided (500 ms) before the monetary outcome (1000

ms). The intertrial interval was jittered (2500 ± 500 ms). Participants were required to return to their starting position (i.e., the center of the board) at the outcome presentation, if a go-response had been made.

This phase had a total duration of 13 minutes, and consisted of 120 instrumental learning trials divided into 6 blocks. The blocks alternated between approach and avoidance action-contexts, with 3 blocks per action-context, each containing 18, 24, and 18 trials respectively. The instrumental targets (gems) consisted of 12 different colored shapes and were randomly assigned to the two blocks, such that different instrumental stimuli occurred in the two blocks. The order of blocks was randomized across participants. To increase ecological validity and participants' motivation during the experimental task, we told participants that they would receive the total amount of monetary gain as a bonus (on top of the reimbursement).

Transfer phase

This crucial phase enabled us to assess the transfer of affective value to instrumental action. The trial events were the same as in the instrumental learning phase, except for two main differences. First, the instrumental target was preceded by an affective (angry/happy) face-stimulus that was presented centrally on the screen. The presentation duration of this face-stimulus varied between 500 and 3000 ms. Second, this phase was in extinction: monetary outcomes were no longer presented. Participants were instructed that their wins and losses for each trial counted toward their total monetary gain (nominal extinction).

Face-stimuli consisted of adult Caucasian faces from 36 models (18 men) from several databases [24–27]. Each model showed two expressions (angry/happy), matched for brightness and contrast. Faces were trimmed to exclude influence from hair and nonfacial contours [28]. Model identity was pseudo-randomized, such that different models occurred in the different action-contexts, but occurred equally often for each type of instrumental response within an action-context. The allocation of models to action-contexts was randomized across participants and balanced across stimulation condition. This phase had a total duration of approximately 25 minutes, and consisted of 216 test trials divided into 6 blocks. The blocks, each consisting of 36 trials, alternated between approach and avoidance action-context.

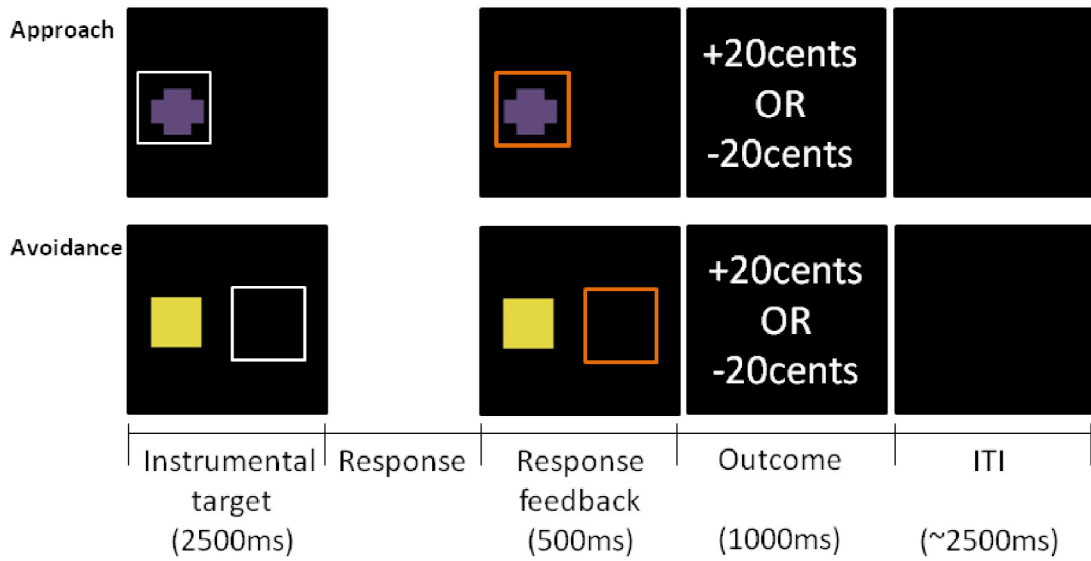
The set-up in this paradigm was the same as in our previous study [18] (Fig. 2B (left)). Participants performed the affective decision making task on a custom-made strain gauge force plate (dimensions: 1 m × 1 m; sampling frequency: 100 Hz), which consisted of four sensors measuring forces in the (vertical) z-direction. To quantify body posture and stepping performance, time series of the center of pressure, for the anterior–posterior and the medio-lateral direction, were derived. Visual stimuli were presented 1 m in front of the participant at eye height on a 22-inch height-adjustable screen.

Data analyses

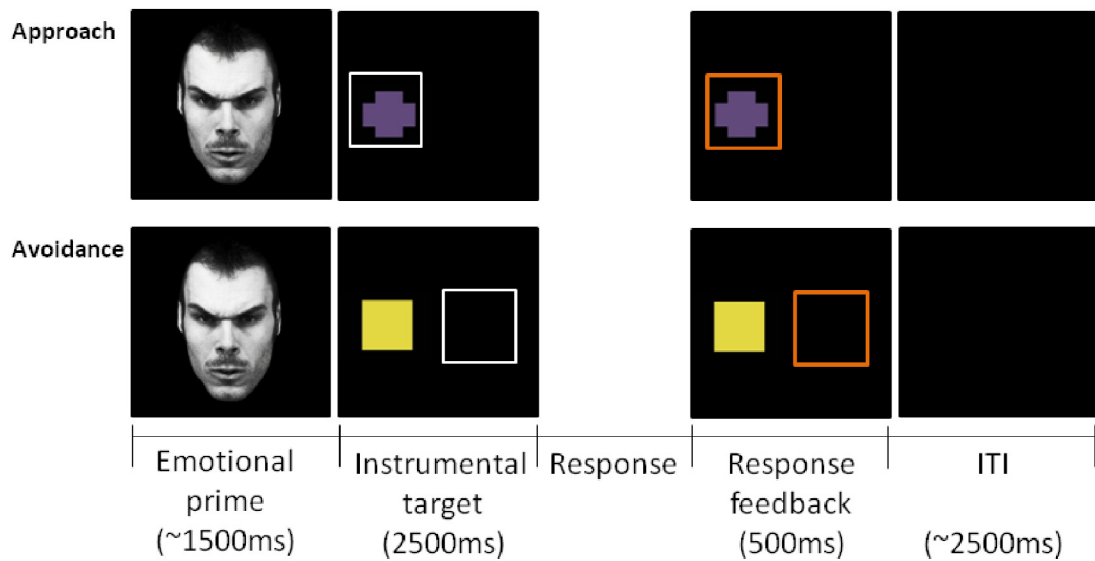
Posturographic data analyses were performed in MATLAB R2009b (The MathWorks, Natick, MA). Statistical analyses were performed using IBM SPSS Statistics 19 (IBM Corp., Armonk, NY). All

Figure 2. (A) Affective decision making task. *Instrumental learning phase*: Trial events from the approach and avoidance block respectively. Upon presentation of the instrumental target, participants were required to make a go- or no go-response within 2500 ms. Response feedback (500 ms) was provided before the monetary outcome (1000 ms). In these examples a go-response had been recorded as indicated by the orange-colored squares during the response feedback phase. The duration of the intertrial interval was 2500 ms on average. *Transfer phase*: Trial events were the same as in the instrumental learning phase, except that the instrumental target was preceded by an affective (angry/happy) face-prime (~1500 ms). (B) Balance board apparatus (left) and examples of a go-response (right) in the approach and the avoidance block respectively. Approach-go: sideway step on the balance board toward the side of the instrumental target. Avoidance-go: sideway step on the balance board away from the side of the instrumental target. Approach-/avoidance-no go-responses involved remaining stationary at the center of the balance board.

A. Instrumental learning phase



Transfer phase



B.



participants complied with the instructions and understood the task as evidenced by the small percentage of errors during the transfer phase ($M_{\text{percentage}} = 0.4$, $SD = 0.6$; range 0–3; an error is defined as making go-responses at the wrong moment or in the wrong direction). Two participants from the cathodal group were excluded from the analyses due to technical errors: (1) displacement of more than 2 cm of the left prefrontal electrode during stimulation; and (2) detachment of the cable from the reference electrode, resulting in abortion of stimulation while performing the task.

The primary analyses that were performed to assess the tDCS effects on the transfer of affective value to instrumental action are described in the following subsection. Additional analyses on the proportion of correct responses (i.e., responses leading to an optimal outcome) were conducted to check whether there was equal (1) performance in terms of accuracy during the instrumental learning phase and (2) generalization of the acquired instrumental responses to the transfer phase between the stimulation groups. All these premises were met (see Supplementary material).

Transfer of affective value to instrumental action

Following our previous study [18], we calculated: (1) the proportion of instrumental go-responses ($P_{\text{go}} = \text{go}/[\text{go} + \text{nogo}]$), and (2) reaction time (RT) of correct instrumental go-responses. Our primary effect measure of interest was the affective bias score, representing affective biasing of instrumental action, and was calculated as follows: (angry_avoidance + happy_approach) minus (angry_approach + happy_avoidance). This effect could be manifested in terms of RT as well as P_{go} [5,18]. Therefore, we computed a composite score of the correct RT and P_{go} [29,30]. To this end, both RT and P_{go} measures were z-scored (RT was reversed so that it indexed speed with higher scores corresponding with vigor), and their sum was divided by 2 to obtain the composite score (Composite = $(-1 * \text{RTz} + P_{\text{goz}})/2$). Subsequently, a mixed design analysis of variance (ANOVA) of the composite scores with affect (angry/happy) \times action-context (approach/avoidance) \times stimulation (anodal/cathodal/sham) was performed. Finally, follow up analyses were performed for RT and P_{go} separately to test whether any significant effects in terms of the composite score were driven by RT and/or P_{go} . The calculation of the composite score and all the following analyses were performed after exclusion of subjects that represented outliers on the basis of the affective bias score in terms of RT and P_{go} . These subjects showed a bias score >3 SD from the mean and influenced the assumptions for parametric tests (Shapiro–Wilks, $p < 0.001$). Age was still comparable between the stimulation groups in this remaining sample (anodal: $n = 36$; cathodal: $n = 34$; sham: $n = 35$; $F_{(2,102)} = 0.886$, $p = 0.415$). For completeness, we also performed an additional nonparametric Kruskal–Wallis test for multiple independent-samples across the whole sample including the outliers. The result of this additional analysis is described in detail

in the Supplementary material and is comparable with the results from the parametric tests.

For all analyses, significant interaction effects were followed up by simple (interaction) effects analyses. Alpha was set at 0.05.

Results

Effects of tDCS on transfer of affective value to instrumental action

Table 1 shows the raw mean data of the transfer phase of the affective decision making task in terms of RT, P_{go} , and composite scores. As expected, prefrontal tDCS reduced affective biasing of instrumental action. An ANOVA of the composite score revealed a significant affect (angry/happy) \times action-context (approach/avoidance) \times stimulation (anodal/cathodal/sham) interaction ($F_{(2,102)} = 5.53$, $p = 0.005$, $\eta_p^2 = 0.08$). However, contrary to our expectations this interaction was driven by the effect of cathodal stimulation (cathodal versus sham: $F_{(1,67)} = 10.35$, $p = 0.002$, $\eta_p^2 = 0.134$; cathodal versus anodal: $F_{(1,68)} = 6.17$, $p = 0.015$, $\eta_p^2 = 0.083$), but not anodal stimulation (anodal versus sham: $F_{(1,69)} = 1.07$, $p = 0.305$, $\eta_p^2 = 0.015$). Consistently, follow up analyses within the stimulation groups revealed significant affective biasing effects in sham and anodal stimulation (affect \times action-context interaction; $F_{(1,34)} = 8.57$, $p = 0.006$, $\eta_p^2 = 0.201$, and $F_{(1,35)} = 4.23$, $p = 0.047$, $\eta_p^2 = 0.108$ respectively) but not in cathodal stimulation ($F_{(1,33)} = 2.06$, $p = 0.161$, $\eta_p^2 = 0.059$). Specifically, angry (versus happy) faces potentiated avoidance (versus approach) actions in sham and anodal, but not in cathodal stimulation. A main effect of action-context in the main ANOVA indicated a go-bias (increased vigor) in the approach versus avoidance action-context ($F_{(1,102)} = 29.5$, $p < 0.001$, $\eta_p^2 = 0.224$).

Follow up analyses showed that the cathodal effects on affective biasing were mainly driven by RT, and not by P_{go} (affect \times action \times stimulation; RT: $F_{(2,102)} = 5.39$, $p = 0.006$, $\eta_p^2 = 0.095$; P_{go} : $F_{(2,102)} = 0.49$, $p = 0.613$, $\eta_p^2 = 0.010$). In line with the analyses above, cathodal tDCS reduced affective biasing of instrumental action in terms of RT compared with sham ($F_{(1,67)} = 9.89$, $p = 0.002$, $\eta_p^2 = 0.129$); other comparisons between stimulation groups were not significant ($F < 3.10$, $p > 0.083$) (Fig. 3). The affective biasing of instrumental action in terms of RT was significant in the sham group ($F_{(1,34)} = 12.82$, $p < 0.001$, $\eta_p^2 = 0.274$), but not in the cathodal group ($F_{(1,33)} = 0.710$, $p = 0.405$, $\eta_p^2 = 0.021$). Affective biasing of instrumental action in terms of RT in the anodal group did not reach significance ($F_{(1,35)} = 2.26$, $p = 0.142$, $\eta_p^2 = 0.061$). To further explore whether the cathodal tDCS effects on affective biasing of instrumental action depended on time, we ran the same ANOVA of RT including time as a within-subject factor (transfer phase blocks: T1/T2/T3). There was no interaction effect of time (affect \times action-context \times time \times stimulation; $F_{(1,102)} = 0.29$, $p = 0.886$, $\eta_p^2 = 0.006$). For the cathodal versus sham comparison only, there

Table 1

Raw mean data on the transfer phase of the affective decision making task.

	Reaction time (ms)		Proportion go (%)		Composite z-score	
	Approach	Avoidance	Approach	Avoidance	Approach	Avoidance
Anodal (N = 36)						
Angry	980(27)	1047(29)	54.6(1.5)	52.1(2.0)	0.17(0.13)	-0.15(0.13)
Happy	976(28)	1065(31)	55.1(1.5)	51.9(2.2)	0.21(0.13)	-0.21(0.14)
Cathodal (N = 34)						
Angry	940(21)	1060(27)	56.2(1.8)	52.7(2.0)	0.37(0.11)	-0.16(0.14)
Happy	954(24)	1059(27)	55.3(1.9)	52.1(2.1)	0.28(0.12)	-0.18(0.14)
Sham (N = 35)						
Angry	1020(29)	1077(26)	55.5(1.5)	51.9(1.9)	0.09(0.12)	-0.25(0.13)
Happy	976(27)	1097(26)	54.7(1.5)	51.0(1.8)	0.19(0.11)	-0.35(0.13)

Values represent the means (SEM) of reaction times, proportion of go responses, and an overall score indexing the ability of making the response (composite z-scores of the reaction time and proportion go).

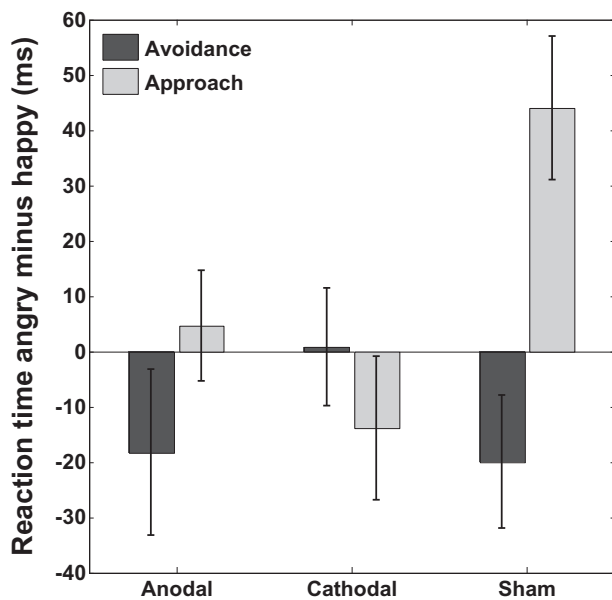


Figure 3. Affective biasing of instrumental action in terms of reaction time for anodal, cathodal and sham tDCS separately. Cathodal (versus sham) tDCS showed reduced degree to which angry (versus happy) faces potentiate avoidance (versus approach) actions, indicating that cathodal tDCS reduced transfer of affective value to instrumental action. Error bars represent standard error of the mean.

was no interaction effect of time either ($F_{(2,66)} = 0.21$, $p = 0.810$, $\eta_p^2 = 0.810$).

Taken together, these results suggest that cathodal tDCS rather than anodal tDCS reduced the transfer of affective value to instrumental action.

Discussion

The main aim of the current study was to assess whether affective biasing of instrumental action can be reduced using prefrontal tDCS. To this end we compared the effects of prefrontal anodal, cathodal and sham tDCS on a task that enables assessment of affective biasing of instrumental action by affective face-stimuli in a double-blind, randomized between-group design. Our data demonstrate that affective biasing of instrumental action can indeed be reduced using prefrontal tDCS, and thus extend previous findings of increased affective biasing of action due to prefrontal brain stimulation [14].

The current finding is particularly relevant in light of psychiatric conditions that are characterized by excessive transfer of affective value to instrumental action [9,31], such as impulse control disorders and addictive disorders [32,33]. This finding opens avenues to start exploring tDCS's effect in these psychiatric conditions. For example, it would be interesting to assess whether tDCS can boost treatment effects in these psychiatric disorders. This is particularly of clinical interest considering the potential of tDCS as a tool for targeting the PFC as opposed to other brain stimulation techniques, such as transcranial magnetic stimulation; tDCS is relatively easy to apply, low in cost and relatively painless.

The mechanisms of the current tDCS effects remain unclear. We describe at least three potential mechanisms below. In contrast with our main prediction, the reduction of affective biasing was obtained with cathodal rather than anodal tDCS. The observation that prefrontal cathodal (rather than anodal) tDCS abolished the transfer of affective value to instrumental action is remarkable given previous work showing that the PFC is involved in instrumental

control and overriding affective biases [13–16,34,35]. Based on these previous findings, we expected to find the opposite – an increase in affective biasing – for cathodal stimulation, which has been suggested to reduce excitability [17]. However, we should also highlight studies that show an important role of PFC regions in Pavlovian-instrumental interactions [36–38]. Indeed, regions of the PFC have been suggested to serve as cognitive control regions by supporting the convergence of disparate information through local connections and interconnections with other brain structures, thereby orchestrating complex behavior, including affective biasing of action [39–42]. Recent findings suggest that, for instance, the ventromedial PFC may function as a hub that integrates input from different systems for value computation, and translates these signals into affective behavior [4,43–45]. Thus, one possibility is that prefrontal cathodal tDCS decreased excitability in neural populations crucial for the integration of Pavlovian and instrumental signals: reduced integration of the affective value from the affective faces at the moment of decision may thus have resulted in decreased biasing of instrumental action by affective value.

Alternatively, the observed effects reflect a paradoxical potentiation of instrumental control per se. Instead of decreasing neural excitability, cathodal tDCS might have paradoxically increased the neural excitability in the targeted brain region. The dichotomy between anode-excitatory and cathode-inhibitory may be an oversimplification of the tDCS mechanisms, and has not been established outside the motor cortex [46]. Moreover, prior work has demonstrated that inhibitory effects of cathodal stimulation can reverse depending on the timing, duration and intensity of stimulation [47,48]. For instance, it has been shown that cathodal tDCS effects (2 mA for 20 min) resembled effects of anodal tDCS and enhanced cortical excitability, whereas cathodal tDCS with lower intensity (1 mA) for the same duration resulted in decreased excitability [47]. However, the fact that we did not observe an effect of anodal tDCS suggests that a different mechanism may underlie the current cathodal effects. In future work, multi-modal imaging methods could be combined with independent measures of goal-directed instrumental control to disentangle the two hypotheses regarding the mechanistic basis of the observed effect of cathodal tDCS.

It is unlikely that cathodal tDCS reduced affective biasing by altering other cognitive functions associated with the PFC, such as attention to the instrumental targets or to the affective faces [49,50]. If cathodal tDCS would have impacted attentional processes, we would have expected reduced accuracy levels. However, we did not observe an effect of tDCS on accuracy in the transfer phase and the transition between the instrumental learning and the transfer phase (see Supplementary material). The lack of these effects suggests that cathodal tDCS did not alter the processing of the instrumental targets themselves.

It is important to note that caution is warranted when ascribing the effects of cathodal tDCS to the modulation of excitability in a specific region of the PFC. Indeed given the complexity and size of the current experiment, we opted not to include yet another stimulation condition to control for anatomical specificity within the PFC. Additionally, we cannot rule out the possibility that prefrontal cathodal tDCS influenced excitability in remote, yet interconnected subcortical areas, such as in the striatum and midbrain [51–54]; these areas are also associated with affective processing and affective modulation of instrumental behavior [3,38,55]. In line with previous suggestions [56–58], we suggest that considerable work is necessary to establish the precise mechanism underlying the effect of our cathodal tDCS protocol.

Taken together, our results demonstrate the potential utility of prefrontal tDCS as a tool for reducing affective biasing of instrumental behavior. Our finding that prefrontal cathodal tDCS abolishes affective biasing of instrumental action strengthens the hypothesis that the PFC plays a crucial role in regulating interactions between

distinct Pavlovian and instrumental control systems [14–16,36,37]. However, unlike prior work [14–16], the present finding raises the possibility that the role of the PFC is not restricted to overriding Pavlovian biases, but extends to promoting synergism between Pavlovian and instrumental systems. Accordingly, the present findings represent an important step in inspiring future research into the mechanisms by which the PFC contributes to regulating affective biases. Finally, given the relevance of enhancing optimal decisions in society and clinical practice, future research, for instance using multi-modal imaging methods to specify the underlying mechanism of the current findings, may have significant theoretical and practical implications.

Authorship

All authors contributed to the study concept and design. V. Ly and N. Usberti were responsible for data-acquisition. V. Ly analyzed and interpreted the data under the supervision of K. Roelofs and R. Cools. V. Ly drafted the manuscript under supervision of R. Cools and K. Roelofs and all others provided critical revisions. All authors approved the final version of the paper prior to submission.

Acknowledgements

This study was supported by the Mosaic grant #017.007.043 from the Netherlands Organization for Scientific Research (NWO) awarded to V. Ly; a starting grant ERC_StG2012_313749 from the European Research Council (ERC) and a VICI grant #453-12-001 (NWO) awarded to K. Roelofs; and a James McDonnell Scholar Award awarded to R. Cools.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.brs.2016.02.002.

References

- Damasio AR. Neuropsychology. Towards a neuropathology of emotion and mood. *Nature* 1997;386:769–70. doi:10.1038/386769a0.
- Dickinson A, Balleine B. Motivational control of goal-directed action. *Anim Learn Behav* 1994;22:1–18. doi:10.3758/BF03199951.
- Cardinal RN, Parkinson JA, Hall J, Everitt BJ. Emotion and motivation the role of the amygdala, ventral striatum, and prefrontal cortex. *Neurosci Biobehav Rev* 2002;26.
- Rangel A, Camerer C, Montague PR. A framework for studying the neurobiology of value-based decision making. *Nat Rev Neurosci* 2008;9:545–56. doi:10.1038/nrn2357.
- Huys QJM, Cools R, Gölzer M, Friedel E, Heinz A, Dolan RJ, et al. Disentangling the roles of approach, activation and valence in instrumental and Pavlovian responding. *PLoS Comput Biol* 2011;7:doi:10.1371/journal.pcbi.1002028.
- Dolan RJ, Dayan P. Goals and habits in the brain. *Neuron* 2013;80:312–25. doi:10.1016/j.neuron.2013.09.007.
- Guitart-Masip M, Duzel E, Dolan R, Dayan P. Action versus valence in decision making. *Trends Cogn Sci* 2014;18:194–202. doi:10.1016/j.tics.2014.01.003.
- Boureau Y-L, Dayan P. Opponency revisited: competition and cooperation between dopamine and serotonin. *Neuropsychopharmacology* 2011;36:74–97. doi:10.1038/npp.2010.151.
- Seymour B, Dolan R. Emotion, decision making, and the amygdala. *Neuron* 2008;58:662–71. doi:10.1016/j.neuron.2008.05.020.
- Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci U S A* 2007;104:19649–54. doi:10.1073/pnas.0707741104.
- Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci* 2011;12:652–69. doi:10.1038/nrn3119.
- Koenigs M, Kruepke M, Newman JP. Economic decision-making in psychopathy: a comparison with ventromedial prefrontal lesion patients. *Neuropsychologia* 2011;48:2198–204. doi:10.1016/j.neuropsychologia.2010.04.012. NIH Public Access.
- Balleine BW, O'Doherty JP. Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology* 2010;35:48–69. doi:10.1038/npp.2009.131.
- Volman I, Roelofs K, Koch S, Verhagen L, Toni I. Anterior prefrontal cortex inhibition impairs control over social emotional actions. *Curr Biol* 2011;21:1766–70. doi:10.1016/j.cub.2011.08.050.
- Guitart-Masip M, Huys QJM, Fuentemilla L, Dayan P, Duzel E, Dolan RJ. Go and no-go learning in reward and punishment: interactions between affect and effect. *Neuroimage* 2012;62:154–66. doi:10.1016/j.neuroimage.2012.04.024.
- Cavanagh JF, Eisenberg I, Guitart-Masip M, Huys Q, Frank MJ. Frontal theta overrides Pavlovian learning biases. *J Neurosci* 2013;33:8541–8. doi:10.1523/JNEUROSCI.5754-12.2013.
- Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 2000;527(Pt 3):633–9. doi:10.1111/j.1469-7793.2000.t01-1-00633.x.
- Ly V, Huys QJM, Stins JF, Roelofs K, Cools R. Individual differences in bodily freezing predict emotional biases in decision making. *Front Behav Neurosci* 2014;8:1–9.
- Rotter NG, Rotter GS. Sex differences in the encoding and decoding of negative facial emotions. *J Nonverbal Behav* 1988;12:139–48. doi:10.1007/BF00986931.
- Herwig U, Satrapi P, Schonfeldt-Lecuona C. Using the international 10–20 EEG system for positioning of transcranial magnetic stimulation. *Brain Topogr* 2003;16:95–9.
- Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: state of the art 2008. *Brain Stimul* 2008;1:206–23. doi:10.1016/j.brs.2008.06.004.
- Nitsche MA, Doemkes S, Karaköse T, Antal A, Liebetanz D, Lang N, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. *J Neurophysiol* 2007;97:3109–17. doi:10.1152/jn.01312.2006.
- Fitzpatrick RC, Day BL. Probing the human vestibular system with galvanic stimulation. *J Appl Physiol* 2004;96:2301–16. doi:10.1152/japplphysiol.00008.2004.
- Ekman P, Friesen W. Pictures of facial affect. Palo Alto, CA: Consulting Psychologist Press; 1976.
- Matsumoto D, Ekman P. Japanese and Caucasian facial expressions of emotion (JACFEE) [slides]. San Francisco, CA: University of California, Human Interaction Laboratory; 1988.
- Martinez A, Benavente R. The AR face database. CVC Technical Report No. 24. 1998.
- Lundqvist D, Flykt A, Ohman A. The Karolinska direct emotional faces (KDEF) [CD ROM]. Sweden: Department of Clinical Neuroscience, Section of Psychology, Karolinska Institute; 1998.
- Van Peer JM, Roelofs K, Rotteveel M, van Dijk JG, Spinhoven P, Ridderinkhof KR. The effects of cortisol administration on approach-avoidance behavior: an event-related potential study. *Biol Psychol* 2007;76:135–46. doi:10.1016/j.biopsycho.2007.07.003.
- Aarts E, Nusslein AA, Smittenaar P, Helmich RC, Bloem BR, Cools R. Greater striatal responses to medication in Parkinson's disease are associated with better task-switching but worse reward performance. *Neuropsychologia* 2014;1–8:doi:10.1016/j.neuropsychologia.2014.05.023.
- Ackerman PL, Cianciolo AT. Cognitive, perceptual-speed, and psychomotor determinants of individual differences during skill acquisition. *J Exp Psychol Appl* 2000;6:259–90.
- Dayan P, Seymour B. Values and actions in aversion. *Neuroeconomics* 2009;175–91. doi:10.1016/B978-0-12-374176-9.00012-9.
- Garofalo S, di Pellegrino G. Individual differences in the influence of task-irrelevant Pavlovian cues on human behavior. *Front Behav Neurosci* 2015;9:1–11. doi:10.3389/fnbeh.2015.00163.
- Everitt BJ, Dickinson A, Robbins TW. The neuropsychological basis of addictive behaviour. *Brain Res Rev* 2001;36:129–38. <http://dx.doi.org/10.1016/S0165-0173(01)00088-1>.
- Balleine BW, Dickinson A. Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. *Neuropharmacology* 1998;37:407–19. doi:10.1016/S0028-3908(98)00033-1.
- Valentin V V, Dickinson A, O'Doherty JP. Determining the neural substrates of goal-directed learning in the human brain. *J Neurosci* 2007;27:4019–26. doi:10.1523/JNEUROSCI.0564-07.2007.
- Homayoun H, Moghaddam B. Differential representation of Pavlovian-instrumental transfer by prefrontal cortex subregions and striatum. *Eur J Neurosci* 2009;29:1461–76. doi:10.1111/j.1460-9568.2009.06679.x.
- Balleine BW, Leung BK, Ostlund SB. The orbitofrontal cortex, predicted value, and choice. *Ann N Y Acad Sci* 2011;1239:43–50. doi:10.1111/j.1749-6632.2011.06270.x.
- Geurts DE, Huys QJ, den Ouden HE, Cools R. Aversive Pavlovian control of instrumental behavior in humans. *J Cogn Neurosci* 2013;1428–41. doi:10.1162/jocn_a_00425.
- Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci* 2001;24:167–202.
- Watanabe M, Sakagami M. Integration of cognitive and motivational context information in the primate prefrontal cortex. *Cereb Cortex* 2007;17:101–9. doi:10.1093/cercor/bhm067.
- Groenewegen HJ, Uylings HBM. The prefrontal cortex and the integration of sensory, limbic and autonomic information. In: Research BT-P in B, editor. Cognition, emotion and autonomic responses: The integrative role of the

- prefrontal cortex and limbic structures, vol. 126. Amsterdam, The Netherlands: Elsevier; 2000. p. 3–28 <[http://dx.doi.org/10.1016/S0079-6123\(00\)26003-2](http://dx.doi.org/10.1016/S0079-6123(00)26003-2)>.
- [42] Gray JR, Braver TS, Raichle ME. Integration of emotion and cognition in the lateral prefrontal cortex. *Proc Natl Acad Sci U S A* 2002;99:4115–20. doi:10.1073/pnas.062381899.
- [43] Kable JW, Glimcher PW. The neural correlates of subjective value during intertemporal choice. *Nat Neurosci* 2007;10:1625–33. doi:10.1038/nn2007.
- [44] Roy M, Shohamy D, Wager TD. Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends Cogn Sci* 2012;16:147–56. doi:10.1016/j.tics.2012.01.005.
- [45] Wunderlich K, Dayan P, Dolan RJ. Mapping value based planning and extensively trained choice in the human brain. *Nat Neurosci* 2012;15:786–91.
- [46] Horvath JC, Forte JD, Carter O. Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review. *Neuropsychologia* 2014;doi:10.1016/j.neuropsychologia.2014.11.021.
- [47] Batsikadze G, Moliadze V, Paulus W, Kuo M-F, Nitsche MA. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *J Physiol* 2013;591:1987–2000. doi:10.1113/jphysiol.2012.249730.
- [48] Pirulli C, Fertonani A, Miniussi C. Is neural hyperpolarization by cathodal stimulation always detrimental at the behavioral level? *Front Behav Neurosci* 2014;8:226. doi:10.3389/fnbeh.2014.00226.
- [49] Daffner KR, Mesulam MM, Scinto LF, Acar D, Calvo V, Faust R, et al. The central role of the prefrontal cortex in directing attention to novel events. *Brain* 2000;123(Pt 5):927–39. doi:10.1093/brain/123.5.927.
- [50] Asplund CL, Todd JJ, Snyder AP, Marois R. A central role for the lateral prefrontal cortex in goal-directed and stimulus-driven attention. *Nat Neurosci* 2010;13:507–12. doi:10.1038/nn.2509.A.
- [51] Takano Y, Yokawa T, Masuda A, Niimi J, Tanaka S, Hironaka N. A rat model for measuring the effectiveness of transcranial direct current stimulation using fMRI. *Neurosci Lett* 2011;491:40–3. doi:10.1016/j.neulet.2011.01.004.
- [52] Chib VS, Yun K, Takahashi H, Shimojo S. Noninvasive remote activation of the ventral midbrain by transcranial direct current stimulation of prefrontal cortex. *Transl Psychiatry* 2013;3:e268. doi:10.1038/tp.2013.44.
- [53] Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J Neurosci* 2001;21:1–4.
- [54] Van Schouwenburg MR, O'Shea J, Mars RB, Rushworth MFS, Cools R. Controlling human striatal cognitive function via the frontal cortex. *J Neurosci* 2012;32:5631–7. doi:10.1523/JNEUROSCI.6428-11.2012.
- [55] Talmi D, Seymour B, Dayan P, Dolan RJ. Human Pavlovian-instrumental transfer. *J Neurosci* 2008;28:360–8. doi:10.1523/JNEUROSCI.4028-07.2008.
- [56] Bestmann S, Feredoes E. Combined neurostimulation and neuroimaging in cognitive neuroscience: past, present, and future. *Ann N Y Acad Sci* 2013;1296:11–30. doi:10.1111/nyas.12110.
- [57] Bikson M, Rahman A, Datta A. Computational models of transcranial direct current stimulation. *Clin EEG Neurosci* 2012;43:176–83. doi:10.1177/1550059412445138.
- [58] Bestmann S, de Berker AO, Bonaiuto J. Understanding the behavioural consequences of noninvasive brain stimulation. *Trends Cogn Sci* 2015;19:13–20. doi:10.1016/j.tics.2014.10.003.