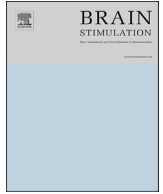




ELSEVIER

Contents lists available at ScienceDirect

## Brain Stimulation

journal homepage: <http://www.journals.elsevier.com/brain-stimulation>

## Stimulating the ventrolateral prefrontal cortex (VLPFC) modulates frustration-induced aggression: A tDCS experiment

Alessia Gallucci <sup>a,\*</sup>, Paolo Riva <sup>a</sup>, Leonor J. Romero Lauro <sup>a</sup>, Brad J. Bushman <sup>b</sup><sup>a</sup> University of Milano-Bicocca, Milan, Italy<sup>b</sup> The Ohio State University, Columbus, OH, USA

## ARTICLE INFO

*Article history:*

Received 7 June 2019

Received in revised form

7 October 2019

Accepted 18 October 2019

Available online xxx

*Keywords:*

Frustration

Aggression

Transcranial direct current stimulation (tDCS)

Ventrolateral prefrontal cortex (VLPFC)

## ABSTRACT

**Background:** The prefrontal cortex is crucial for top-down regulation of aggression, but the neural underpinnings of aggression are still poorly understood. Past research showed the transcranial direct current stimulation (tDCS) over the ventrolateral prefrontal cortex (VLPFC) modulates aggression following exposure to risk factors for aggression (e.g., social exclusion, violent media). Although frustration is a key risk factor for aggression, no study to date has examined the modulatory role of tDCS on frustration-induced aggression.

**Objectives:** By exploring the VLPFC involvement in frustration-aggression link, we tested the hypothesis that the anodal tDCS over right and left VLPFC modulates frustration-induced aggression. We also explored whether tDCS interacts with gender to influence frustration-induced aggression.

**Methods:** 90 healthy participants (45 men) were randomly assigned to receive anodal or sham tDCS over the right or left VLPFC before being frustrated by an accomplice. To increase reliability, several tasks were used to measure aggression.

**Results:** We found that anodal tDCS over the left VLPFC, compared to sham stimulation, increased aggression. Unexpectedly, no main effect was found following tDCS of right VLPFC. However, we also found a significant interaction between gender and tDCS, showing that males were more aggressive than females following sham stimulation, but females became as aggressive as males following active tDCS.

**Conclusion:** Overall, these results shed light on the neural basis of frustration-induced aggression, providing further evidence for the involvement of VLPFC in modulating aggressive responses, and on gender differences in aggression. Future research should further investigate the role of stimulating the VLPFC on frustration-induced aggression.

© 2019 Elsevier Inc. All rights reserved.

### Stimulating the ventrolateral prefrontal cortex (VLPFC) modulates frustration-induced aggression: a tDCS experiment

“Frustration is the wet nurse of violence.”

— David Abrahamsen, Norwegian forensic psychiatrist

One of the earliest proposed causes of aggression was frustration, defined as blocking or obstructing goal-directed behavior [1].

Despite the prominent role of frustration on aggression, no research has examined the neural mechanisms involved.

#### *The regulatory role of the pre-frontal cortex on aggression*

Past research has examined the role of the prefrontal cortex on aggression and violence [2–5]. The prefrontal network is crucial for a top-down control over subcortical regions involved in processing threatening stimuli, including frustrations [6–8]. Particularly, the ventrolateral prefrontal cortex (VLPFC) is critical for self-control and emotion regulation processes [9–13] including control over aggressive impulses.

Both hemispheres are involved. Studies of the right hemisphere show that the rVLPFC can play a role in decreasing a wide range of negative emotions that can trigger aggression [12,14–21]. Studies also show that the degree of rVLPFC activity, as well as the degree of

\* Corresponding author.

E-mail addresses: [a.gallucci@campus.unimib.it](mailto:a.gallucci@campus.unimib.it) (A. Gallucci), [paolo.riva1@unimib.it](mailto:paolo.riva1@unimib.it) (P. Riva), [l.romerolauro@gmail.com](mailto:l.romerolauro@gmail.com) (L.J. Romero Lauro), [bushman.20@osu.edu](mailto:bushman.20@osu.edu) (B.J. Bushman).

<https://doi.org/10.1016/j.brs.2019.10.015>

1935-861X/© 2019 Elsevier Inc. All rights reserved.

negative interplay between the rVLPFC and the amygdala, significantly correlated with self-reported negative emotions [13,22–24]. The rVLPFC is also involved in controlling the impulses [25–30], which might include aggressive impulses.

Studies of the left hemisphere show that the lVLPFC is recruited especially in reappraisal-related emotion regulation strategies [16,31,32], and impulsivity control [29,30,33]. Moreover, it has been hypothesized that the rVLPFC is involved in both conscious and unconscious control, whereas the lVLPFC is only involved in conscious control [34]. Self-control is critical when it comes to inhibiting aggressive impulses. Indeed aggression often starts when self-control stops [35].

Anger is associated with approach motivation [64]. Approach motivational processes are associated with greater left than right frontal activity, whereas avoidance motivational processes are associated with greater right than left frontal activity. This asymmetric frontal cortical activity could affect the onset of aggressive responses. Thus, this experiment examines the role of both hemispheres on frustration-induced aggression.

#### Using tDCS over the pre-frontal cortex to study aggression

The neural mechanisms of aggression can be studied using non-invasive brain stimulation approach, such as Transcranial Direct Current Stimulation (tDCS). tDCS is a noninvasive neuromodulatory technique that delivers weak electrical currents through a pair of electrodes placed on the scalp. The electrical currents affect the excitability of cortical neurons beneath the electrodes in a polarity-dependent fashion: anodal stimulation typically enhances neural excitability, whereas cathodal stimulation reduces it [36].

Focusing on the modulation of aggression, past research has found that anodal tDCS applied over the rVLPFC decreases aggressive reactions elicited by several stimuli, including social rejection [38] and exposure to violent video games [39]. These results suggest that it is possible to influence the neurocircuitry implicated in successful self-regulation by modulating the cortical excitability of brain regions involved in the top-down regulation of aggression. However, to our knowledge, no study has tested whether tDCS applied over the VLPFC modulates frustration-induced aggression. This study attempts to fill this gap in the literature, exploring whether the effects of tDCS on aggression can be differently modulated by the type of aversive stimuli, in this case frustration, as compared to other stimuli investigated in past studies, such as social exclusion or video games [38,39].

Studies of the left hemisphere show that applying tDCS to increase relative left frontal cortical activity results in angry people behaving more aggressively [40,41]. Particularly, receiving a provocation after tDCS stimulation to left frontal cortex leads people to choose louder and longer noise blasts towards an ostensible partner [40], and reduces aggression inhibitions [41].

#### Gender differences in frustration-induced aggression

Previous research has shown that males are less tolerant of frustration than females [42,43]. However, no study has investigated whether tDCS can affect gender differences in frustration-induced aggression.

Previous research has found that tDCS interacts with gender to strengthen some crucial cognitive abilities. For instance, one study found that anodal tDCS over the medial prefrontal cortex enhanced performance on a theory of mind task in females more than males [44]. Another study found that anodal tDCS of the left temporal cortex improved emotion detection abilities in females more than males [45]. Still another study found that anodal stimulation

applied over the VPFC increased utilitarian responses on a moral judgment task in females more than males [46]. In this study, we explored the possibility that tDCS stimulation might influence the gender differences in frustration-induced aggression.

#### Overview

This study investigated the modulatory role of the VLPFC on the link between frustration and aggression. Participants were first frustrated by means of an unsolvable task and were then randomly assigned to receive either anodal tDCS to the rVLPFC, anodal tDCS to the lVLPFC, or sham tDCS. Following stimulation, aggression was measured using three well-validated behavioral paradigms. In line with previous studies, we predicted a decrease in aggression following anodal stimulation of the rVLPFC [38,39]. Based on other studies, we also predicted that anodal tDCS to the lVLPFC would increase aggression [40,41,47,48]. Finally, we explored gender differences in the effects of tDCS on frustration-induced aggression.

#### Method

##### Participants

Participants were 90 healthy adults from Milan, Italy (45 males and 45 females, mean age = 22.27,  $SD = 2.46$ ). Of these, 73% were university students. However, we excluded psychology students who might be suspicious about procedures. Because results were similar for university students and non-students, data from the two groups were combined. All participants had normal or corrected to normal vision, and reported no history of neurological or psychiatric disorders, and no contraindications to tDCS [49]. Participants received 10€ (about \$11) in exchange for their voluntary participation. The study was approved by the ethics committee of the University of Milano-Bicocca and conducted in accordance with the ethical standards of the revised Helsinki Declaration.

##### Frustration task

To induce frustration, participants were asked to solve number sequences that were unsolvable [50]. Specifically, participants were asked to complete 6 numerical sequences that an online partner of the same gender chose for them. The partner could select among 6 easy sequences (e.g. 16-14-12-10-8-6-4-?) and 6 difficult sequences (e.g. 9-6-18-19-7-5-10-?). The “difficult” sequences were actually unsolvable. The ostensible partner chose 6 difficult sequences and 0 easy sequences for the participant to solve. Participants had up to 30 s to solve each number sequence. To increase stress, a digital clock showed the time counting down. After 30 s, participants saw the message “incorrect response”. To increase motivation, participants were told that they could earn an extra 1€ for each sequence they solved (in actually, all participants received 10€). Participants were given two easy training sequences to solve to make sure they understood the procedure. There actually was no partner; the task was controlled by a computer. To assess whether the frustrating task induced more negative emotions than positive emotions, participants completed an adjective checklist that contained 9 negative emotions (*angry, anxious, hurt, injured, irritated, mad, nervous, pained, tense*; Cronbach  $\alpha = 0.91$ ) and 3 positive emotions (*cheerful, delighted, happy*; Cronbach  $\alpha = .93$ ) on a scale ranging from 1 (*not at all*) to 7 (*extremely*).

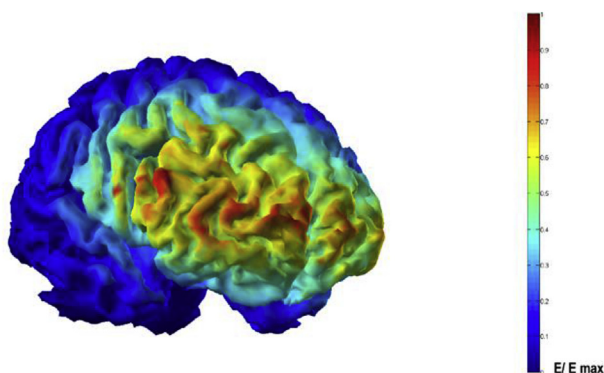
##### tDCS

tDCS was delivered using a battery-driven, constant current stimulator (BrainStim, EMS, Bologna, Italy, <http://brainstim.it>),

through a pair of saline-soaked sponge electrodes. Participants were randomly assigned to one of three conditions: (a) anodal tDCS over the rVLPFC, (b) anodal tDCS over the lVLPFC, or (c) sham tDCS. In accordance with tDCS safety standards [49,51], the 20 min of stimulation was administered at 1.5 mA, with a  $5 \times 5$  anode (0.06 mA/cm<sup>2</sup> current density) and a  $7 \times 5$  cathode (0.042 mA/cm<sup>2</sup> current density). A fade-in/fade-out phase of 10 s was used at the beginning/end of the stimulation to diminish its perception. The 10–20 system was used to place electrodes. To stimulate the rVLPFC, the anode was placed over F6 (Montreal Neurological Institute coordinates: 58, 30, 8; 6); the contralateral homolog area (F5) was targeted for the stimulation of the lVLPFC. In both conditions, the cathodal reference electrode was placed over the contralateral supraorbital area. Fig. 1 shows a three-dimensional (3D) numerical computation of the electric field generated by tDCS according to the used montage, based on an MR-derived finite element model and computed using Comets Matlab toolbox ([52] <http://www.COMETStool.com>). For sham tDCS, the same electrode montage was used, placing the anode over one of the target areas, which was randomized across participants. However, the stimulation was active only for 10 s at the beginning and 10 s at the end of the 20 min stimulation period, which ensured that participants felt the initial itching sensation without any modulation of cortical excitability [53]. To keep both the experimenter and the participant blind to condition, condition codes were set through the BrainStim software, which controlled the tDCS device. At the end of the experimental session, participants were asked to rate how much pain they experienced (0 = no pain to 10 = the maximum conceivable pain).

### Procedure

The experiment was conducted in two sessions (see Fig. 2). In the first session, participants completed online three self-report questionnaires thought to measure individual difference relevant to frustration-induced aggression: (a) the Physical Aggression subscale of the Buss Perry Aggression Questionnaire [54,55], which consists of 9-items (e.g. “Sometimes it happens to me that I am not able to control the desire to beat another person”; Cronbach  $\alpha=.78$ ); (b) the Negative Urgency subscale of the Urgency, Pre-mediation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale [56,57], which consists



**Fig. 1. Computational model of tDCS-induced electric field.** A simulation of the electrical field induced by tDCS over the rVLPFC was computed using Comets. The anode (25 cm<sup>2</sup>) was placed over the rVLPFC, corresponding to F6 electrode according to the 10–20 EEG system. The cathode (35 cm<sup>2</sup>) was placed on the contralateral supraorbital area. Red parts indicate the strongest electrical field, occurring over the lateral and ventral portion of the right prefrontal cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

of 12-items (e.g. “I have difficulty controlling my impulses”; Cronbach  $\alpha=.87$ ); and (c) the Trait Anger Scale [58], which consists of 10-items (e.g. “I am a hot-headed person”; Cronbach  $\alpha=.85$ ). All items were scored using a 7-point scale (1 = not at all to 7 = extremely). We used these three questionnaires to ensure that the groups did not differ on these traits prior to receiving tDCS stimulation.

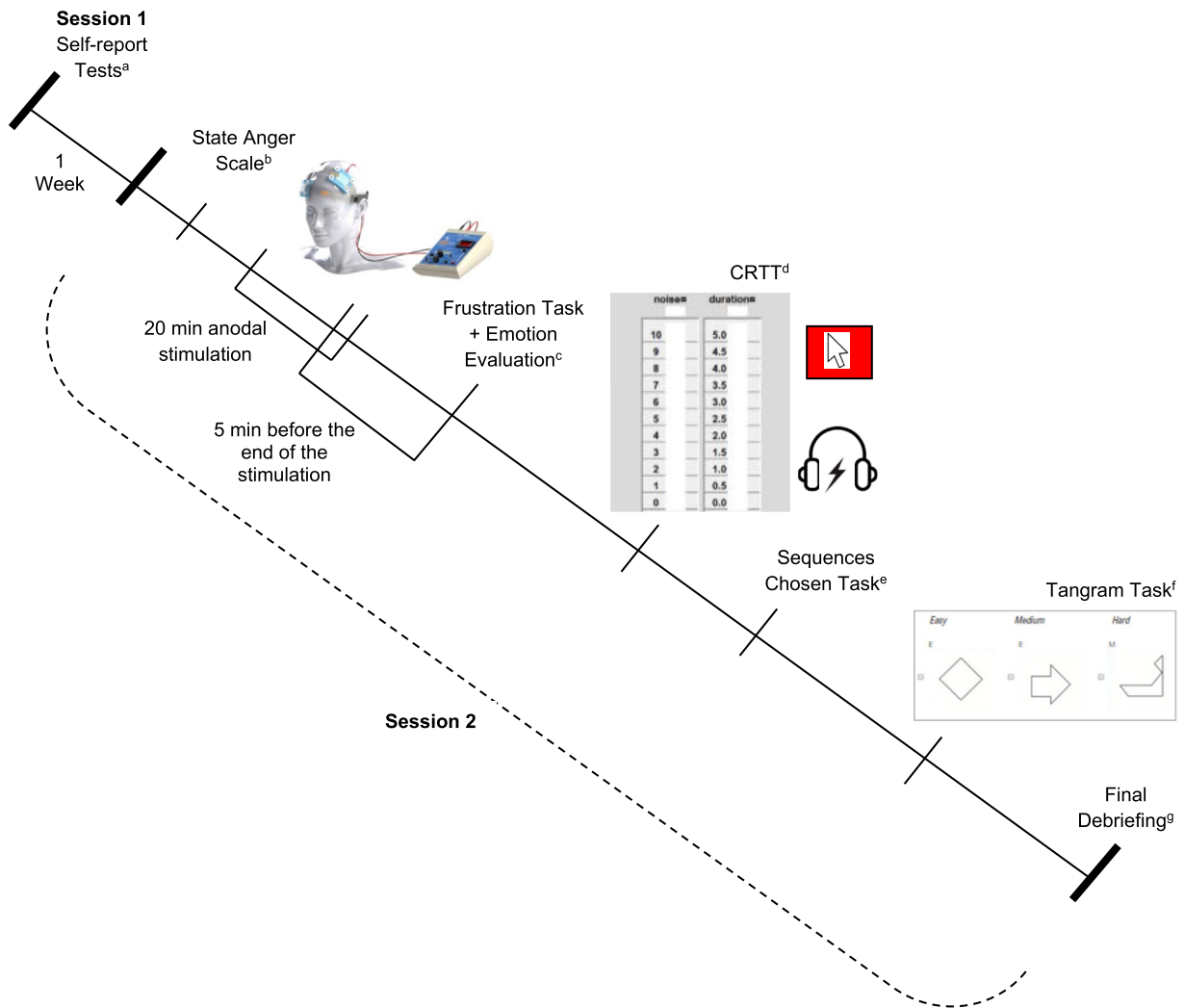
The second session occurred a week later in a laboratory at the Department of Psychology, University of Milano-Bicocca. To determine whether anger levels were similar before the frustration induction, participants first completed the State Anger Scale [58], which contains 7 items used to describe how they felt at that moment (e.g., “Angry”; 1 = not at all to 7 = extremely; Cronbach  $\alpha=.92$ ). Next, tDCS stimulation was administered. As a cover story, participants were told that the researchers were studying the effects of non-invasive stimulation on mental visualization on a series of tasks. Five minutes before the end of the tDCS stimulation, participants completed the frustration task. Following tDCS stimulation, three tasks were used to measure aggression. The first task was the competitive reaction-time task (CRTT; [59]), which was supposedly completed with an ostensible partner of the same gender. The task, which took about 8 min to complete, required the participant and the partner to press a button as fast as possible on each of 9 trials. The winner on each trial gave the loser noise blasts through headphones. The noise was a mixture of unpleasant noises (e.g., finger nails scratching on chalk boards, dentist drills, blow horns, sirens). Before each trial, participants set the level (ranging from 60 dB - level 1 – 105 dB - level 10) and the duration (from 0.5 to 5 s) of noise their partner would receive if their partner lost that trial. A non aggressive no-noise option (level 0) was also provided. At the end of each trial, participants saw the noise intensity and duration levels the partner set. Before the competition, participants received sample noise blasts at levels 2 (low noise) and 8 (high noise) to ensure they knew the noise was indeed unpleasant. The first trial was used to assess unprovoked aggression because participants had not received any noise blasts yet, and the following 8 trials were used to assess provoked aggressiveness. The partner set the maximum intensity and duration of noise on trial 1, and random noise levels on the remaining 8 trials. The participants lost trial 1, and half of the remaining 8 trials (randomly determined). The intensities and durations of noise participants set for their partner across all trials were the first aggression measure.

In the second task, participants chose 6 numerical sequences for their partner to solve among the 6 easy and 6 “difficult” (actually impossible) sequences. The number of “difficult” sequences participants chose for their partner was used as the second aggression measure.

In the third task, participants chose 11 Tangram puzzles for their partner to solve [60]. Participants could select the level of difficulty of the Tangram puzzles among 30 puzzles (10 easy, 10 medium, 10 difficult). Participants were informed that the partner could win 10€ if they successfully solved all 11 Tangram puzzles within 10 min. The number of difficult Tangram puzzles participants chose for their partner was the third aggression measure. A debriefing followed.

### Statistical analyses

Data were analyzed using SPSS Statistics (Version 25.0). We considered three indices of aggressiveness (i.e., mean of intensities and durations across all 9 trials on the CRTT, number of impossible number sequences, number of difficult Tangram puzzles). The correlations between these aggression indices were quite strong (see Table 1). The three measures had good internal reliability (Cronbach  $\alpha=.72$ ). A principal component analysis also obtained a



<sup>a</sup> Physical Aggression subscale (Buss Perry Aggression Questionnaire [54,55]; Negative Urgency subscale (Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale [56,57]); Trait Anger Scale [58].

<sup>b</sup> The State Anger Scale [58] evaluates the anger levels from 1 (*not at all*) to 7 (*extremely*).

<sup>c</sup> The 6 impossible sequences chosen for participants by the ostensible partner. An evaluation of the positive and negative emotions caused by the task followed.

<sup>d</sup> The 9 trials of the CRTT [59].

<sup>e</sup> The 6 numerical sequences (easy versus impossible) chosen for the ostensible partner by participants.

<sup>f</sup> The 11 Tangram [60] puzzles (easy versus medium versus difficult) chosen for the ostensible partner by participants.

<sup>g</sup> Participants were debriefed about the experimental procedure and the mental visualization cover story.

**Fig. 2.** Schematic experimental procedure.

single factor of aggression, which explained 64% of the variance. To obtain a more reliable measure of aggression, the three indices were standardized and averaged (see Supplementary Materials for analyses of each aggression measure separately).

Data were analyzed using a 3 (stimulation condition: tDCS to the rVLPFC, tDCS to the IVLPFC, sham tDCS) x 2 (gender: male, female) between-subjects Analysis of Variance (ANOVA). Fisher's Least Significant Difference (LSD) was used for post hoc comparisons.



**Table 1**  
Pearson correlations between aggression outcomes.

	Impossible sequences	Difficult Tangram puzzles	CRTT noise all trials
Impossible sequences	1	.54**	.48**
Difficult Tangram puzzles		1	.36**
CRTT noise all trials			1

Note. All outcomes were standardized. CRTT = competitive reaction time task. \*\* $p < .01$  (2-tailed).

## Results

### Preliminary analyses

#### Individual differences

ANOVA found that trait anger [ $F(2, 86) = 2.85, p = .06$ ], physical aggressiveness [ $F(2, 86) = 0.32, p = .73$ ], and negative urgency scores [ $F(2, 86) = 1.84, p = .17$ ] did not significantly differ across conditions. Thus, the groups were similar in their initial level of aggressiveness before the frustration induction.

#### State Anger Scale

ANOVA found that state anger levels did not differ across the three tDCS conditions [ $F(2, 87) = 0.10, p = .90$ ]. Thus, initial anger levels were similar across conditions.

#### Frustration task

As expected, participants experienced more negative ( $M = 3.44, SD = 1.51$ ) than positive emotions ( $M = 1.70, SD = 1.03$ ) following the induction of frustration,  $t(89) = 7.933, p < .001, d = 1.35$ . Thus, it appears that the frustration task produced negative feelings.

#### Pain from electrodes

Similar to past research (Nitsche et al., 2008), participants reported experiencing slight pain from the electrodes ( $M = 1.65, SD = 1.36$ ). Crucially, self-reported pain did not vary across the three experimental conditions,  $\chi^2(2) = 0.86, p = .65$ . Thus, the sham condition was successful.

#### Primary analyses

ANOVA found a main effect for stimulation condition,  $F(2,84) = 3.57, p = .033$ . Post hoc comparisons showed that participants who received anodal stimulation to the IVPFC behaved more aggressively ( $M = 0.24, SD = 0.14$ ) than participants who received sham stimulation ( $M = -0.28, SD = 0.14, p = .009, d = 3.78$ ). Unexpectedly, we did not find differences between rVLPFC tDCS and sham stimulation ( $p = .17, d = 1.98$ ), or between rVLPFC tDCS and IVPFC tDCS ( $p = .22, d = 1.80$ ). Analysis showed a significant main effect of gender, with higher levels of aggression in males ( $M = 0.15, SD = 0.11$ ) than in females ( $M = -0.18, SD = 0.11$ ),  $F(1,84) = 4.24, p = .043, d = 3.03$ . However, active stimulation seemed to reduce the gender difference, as indicated by a significant tDCS by gender interaction,  $F(2,84) = 3.52, p = .034$  (Fig. 3). Males were more aggressive than females following sham stimulation ( $p = .002, d = 4.82$ ), but females were not less aggressive than males following active tDCS, regardless of whether it was administered to the left ( $p = .002, d = 4.61$ ) or right ( $p = .007, d = 4.07$ ) hemisphere.

## Discussion

Although past research has found that frustration increases aggression [1], the neural mechanisms of the frustration-aggression link have not been fully investigated. To our knowledge, this is the first study to test the effect of non-invasive brain

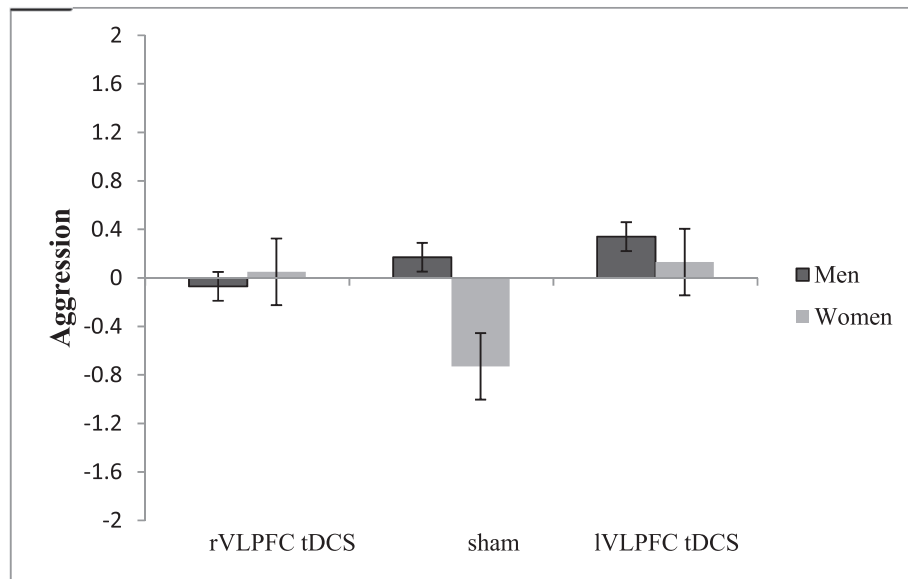
stimulation effects on frustration-induced aggression. We explored the possible modulatory role of the anodal tDCS applied to the VLPFC, a cortical area involved in self-control [10,13,18,34], on frustration-induced aggression.

We found that increasing the cortical excitability of the IVPFC significantly increased aggression following frustration. This result is consistent with the motivational direction model of frontal asymmetry [61], in which approach motivations are related to greater left than right frontal activity [47,48,62,63]. According to this model, because anger is associated with approach motivations, people are more likely to behave aggressively when angry [40,41,64]. In our study, we first exposed participants to frustration, which is known to be associated with anger, and then gave them a chance to aggress against the fictitious partner who had frustrated them on several standard laboratory aggression paradigms. Our results suggest that anodal stimulation over IVPFC likely enhanced the approach motivations as shown by an increase in aggressive reactions.

Moreover, we found a significant interaction between gender and tDCS on frustration-induced aggression. Specifically, we replicated the finding that males are more aggressive than females in the sham (control) condition [42,43]. Importantly, our study is the first to show that left- and right-side stimulation eliminated this gender difference, because after tDCS males were no more aggressive than females. Different explanations might account for these null gender differences. One possibility is that the way females handle environmental demands becomes more similar to that of males after tDCS, even at the expense of socially acceptable behaviors. This explanation is consistent with the findings from a moral judgment study that found gender differences in utilitarian and socially desirable responses were eliminated after anodal stimulation of the ventral prefrontal cortex [46]. We can hypothesize that anodal tDCS drives females to adopt an “eye for an eye” strategy following frustration, overcoming their tendency to behave in a less aggressive and more socially desirable manner.

Second, it could be that tDCS is more effective for females than males. It is well known that there is high variability in the tDCS effects on cognition and behavior (for a review see Ref. [65]) and that many inter-individual factors moderate these effects, including gender (e.g. Refs. [66,67]). Previous research has found greater effects of tDCS on females than males across several tasks (e.g., go-no-go, Theory of Mind; [44,45]). However, the existence of a differential effect of tDCS on males versus females can be clearly inferred only when the outcome measures are the same at a baseline (i.e. are not influenced by gender). This was not the case in our study. Another possibility is that the strong difference between males and females' aggressive reactions we found at the baseline could conceivably be a possible ceiling effect for males, nullifying any modulatory effects of tDCS.

Regarding the right hemisphere, we expected to find that anodal stimulation decreases aggression. However, our current results are inconsistent with previous findings [37–39]. Two possible explanations could account for this unexpected result. First, previous studies focused on affective valence, such as by asking participants only to rate their negative emotions following the experimental task [37], whereas the present study focused on approach



**Fig. 3.** Composite aggression index scores (i.e., mean of standardized aggression outcomes: CRTT all trials; the number of impossible sequences; the number of difficult Tangram puzzles) of males and females in the tDCS conditions. Capped vertical bars denote standard error.

motivation. When the focus is on affective valence, negative emotions are more likely related to greater right than left frontal activity. However, when the focus is on motivation direction (e.g., approach), negative emotions are more likely related to left than right frontal activity [64]. Several studies have demonstrated that the chance of tDCS long-lasting effects, likely affecting brain plasticity, relies upon ongoing brain activity [68,69]. TDCS stimulation depends upon the functional networks active while processing aversive stimuli. Therefore, applying tDCS over rVLPFC during tasks involving either affective valence or motivation direction could lead to different results. During tasks involving affective valence, tDCS over the rVLPFC did effectively decrease negative emotions evaluation (e.g. Refs. [21,37]). In our experiment, because the focus was on motivation direction (i.e., a “partner” first frustrated participants, and then we allowed them to aggress against their “partner”), consistent with the model of prefrontal asymmetry, we found a significant effect of anodal tDCS over IVLPFC on aggression, but no effect of anodal tDCS over rVLPFC on aggression.

A second explanation is that frustration is qualitatively different from other factors known to cause aggression (e.g., social exclusion, violent video games). Several fMRI studies reported specific abnormal activations in the prefrontal network in response to frustration [70]. However, results are still inconsistent. Indeed, some studies showed a decrease of activation in the frontal regions [71], whereas other studies showed an increase of activation in the right ventral prefrontal, medial prefrontal, anterior cingulate and dorsolateral prefrontal cortex in response to frustration [72,73]. Moreover, frustration-related neural responses are not linear, because several factors affect their variability, including trait aggressiveness [71] and susceptibility to frustration [73]. Thus, future research is needed to investigate the neural mechanisms involved in aggressive responses to frustration, compared to other factors linked to aggression. We believe that this will allow researchers to build more precise models of the neural underpinning of aggression when triggered by different factors.

This study, like all studies, has limitations. Our design allowed us to test the effects of frustration on aggression above and beyond the effects of provocation, which was held constant across conditions

(i.e., all participants were provoked on the first trial of the CRTT). However, the first limitation is that we did not include a no-frustration control condition. Because all participants were frustrated, we could not explore possible stimulation differences across our three stimulation groups between frustrated and non-frustrated participants. Including a no-frustration control condition would be key for future studies. Future studies could also take advantage of the possibility of assessing baseline levels of negative emotions and aggressiveness to detect changes over time linked with frustration and neuromodulation.

Another possible methodological limitation is that we did not consider a third group of participants comparing the stimulation of the VLPFC with stimulation of a control area. Future studies with larger samples could stimulate different cortical areas. For example, posterior regions, such as the temporoparietal junction, which is involved in the mentalizing network, could affect frustration-induced aggression [74]. In our study, we asked the participants to report previous neurological and psychiatric disorders. Although this procedure is common when testing healthy participants, we can not rule out the presence of anxiety or depressive disorders the participants were not aware of. Future research should also consider running a proper battery of tests screening for clinical, neurological and psychiatric disorders rather than relying on self-reports.

Another possible limitation is the well-known low spatial resolution of tDCS. Although in the present experiment a larger amount of current was caused by the small distance between the two electrodes, computational models of current flow have shown that tDCS usually results in a spread of electric fields that occur underneath the stimulating electrodes as well as in the regions between them [75]. Thus, we cannot rule out the possibility that the stimulation affected other areas within the prefrontal cortex, such as the dorsolateral prefrontal cortex, that have a key role for top-down monitoring [10,11,13]. Further research with more focal techniques (e.g., TMS) could specify our results. Future research should also consider adopting cathodal stimulation over the target regions to test for differential effects linked with tDCS polarity.

## Conclusion

Our results show that modulating the cortical excitability of left and right VLPFC affects frustration-related aggression. Our experiment extends previous research on the modulatory role of VLPFC in a wide range of domains [9,11–13,76]. It also extends previous research on gender differences in aggression. More generally, our results support the feasibility of applying non-invasive brain stimulation techniques to study self-regulation processing and contribute to the growing knowledge about the neural underpinnings of aggression regulation. However, the lack of a reduction on aggressive tendencies in the context of frustration suggests that caution should be exercised when considering clinical or therapeutic uses of tDCS to address anger and aggression.

## Author notes

This work was supported by a Grant from the National Science Foundation (USA) titled “Aggressive Impulse Management” (BCS-1348553). The authors have no conflicts of interest to declare. Correspondence concerning this article should be addressed to Alessia Gallucci, University of Milano-Bicocca, Department of Psychology, Piazza Ateneo Nuovo, 1, 20126 – Milano, ITALY. E-mail: a.gallucci@campus.unimib.it.

## Declaration of competing interestCOI

The authors declare no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2019.10.015>.

## References

- [1] Dollard J, Doob L, Miller N, Mowrer O, Sears R. Frustration and aggression: definitions. In: Davies JC, editor. *When men revolt-and why*. New York: Free Press; 1971.
- [2] Giancola PR, Mezzich AC, Tarter RE. Executive cognitive functioning, temperament, and antisocial behavior in conduct-disordered adolescent females. *J Abnorm Psychol* 1998. <https://doi.org/10.1037/0021-843X.107.4.629>.
- [3] Keune PM, van der Heiden L, Várkuti B, Konicar L, Veit R, Birbaumer N. Prefrontal brain asymmetry and aggression in imprisoned violent offenders. *Neurosci Lett* 2012. <https://doi.org/10.1016/j.neulet.2012.03.058>.
- [4] Potegal M. Temporal and frontal lobe initiation and regulation of the top-down escalation of anger and aggression. *Behav Brain Res* 2012. <https://doi.org/10.1016/j.bbr.2011.10.049>.
- [5] Walters RP, Harrison PK, Campbell RW, Harrison DW. Frontal lobe regulation of blood glucose levels: support for the limited capacity model in hostile violence-prone men. *Brain Inf* 2016. <https://doi.org/10.1007/s40708-016-0034-6>.
- [6] Berkman ET. The neuroscience of self-control. In: Routledge Int. Handb. Self-Control Heal. Well-Being; 2018. <https://doi.org/10.4324/9781315648576-10>.
- [7] Kelley WM, Wagner DD, Heatherton TF. In search of a human self-regulation system. *Annu Rev Neurosci* 2015. <https://doi.org/10.1146/annurev-neuro-071013-014243>.
- [8] Meyer HC, Bucci DJ. Imbalanced activity in the orbitofrontal cortex and nucleus accumbens impairs behavioral inhibition. *Curr Biol* 2016. <https://doi.org/10.1016/j.cub.2016.08.034>.
- [9] Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. *Trends Cogn Sci* 2004. <https://doi.org/10.1016/j.tics.2004.02.010>.
- [10] Berkman ET, Lieberman MD. Using neuroscience to broaden emotion regulation: theoretical and methodological considerations. *Soc Personal Psychol Compass* 2009. <https://doi.org/10.1111/j.1751-9004.2009.00186.x>.
- [11] Braver TS, Reynolds JR, Donaldson DI. Neural mechanisms of transient and sustained cognitive control during task switching. *Neuron* 2003. [https://doi.org/10.1016/s0896-6273\(03\)00466-5](https://doi.org/10.1016/s0896-6273(03)00466-5).
- [12] Sang HK, Hamann S. Neural correlates of positive and negative emotion regulation. *J Cogn Neurosci* 2007. <https://doi.org/10.1162/jocn.2007.19.5.776>.
- [13] Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron* 2008. <https://doi.org/10.1016/j.neuron.2008.09.006>.
- [14] Eisenberger NI, Lieberman MD. Does rejection hurt? An FMRI study of social exclusion. *Science* 2003. <https://doi.org/10.1126/science.1089134>.
- [15] Eisenberger NI, Taylor SE, Gable SL, Hilmert CJ, Lieberman MD. Neural pathways link social support to attenuated neuroendocrine stress responses. *Neuroimage* 2007. <https://doi.org/10.1016/j.neuroimage.2007.01.038>.
- [16] Kalisch R, Wiech K, Critchley HD, Seymour B, O'Doherty JP, Oakley DA, et al. Anxiety reduction through detachment: subjective, physiological, and neural effects. *J Cogn Neurosci* 2005. <https://doi.org/10.1162/0898929054021184>.
- [17] Kross E, Egner T, Ochsner K, Hirsch J, Downey G. Neural dynamics of rejection sensitivity. *J Cogn Neurosci* 2007. <https://doi.org/10.1162/jocn.2007.19.6.945>.
- [18] Ochsner KN, Chopra S, Gabrieli JDE, Ray RD, Gross JJ, Cooper JC, et al. For better or for worse: neural systems supporting the cognitive down-and-up-regulation of negative emotion. *Neuroimage* 2004. <https://doi.org/10.1016/j.neuroimage.2004.06.030>.
- [19] Onoda K, Okamoto Y, Nakashima K, Nittono H, Ura M, Yamawaki S. Decreased ventral anterior cingulate cortex activity is associated with reduced social pain during emotional support. *Soc Neurosci* 2009. <https://doi.org/10.1080/17470910902955884>.
- [20] Onoda K, Okamoto Y, Nakashima K, Nittono H, Yoshimura S, Yamawaki S, et al. Does low self-esteem enhance social pain? The relationship between trait self-esteem and anterior cingulate cortex activation induced by ostracism. *Soc Cogn Affect Neurosci* 2010. <https://doi.org/10.1093/scan/nsq002>.
- [21] Vergallito A, Riva P, Pisoni A, Romero Lauro LJ. Modulation of negative emotions through anodal tDCS over the right ventrolateral prefrontal cortex. *Neuropsychologia* 2018. <https://doi.org/10.1016/j.neuropsychologia.2018.07.037>.
- [22] Banks SJ, Eddy KT, Angstadt M, Nathan PJ, Luan Phan K. Amygdala-frontal connectivity during emotion regulation. *Soc Cogn Affect Neurosci* 2007. <https://doi.org/10.1093/scan/nsm029>.
- [23] Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhdé TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. *Biol Psychiatry* 2005. <https://doi.org/10.1016/j.biopsych.2004.10.030>.
- [24] Wager TD, Jonides J, Reading S. Neuroimaging studies of shifting attention: a meta-analysis. *Neuroimage* 2004;22:1679–93. <https://doi.org/10.1016/j.neuroimage.2004.03.052>.
- [25] Cohen MX, Heller AS, Ranganath C. Functional connectivity with anterior cingulate and orbitofrontal cortices during decision-making. *Cogn Brain Res* 2005. <https://doi.org/10.1016/j.cogbrainres.2005.01.010>.
- [26] Ernst M, Bolla K, Mouratidis M, Contoreggi C, Matochik JA, Kurian V, et al. Decision-making in a risk-taking task: a PET study. *Neuropsychopharmacology* 2002. [https://doi.org/10.1016/S0893-133X\(01\)00414-6](https://doi.org/10.1016/S0893-133X(01)00414-6).
- [27] Floden D, Alexander MP, Kubu CS, Katz D, Stuss DT. Impulsivity and risk-taking behavior in focal frontal lobe lesions. *Neuropsychologia* 2008. <https://doi.org/10.1016/j.neuropsychologia.2007.07.020>.
- [28] McClure SM, Laibson DI, Loewenstein G, Cohen JD. Separate neural systems value immediate and delayed monetary rewards. *Science* 2004. <https://doi.org/10.1126/science.1100907>.
- [29] Tanaka SC, Doya K, Ueda K, Okamoto Y, Yamawaki. Prediction of immediate and future rewards differentially recruits cortico-basal ganglia loops. *Nat Neurosci* 2004. <https://doi.org/10.1038/nn1279>.
- [30] Wittmann M, Leland DS, Paulus MP. Time and decision making: differential contribution of the posterior insular cortex and the striatum during a delay discounting task. *Exp Brain Res* 2007. <https://doi.org/10.1007/s00221-006-0822-y>.
- [31] Goldin PR, McRae K, Ramel W, Gross JJ. The neural bases of emotion regulation: reappraisal and suppression of negative emotion. *Biol Psychiatry* 2008. <https://doi.org/10.1016/j.biopsych.2007.05.031>.
- [32] McRae K, Hughes B, Chopra S, Gabrieli JDE, Gross JJ, Ochsner KN. The neural bases of distraction and reappraisal. *J Cogn Neurosci* 2010. <https://doi.org/10.1162/jocn.2009.21243>.
- [33] Monterosso JR, Ainslie G, Xu J, Cordova X, Domier CP, London ED. Frontoparietal cortical activity of methamphetamine-dependent and comparison subjects performing a delay discounting task. *Hum Brain Mapp* 2007. <https://doi.org/10.1002/hbm.20281>.
- [34] Cohen JR, Berkman ET, Lieberman MD. Intentional and incidental self-control in ventrolateral PFC. In: Stuss DT, Knight RT, editors. *Principles of frontal lobe function*. second ed. Oxford: Oxford University Press; 2013.
- [35] Gottfredson MR, Hirschi T. *A general theory of crime*. Stanford, CA: Stanford University Press; 1990.
- [36] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 2000. <https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x>.
- [37] Riva P, Romero Lauro LJ, DeWall CN, Bushman BJ. Buffer the pain away: stimulating the right ventrolateral prefrontal cortex reduces pain following social exclusion. *Psychol Sci* 2012. <https://doi.org/10.1177/0956797612450894>.
- [38] Riva P, Lauro LJR, Nathan DeWall C, Chester DS, Bushman BJ. Reducing aggressive responses to social exclusion using transcranial direct current stimulation. *Soc Cogn Affect Neurosci* 2013. <https://doi.org/10.1093/scan/nsu053>.
- [39] Riva P, Gabbadini A, Romero Lauro LJ, Andrighetto L, Volpato C, Bushman BJ. Neuromodulation can reduce aggressive behavior elicited by violent video games. *Cognit Affect Behav Neurosci* 2017. <https://doi.org/10.3758/s13415-016-0490-8>.

- [40] Hortensius R, Schutter DJLG, Harmon-Jones E. When anger leads to aggression: induction of relative left frontal cortical activity with transcranial direct current stimulation increases the anger-aggression relationship. *Soc Cogn Affect Neurosci* 2012. <https://doi.org/10.1093/scan/nsr012>.
- [41] Kelley NJ, Hortensius R, Harmon-Jones E. When anger leads to rumination: induction of relative right frontal cortical activity with transcranial direct current stimulation increases anger-related rumination. *Psychol Sci* 2013. <https://doi.org/10.1177/0956797612457384>.
- [42] Bettencourt BA, Miller N. Gender differences in aggression as a function of provocation: a meta-analysis. *Psychol Bull* 1996. <https://doi.org/10.1037/0033-2909.119.3.422>.
- [43] Verona E, Curtin JJ. Gender differences in the negative affective priming of aggressive behavior. *Emotion* 2006. <https://doi.org/10.1037/1528-3542.6.1.115>.
- [44] Adenzato M, Brambilla M, Manenti R, De Lucia L, Trojano L, Garofalo S, et al. Gender differences in cognitive Theory of Mind revealed by transcranial direct current stimulation on medial prefrontal cortex. *Sci Rep* 2017. <https://doi.org/10.1038/srep41219>.
- [45] Boggio PS, Rocha RR, da Silva MT, Fregni F. Differential modulatory effects of transcranial direct current stimulation on a facial expression go-no-go task in males and females. *Neurosci Lett* 2008. <https://doi.org/10.1016/j.neulet.2008.10.009>.
- [46] Fumagalli M, Vergari M, Pasqualetti P, Marceglia S, Mameli F, Ferrucci R, et al. Brain switches utilitarian behavior: does gender make the difference? *PLoS One* 2010. <https://doi.org/10.1371/journal.pone.0008865>.
- [47] Harmon-Jones E, Allen JJB. Behavioral activation sensitivity and resting frontal EEG asymmetry: covariation of putative indicators related to risk for mood disorders. *J Abnorm Psychol* 1997. <https://doi.org/10.1037/0021-843X.106.1.159>.
- [48] Harmon-Jones E, Lueck L, Fearn M, Harmon-Jones C. The effect of personal relevance and approach-related action expectation on relative left frontal cortical activity. *Psychol Sci* 2006. <https://doi.org/10.1111/j.1467-9280.2006.01724.x>.
- [49] Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Res Bull* 2007. <https://doi.org/10.1016/j.brainresbull.2007.01.004>.
- [50] Lutz J. The validity of crowdsourcing data in studying anger and aggressive behavior: a comparison of online and laboratory data. *Soc Psychol* 2016. <https://doi.org/10.1027/1864-9335/a000256>.
- [51] 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. <https://doi.org/10.1016/j.brs.2008.06.004>.
- [52] Jung YJ, Kim JH, Im CH. COMETS: a MATLAB toolbox for simulating local electric fields generated by transcranial direct current stimulation (tDCS). *Biomed Eng Lett* 2013. <https://doi.org/10.1007/s13534-013-0087-x>.
- [53] Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin Neurophysiol* 2006. <https://doi.org/10.1016/j.clinph.2005.12.003>.
- [54] Bryant FB, Smith BD. Refining the architecture of aggression: a measurement model for the buss-perry aggression questionnaire. *J Res Personal* 2001. <https://doi.org/10.1006/jrpe.2000.2302>.
- [55] Buss AH, Perry M. The aggression questionnaire. *J Personal Soc Psychol* 1992. <https://doi.org/10.1037/0022-3514.63.3.452>.
- [56] Whiteside SP, Lynam DR. The five factor model and impulsivity: using a structural model of personality to understand impulsivity. *Personal Individ Differ* 2001. [https://doi.org/10.1016/S0191-8869\(00\)00064-7](https://doi.org/10.1016/S0191-8869(00)00064-7).
- [57] Whiteside SP, Lynam DR, Miller JD, Reynolds SK. Validation of the UPPS impulsive behaviour scale: a four-factor model of impulsivity. *Eur J Personal* 2005. <https://doi.org/10.1002/per.556>.
- [58] Spielberger CD. Professional manual for the state-trait anger expression inventory-2 (STAXI-2). 1999. <https://doi.org/10.1016/j.psychsport.2014.07.004>. Odessa, FL.
- [59] Warburton WA, Bushman BJ. The competitive reaction time task: the development and scientific utility of a flexible laboratory aggression paradigm. *Aggress Behav* 2019. <https://doi.org/10.1002/ab.21829>.
- [60] Saleem M, Barlett CP, Anderson CA, Hawkins I. Helping and hurting others: person and situation effects on aggressive and prosocial behavior as assessed by the Tangram task. *Aggress Behav* 2017. <https://doi.org/10.1002/ab.21669>.
- [61] Harmon-Jones E. Clarifying the emotive functions of asymmetrical frontal cortical activity. *Psychophysiology* 2003. <https://doi.org/10.1111/1469-8986.00121>.
- [62] Peterson CK, Gravens LC, Harmon-Jones E. Asymmetric frontal cortical activity and negative affective responses to ostracism. *Soc Cogn Affect Neurosci* 2011. <https://doi.org/10.1093/scan/nsq027>.
- [63] Sutton SK, Davidson RJ. Prefrontal brain asymmetry: a biological substrate of the behavioral approach and inhibition systems. *Psychol Sci* 1997. <https://doi.org/10.1111/j.1467-9280.1997.tb00413.x>.
- [64] Harmon-Jones E, Gable PA, Peterson CK. The role of asymmetric frontal cortical activity in emotion-related phenomena: a review and update. *Biol Psychol* 2010. <https://doi.org/10.1016/j.biopsycho.2009.08.010>.
- [65] Li LM, Uehara K, Hanakawa T. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Front Cell Neurosci* 2015. <https://doi.org/10.3389/fncel.2015.00181>.
- [66] Chaieb L, Antal A, Paulus W. Gender-specific modulation of short-term neuroplasticity in the visual cortex induced by transcranial direct current stimulation. *Vis Neurosci* 2008. <https://doi.org/10.1017/S0952523808080097>.
- [67] Meiron O, Lavidor M. Unilateral prefrontal direct current stimulation effects are modulated by working memory load and gender. *Brain Stimul* 2013. <https://doi.org/10.1016/j.brs.2012.05.014>.
- [68] Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, Lu B. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron* 2010. <https://doi.org/10.1016/j.neuron.2010.03.035>.
- [69] Pisoni A, Mattavelli G, Papagno C, Rosanova M, Casali AG, Lauro LJR. Cognitive enhancement induced by anodal tDCS drives circuit-specific cortical plasticity. *Cerebr Cortex* 2018. <https://doi.org/10.1093/cercor/bhx021>.
- [70] Blair RJR. Psychopathy, frustration, and reactive aggression: the role of ventromedial prefrontal cortex. *Br J Psychol* 2010. <https://doi.org/10.1348/000712609X418480>.
- [71] Pawliczek CM, Derntl B, Kellermann T, Gur RC, Schneider F, Habel U. Anger under control: neural correlates of frustration as a function of trait aggression. *PLoS One* 2013. <https://doi.org/10.1371/journal.pone.0078503>.
- [72] Abler B, Walter H, Erk S. Neural correlates of frustration. *Neuroreport* 2005. <https://doi.org/10.1097/00001756-200505120-00003>.
- [73] Siegrist J, Menrath I, Stöcker T, Klein M, Kellermann T, Shah NJ, et al. Differential brain activation according to chronic social reward frustration. *Neuroreport* 2005. <https://doi.org/10.1097/01.wnr.0000186601.50996.f7>.
- [74] Beyer F, Münte TF, Erdmann C, Krämer UM. Emotional reactivity to threat modulates activity in mentalizing network during aggression. *Soc Cogn Affect Neurosci* 2013. <https://doi.org/10.1093/scan/nst146>.
- [75] Miranda PC, Mekonnen A, Salvador R, Ruffini G. The electric field in the cortex during transcranial current stimulation. *Neuroimage* 2013. <https://doi.org/10.1016/j.neuroimage.2012.12.034>.
- [76] Berkman ET, Burklund L, Lieberman MD. Inhibitory spillover: intentional motor inhibition produces incidental limbic inhibition via right inferior frontal cortex. *Neuroimage* 2009;47:705–12. <https://doi.org/10.1016/j.neuroimage.2009.04.084>.