Modulation of cue-guided choices by transcranial direct current stimulation

Garofalo, S., Battaglia, S., Starita, F., & di Pellegrino, G. (2021). Modulation of cue-guided choices by transcranial direct current stimulation. *Cortex*, *137*, 124–137.

https://doi.org/10.1016/j.cortex.2021.01.004

Modulation of cue-guided choices by transcranial direct current stimulation

Sara Garofalo[1*], Simone Battaglia[1], Francesca Starita[1], and Giuseppe di Pellegrino[1]

[1]Department of Psychology, University of Bologna, Cesena, Italy

* Corresponding author:
Sara Garofalo
Department of Psychology, University of Bologna
Piazza Aldo Moro, 90
47521, Cesena (FC), Italy
sara.garofalo@unibo.it

Abstract

Environmental cues may anticipate the availability of rewards, thus acting as a guide towards a specific choice (i.e. cue-guided choices). Despite the lateral prefrontal cortex having a critical role in using past learning and flexibly selecting relevant information to guide behavior, the literature on the neural basis of human cue-guided choice mainly focused on the subcortical brain structures implicated, while the specific role of cortical areas remained unclear. The present study aimed to provide causal evidence for the involvement of the lateral prefrontal cortex in two forms of human cue-guided choice, namely outcome-specific and general. To do this, 2 mA cathodal, anodal or sham transcranial direct current stimulation was applied over the lateral prefrontal cortex (with the posterior parietal cortex serving as control region) in three separate groups performing a Pavlovian-to-Instrumental Transfer task. Results showed, for the first time, a dissociation in the cortical structures involved in human cue-guided choice. Cathodal stimulation of the lateral prefrontal cortex reduced the outcome-specific transfer. In striking contrast, there was no influence on the general transfer. These results argue in favor of the presence of at least two possible neural pathways underlying cue-guided choices.

Keywords: Cue-guided choice; lateral prefrontal cortex; Pavlovian-to-Instrumental Transfer; tDCS.

Introduction

Environmental cues - like a logo or a jingle – can be powerful modulators of choice, even when apparently irrelevant (Doya, 2008; Miller, 2000). In fact, they can anticipate the presence of associated rewards or punishments and guide action to obtain or avoid them. For example, as we are walking to an appointment, seeing the logo of a fast-food diner may remind us that we are hungry, or even lead us through the diner's door to buy food. These can be defined as cue-guided choices and they come in two forms. In the sensory-specific form, a reward-associated cue activates the sensory-specific features of the reward, thus triggering the action associated with that specific reward (Corbit & Balleine, 2011, 2015). In the general form, a reward-associated cue can produce a general increase in motivation, biasing choice towards different kinds of rewards that share the same appetitive value. For example, the presence of a cue predicting the delivery of dark chocolate can either increase actions to obtain precisely dark chocolate (outcome-specific form) or any kind of food (general form). In this sense, the first one may be intended as a sensory-motor bias mediated by the specific sensory properties of the outcome, while the second one as a bias on choice based on the general value of the outcome (e.g., appetitive or aversive).

Cue-guided choices are often intended as automatic and possibly maladaptive, in that they can lead to an inflexible association when a response is perseverated in absence of a reward or despite its negative consequence, as observed in compulsive or addictive conducts (Dolan & Dayan, 2013; Everitt & Robbins, 2016; Hogarth et al., 2010; Holland, 2004; Watson et al., 2014). Nevertheless, environmental cues can also provide useful information to strategically guide behavior according to the context (Lee et al., 2007). In doing so, a number of value computations need to be performed by different areas of the brain (Kennerley & Walton, 2011). Former studies mainly focused on the role of limbic and basal ganglia structures (Bray et al., 2008; Mendelsohn et al., 2014; Prévost et al., 2012; Talmi et al., 2008; van Steenbergen et al., 2017), which may be only a part of the broader neural network involved in cue-guided choice, also comprising cortical structures like medial and lateral prefrontal regions (Cavanagh et al., 2013; Guitart-Masip et al., 2012; Hayashi et al., 2013; Swart et al., 2018). These studies highlighted the presence of neural (Bray et al., 2008; Garofalo et al., 2017; Lewis et al., 2013; Morris et al., 2015; Prévost et al., 2012; Talmi et al., 2008) - as well as behavioral (Garofalo et al., 2019, 2020; Garofalo & di Pellegrino, 2015, 2017; Garofalo & Robbins, 2017) - dissociations between general and outcome-specific cue guided choice (Corbit & Balleine, 2005; Dolan & Dayan, 2013; Garofalo et al., 2019, 2020; Garofalo & di Pellegrino, 2017; Garofalo & Robbins, 2017). Notably, the limbic system and the basal ganglia are strongly interconnected with the prefrontal cortex and exchange relevant information for decision-making (Alexander & Crutcher, 1990; Haber et al., 2006; Jarbo & Verstynen, 2015; Makino et al., 2016; Moustafa et al., 2013; van Holstein et al., 2018). The lateral prefrontal cortex (comprising both ventral and dorsal parts), in particular, is primarily involved when contextual information is used to guide behavior and to resolve uncertainty about stimulus-response contingencies (Battaglia et al., 2018; Huettel et al., 2005; Kennerley & Walton, 2011; Lee et al., 2007; Miller, 2000; Miller & Cohen, 2001; Xue et al., 2012). More specifically, information from the basal ganglia to the prefrontal cortex, via the thalamus, is known to be at the core of the formation of dedicated sensory-motor pathways linking together sensorial information and motor action (Makino et al., 2016). Based on this evidence, we argue that sensory-specific cue-guided choice is likely to rely on the lateral prefrontal cortex for the active

maintenance of a detailed representation of the sensory properties of each choice-reward pairing elicited by the cue which are, in turn, used to direct choice. In line with this, previous studies showed that high-level cognitive abilities, such as working memory (Garofalo et al., 2019), and supraliminal (vs subliminal) presentation of the reward-associated cue (Garofalo et al., 2020) are crucial for the expression of outcome specific, but not general transfer. In contrast, such area may not be as crucial for the general form of cue-guided choices which results from an increase in motivation towards obtaining any reward, and may rather rely on subcortical areas (Corbit & Balleine, 2015; Dolan & Dayan, 2013; Holland, 2004). However, which cortical structures mediate cue-guided choice in humans remains elusive and the specific role of the lateral prefrontal cortex unclear.

The present study aims to provide causal evidence for the involvement of the lateral prefrontal cortex in human cue-guided choice, anticipating a causal role of this area in the sensory-specific, but not in the general form. To test this hypothesis, participants completed a Pavlovian-to-Instrumental Transfer (PIT) task. Following instrumental and Pavlovian learning, this task enables to observe the biasing effect of reward-associated Pavlovian cues on instrumental responses (i.e. transfer effect) to obtain the exact same reward (also sharing the sensory properties, i.e. outcome-specific transfer) or a motivationally similar reward (sharing the same appetitive value, i.e. general transfer) associated with the cue. Three groups of participants received 2 mA cathodal, anodal, or sham transcranial direct current stimulation (tDCS) over the lateral prefrontal cortex before the transfer phase of the PIT task. Given the different nature of the two forms of transfer, we anticipated an effect of tDCS on outcome-specific transfer, rather than general transfer. Specifically, we expected cathodal stimulation to interfere with the outcome representation needed to guide choice, thus reducing the biasing effect of Pavlovian cues in outcome-specific transfer. Given the strong imbalance between congruent and incongruent responses normally observed in this task, we did not expect anodal stimulation to increase outcome-specific transfer due to a possible ceiling effect. Thus, rather than testing polarity-specific effects, the "anodal" condition was actually designed to test the effects of cathodal tDCS above a control (parietal) region (details in methodology section).

Methods

We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

Participants

Sixty-four participants took part in the study. Four participants did not complete the task due to intolerance to tDCS. Thus, sixty participants were included in the study sample. Participants were randomly assigned to receive either active cathodal stimulation over the left lateral prefrontal cortex (cathodal group: n=20, 10 females, age in years M=22.70, SD=2.27, education in years M=15.15, SD=1.75), active anodal stimulation over the left prefrontal cortex (anodal group: n=20, 10 females, age in years M=22.85, SD=2.01; education in years M=15.50, SD=1.88) or sham stimulation (sham group: n=20, 10 females, age in years M=23.45, SD=2.85; education in years M=15.60, SD=1.93). Groups did not differ on age or years of education (One-Way ANOVA, all $p \geq 0.583$). Additionally,

since previous evidence found a relationship between working memory and outcome-specific transfer (Garofalo et al., 2019), the groups were compared on working memory capacity as measured by the Automated Operational SPAN task (Unsworth et al., 2005) performed before the experimental task. The statistical analysis showed no difference between the groups (one-way ANOVA, $p=0.58$, $N = 54$). Participants had a normal or corrected-to-normal vision and were screened for any contraindications to non-invasive brain stimulation (Brunoni et al., 2011) using the questionnaire developed by Rossi and colleagues (Rossi et al., 2009). No participant was on medication at the time of the experiment or reported a history of neurological or psychiatric disorders. All participants gave informed written consent to participate after being informed about the procedure of the study. All participants were naïve to the purposes of the study. The study was approved by the University of Bologna Bioethics Committee and conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki (World Health Organisation, 2013).

Pavlovian-to-Instrumental Transfer task

The task included three consecutive phases and mirrored the structure used in previous studies (Bray et al., 2008; Garofalo et al., 2019; Garofalo & di Pellegrino, 2015; Garofalo & Robbins, 2017; Prévost et al., 2012; Talmi et al., 2008): (1) Instrumental training, in which participants learned a response-contingent reward or no-reward outcome; (2) Pavlovian training, in which participants learned a cue-contingent reward or no-reward outcome; (3) Transfer test, during which the influence of task-irrelevant Pavlovian cues on instrumental responding was tested. During the task, the participant was invited to perform as many responses as possible to collect more rewards. Nevertheless, at the end of the task, participants received the same amount of reward, irrespective of their performance.

A computer running OpenSesame software (Mathôt et al., 2012) controlled stimulus presentation. The same visual settings were used in all three phases (see Fig. 1). Five black squares (4 cm^2) surrounded by a white frame (2mm thickness) were displayed on a 15.6-inch color monitor with a black background. One frame was positioned in the upper portion of the screen, indicating the area where the Pavlovian conditioned cues would be displayed during Pavlovian training and transfer test. Three frames were positioned horizontally next to each other in the middle portion of the screen, indicating the areas of the screen to be clicked with the mouse to make a response during instrumental training and transfer test. One frame was positioned in the bottom portion of the screen, indicating the area where the outcome would be displayed during instrumental training, Pavlovian training, and transfer test.

Instrumental training. This training aimed to teach the association between a specific instrumental response and its corresponding outcome. In each trial, participants made a response, i.e. they clicked on one of the three frames placed in the middle portion of the screen. Two responses ($R+_1$ and $R+_2$) were each paired with one of the two different reward outcomes (O_1 and O_2 respectively), while a third response (R-) was always paired with the no-reward outcome (NR, i.e. picture of an ‘X’). The response-outcome association was counterbalanced across participants. In each trial, only two out of the three responses were available. Available responses were indicated to participants by a white patch appearing within the square. After each choice, a corresponding no-reward or reward outcome appeared for 600ms in the bottom square. Reward-associated responses followed a partial reinforcement schedule, such that when a specific response was rewarded, the same response would not be rewarded for the following 2 to 4 seconds (jittered interval). The instrumental conditioning

phase consisted of a total of 27 trials (9 trials for each pair of responses), each lasting 10 seconds, during which participants were free to perform as many responses as they wished (i.e. mouse clicks). A jittered 500-1500ms inter-trial-interval followed each trial. Three example trials were performed before beginning. This phase lasted about 6 minutes.

---------- FIGURE 1 ----------

Pavlovian training. This training aimed to teach the association between a specific conditioned cue and its corresponding outcome. In each trial, one of three conditioned cues (CS, i.e. fractal images balanced for luminance, complexity, and color saturation) appeared within the upper frame for 5 seconds. Then, a white patch appeared within the bottom square. Participants were instructed to press the left-Ctrl button on the computer keyboard as quickly as possible to remove the patch and discover the outcome hidden behind it. The outcome was presented for 1 second. Two of the CSs ($CS+_1$ and $CS+_2$) were associated with a rewarding outcome (O_1 and O_2 respectively) on 80% of trials and with the no-reward outcome (NR, i.e. picture of an 'X') in the remaining 20% of trials. The third CS (CS-) was associated with the no-reward outcome on all trials. The cue-outcome association was counterbalanced across participants. The task consisted of 75 trials (25 per each visual cue) each followed by a jittered 500-1500ms inter-trial-interval. Three example trials (one for each CS) were performed before beginning. This phase lasted about 8 minutes.

This Pavlovian speeded reaction-time response has been successfully used to obtain a behavioral measure of Pavlovian learning (Garofalo et al., 2019, 2020; Garofalo & di Pellegrino, 2015; Talmi et al., 2008). To avoid a possible instrumental component, participants were explicitly told and demonstrated that reward delivery was not dependent upon their response. Even without a button press, the patch would disappear after 3 seconds and reveal the hidden outcome. The main reason for using a speeded response was to mirror PIT studies on animals, in which Pavlovian training is measured by a behavior performed to gain the reward (Corbit & Balleine, 2005; Dickinson et al., 2000; Holland, 2004). The rationale was to observe faster reaction times when a reward was predicted contingent to CS+ presentation, as compared to when no-reward was predicted contingent to CS− presentation.

As a further measure of learning, subjective liking for each CSs was rated by participants on a 9-items Likert scale ranging from 1 (very little) to 9 (very much), before the beginning of the task and after Pavlovian training. The rationale was to observe an increase in liking scores after Pavlovian training for $CS+_1$ and $CS+_2$, as compared to CS-.

Explicit learning assessment. At the end of the two training sessions, explicit learning was assessed. Participants saw each response option and CS separately and had to associate them with their corresponding outcome, pressing the corresponding button on the keyboard.

Transfer test. This phase aimed to test the influence of the Pavlovian CSs on instrumental responses. The task mirrored instrumental training, with two differences. First, while performing responses, task-irrelevant Pavlovian CSs were presented within the upper square, at the beginning of the trial. Second, the whole task was performed under extinction, so that no reward was ever delivered. Extinction is a

standard procedure to assess transfer effects, both in human and animal research, as it allows to test the influence of Pavlovian cues on instrumental responding without the confounding effects of reward presentation (Bray et al., 2008; Rescorla, 1994; Talmi et al., 2008). The task consisted of 36 trials of 10 seconds (6 trials for each association of cue and response pair, see Table 1), during which subjects were free to perform as many responses (mouse clicks) as they wished. This phase lasted about 7 minutes.

tDCS

tDCS was delivered using a battery-driven Eldith constant direct current stimulator (neuroConn GmbH). A pair of surface sponge electrodes were soaked in a standard saline solution (NaCl 0.9%) and held in place with elastic rubber bands. For the cathodal group, the cathodal electrode (25 cm^2) was applied over the left prefrontal cortex (Dedoncker et al., 2016; Filmer et al., 2013; Metuki et al., 2012; Pope & Miall, 2012) and the reference electrode (35 cm^2) over the right posterior parietal cortex (control region). For the anodal group, the anodal electrode (35 cm^2) was applied over the left prefrontal cortex (target region) and the reference electrode (25 cm^2) right posterior parietal cortex (control region). Regarding the Sham stimulation group, the anodal group montage was used for half of the participants, while the cathodal group montage for the other half. The choice to apply the tDCS stimulation to the left lateral prefrontal cortex only was guided by evidence showing an association between left frontal activity and the approach motivational system, as compared to right frontal activity associated with avoidance motivation (Fetterman et al., 2013; Kelley et al., 2017).

tDCS electrode positions were identified on each participant's scalp in F3 (corresponding to the Brodmann area 9) position based on the international 10–20 electroencephalogram (EEG) system, as used in previous studies targeting the left lateral prefrontal cortex (Dedoncker et al., 2016). Due to our a priory hypothesis of the sensory-specific cue-guided choice is likely to rely on the lateral prefrontal cortex, the F3 electrode has been chosen as the middle crossing point of the lateral surface of PFC (Conson et al., 2015; Xue et al., 2012). Consequently, the reference site was identified on P4 (Brodmann area 40) (Kajimura & Nomura, 2015) so that would be on the very far and opposite from the target region of interest (F3) to prevent as much interference as possible given cortical stimulation (Ziemann et al., 2008).

Figure 2 represents the tDCS montage (panel a) and the computational model of voltage distribution of the electric field induced by tDCS. The Realistic vOlumetric-Approach to Simulate Transcranial electric stimulation (ROAST, panels b and d) was used to segment the full head from an MRI structural image, place virtual electrodes, generate a FEM mesh, and solve for voltage field distribution at 1 mm resolution (Dmochowski et al., 2011; Huang et al., 2016, 2019). The normal component of the electric field is believed to be the effective component of the electric field, with negative (cathodal) currents flowing outwards, and positive (anodal) currents flowing inwards (Csifcsák et al., 2018). SimNIBS v3.2.1 (Saturnino et al., 2019) was used to estimate the normal component of electric field distribution and for automatic skull segmentation from MR images (Nielsen et al., 2018). Conductivities for different tissue compartments were set as follows: 0.465 S/m (skin), 0.01 S/m (skull), 0.5 S/m (eyeballs), 1.654 S/m (cerebrospinal fluid), 0.275 S/m (gray matter) and 0.126 S/m (white matter). One electrode was set as 5 x 5 (25 cm^2) and the other was set as a 7 x 5 (35 cm^2), both with 1 mm of thickness and 3 mm of sponge thickness. Stimulation intensity for the anode was set to 2 mA, with equal distribution of return currents for the cathode (-2 mA) and

reversed for the opposite montage used. Overall, the simulation showed an accurate propagation of the stimulation over the lateral prefrontal cortex, hence supporting the tDCS setup used (Fig. 2).

For the anodal and cathodal groups, tDCS was delivered with a constant current of 2 mA (current density ~0.08 mA/cm2), complying with current safety guidelines (Nitsche et al., 2003; Poreisz et al., 2007). Stimulation lasted for 15 min, plus 23 s of ramp-up and ramp-down at the beginning and end of stimulation. Impedance was constantly monitored and kept below 5 kOhm. This protocol is known to affect cortical excitability for more than 30 min after the end of stimulation (Nitsche et al., 2008; Nitsche & Paulus, 2011), thus covering the entire duration of the transfer test. For the sham group, the current was turned on at the beginning of the session and then turned off in a ramp-shaped fashion (fade in/out: 30 s), so that participants experienced the sensations initially associated with the onset of stimulation (mild local tingling), without inducing any effective modulation of cortical excitability (Avenanti et al., 2018). This procedure ensures the successful blinding of participants (Ambrus et al., 2012; Gandiga et al., 2006).

---------- FIGURE 2 ----------

Procedure

On arrival, participants were seated in a silent room and their position was centered relative to the screen, at a viewing distance of 50 cm from the screen. Before starting the experimental task, participants performed a food rating, to find the food-reward most liked and wanted by each participant. Each participant saw pictures of 12 savory and 12 sweet foods and rated their subjective wanting on a 10-point Likert scale, ranging from 0 (I do not care) to 10 (I want it now). Based on the subjective preference expressed, one savory and one sweet food with similar wanting ratings were used as rewards. Thus, food rewards were tailored for each participant. Groups did not differ on mean wanting rating (cathodal: M=6.37, SD=2.08; anodal: M=6.42, SD=2.52; sham: M=6.85, SD=2.32; one way ANOVA: p=0.777) Participants were told that during the task they would be collecting "food points" based on their responses and receive a corresponding amount of such food at the end of the task. Successively participants completed the experimental task. Detailed instructions are available in the Supplementary Materials. In each phase, participants were required to pay attention to the screen and follow the instructions reported at the beginning of the task. To avoid possible experimenter's interference, instructions were written, and each participant read them before each phase. After the Pavlovian training, tDCS was performed. Participants then completed the transfer test. Finally, to test whether sham or active tDCS induced different scalp sensations, participants evaluated the discomfort caused by the stimulation on a 5-point Likert scale ranging from 1 (not unpleasant at all) to 5 (extremely unpleasant). Groups did not differ in mean rating of experienced discomfort (cathodal: M=1.70, SD=1.08; anodal: M=1.55, SD=0.55; sham: M=1.25, SD=0.55; one way ANOVA: p=0.240.

Dependent measures

Acquisition of instrumental learning. To assess the implicit acquisition of instrumental learning, for each participant, we calculated the mean number of responses across trials for each type of response (i.e. $R+_1$, $R+_2$, and R-), during instrumental training. We expected more $R+_1$ and $R+_2$ than R-. To assess the explicit acquisition of instrumental learning, for each participant, we calculated the number of correct answers given during the explicit learning assessment.

Acquisition of Pavlovian learning. To assess the implicit acquisition of Pavlovian learning, for each participant, we calculated the mean reaction time to the presentation of each conditioned cue (i.e. $CS+_1$, $CS+_2$, and CS-), during Pavlovian training. Note that for each subject, we excluded trials whose reaction time was greater than ±2SD from that subject's mean reaction time. We expected faster mean reaction time to $CS+_1$ and $CS+_2$ than CS-. In addition, from the liking Likert scale, we calculated the subjective liking for each CSs, before and after Pavlovian training. We expected an increase in liking after Pavlovian training for $CS+_1$ and $CS+_2$, as compared to CS-. To assess the explicit acquisition of Pavlovian learning, for each participant, we calculated the number of correct answers given during the explicit learning assessment.

Outcome-specific transfer. To assess outcome-specific transfer we considered responses for trials on which participants were presented with a CS+ ($CS+_1$ or $CS+_2$) while having to choose between $R+_1$ and $R+_2$, during the transfer test. Importantly, responses were classified as congruent or incongruent. Specifically, choosing $R+_1$ in presence of $CS+_1$ would constitute a congruent response - as both $R+_1$ and $CS+_1$ had been associated with O_1 -, while choosing $R+_2$ would constitute an incongruent response. Similarly, choosing $R+_2$ in presence of $CS+_2$ would constitute a congruent response - as both $R+_2$ and $CS+_2$ had been associated with O_2 -, while choosing $R+_1$ would constitute an incongruent response (see Table 1 for a detailed description of trials). Outcome specific transfer was calculated as the difference between congruent and incongruent responses. Thus, a positive difference would be evidence of outcome-specific transfer, with greater difference indicating greater transfer effect.

General transfer. General transfer was calculated as the mean number of R+ responses for trials on which participants were presented with a CS ($CS+_1$, $CS+_2$, or CS-) while having to choose between the two responses that had never been paired with the presented CS. Specifically, if $CS+_1$ was presented, participants chose between $R+_2$ and R-; if $CS+_2$ was presented, participants chose between $R+_1$ and R-; if CS- was presented participants, chose between either $R+_1$ and R- or $R+_2$ and R-. A higher number of R+ responses during the presentation of CS+ than CS- would be evidence of general transfer (see Table 1 for a detailed description of trials).

Table 1 – Trial composition for all task phases

TRIALS	CONTINGENCY
Instrumental training	$R+_1 \rightarrow O1$ $R+_2 \rightarrow O2$ $R- \rightarrow NR$

Pavlovian training		$CS+_1 \rightarrow O1$ $CS+_2 \rightarrow O2$ $CS- \rightarrow NR$		
Transfer	Outcome-specific	$CS+_1$: R_1 (congruent)	vs	R_2 (incongruent)
		$CS+_2$: R_1 (incongruent)	vs	R_2 (congruent)
	General	$CS+_1$: R_2 vs R- $CS+_2$: R_1 vs R-	vs	CS-: R_2 vs R- CS-: R_1 vs R-

Note: R, response; CS, conditioned stimulus; O, outcome; +, rewarded; -, unrewarded, NR, no reward.

Statistical analyses

Statistical analyses included both Null Hypothesis Significance Testing (NHST) and Bayesian approaches. Analyses were performed with JASP 0.12.2.0. Analyses of variance (ANOVA) was used to investigate differences within and between groups with a significance threshold of $p<0.05$. Degrees-of-freedom were Greenhouse–Geisser corrected, whenever a violation of the sphericity assumption occurred. Partial η^2 is reported as a measure of effect size for the main effects and interactions. Post hoc comparisons were performed using Bonferroni tests to correct for multiple comparisons. The Bayes Factor is reported for all analyses as the probability associated with the alternative hypothesis over the null hypothesis (BF_{10}). The number of Monte Carlo samples was always 10000. The estimated proportional error (err%) associated with the Bayes Factor is reported only if higher than 1. Post hoc comparisons were performed using default JASP parameters. Cumming estimation plots (Ho et al., 2019) were used for estimation and to illustrate the data, whenever appropriate. Data and code are publicly available on https://osf.io/m9sb2/. No part of the study procedures or analysis plans was preregistered in an institutional registry prior to the research being conducted.

Results

Instrumental training lead to the acquisition of response-outcome contingencies

First, we assessed whether participants showed evidence of implicit instrumental learning. The 3x3 mixed ANOVA - independent variables: group (cathodal, anodal, sham) and response type (R-, $R+_1$, $R+_2$) - on mean number of responses when choosing between R- and $R+_1$ or $R+_2$ showed a main effect of response type ($F_{(1.07, 61.08)}=115.46$, $p < 0.001$, $\eta_p^2=0.67$; $BF_{10}=8.33*10^{28}$; Fig. 3a). Participants gave more rewarded than non-rewarded responses and showed no difference in rewarded responses ($R+_1$: M=8.10, SD=3.07; $R+_2$: M=8.32, SD=2.90; R-: M=2.63, SD=1.59; R+1 vs R-: $p < 0.001$, $BF_{10}=1.74*10^{12}$; $R+_2$ vs R-: $p < 0.001$, $BF_{10=}9.27*10^{13}$; $R+_1$ vs $R+_2$: p=.208, $BF_{10}=0.08$). No other effect emerged (group: $F_{(2, 57)}=0.14$, p=0.872, $\eta_p^2=0.00$; $BF_{10}=0.08$, err%=1.70; response type by group: $F_{(2.14, 61.08)}=0.12$, p=0.900, $\eta_p^2=0.00$; $BF_{10=}4.14*10^{26}$, err%=1.09). Note that, despite the BF of the interaction supporting the alternative hypothesis, this was outperformed by the response type main effect, as clarified by post-hoc analysis reporting a difference between R- and $R+_1$ ($BF_{10}=1738e+12$), R- and $R+_2$ ($BF_{10}=9267e+13$) and no difference between $R+_1$ and $R+_2$ ($BF_{10}=0.69$), but not between

cathodal and anodal (BF_{10}=0.21), cathodal and sham (BF_{10}=0.21), and anodal and sham(BF_{10}=0.19) groups. These results are also confirmed by the estimation provided in Figure 3A, where the confidence interval reporting the difference between R- and both $R+_1$ and $R+_2$ do not include zero. Additionally, the 2x3 mixed-design ANOVA - independent variables: group (cathodal, anodal, sham) and response type ($R+_1$, $R+_2$) - on mean number of responses when choice was limited to $R+_1$ and $R+_2$, showed no effect (response type: $F_{(1, 57)}$=2.56, p=0.116, η_p^2=2.55; BF_{10}=1.09, err%=1.28; group: $F_{(2, 57)}$=0.32, p=0.726, η_p^2=0.01; BF_{10}=0.11; response type by group: $F_{(2, 57)}$=0.34, p=0.714, η_p^2=0.01; BF_{10}=0.02, err%=1.42, Fig. 3b). These results are also confirmed by the estimation provided in Figure 3B, where the confidence intervals reporting the difference between $R+_1$ and $R+_2$ includes zero.

Thus, overall, there was a preference for rewarded over non-rewarded responses and no difference between rewarded responses.

Then, we assessed whether participants showed evidence of explicit instrumental learning. When examining the number of correct answers given during the explicit learning assessment, 73.3% of participants correctly reported all response-outcome associations (Anodal: 60%, Cathodal: 85%, Sham: 75%), 6.67% correctly reported 2 out of three associations (Anodal: 10%, Cathodal: 5%, Sham: 5%), 16.67% correctly reported 1 out of three associations (Anodal: 25%, Cathodal: 10%, Sham: 15%), and 3.33% did not answer correctly on any association (Anodal: 5%, Cathodal: 0%, Sham: 5%).

Together these results indicate successful acquisition of instrumental learning on an implicit and explicit level with no difference between groups.

---------- **FIGURE 3** ----------

Pavlovian training lead to the acquisition of stimulus-outcome contingencies

Next, we assessed whether participants showed evidence of implicit Pavlovian learning. The 3x3 mixed-design ANOVA - independent variables: group (cathodal, anodal, sham) and stimulus type (CS-, $CS+_1$, $CS+_2$) - on reaction times showed a main effect of stimulus type ($F_{(2, 114)}$=3.62, p=0.030, η_p^2=0.06; BF_{10}=1.21, err%=1.35). Participants responded faster in presence of $CS+_1$ (M=270.21ms, SD=62.67ms) than CS- (M=279.24ms, SD=75.82; p=0.031, BF_{10}=4.12) and in presence of $CS+_2$ (M=276.71ms, SD=62.60ms) than CS- although this last comparison was not supported by statistical analyses (p=1.000, BF_{10}=0.18) and the RT difference was very small (<3ms). No other effect emerged (group: $F_{(2 ,57)}$=0.55, p=0.581, η_p^2=0.02; BF_{10}=0.56, err%=3.58; stimulus type by group: $F_{(4, 114)}$=1.35, p=0.255, η_p^2=0.04; BF_{10}=0.15, err%=7.81).

Additionally, the 3x3x2 mixed-design ANOVA - independent variables: group (cathodal, anodal, sham), stimulus type (CS-, $CS+_1$, $CS+_2$), and time of rating (before, after Pavlovian training) - on liking scores showed a main effect of time of rating following NHST but not Bayesian analysis ($F_{(1, 57)}$=4.56, p=0.037, η_p^2=0.07; BF_{10}=0.26, err%=1.04) and a main effect of stimulus type ($F_{(2, 114)}$=3.84, p=0.024, η_p^2=0.06; BF_{10}=8.44). Crucially, these were qualified by a time of rating by stimulus type interaction ($F_{(2, 114)}$=13.85, p<0.001, η_p^2=0.20; BF_{10}=177.28, err%=2.00; Fig. 4). Before Pavlovian training, there was no difference in liking between CSs (CS-: M=5.85, SD=1.95; $CS+_1$: M=5.85,

SD=2.22; CS+$_2$: M=5.67, SD=1.85; all p=1.000, all BF_{10}≤0.18). In contrast, after Pavlovian training, CSs+ were liked more than CS- (CS-: M=5.13, SD=2.26; CS+$_1$: M=6.50, SD=1.81; CS+$_2$: M=6.40, SD=1.95; both p<0.001, both BF_{10}≥19.36), with no difference in liking between CS+$_1$ and CS+$_2$ (p=1.000, BF_{10}=0.15). Also, while liking increased for both CS+ from before to after Pavlovian training (both p≤0.030, both BF_{10}≥8.35), it decreased for the CS- (p=0.010, BF_{10}=12.38). No other effect emerged (group: $F_{(2, 57)}$=0.70, p=0.502, η_p^2=0.02; BF_{10}=0.19, err%=4.00; stimulus type by group: $F_{(4, 114)}$=1.16, p=0.332, η_p^2=0.04; BF_{10}=0.46, err%=1.48; time by group: $F_{(2, 57)}$=0.70, p=0.499, η_p^2=0.02; BF_{10}=0.00, err%=1.26; stimulus type by time by group: $F_{(4, 114)}$=1.08, p=0.369, η_p^2=0.04; BF_{10}=0.07, err%=2.36). These results are also confirmed by the estimation provided in Figure 4, where all confidence intervals reporting the difference between after and before conditioning for all CSs do not include zero. Thus, after Pavlovian training, participants increased liking for rewarded CSs and liked them more than non-rewarded CSs, with no difference between rewarded CSs.

Then, we assessed whether participants showed evidence of explicit Pavlovian learning. When examining the number of correct answers given during the explicit learning assessment of all participants, 83.3% correctly reported all CS-outcome associations (Anodal: 80%, Cathodal: 85%, Sham: 85%), 13.33% correctly reported 1 out of three associations (Anodal: 15%, Cathodal: 15%, Sham: 10%), and 3.33% did not answer correctly on any association (Anodal: 5%, Cathodal: 0%, Sham: 5%).

Together these results indicate successful acquisition of Pavlovian learning on an implicit and explicit level with no difference in learning between groups.

---------- FIGURE 4 ----------

Cathodal tDCS over lateral prefrontal cortex reduced outcome-specific but not general transfer

Finally, we tested our main hypothesis, namely that cathodal tDCS over lateral PFC may reduce outcome specific transfer. The one-way ANOVA – independent variables: group (cathodal, anodal, sham) - on the mean difference (congruent – incongruent) of number of responses showed a main effect of group F(2, 57)=10.87, p<0.001, ηp^2=0.28; BF_{10}=250.31). While the difference between congruent and incongruent responses was lower in the cathodal group (M=1.25, SD=5.72) as compared to both the sham (M=5.93, SD=4.45; p≤0.006, BF_{10}=7.06) and anodal (M=7.85, SD=3.34; p≤0.006, BF_{10}=288.862) groups, no difference between the sham and anodal groups (p=0.58, BF_{10}=0.79) was found. These results are also confirmed by the estimation provided in Figure 5A, where the confidence intervals reporting the difference between congruent and incongruent response include zero in the cathodal group only. Additionally, the confidence interval in this group does not overlap with those reported by the anodal and sham groups.

Regarding general transfer, the 3x2 mixed ANOVA - independent variables: group (cathodal, anodal, sham) and stimulus type (CS+, CS-) - on mean number of rewarded responses in presence of CS+ rather than CS- showed only a main effect of stimulus type ($F_{(1, 57)}$=20.21, p < 0.001, η_p^2=0.26; BF_{10}=568.82, Fig. 5b). Participants made more rewarded responses when in presence of the CS+ (M=7.97, SD=3.16) rather than the CS- (M=5.99, SD=4.19; p<0.001, BF_{10}=641.187). The main effect

of group or the stimulus type by group interactions were not significant (group: $F_{(2, 57)}$=0.84, p=0.437, η_p^2=0.03; BF_{10}=0.30; stimulus type by group: $F_{(2, 57)}$=0.77, p=0.468, η_p^2=0.03; BF_{10}=48.64, err%=2.77). Note that, despite the BF of the interaction supporting the alternative hypothesis, this was outperformed by the stimulus type main effect, as clarified by post-hoc analysis reporting a difference between the two response types (BF_{10}=641.19) but not between cathodal and anodal (BF_{10}=0.69), cathodal and sham (BF_{10}=0.36), and anodal and sham (BF_{10}=0.27) groups. These results are also confirmed by the estimation provided in Figure 5B, where all confidence intervals reporting the difference between CS+ and CS- do not include zero in any group. Although the cathodal group is very close to zero, its confidence interval overlaps with that of the other two groups, thus indicating comparable effects among groups.

Together these results indicate that cathodal tDCS over the lateral prefrontal cortex reduces outcome-specific transfer. The cathodal group showed no evidence of outcome-specific transfer, which was instead evident in the sham and anodal group. In contrast, there was no effect of the tDCS on general transfer, whose analysis showed no effect of group.

---------- FIGURE 5 ----------

Discussion

The present study provides evidence for the causal role of the lateral prefrontal cortex in cue-guided choice. After comparable instrumental (response-outcome) and Pavlovian (stimulus-outcome) learning, participants receiving cathodal - as compared to sham or anodal - tDCS over the lateral prefrontal cortex selectively reduced outcome-specific transfer (Fig. 5). In contrast, general transfer was not modulated by this stimulation. In other terms, following cathodal stimulation over the lateral prefrontal cortex, the biasing effect of Pavlovian cues was reduced on choices associated with the exact same reward (i.e. sharing the sensory properties, outcome-specific transfer), but not on choices associates with a motivationally similar reward (i.e. sharing the appetitive value, general transfer). These results are in line with and extend the current literature on cue-guided choice, supporting the idea that separate neural substrates underpin these two effects and further highlighting a dissociation between outcome-specific and general transfer (Bray et al., 2008; Garofalo et al., 2017, 2019, 2020; Garofalo & di Pellegrino, 2015, 2017; Garofalo & Robbins, 2017; Lewis et al., 2013; Morris et al., 2015; Prévost et al., 2012; Talmi et al., 2008). Moreover, the present results shed new light on the cortical structures involved in cue-guided choice by providing the first evidence for direct involvement of the lateral prefrontal cortex in outcome-specific transfer.

To determine the optimal choice, the lateral prefrontal cortex evaluates the state of the environment by accumulating the sensory evidence and retaining the necessary information in working memory to control task performance (Kennerley & Walton, 2011; Lee et al., 2007). In doing so, it contributes to the transformation of perceptual information into motor outputs (Kennerley & Walton, 2011; Lee et al., 2007). Indeed, when learning a stimulus-response association, neural activity emerges early in the basal ganglia and then transfers to the lateral prefrontal cortex (Pasupathy & Miller, 2005), where a specific sensory-motor combination is selected and maintained (Makino et al., 2016; Schoenbaum et

al., 2009). Collectively, this evidence resonates with the main finding here reported. To trigger outcome-specific transfer, a representation of the sensory-specific properties of the reward – and the associated response – recalled by the cue needs to be actively maintained (Corbit & Balleine, 2015; Dolan & Dayan, 2013; Holland, 2004; Miller & Cohen, 2001). The lateral prefrontal cortex may have a role in holding the internal representation of the mappings between sensory inputs and motor actions (Miller, 2000; Miller & Cohen, 2001; Morris et al., 2014) needed to select an action based on the information provided by the cue (Huettel et al., 2005; Morris et al., 2014). In contrast, when the biasing effect of the cue simply boost choice towards any outcome sharing its appetitive value (i.e., general transfer), neural regions processing the value of the outcome are more likely involved, such as striatum and amygdala (Schoenbaum et al., 1998; Wallis & Miller, 2003). In line with this, the present findings argue in favor of two dissociated neural pathways underlying cue-guided choice: one sensory-motor - sensory-specific information about the outcome mediated by the prefrontal cortex - and one value-based (Dolan & Dayan, 2013; Garofalo et al., 2019, 2020; Garofalo & di Pellegrino, 2015, 2017; Garofalo & Robbins, 2017). Such dissociation has been previously reported for subcortical structures, with outcome-specific transfer involving the basolateral amygdala and nucleus accumbens shell, and general transfer involving the central nucleus of the amygdala and the nucleus accumbens core (Cartoni et al., 2016; Holmes et al., 2010). We extend such evidence adding that a dissociation also concerns the lateral prefrontal cortex.

The lateral prefrontal cortex may use environmental cues and contextual information to guide choice. Importantly, such external information can either match or conflict with the instrumental action required by the task at hand (Miller & Cohen, 2001). For example, if the presence of the cue signaled the availability of reward, using it as guidance to inform action selection becomes adaptive; otherwise it should be inhibited to avoid a maladaptive bias. Within this scenario, the lateral prefrontal cortex may support decision making by flexibly inhibiting information provided by the cue that conflicts with the goal of the instrumental task, or exploiting information that matches with the task goal (Hare et al., 2009; Makino et al., 2016; Morris et al., 2014; Xue et al., 2012). Related to this, prior studies employing a motivational Go/NoGo task showed that, among other areas, activation of the lateral prefrontal cortex predicts the reduced impact of maladaptive Pavlovian biases over choice (Swart et al., 2018). The present results extend this evidence by showing that the lateral PFC also plays a role in exploiting information useful to achieve the task goal, hence promoting an adaptive Pavlovian bias. Indeed, the temporary inhibition of the lateral prefrontal cortex reduced the adaptive exploitation of external information potentially useful to complete the task (i.e. earning as much food as possible), resulting in a reduction of outcome specific transfer. Relatedly, high-level cognitive abilities, such as working memory (Garofalo et al., 2019), and supraliminal (vs subliminal) presentation of the reward-associated cue (Garofalo et al., 2020) have been reported as crucial for the expression of outcome specific, but not general transfer. In turn, by encoding the value of the expected outcome (Kennerley & Walton, 2011; Lee et al., 2007; Morris et al., 2014; Schoenbaum et al., 2009) irrespective of the sensory-motor combination, activity in the medial prefrontal cortex and the amygdala may mediate the value-based cue-guided choice characterizing general transfer.

To note, if the evidence here provided confirms the role of the lateral prefrontal cortex in the initial stages of cue-guided choices, no conclusion can be drawn on how it may evolve in time. One influential hypothesis posits that addictive and compulsive behaviors are rooted in a transition from voluntary to habitual actions, which is neurally paralleled by a transition from prefrontal cortical areas

to striatal control over choice (Everitt & Robbins, 2016). In outcome-specific transfer, the lateral prefrontal cortex may support a strategic use of the information provided by environmental cues when the stimulus-response association is mediated by a specific outcome (i.e., a goal). With time and practice, however, the role of the lateral prefrontal cortex may gradually decrease, shifting towards a more habit-like control over choice. Future studies should address such a hypothesis directly.

Finally, some limitations of the study shall be taken into account. This experiment employed tDCS to modulate brain activity. While cathodal stimulation reduces neuronal firing rates and excitability, anodal tDCS stimulation increases them (Nitsche & Paulus, 2011). In the experimental group receiving cathodal stimulation over the lateral prefrontal cortex, the reference electrode (anode) was placed on the parietal cortex. Although it cannot be excluded that the modulation of any area affected by the stimulation may have played a role in the reduction of outcome-specific transfer (Corlett et al., 2006; Makino et al., 2016), the parietal cortex was chosen as a reference because it has never been implicated in the cortico-striatal circuits underlying cue-guided choice (Cartoni et al., 2016; Holmes et al., 2010) and because it allowed the best montage to target the lateral prefrontal cortex (see Fig. 2). Importantly, it should be noted that, given the role of the parietal cortex in attentional processes, putative excitation of this area by the anodal stimulation should have enhanced attention toward the Pavlovian cue (Jarbo & Verstynen, 2015) and, hence, increased the biasing effect on choice rather than decreased it, as found in the present results . Moreover, cathodal stimulation of the lateral prefrontal cortex did not result in reduced responding compared to anodal and sham stimulation, thus excluding the possibility that the observed effect is due to a general decrease in response rate. Regarding the absence of increased outcome-specific transfer associated with anodal stimulation over the later prefrontal cortex, this may be easily explained by the presence of a ceiling effect. In fact, although control site-effects are not clearly distinguishable from polarity-reversal effects (as it is also evident from Fig. 2), the "anodal" condition was designed to test the effects of cathodal tDCS above a control (parietal) region, rather than testing polarity-specific effects of lateral PFC stimulation. On a final note, although widely used in the literature to assess blinding, the measure of discomfort level used in the present study may not have ensued full blinding between the groups (Turi et al., 2019).

In conclusion, the present findings constitute the first evidence of the causal role of the lateral prefrontal cortex in outcome-specific transfer and provide support to the hypothesis that two separate neural and functional mechanisms underlie cue-guided choice. Such dissociation is crucial to shed new light on the mechanisms at the core of cue-guided choice. Additionally, the vast implications in daily life and clinical conditions warrants future studies to explore the adaptive and maladaptive implications of cue-guided choices.

Acknowledgments

The authors thank Francesco Padovani, Sofia Rivaira, and Chiara Di Fazio for their contribution to data collection. This work was supported by the FLAG-ERA grant MoDeM by MIUR.

Credit Author Statement

Sara Garofalo: conceptualization, formal analysis, methodology, software, writing - original draft, writing - review & editing. **Simone Battaglia**: data curation, investigation, formal analysis, methodology, software. **Francesca Starita**: formal analysis, writing - review & editing. **Giuseppe di Pellegrino**: conceptualization, project administration, resources, supervision, writing - review & editing.

Additional Information

Competing Interests: authors declare no competing interests.

Data availability statement

Data and code are publicly available on https://osf.io/m9sb2/.

References

Alexander, G. E., & Crutcher, M. D. (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends in Neurosciences*, *13*(7), 266–271. https://doi.org/10.1016/0166-2236(90)90107-L

Ambrus, G. G., Al-Moyed, H., Chaieb, L., Sarp, L., Antal, A., & Paulus, W. (2012). The fade-in - Short stimulation - Fade out approach to sham tDCS - Reliable at 1 mA for naïve and experienced subjects, but not investigators. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2011.12.001

Avenanti, A., Paracampo, R., Annella, L., Tidoni, E., & Aglioti, S. M. (2018). Boosting and decreasing action prediction abilities through excitatory and inhibitory tDCS of inferior frontal cortex. *Cerebral Cortex*, *28*(4), 1282–1296. https://doi.org/10.1093/cercor/bhx041

Battaglia, S., Garofalo, S., & di Pellegrino, G. (2018). Context-dependent extinction of threat memories: influences of healthy aging. *Scientific Reports*, *8*(1), 12592. https://doi.org/10.1038/s41598-018-31000-9

Bray, S., Rangel, A., Shimojo, S., Balleine, B., & O'Doherty, J. P. (2008). The neural mechanisms underlying the influence of pavlovian cues on human decision making. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *28*(22), 5861–5866. https://doi.org/10.1523/JNEUROSCI.0897-08.2008

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *The International Journal of Neuropsychopharmacology*, *14*(8), 1133–1145. https://doi.org/10.1017/S1461145710001690

Cartoni, E., Balleine, B., & Baldassarre, G. (2016). Appetitive Pavlovian-instrumental Transfer: A review. *Neuroscience and Biobehavioral Reviews*, *71*, 829–848. https://doi.org/10.1016/j.neubiorev.2016.09.020

Cavanagh, J. F., Eisenberg, I., Guitart-Masip, M., Huys, Q., & Frank, M. J. (2013). Frontal Theta Overrides Pavlovian Learning Biases. *Journal of Neuroscience*, *33*(19), 8541–8548. https://doi.org/10.1523/JNEUROSCI.5754-12.2013

Conson, M., Errico, D., Mazzarella, E., Giordano, M., Grossi, D., & Trojano, L. (2015). Transcranial electrical stimulation over dorsolateral prefrontal cortex modulates processing of social cognitive and affective information. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0126448

Corbit, L. H., & Balleine, B. W. (2005). Double dissociation of basolateral and central amygdala lesions on the general and outcome-specific forms of pavlovian-instrumental transfer. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *25*(4), 962–970. https://doi.org/10.1523/JNEUROSCI.4507-04.2005

Corbit, L. H., & Balleine, B. W. (2011). The general and outcome-specific forms of Pavlovian-instrumental transfer are differentially mediated by the nucleus accumbens core and shell. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *31*(33), 11786–11794. https://doi.org/10.1523/JNEUROSCI.2711-11.2011

Corbit, L. H., & Balleine, B. W. (2015). Learning and Motivational Processes Contributing to Pavlovian–Instrumental Transfer and Their Neural Bases: Dopamine and Beyond. In *Brain Imaging in Behavioral Neuroscience* (Issue November 2011, pp. 259–289). https://doi.org/10.1007/7854_2015_388

Corlett, P. R., Honey, G. D., Aitken, M. R. F., Dickinson, A., Shanks, D. R., Absalom, A. R., Lee,

M., Pomarol-Clotet, E., Murray, G. K., McKenna, P. J., Robbins, T. W., Bullmore, E. T., & Fletcher, P. C. (2006). Frontal Responses During Learning Predict Vulnerability to the Psychotogenic Effects of Ketamine. *Archives of General Psychiatry*, *63*(6), 611. https://doi.org/10.1001/archpsyc.63.6.611

Csifcsák, G., Boayue, N. M., Puonti, O., Thielscher, A., & Mittner, M. (2018). Effects of transcranial direct current stimulation for treating depression: A modeling study. *Journal of Affective Disorders*, *234*(February), 164–173. https://doi.org/10.1016/j.jad.2018.02.077

Dedoncker, J., Brunoni, A. R., Baeken, C., & Vanderhasselt, M. A. (2016). A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) Over the Dorsolateral Prefrontal Cortex in Healthy and Neuropsychiatric Samples: Influence of Stimulation Parameters. In *Brain Stimulation* (Vol. 9, Issue 4, pp. 501–517). Elsevier Inc. https://doi.org/10.1016/j.brs.2016.04.006

Dickinson, A. D., Smith, J., & Mirenowicz, J. (2000). Dissociation of Pavlovian and instrumental incentive learning under dopamine antagonists. *Behavioral Neuroscience*, *114*(3), 468–483. https://doi.org/10.1037/0735-7044.114.3.468

Dmochowski, J. P., Datta, A., Bikson, M., Su, Y., & Parra, L. C. (2011). Optimized multi-electrode stimulation increases focality and intensity at target. *Journal of Neural Engineering*, *8*(4), 046011. https://doi.org/10.1088/1741-2560/8/4/046011

Dolan, R. J., & Dayan, P. (2013). Goals and Habits in the Brain. *Neuron*, *80*(2), 312–325. https://doi.org/10.1016/j.neuron.2013.09.007

Doya, K. (2008). Modulators of decision making. *Nature Neuroscience*, *11*(4), 410–416. https://doi.org/10.1038/nn2077

Everitt, B. J., & Robbins, T. W. (2016). Drug Addiction: Updating Actions to Habits to Compulsions Ten Years On. *Annual Review of Psychology*, *67*(1), 23–50. https://doi.org/10.1146/annurev-psych-122414-033457

Fetterman, A. K., Ode, S., & Robinson, M. D. (2013). For which side the bell tolls: The laterality of approach-avoidance associative networks. *Motivation and Emotion*, *37*(1), 33–38. https://doi.org/10.1007/s11031-012-9306-5

Filmer, H. L., Mattingley, J. B., & Dux, P. E. (2013). Improved multitasking following prefrontal tDCS. *Cortex*. https://doi.org/10.1016/j.cortex.2013.08.015

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2005.12.003

Garofalo, S., Battaglia, S., & di Pellegrino, G. (2019). Individual differences in working memory capacity and cue-guided behavior in humans. *Scientific Reports*, *9*(1), 7327. https://doi.org/10.1038/s41598-019-43860-w

Garofalo, S., & di Pellegrino, G. (2015). Individual differences in the influence of task-irrelevant Pavlovian cues on human behavior. *Frontiers in Behavioral Neuroscience*, *9*(June), 163. https://doi.org/10.3389/fnbeh.2015.00163

Garofalo, S., & di Pellegrino, G. (2017). Commentary: Monetary, Food, and Social Rewards Induce Similar Pavlovian-to-Instrumental Transfer Effects. *Frontiers in Behavioral Neuroscience*, *11*(July), 247. https://doi.org/10.3389/fnbeh.2017.00136

Garofalo, S., Justicia, A., Arrondo, G., Ermakova, A. O., Ramachandra, P., Tudor-Sfetea, C., Robbins, T. W., Barker, R. A., Fletcher, P. C., & Murray, G. K. (2017). Cortical and Striatal

Reward Processing in Parkinson's Disease Psychosis. *Frontiers in Neurology*, *8*(April), 1–11. https://doi.org/10.3389/fneur.2017.00156

Garofalo, S., & Robbins, T. W. (2017). Triggering Avoidance: Dissociable Influences of Aversive Pavlovian Conditioned Stimuli on Human Instrumental Behavior. *Frontiers in Behavioral Neuroscience*, *11*(April), 1–11. https://doi.org/10.3389/fnbeh.2017.00063

Garofalo, S., Sagliano, L., Starita, F., Trojano, L., & di Pellegrino, G. (2020). Subliminal determinants of cue-guided choice. *Scientific Reports*, 14. https://doi.org/10.1038/s41598-020-68926-y

Guitart-Masip, M., Huys, Q. J. M., Fuentemilla, L., Dayan, P., Duzel, E., & Dolan, R. J. (2012). Go and no-go learning in reward and punishment: Interactions between affect and effect. *NeuroImage*, *62*(1), 154–166. https://doi.org/10.1016/j.neuroimage.2012.04.024

Haber, S. N., Kim, K.-S., Mailly, P., & Calzavara, R. (2006). Reward-Related Cortical Inputs Define a Large Striatal Region in Primates That Interface with Associative Cortical Connections, Providing a Substrate for Incentive-Based Learning. *Journal of Neuroscience*, *26*(32), 8368–8376. https://doi.org/10.1523/JNEUROSCI.0271-06.2006

Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-Control in Decision-Making Involves Modulation of the vmPFC Valuation System. *Science*, *324*(5927), 646–648. https://doi.org/10.1126/science.1168450

Hayashi, T., Ko, J. H., Strafella, A. P., & Dagher, A. (2013). Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of cigarette craving. *Proceedings of the National Academy of Sciences*, *110*(11), 4422–4427. https://doi.org/10.1073/pnas.1212185110

Ho, J., Tumkaya, T., Aryal, S., Choi, H., & Claridge-Chang, A. (2019). Moving beyond P values: data analysis with estimation graphics. *Nature Methods*, *16*(7), 565–566. https://doi.org/10.1038/s41592-019-0470-3

Hogarth, L., Dickinson, A., & Duka, T. (2010). The associative basis of cue-elicited drug taking in humans. *Psychopharmacology*, *208*(3), 337–351. https://doi.org/10.1007/s00213-009-1735-9

Holland, P. C. C. (2004). Relations between Pavlovian-instrumental transfer and reinforcer devaluation. *Journal of Experimental Psychology. Animal Behavior Processes*, *30*(2), 104–117. https://doi.org/10.1037/0097-7403.30.2.104

Holmes, N. M., Marchand, A. R., & Coutureau, E. (2010). Pavlovian to instrumental transfer: a neurobehavioural perspective. *Neuroscience and Biobehavioral Reviews*, *34*(8), 1277–1295. https://doi.org/10.1016/j.neubiorev.2010.03.007

Huang, Y., Datta, A., Bikson, M., & Parra, L. C. (2019). Realistic volumetric-approach to simulate transcranial electric stimulation — ROAST — a fully automated open-source pipeline. *Journal of Neural Engineering*, *16*(5). https://doi.org/10.1088/1741-2552/ab208d

Huang, Y., Parra, L. C., & Haufe, S. (2016). The New York Head—A precise standardized volume conductor model for EEG source localization and tES targeting. *NeuroImage*, *140*, 150–162. https://doi.org/10.1016/j.neuroimage.2015.12.019

Huettel, S. A., Song, A. W., & McCarthy, G. (2005). Decisions under uncertainty: Probabilistic context influences activation of prefrontal and parietal cortices. *Journal of Neuroscience*, *25*(13), 3304–3311. https://doi.org/10.1523/JNEUROSCI.5070-04.2005

Jarbo, K., & Verstynen, T. D. (2015). Converging Structural and Functional Connectivity of Orbitofrontal, Dorsolateral Prefrontal, and Posterior Parietal Cortex in the Human Striatum. *Journal of Neuroscience*, *35*(9), 3865–3878. https://doi.org/10.1523/JNEUROSCI.2636-14.2015

Kajimura, S., & Nomura, M. (2015). Decreasing propensity to mind-wander with transcranial direct current stimulation. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2015.07.013

Kelley, N. J., Hortensius, R., Schutter, D. J. L. G., & Harmon-Jones, E. (2017). The relationship of approach/avoidance motivation and asymmetric frontal cortical activity: A review of studies manipulating frontal asymmetry. *International Journal of Psychophysiology*, *119*, 19–30. https://doi.org/10.1016/j.ijpsycho.2017.03.001

Kennerley, S. W., & Walton, M. E. (2011). Decision making and reward in frontal cortex: Complementary evidence from neurophysiological and neuropsychological studies. *Behavioral Neuroscience*, *125*(3), 297–317. https://doi.org/10.1037/a0023575

Lee, D., Rushworth, M. F. S., Walton, M. E., Watanabe, M., & Sakagami, M. (2007). Functional specialization of the primate frontal cortex during decision making. *Journal of Neuroscience*, *27*(31), 8170–8173. https://doi.org/10.1523/JNEUROSCI.1561-07.2007

Lewis, A. H., Niznikiewicz, M. A., Delamater, A. R., & Delgado, M. R. (2013). Avoidance-based human Pavlovian-to-instrumental transfer. *European Journal of Neuroscience*, *38*(12), 3740–3748. https://doi.org/10.1111/ejn.12377

Makino, H., Hwang, E. J., Hedrick, N. G., & Komiyama, T. (2016). Circuit Mechanisms of Sensorimotor Learning. *Neuron*, *92*(4), 705–721. https://doi.org/10.1016/j.neuron.2016.10.029

Mathôt, S., Schreij, D., & Theeuwes, J. (2012). OpenSesame: An open-source, graphical experiment builder for the social sciences. *Behavior Research Methods*, *44*(2), 314–324. https://doi.org/10.3758/s13428-011-0168-7

Mendelsohn, A., Pine, A., & Schiller, D. (2014). Between Thoughts and Actions: Motivationally Salient Cues Invigorate Mental Action in the Human Brain. *Neuron*, *81*(1), 207–217. https://doi.org/10.1016/j.neuron.2013.10.019

Metuki, N., Sela, T., & Lavidor, M. (2012). Enhancing cognitive control components of insight problems solving by anodal tDCS of the left dorsolateral prefrontal cortex. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2012.03.002

Miller, E. K. (2000). The prefontral cortex and cognitive control. *Nature Reviews Neuroscience*, *1*(1), 59–65. https://doi.org/10.1038/35036228

Miller, E. K., & Cohen, J. D. (2001). An Integrative Theory of Prefrontal Cortex Function. *Annual Review of Neuroscience*, *24*(1), 167–202. https://doi.org/10.1146/annurev.neuro.24.1.167

Morris, R. W., Dezfouli, A., Griffiths, K. R., & Balleine, B. W. (2014). Action-value comparisons in the dorsolateral prefrontal cortex control choice between goal-directed actions. *Nature Communications*, *5*. https://doi.org/10.1038/ncomms5390

Morris, R. W., Quail, S., Griffiths, K. R., Green, M. J., & Balleine, B. W. (2015). Corticostriatal control of goal-directed action is impaired in schizophrenia. *Biological Psychiatry*, *77*(2), 187–195. https://doi.org/10.1016/j.biopsych.2014.06.005

Moustafa, A. A., Gilbertson, M. W., Orr, S. P., Herzallah, M. M., Servatius, R. J., & Myers, C. E. (2013). A model of amygdala-hippocampal-prefrontal interaction in fear conditioning and extinction in animals. *Brain and Cognition*, *81*(1), 29–43. https://doi.org/10.1016/j.bandc.2012.10.005

Nielsen, J. D., Madsen, K. H., Puonti, O., Siebner, H. R., Bauer, C., Camilla, G., Saturnino, G. B., & Thielscher, A. (2018). Automatic skull segmentation from MR images for realistic volume conductor models of the head : Assessment of the state-of-the-art. *NeuroImage*, *174*(February), 587–598. https://doi.org/10.1016/j.neuroimage.2018.03.001

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P. S., Fregni, F., & Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, *1*(3), 206–223. https://doi.org/10.1016/j.brs.2008.06.004

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., Henning, S., Tergau, F., & Paulus, W. (2003). Pharmacological Modulation of Cortical Excitability Shifts Induced by Transcranial Direct Current Stimulation in Humans. *The Journal of Physiology*, *553*(1), 293–301. https://doi.org/10.1113/jphysiol.2003.049916

Nitsche, M. A., & Paulus, W. (2011). Transcranial direct current stimulation--update 2011. *Restorative Neurology and Neuroscience*, *29*(6), 463–492. https://doi.org/10.3233/RNN-2011-0618

Pasupathy, A., & Miller, E. K. (2005). Different time courses of learning-related activity in the prefrontal cortex and striatum. *Nature*. https://doi.org/10.1038/nature03287

Pope, P. A., & Miall, R. C. (2012). Task-specific facilitation of cognition by cathodal transcranial direct current stimulation of the cerebellum. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2012.03.006

Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin*, *72*(4–6), 208–214. https://doi.org/10.1016/j.brainresbull.2007.01.004

Prévost, C., Liljeholm, M., Tyszka, J. M., O'Doherty, J. P., Prevost, C., Liljeholm, M., Tyszka, J. M., O'Doherty, J. P., Prévost, C., Liljeholm, M., Tyszka, J. M., & O'Doherty, J. P. (2012). Neural correlates of specific and general Pavlovian-to-Instrumental Transfer within human amygdalar subregions: a high-resolution fMRI study. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *32*(24), 8383–8390. https://doi.org/10.1523/JNEUROSCI.6237-11.2012

Rescorla, R. A. (1994). Control of instrumental performance by Pavlovian and instrumental stimuli. *Journal of Experimental Psychology: Animal Behavior Processes*, *20*(1), 44–50. https://doi.org/10.1037/0097-7403.20.1.44

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., Avanzini, G., Bestmann, S., Berardelli, A., Brewer, C., Canli, T., Cantello, R., Chen, R., Classen, J., Demitrack, M., Di Lazzaro, V., Epstein, C. M., George, M. S., Fregni, F., Ilmoniemi, R., Jalinous, R., … Ziemann, U. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. In *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2009.08.016

Saturnino, G. B., Puonti, O., Nielsen, J. D., Antonenko, D., Madsen, K. H., & Thielscher, A. (2019). SimNIBS 2.1: A Comprehensive Pipeline for Individualized Electric Field Modelling for Transcranial Brain Stimulation. In *Brain and Human Body Modeling* (pp. 3–25). Springer International Publishing. https://doi.org/10.1007/978-3-030-21293-3_1

Schoenbaum, G., Chiba, A. A., & Gallagher, M. (1998). Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. *Nature Neuroscience*, *1*(2), 155–159. https://doi.org/10.1038/407

Schoenbaum, G., Roesch, M. R., Stalnaker, T. A., Takahashi, Y. K., & Yuji, K. (2009). A new perspective on the role of the orbitofrontal cortex in adaptive behaviour. *Nature Review Neuroscience*, *10*(12), 885–892. https://doi.org/10.1038/nrn2753.A

Seabrooke, T., Le Pelley, M. E., Hogarth, L., & Mitchell, C. J. (2017). Evidence of a goal-directed

process in human pavlovian-instrumental transfer. *Journal of Experimental Psychology: Animal Learning and Cognition*, *43*(4), 377–387. https://doi.org/10.1037/xan0000147

Swart, J. C., Frank, M. J., Määttä, J. I., Jensen, O., Cools, R., & den Ouden, H. E. M. (2018). Frontal network dynamics reflect neurocomputational mechanisms for reducing maladaptive biases in motivated action. *PLoS Biology*, *16*(10), 1–25. https://doi.org/10.1371/journal.pbio.2005979

Talmi, D., Seymour, B., Dayan, P., & Dolan, R. J. (2008). Human Pavlovian Instrumental Transfer. *Journal of Neuroscience*, *28*(2), 360–368. https://doi.org/10.1523/JNEUROSCI.4028-07.2008

Turi, Z., Csifcsák, G., Boayue, N. M., Aslaksen, P., Antal, A., Paulus, W., Groot, J., Hawkins, G. E., Forstmann, B., Opitz, A., Thielscher, A., & Mittner, M. (2019). Blinding is compromised for transcranial direct current stimulation at 1 <scp>mA</scp> for 20 min in young healthy adults. *European Journal of Neuroscience*, *50*(8), 3261–3268. https://doi.org/10.1111/ejn.14403

Unsworth, N., Heitz, R. P., Schrock, J. C., & Engle, R. W. (2005). An automated version of the operation span task. *Behavior Research Methods*, *37*(3), 498–505. https://doi.org/10.3758/BF03192720

van Holstein, M., Froböse, M. I., O'Shea, J., Aarts, E., & Cools, R. (2018). Controlling striatal function via anterior frontal cortex stimulation. *Scientific Reports*, *8*(1), 3312. https://doi.org/10.1038/s41598-018-21346-5

van Steenbergen, H., Watson, P., Wiers, R. W., Hommel, B., & de Wit, S. (2017). Dissociable corticostriatal circuits underlie goal-directed vs. cue-elicited habitual food seeking after satiation: evidence from a multimodal MRI study. *European Journal of Neuroscience*, *46*(2), 1815–1827. https://doi.org/10.1111/ejn.13586

Wallis, J. D., & Miller, E. K. (2003). Neuronal activity in primate dorsolateral and orbital prefrontal cortex during performance of a reward preference task. *European Journal of Neuroscience*, *18*(7), 2069–2081. https://doi.org/10.1046/j.1460-9568.2003.02922.x

Watson, P., Wiers, R. W. W., Hommel, B., & De Wit, S. (2014). Working for food you don't desire. Cues interfere with goal-directed food-seeking. *Appetite*, *79*(February 2016), 139–148. https://doi.org/10.1016/j.appet.2014.04.005

Xue, G., Juan, C.-H., Chang, C.-F., Lu, Z.-L., & Dong, Q. (2012). Lateral prefrontal cortex contributes to maladaptive decisions. *Proceedings of the National Academy of Sciences*, *109*(12), 4401–4406. https://doi.org/10.1073/pnas.1111927109

Ziemann, U., Paulus, W., Nitsche, M. A., Pascual-Leone, A., Byblow, W. D., Berardelli, A., Siebner, H. R., Classen, J., Cohen, L. G., & Rothwell, J. C. (2008). Consensus: Motor cortex plasticity protocols. In *Brain Stimulation* (Vol. 1, Issue 3, pp. 164–182). https://doi.org/10.1016/j.brs.2008.06.006

FIGURE CAPTIONS

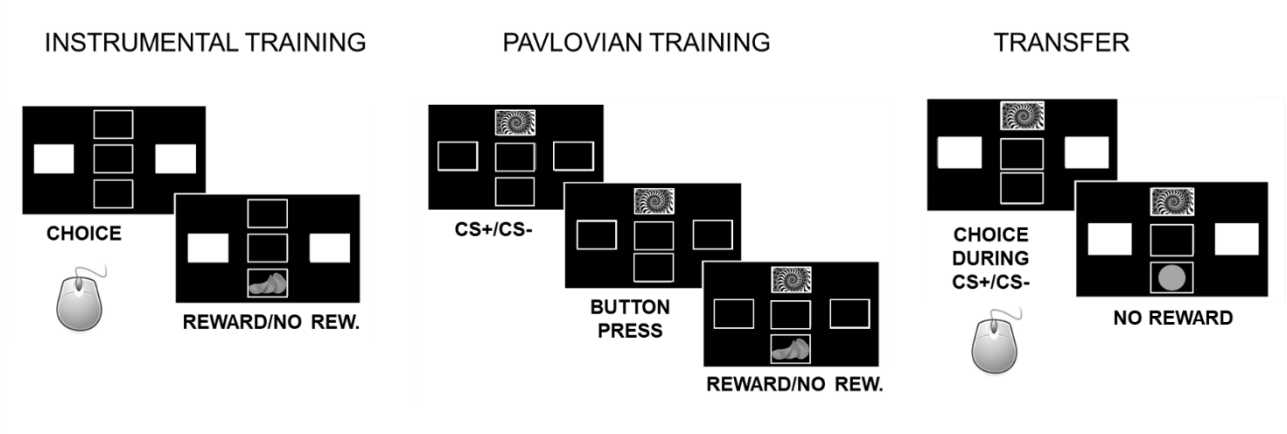

Figure 1. Pavlovian-to-Instrumental Transfer (PIT) task. Visual representation of the three task phases to test for the PIT effect. During instrumental conditioning, participants learned the association between three instrumental responses and the associated reward or neutral outcome. During Pavlovian conditioning, the same rewards were associated with visual stimuli. During PIT, participants were asked to perform the again an instrumental choice under extinction (i.e., in the absence of rewards) while being presented with task-irrelevant Pavlovian stimuli.

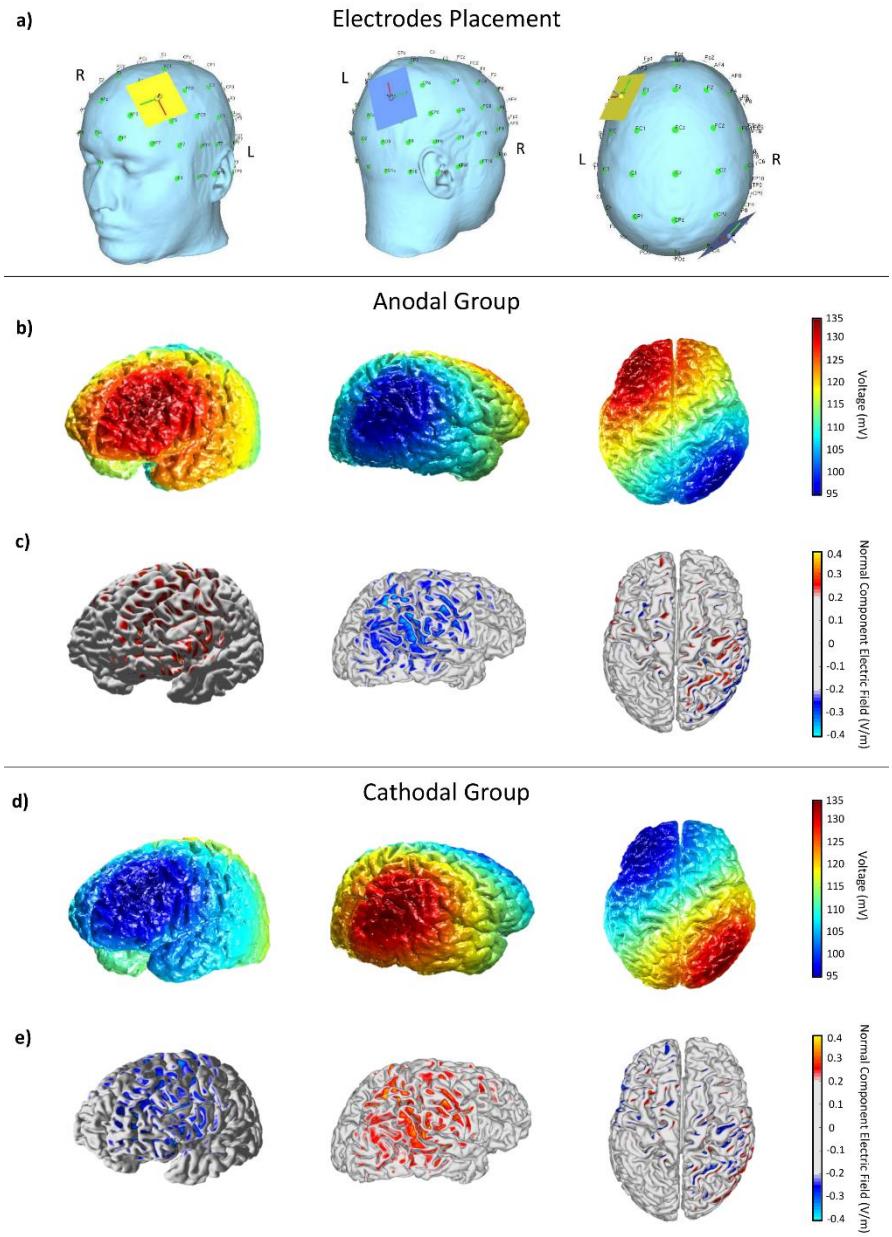

Figure 2. tDCS montage and stimulation. Representation of electrodes placement (panel a), computational models of voltages distribution (panels b and d) and normal component of electric field induced by tDCS (panels c and e) for the anodal and cathodal groups, respectively.

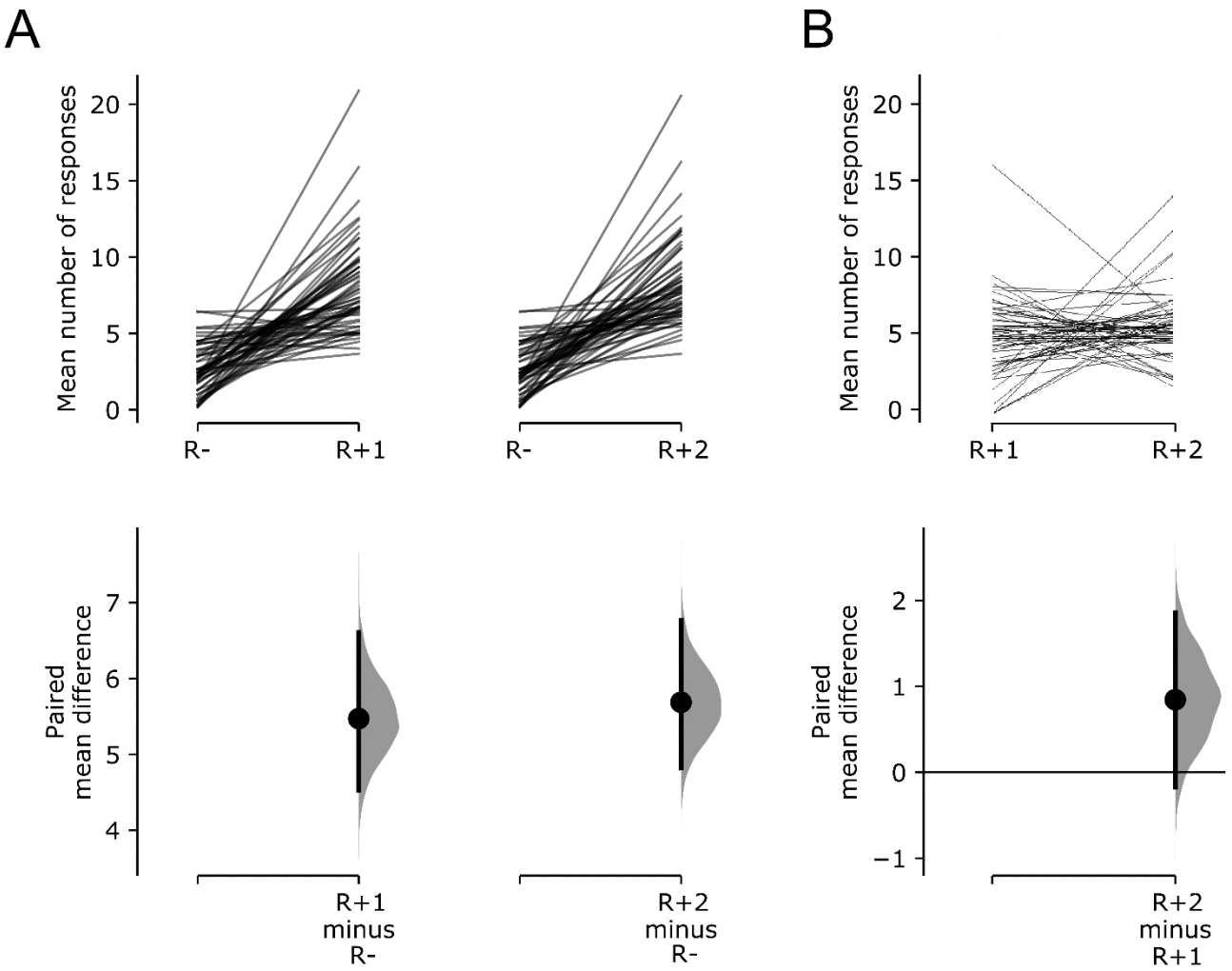

Figure 3. Acquisition of instrumental learning. Cumming estimation plots showing raw data on the upper axes and paired mean difference between (A) rewarded (R+1 and R+2) and non-rewarded (R-) responses and (B) between the two rewarded responses during instrumental training. On the upper axes, each paired set of observations is connected by a line. On the lower axes, 95% confidence intervals are indicated by vertical error bars, and mean differences, plotted as a bootstrap sampling distribution (5000 samples), are depicted as dots. Confidence intervals of the paired mean difference show (A) more rewarded than non-rewarded responses during instrumental learning, and (B) no difference in the number of rewarded responses.

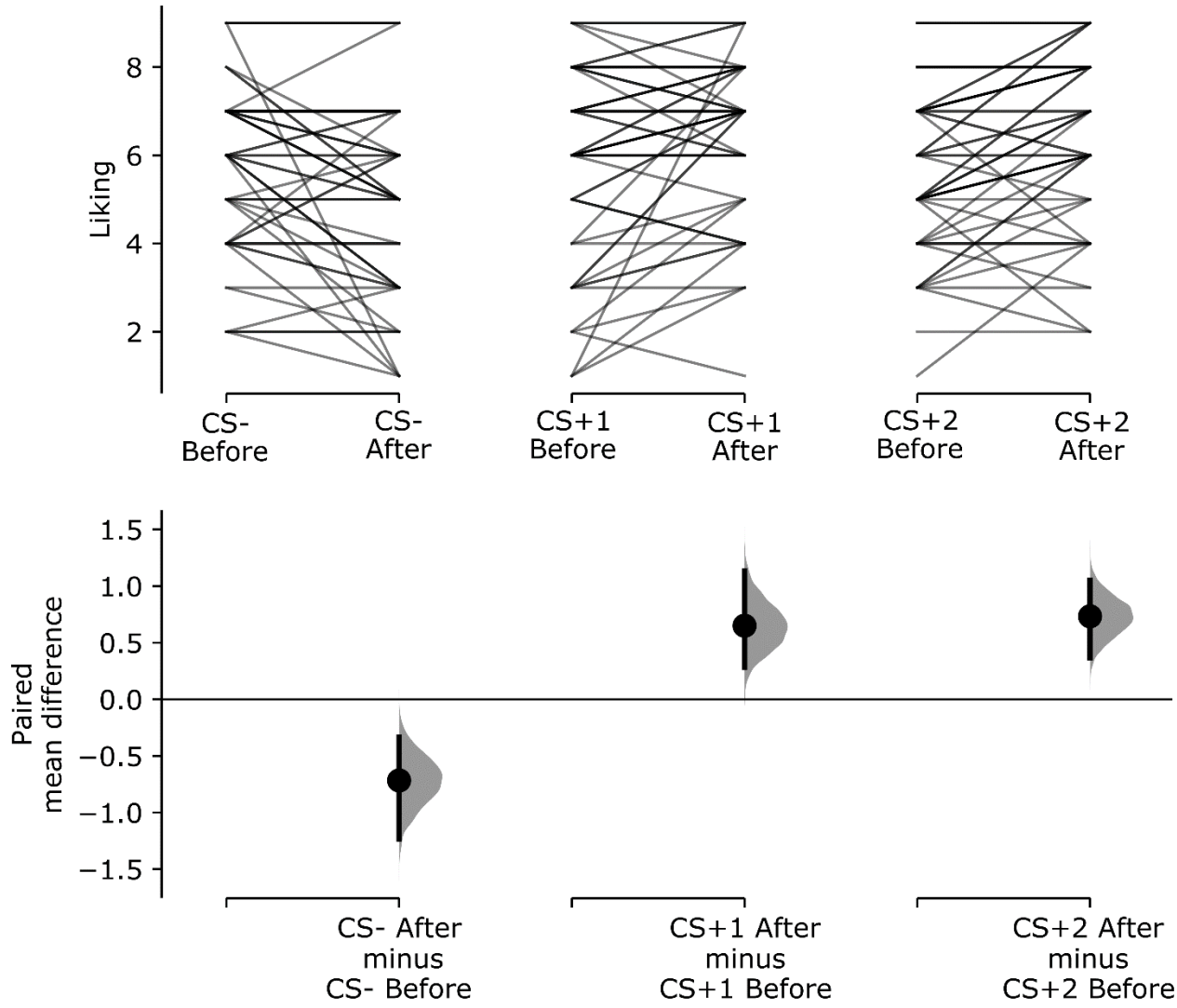

Figure 4. Acquisition of Pavlovian learning. Cumming estimation plots showing raw data on the upper axes and paired mean difference of liking rating between after and before Pavlovian training, for each CS. On the upper axes, each paired set of observations is connected by a line. On the lower axes, 95% confidence intervals are indicated by vertical error bars, and mean differences, plotted as a bootstrap sampling distribution (5000 samples) are depicted as dots. Confidence intervals of the paired mean difference show a decrease in liking for the CS- and an increase in liking for CS+1 and CS+2 after Pavlovian training.

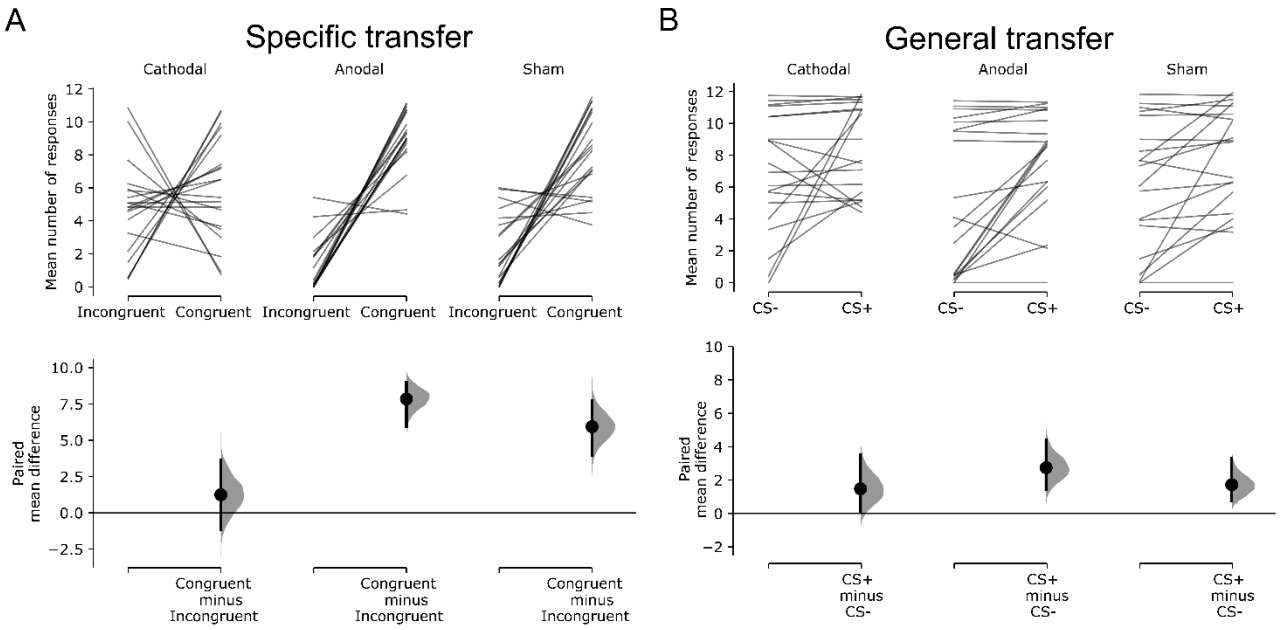

Figure 5. Transfer effect. Cumming estimation plots showing raw data on the upper axes and paired mean difference in the mean number of (A) congruent vs. incongruent responses and (B) rewarded responses when seeing a CS+ and CS- for each group. On the lower axes, 95% confidence intervals are indicated by vertical error bars, and mean differences, plotted as a bootstrap sampling distribution (5000 samples) are depicted as dots. Confidence intervals of the paired mean difference show (A) more congruent than incongruent responses (i.e. outcome-specific transfer) in the Anodal and Sham groups but not in the Cathodal group and (B) more rewarded responses when in presence of CS+ than CS- (i.e. general transfer) in all groups.