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Anodal tDCS over the dorsolateral prefrontal cortex reduces Stroop errors. A comparison of different tasks and designs

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ABSTRACT

In the present work, we evaluated the possibility to induce changes in the inhibitory control through non-invasive excitatory stimulation of the prefrontal cortex (PFC). To this aim, different montages of the trans-cranial direct current stimulation (tDCS) were adopted in three separate experiments, wherein different cognitive tasks were performed before and after the stimulation. In the first experiment, participants performed a visual Go/no-go task, and a bilateral anodic or sham stimulation was provided over the scalp area corresponding to the inferior frontal gyrus (IFG). In the second experiment, the IFG was stimulated unilaterally over the right hemisphere, and participants performed a Stroop task combined with a concurrent n-back task, which was aimed at overloading PFC activity. Since no behavioral effects of tDCS were observed in both experiments, we conducted a third experiment with different montage and paradigm. Stimulation was provided bilaterally over the dorsolateral PFC (DLPFC) in the context of a classic Stroop task: results indicated that anodal stimulation favored a reduction of errors. Present findings suggest that the bihemispheric stimulation of the DLPFC might be effective to increase inhibition in healthy subjects, and that this effect might be mediated by the implementation of sustained attention, as predicted by the attentional account of the inhibitory control.

1. General introduction

Executive functions are essential to process high-order cognitions: differently from bottom-up and automatic processes, executive functions involve the representation of goals and rules, which allow the brain to implement controlled strategies [1,2]. Inhibitory control can be considered in this framework, as it allows to inhibit an impellent response according to internal goals (e.g. [3–5]). Inhibition of a prepotent response tendency is a crucial skill of the human being, which is needed to withhold inappropriate actions or to suppress automatic processes [1]. It has been investigated in terms of cognitive control, with the putative existence of a dual mechanism of control (DMC [6,7]), suggesting the existence of a proactive and a reactive control mode. The former is intended as a future oriented control, activated prior to imperative stimuli, while the latter represents a just-in time form of regulation activated after stimulus presentation. However, some authors did not agree on such a sharp separation [8–10], and a unitary view of inhibition has also been proposed. For instance, according to the attentional inhibitory control (AIC) model [11], inhibition represents a default state of the human brain, and what was referred to as proactive and reactive mechanisms would reflect the contribution of the sustained and the selective attention in the implementation of the inhibitory control. Several authors agree in claiming that the main neural areas involving inhibition dwell in the dorsolateral prefrontal cortex (DLPFC), typically recruited during different executive tasks involving working memory, sustained or selective attention [12–20]. Further, particular attention in this field has been posed on a specific portion of the PFC, that is the right inferior frontal gyrus (rIFG [4,5,21–24],). The rIFG plays a key-role in attentional control [25–27] and represents the core area of the inhibitory network, which includes also the supplementary motor area (SMA), the sub-thalamic nucleus (STN) and the striatum (see Refs. [5,28] for reviews). Following these evidence, previous studies suggested the possibility to influence the inhibitory control of the PFC through neurostimulation in healthy and clinical populations (see

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Ref. [29] for a review). Among these, the transcranial direct current stimulation (tDCS) is the most cost-effective technique, which allows to stimulate the brain by modulating the intrinsic cortical activity [30,31]. In fact, it is well accepted that the tDCS might not directly provoke a depolarization of the membrane potential, but might, instead, increase the resting potential of the pyramidal neurons [30,32]. Conventionally, the tDCS stimulation is distinguished between anodal and cathodal: the former is usually associated with an enhancement of the cortical excitability, while the latter is often associated with a reduction of the cortical excitability [32].

The present study focuses on the role of prefrontal regions in processing inhibitory mechanisms. This topic has been previously addressed by transcranial magnetic stimulation (TMS) studies, showing that the stimulation of the IFG can alter inhibition [33,34]. However, experimental effects induced by the neurostimulation of the IFG are manifold, as it was suggested that both unilateral and bilateral stimulation of the IFG might affect inhibition [35]. As for the tDCS, electrode montage is a critical issue for the effective stimulation. According to some authors, the stimulation intensities do not necessarily follow a proportional relation with the efficacy of the stimulation: for instance, stimulating at 1 mA can induce larger improvements in cognitive performance than stimulating at 2 mA [36]. Despite contradictory results, several evidence relate anodal tDCS stimulation over the rIFG with improved inhibitory control [37–39]. Inhibition of motor response has been investigated using different tasks, such as the Go/no-go [40,41], the Stop signal [9,42,43], and the Stroop task [44–46]. Generally, a behavioral pattern of higher accuracy has been interpreted as increased inhibitory control, which could also be interpreted in terms of increased top-down attentional control [11,78,47]. Several researchers tried also to affect the level of inhibition by modifying the proportion of congruent and incongruent stimuli [45,46,48,49] or combining different tasks, such as the Stroop test and the 3-back task with the aim to increase working memory (WM [46,50,51]). However, it is also worth noting that empirical studies often revealed no effects of tDCS on cognitive skills in healthy subjects [52–55]. In fact, the neural mechanisms underlying the effectiveness of tDCS are still debated: contrasting findings are probably related to the large number of variables implicated in the experimental protocols, the role of the specific tasks and site of stimulation (IFG or DLPFC), as well as the polarity of the stimulation. For example, it was shown that cathodal stimulation of the left DLPFC disrupted interference processing of the Stroop task [16], while tDCS over the right DLPFC decreased and increased the Stop signal task performance when provided with cathodal and anodal polarity respectively [43,17].

The present study aims at understanding the efficacy of the tDCS on inhibition. The efficacy of tDCS is evaluated by varying the task and the montage across three experiments, with the second and the third planned in sequence due to the lack of results from experiment one. In particular, in the first experiment we adopted a Go/no-go task and tried to alter inhibition by administering bilateral stimulation with anode over the rIFG in a within-subject design. We expected to observe an increased inhibitory control, characterized by slow response time and high accuracy of the response. In the second experiment, we manipulated the cognitive load combining a Stroop test with a 3-back task, maintaining the within-subject design, but adopting a unilateral stimulation of the rIFG. Challenging cognitive demand is expected to be an important factor to reveal the effectiveness of the tDCS in healthy subjects. In fact, when the cognitive load is increased, the proactive inhibition should be less efficient, revealing higher error rates. In the third experiment, we investigated the role of the rDLPFC with a classic Stroop task, favoring a between-subject design in order to reduce the learning effect and to prevent any possible confounding factor associated to a concomitant task, like in experiment 2. Also, considering both the key-role of the rDLPFC in sustained attention [56] and the relationship between the sustained attention and the inhibitory control [11,47], we assumed that the stimulation of this cortical area would be effective in enhancing accuracy performances, as effects of the enhanced top-down attentional control. Moreover, the inhibitory effect of the DLPFC stimulation would be consistent with the extensive literature indicating the therapeutic efficacy of the tDCS in the clinical population (for a review see Ref. [57]). Therefore, we attempted to investigate whether similar montage might be effective in healthy subjects as well.

2. Experiment 1

2.1. Introduction

The Go/no-go task has been widely used in order to verify the efficiency of executive functions in healthy subjects, with a particular focus on motor/cognitive inhibition abilities [22,39,58,59]. This task has been adopted by previous studies that investigated the effect of tDCS stimulation over the PFC; however, results were not always consistent. For example, Cunillera and colleagues (2014) observed increased reaction times as effect of anodal stimulation of the rIFG, but the same authors failed to replicate their findings, showing only electrophysiological changes, with reference electrode over the lIFG and direct current of 1.5 mA in both studies [39]. To clarify this issue, we also adopted the tDCS for stimulating offline and bilaterally the IFG (right anodal/left cathodal) during a Go/no-go task. To this aim, we adopted 9 cm^2 electrodes that should lead to a more focal effect on the stimulated cortical area. This montage is supposed to limit the current distribution of the neurostimulation on other areas of the PFC. After the anodic stimulation of the rIFG, we expect slower response times (RT) and, especially, enhanced level of accuracy, which could be interpreted as an enhanced proactive inhibitory control, compared to the sham session.

2.2. Methods

2.2.1. Participants

Twelve subjects participated in the study (6 females, 26±4.2 years). They had normal or corrected-to-normal vision, no auditory deficits, and they did not report any neurological or psychological disorders. All participants were right-handed (Edinburgh Handedness Inventory, Oldfield, 1971[82]).

All participants received anodal and sham stimulation in a counterbalanced random order in two separate days. After explanations of the procedures, written informed consent was obtained from all participants according to the Declaration of Helsinki after approval of the Santa Lucia Foundation Ethical Committee.

2.2.2. Stimuli and procedure

Visual stimuli consisted of four squared figures made by vertical and horizontal bars randomly displayed for 250 ms on a dark gray background with equal probability ($p = 0.25$); the stimulus-onset asynchrony varied from 1 to 2 s. Two stimuli were defined as go (target stimuli; $p = 0.5$) and two as no-go (non-target stimuli; $p = 0.5$). The fixation point was a yellow circle (diameter $0.15^\circ \times 0.15^\circ$ of visual angle) in the center of the computer monitor. Stimuli were presented via Presentation Software.

Participants were asked to respond as soon as possible to target stimuli, and to withhold the response when the non-target appeared: response speed and response accuracy were equally emphasized in the task instruction. The order of presentation was randomized within blocks and across participants. A total of 5 runs and 400 trials (i.e. 200 go and 200 no-go) were presented in the experiment; 40 warm-up trials were also provided at the beginning of the session. The duration of each run was approximately 3 min with a pause interleaved. The total duration of the experiment was about 20 min.

Each participant was enrolled in two sessions (within-subjects design) spaced 1 week apart: in the first session they performed the Go/no-go task before and after anodal stimulation, whereas in the second session they performed the same task before and after sham stimulation: the order of sessions was counterbalanced across participants (see

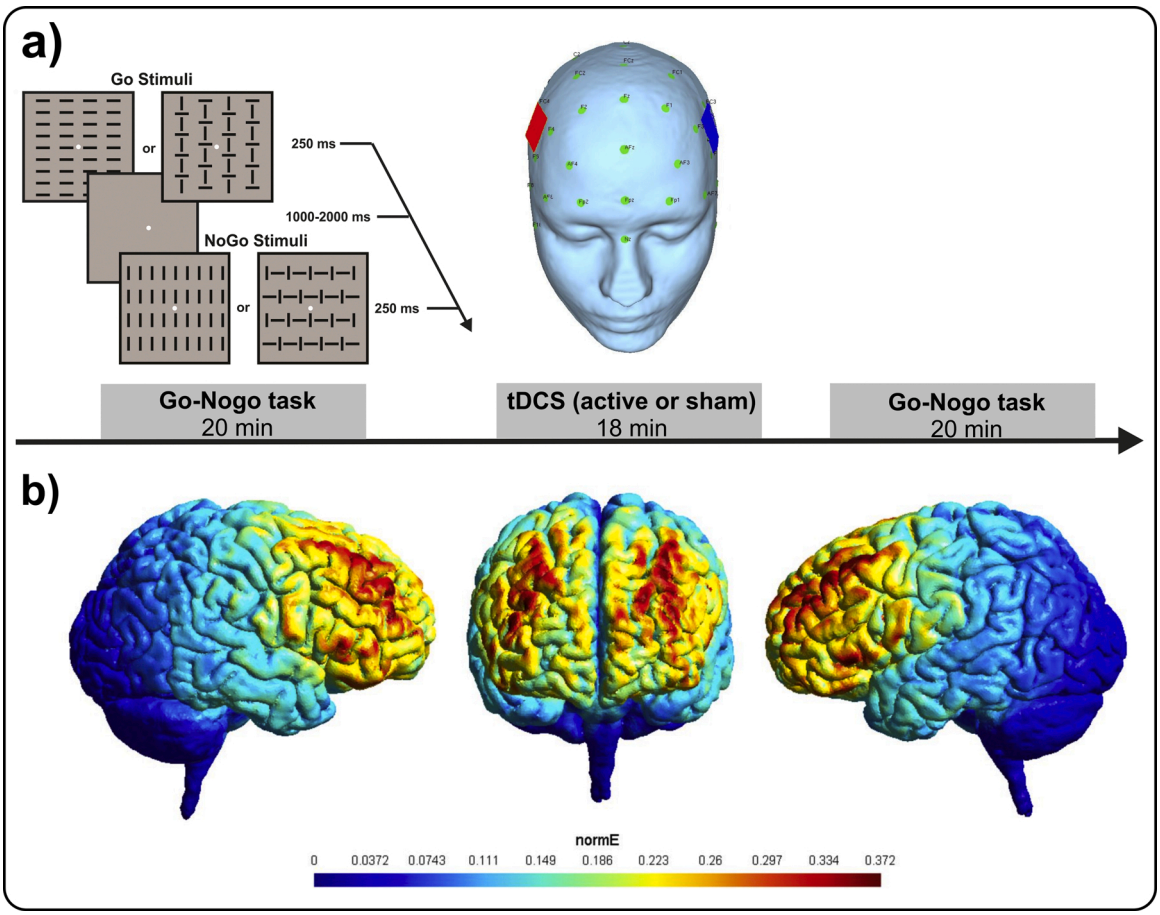

Fig. 1. Experiment 1: a) schematic representation of the Go/no-go task. Bilateral montage (right anodal/left cathodal) with 9 cm^2 electrodes was adopted for the tDCS stimulation of the PFC; b) Electric field modeling performed with SimNIBS 3.2.

Fig. 1a for stimuli and procedure). In both sessions, they were seated in front of a computer screen at a distance of 114 cm with their left arm relaxed and their right arm positioned palm down on a push button board.

2.2.3. Transcranial direct current stimulation

Direct current was transferred by a saline-soaked pair of surface sponge electrodes (9 cm^2) and delivered by a battery-driven constant current stimulator. Following Cunillera et al. [38], the anodal electrode was placed on the crossing point between the lines connecting T4-Fz and F8-Cz positions of the 10–20 International system, whereas the cathodal electrode was placed on the crossing point between the lines connecting T3-Fz and F7-Cz positions, corresponding to the scalp location of the right and left IFG respectively.

In the anodal stimulation, the current intensity was gradually increased for 10 s at the beginning of the stimulation session (ramp up), delivered at 1.5 mA for 18 min (current density 0.16 mA/cm^2), and decreased for 10 s at the end of the session (ramp down) to diminish its perception.

In the sham stimulation, the ramp up was delivered for 10 s until reaching 1.5 mA, the current was transferred for 7 s, and it was followed by a ramp down lasting 10 s. Then, after 18 min of no-stimulation, the ramp up-ramp down cycle was repeated at the end of the session. An electric field simulation for the tDCS was performed using SimNIBS 3.2 [60] as reported in Fig. 1b.

2.2.4. Behavioral data

For each participant, the behavioral measures included the median response time (RT) for correct go trials and the percentage of commission errors (CE, responses to no-go stimuli).

2.2.5. Data analysis

Statistical analyses were performed with Statistica 6.1 (StatSoft, Inc. 2004[83]). All behavioral outcomes were submitted to repeated-measure ANOVAs with Stimulation (Sham vs Anodal) and Session (Pre- vs Post-stimulation) as repeated factors. The overall alpha level was fixed at 0.05. Post-hoc comparisons were carried out using Bonferroni correction.

2.3. Results

Behavioral data of the Go/no-go task are reported in Table 1 for the pre- and the post-stimulation for sham and anodal stimulation. Statistical analysis on the response times did not reveal significant effect of Stimulation ($F_{1,11} = 1.64$; $p > 0.05$) or Session ($F_{1,11} = 4.66$; $p > 0.05$). Also, the Session X Time interaction did not reach significance ($F_{1,11} = 0.38$; $p > 0.05$). Statistical analysis on commission error did not reveal any significance of Stimulation ($F_{1,11} = 2.91$; $p > 0.05$) and Session ($F_{1,11} = 0.29$; $p > 0.05$). Similarly, no Session X Time interaction effect

Table 1
Behavioral data of the Go/no-go task for the pre- and the post-stimulation in the sham and anodal session. Group mean (± SD) is reported.

	Sham		Anodal	
	Pre	Post	Pre	Post
RT	406 (54)	356 (40)	420 (60)	406 (48)
CE	5.1(5)	4.8 (4)	7.6 (4)	6 (2.0)

was found ($F_{1,11} = 0.15$; $p > 0.05$).

As additional control, the same ANOVA was performed including also Order of stimulation (anodal-sham vs sham-anodal) as between-subjects factor, but no significant effects emerged for all considered variables (all ps>0.05).

2.4. Discussion

We failed to replicate results of Cunillera et al. [38] about the inhibitory effects of tDCS over the rIFG. It is conceivable that a learning effect associated to task repetition (4 times across the 2 sessions for a total of 800 trials) may have masked any possible effect of stimulation on the task performance. As an alternative hypothesis, and contrary to our expectation, the reduced surface of the electrodes (9 cm^2) did not help to increase the inhibitory performance, but, at the opposite, may have attenuated the inhibitory effect of the tDCS by limiting the current distribution on other PFC areas. This latter hypothesis also opens the question of the most suitable montage for effectively enhancing inhibitory control.

At last, our choice to present go and no-go stimuli with equal distribution should have reduced the need of inhibitory control, while an higher proportion of no-go stimuli (e.g., 80 %) probably could have brought out more the effect of stimulation on the level of inhibition. Future studies could test this hypothesis.

3. Experiment 2

3.1. Introduction

To overcome the possible limitations of experiment 1, in the present study we provided anodal and sham stimulations with larger electrodes (25 cm^2) than experiment 1. In particular, according to findings of Leite et al. [35], we provided unihemispheric stimulation of the rIFG with the reference electrode placed on the left supra-orbital cortex. The rationale was that, since the left IFG might be also involved in inhibition, the bihemispheric stimulation with right anodal/left cathodal could have canceled out the contribution to the lIFG on inhibitory control [35]. Further, in order to increase the task difficulty, we adopted a Stroop test combined with a task characterized by two different cognitive loads [45, 49] that required both inhibition and working memory. In particular, we provided a paradigm similar to Kalanthroff et al. [46], that is a Stroop test administered in a “simple” and a “complex” version. What made the task more demanding was the combination of the Stroop task with the 3-back task. As suggested by Kalanthroff et al. [45,46], the use of a dual cognitive task represents a strategy to add an extra load on working memory: enhanced requirement of working memory should impair the proactive control and, at behavioral level, this should lead to shorter reaction times and reduced accuracy. In experiment 2, we tried to replicate these results, hypothesizing an impairment in working memory as effects of the extra workload induced by the 3-back task. In particular, an increased interference effect for the Stroop test is expected consisting in slower RTs for incongruent than neutral stimuli, and a reduction of Stroop facilitation with slower RTs for congruent than neutral stimuli. The high demanding task should provoke a working memory overload, which in turn might impair the proactive control. We hypothesize that active stimulation may counteract the high cognitive load by reducing the error rates as a result of the enhanced attentional and inhibitory control of the right PFC.

3.2. Methods

3.2.1. Participants

Nineteen young adults were recruited, (11 females, 8 males, 22,45±2.40 years), who did not take part to experiment 1. They had normal or corrected-to-normal vision, and they did not report any neurological or psychological disorders. All participants were right-handed (Edinburgh Handedness Inventory, Oldfield, 1971[82]).

All participants received anodal and sham stimulation in a counterbalanced order, with random assignment, in two separate days (within-subjects design). After explanation of the procedures, informed consent was obtained from all participants according to the Declaration of Helsinki after approval by the Santa Lucia Foundation Ethical Committee.

3.2.2. Stimuli and procedure

As reported in Fig. 2a and b, the paradigm consisted of two combined tasks: the n-back and the Stroop task, provided in the simple and the complex modality defined on the basis of the n-back task version. For the Stroop task, which remained the same in the two task modalities, stimuli consisted of words in a colored ink presented 0.5 cm above a white fixation cross (diameter 0.15° × 0.15° of visual angle) in the center of a gray computer screen. Word stimuli for the Congruent and Incongruent conditions were Italian translation of the words: RED, BLUE, YELLOW and GREEN. Word stimuli for the Neutral condition were TIME, EPOCH, HIT, RIGID (chosen to match the Italian version of color–words for length according to the Thorndike General Count wGx, [61]). The words subtended approximately 1.00° visual angle horizontally and 0.30° vertically. Participants were instructed to respond by pushing one of four buttons on the keyboard corresponding to each of the four colors. The buttons were operated with the index and middle fingers of both hands. Participants were instructed to constantly look at the fixation cross and respond to stimuli as quickly and accurately as possible by pushing the colored button matching the ink color of the delivered words. For the Stroop task, congruent, neutral and incongruent trials were equally presented (0.33 probability) and randomly intermixed in the task: each stimulus was displayed for 750 ms. For the n-back task, visual stimuli consisted of two squared figures made either by vertical and horizontal bars randomly displayed for 750 ms before and after two Stroop stimuli. In each trial, the Stroop stimuli were mixed with the stimuli of the n-back task, for a total of 4 stimuli with the following order: n-back, stroop, stroop, n-back. The inter-stimulus interval (ISI) ranged from 1.5 to 2.5 s for an average duration of 9 s for each trial. A total of 20 trials were provided in each run, and the experimental block consisted of 4 runs (N = 160 stroop stimuli, N = 160 n-back stimuli), for a total duration of about 12 min plus a few seconds rest between runs. Each experimental block was administered in two modalities: simple and complex. In the simple version, participants had to press the space bar on the keyboard every time the second n-back stimulus (horizontal or vertical) appeared; in the complex version of the task, they had to press the space bar only when the visual configuration of the second n-back stimulus matched the configuration of the n-3 stimulus (i.e. horizontal-horizontal, vertical-vertical), that is the target stimulus. When the visual configuration of the second n stimulus did not match the configuration of the n-3 stimulus (i.e. horizontal-vertical, vertical-horizontal) participants had to refrain from responding (no-target). Both the simple and the complex tasks were administered twice in each session: before and after the stimulation. The two sessions (anodic and sham tDCS) were provided at a distance of approximately 1 week. The order of sessions was counterbalanced across participants.

3.2.3. Transcranial direct current stimulation

Direct current was transferred by a saline-soaked pair of surface sponge electrodes (25 cm^2) and delivered by a battery-driven constant current stimulator. The anodal electrode was placed, as the previous experiment 1, on the crossing point between the lines connecting T4-Fz and F8-Cz positions of the 10–20 international system, whereas the cathodal electrode was placed, according to Jacobson et al. [37], above the left eyebrow. This positioning corresponded to the location of the rIFG and the left orbitofrontal cortex (lOFC) on the scalp, respectively (see Fig. 2c). The choice of using larger electrodes than in experiment 1 reflects the intention to widen the current flow with a minor focus on a specific area. Since both inhibition and working memory should be

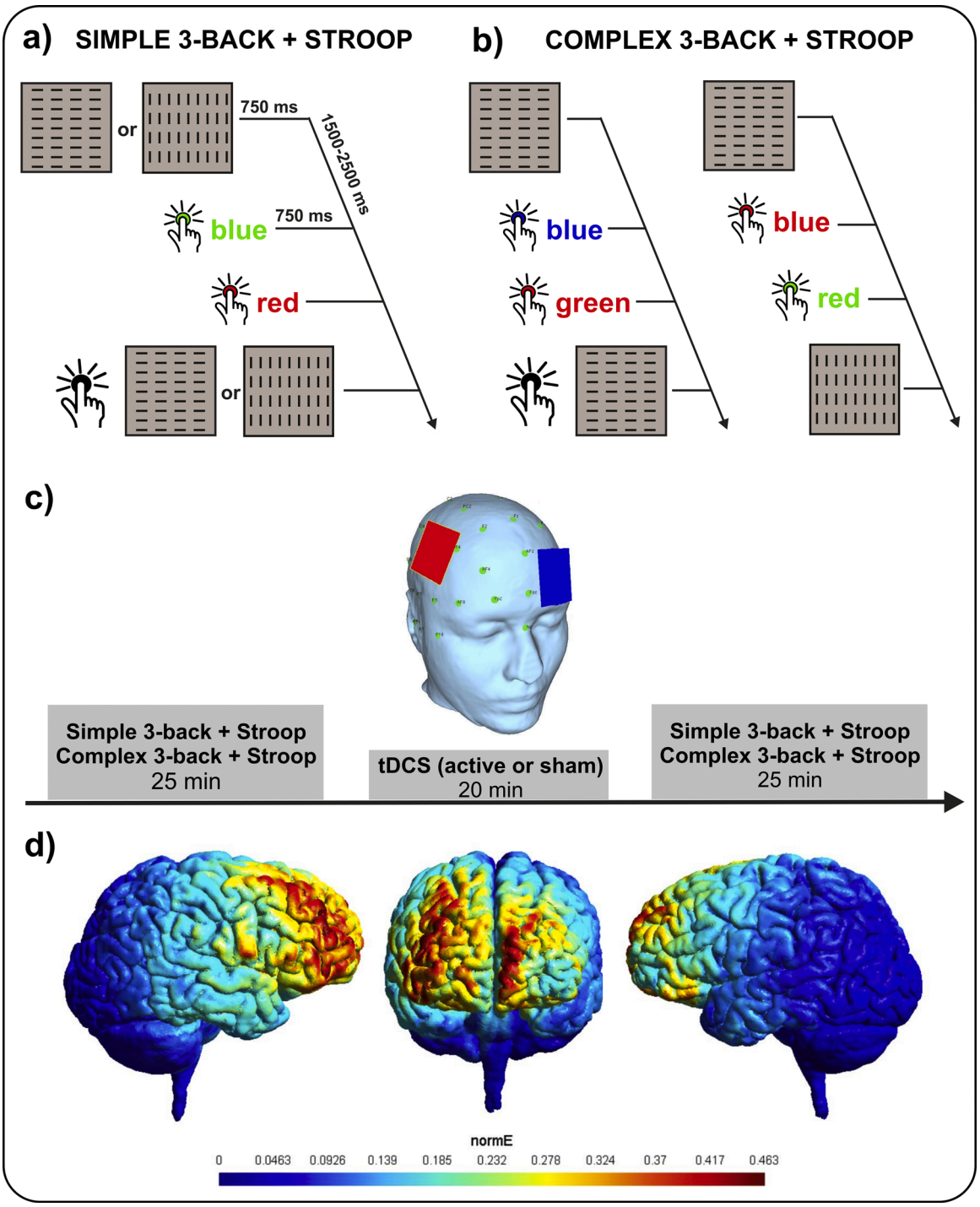

Fig. 2. Experiment 2: schematic representation of a trial in the a) simple version of the 3-back + Stroop task, and in the b) complex version of the 3-back + Stroop task. **c)** Unilateral montage with 25 cm^2 electrodes was adopted for the tDCS stimulation of the right inferior frontal gyrus. Red = anode; blue = cathode). d) Electric field modeling performed with SimNIBS 3.2.

involved in the present task, a wider distribution of current flow on the lateral prefrontal cortex could better enhance the behavioral effects of stimulation. For the active stimulation, the current intensity was gradually increased for 10 s at the beginning of the stimulation session (ramp up), delivered at 2.0 mA for 20 min, and decreased for 10 s at the end of the session (ramp down) to diminish its perception. In the sham stimulation, the ramp up was delivered for 10 s until reaching 2.0 mA, the current was transferred for 7 s, and it was followed by a ramp down lasting 10 s. Then, after 20 min of no-stimulation, the ramp up-ramp down cycle was repeated at the end of the session. In the sham stimulation, the ramp up was delivered for 10 s until reaching 2.0 mA, the current was transferred for 7 s, and it was followed by a ramp down lasting 10 s. Then, after 20 min of no-stimulation, the ramp up-ramp down cycle was repeated at the end of the session.

3.2.4. *Behavioral data*

The following measures were considered for the Stroop task: individual median RT and percentage of errors (ERR) for congruent, neutral and incongruent trials. Further, the RTs of each category were adopted to calculate the main effects of the Stroop task as follows: facilitation

(neutral minus congruent), interference (incongruent minus neutral), and inhibition (incongruent minus congruent). For the n-back task, RT was calculated for all stimuli in the simple version, and only for targets in the complex version, for which the percentage of errors (ERR) was considered as well.

3.2.5. Data analysis

Statistical analyses were carried out using the software Statistica 6.1 (StatSoft, Inc. 2004[83]). All the considered behavioral variables were submitted to separated repeated-measure ANOVAs for simple and complex tasks, with stimulation (Sham vs Anodal) and session (Pre vs Post) as factors. For the Stroop test, ANOVAs were separately repeated for each category (congruent, incongruent, neutral). Overall alpha level was fixed at 0.05. When appropriate, post-hoc comparisons were carried out using Bonferroni.

3.3. Results

No significant effects emerged from statistical analysis of the Stroop task (all ps>0.05) and the 3-back task (all ps>0.05), neither for the simple nor for the complex version. Behavioral data and statistical values of the Stimulation X Session ANOVA (df = 1,18) are reported in Tables 2 and 3 the simple and the complex version of the task respectively.

3.4. Additional control analysis

In order to exclude that order of stimulation (anode or sham first) produced any effect, the same ANOVAs were repeated including Order (anodal-sham vs sham-anodal) as between-subjects factor. However, no significant effects emerged from this analysis (all ps >0.05), confirming that the order of stimulation did not account for any behavioral change in this task.

3.5. Discussion

We failed to replicate the findings of Kalanthroff et al. [46] on the interference effect and reverse facilitation for the complex version of the combined Stroop and 3-back tasks. Moreover, unihemispheric anodic stimulation of the rIFG did not produce any behavioral difference between tasks, neither for the response speed nor for the accuracy level.

Table 2
Behavioral data of the Stroop task and 3-back task in the simple version for the pre- and the post-stimulation condition in the sham and anodal session. Mean (± SD) are reported. ANOVA refers to the Stimulation X Session interaction.

	Sham		Anodal		ANOVA
	Pre	Post	Pre	Post	
RT Congruent	583 (60.61)	573 (51.55)	580 (50.98)	563 (48.47)	F = 1.45; p = 0.24
RT Incongruent	656 (79.31)	630 (82.88)	669 (73.18)	618 (63.54)	F = 0.06; p = 0.81
RT Neutral	594 (51.35)	559 (49.03)	584 (46.21)	559 (53.68)	F = 0.14; p = 0.70
ERRincongruent	21.47 (19.40)	18.10 (21.21)	18.26 (17.28)	15.86 (19.14)	F = 1.79; p = 0.19
ERR congruent	8.65 (7.15)	7.85 (5.58)	7.53 (5.48)	5.60 (5.61)	F = 1.30; p = 0.26
ERR neutral	5.76 (4.51)	4.16 (4.33)	6.73 (4.97)	3.52 (3.54)	F = 0.56; p = 0.46
Facilitation	11.61 (27.23)	−13.3 (27.23)	4.58 (36.65)	−4.16 (28.19)	F = 0.06; p = 0.81
Inhibition	73.37 (53.30)	57.08 (63.79)	89.31 (56.31)	54.44 (36.75)	F = 1.69; p = 0.20
Interference	61.75 (53.23)	70.45 (74.59)	84.73 (74.42)	58.60 (41.12)	F = 2.34; p = 0.14
RT 3-back	348 (56.28)	334 (38.42)	350 (45.15)	347 (45.92)	F = 1.45; p = 0.56

The reasons of these negative results may be manifold: i) although more difficult than the paradigm of experiment 1, the high number of trials might have produced a learning effect; ii) the concurrent n-back task may have increased the working memory load to such an extent that the speed disposition in the Stroop task was not so strong to enroll high levels of inhibition: as a consequence, the weak effect of the tDCS was not enough to significantly increase the accuracy level. This interpretation would be supported by findings of Leite et al. [35], who obtained results only when stimulating the IFG in a Prepotent response inhibition task, but not in other tasks such as the choice reaction time and the equiprobable Go/no-go; iii) contrary to our expectation, it is possible that the unihemispheric stimulation of the rIFG was not the best montage for enhancing inhibitory control. Finally, since recent studies revealed that working memory functions are lateralized in the brain [62, 63], it might be useful for future studies to investigate whether stimulation of the left (and not right) DLPFC is more effective in improving performance in such a paradigm (see e.g. Ref. [18] for similar results in a verbal n-back task).

4. Experiment 3

4.1. Introduction

In light of the previous failure to replicate findings on the efficacy of the tDCS to increase inhibition, in the following experiment we manipulated some methodological details that may have weakened the results of previous experiments. First of all, we decided to adopt a between-subject design to diminish the possible leaning effects encountered in experiments 1 and 2 (present subjects were assigned to anodal or sham group). Second, the anode was placed over a different portion of the PFC, that is the rDLPFC (F4 site of the 10–20 system, with the reference on the contralateral site), whose stimulation was recently shown to be effective in increasing inhibition in healthy subjects [43]. Noteworthy, the DLPFC is the target area of an extensive literature investigating clinical effects of the tDCS in the treatment of behavioral and substance addictions, for which an increase in the metacognitive control of inhibition is showed to be effective (for reviews see Refs. [57, 64,65]). Finally, differently from experiment 2, we administered the classic version of the Stroop test in order to reduce any possible confounding effect of the dual task. Again, we expected to observe an increase of accuracy as an effect of the anodal stimulation of the right DLPFC.

4.2. Method

4.2.1. Participants

Seventeen participants were recruited (14 females, 3 males), who did not take part to experiment 1 and 2. Participants were randomly assigned to the anodal (n = 9; age = 31.1±16 years; females = 6) or the sham group (n = 8; age 23.25±5 years; females = 8). They had normal or corrected-to-normal vision, and they did not report any neurological or psychological disorder. All participants were right-handed (Edinburgh Handedness Inventory, Oldfield, 1971[82]). After explanations of the procedures, informed consent was obtained from all participants according to the Declaration of Helsinki after approval by the Santa Lucia Foundation Ethical Committee.

4.2.2. Stimuli and procedure

Stimuli and procedure of the Stroop task were the same as the experiment 2, except for the n-back task that was excluded from the present experiment.

4.2.3. Transcranial direct current stimulation

Direct current was transferred with the same parameters used in experiment 2. As shown in Fig. 3, the anodal electrode was placed over the F4 site, and the cathode on F3, corresponding to the scalp location of

Table 3
Behavioral data of the Stroop task and 3-back task in the complex version for the pre- and the post-stimulation condition in the sham and anodal session. Mean (± SD) are reported. ANOVA refers to the Stimulation X Session interaction.

	Sham		Anodal		ANOVA
	Pre	Post	Pre	Post	
RT Congruent	584 (45)	583 (51.04)	578 (42.98)	577 (52.42)	$F = 2.94$; $p = 0.10$
RT Incongruent	642 (88)	638 (83.95)	649 (42.69)	629 (64.29)	$F = 2.26$; $p = 0.14$
RT Neutral	586 (54)	574 (57.64)	587 (54.11)	570 (56.10)	$F = 0.78$; $p = 0.38$
ERR incongruent	16.66 (9.60)	13.71 (7.61)	16.49 (11.69)	14.93 (13.55)	$F = 0.71$; $p = 0.41$
ERR congruent	8.15 (8.11)	8.50 (6.11)	7.11 (5.13)	7.46 (4.56)	$F = 0.45$; $p = 0.51$
ERR neutral	8.33 (7.48)	6.07 (5.13)	7.46 (5.28)	4.51 (3.75)	$F = 1.26$; $p = 0.27$
Facilitation	2.19 (26.18)	−8.97 (21.05)	9.14 (23.54)	−7.22 (25.07)	$F = 0.08$; $p = 0.77$
Inhibition	58.63 (73.06)	55.07 (65.65)	61.98 (43.85)	52.09 (41.93)	$F = 0.66$; $p = 0.42$
Interference	56.44 (73.06)	64.04 (63.65)	71.12 (43.85)	59.31 (43.10)	$F = 0.96$; $p = 0.33$
RT 3-back	439 (58.64)	425 (68.10)	422 (33.95)	419 (56.16)	$F = 1.78$; $p = 0.76$
ERR 3-back	34.86 (15.34)	33.11 (20.85)	27.85 (19.80)	25.87 (17.44)	$F = 1.32$; $p = 0.34$

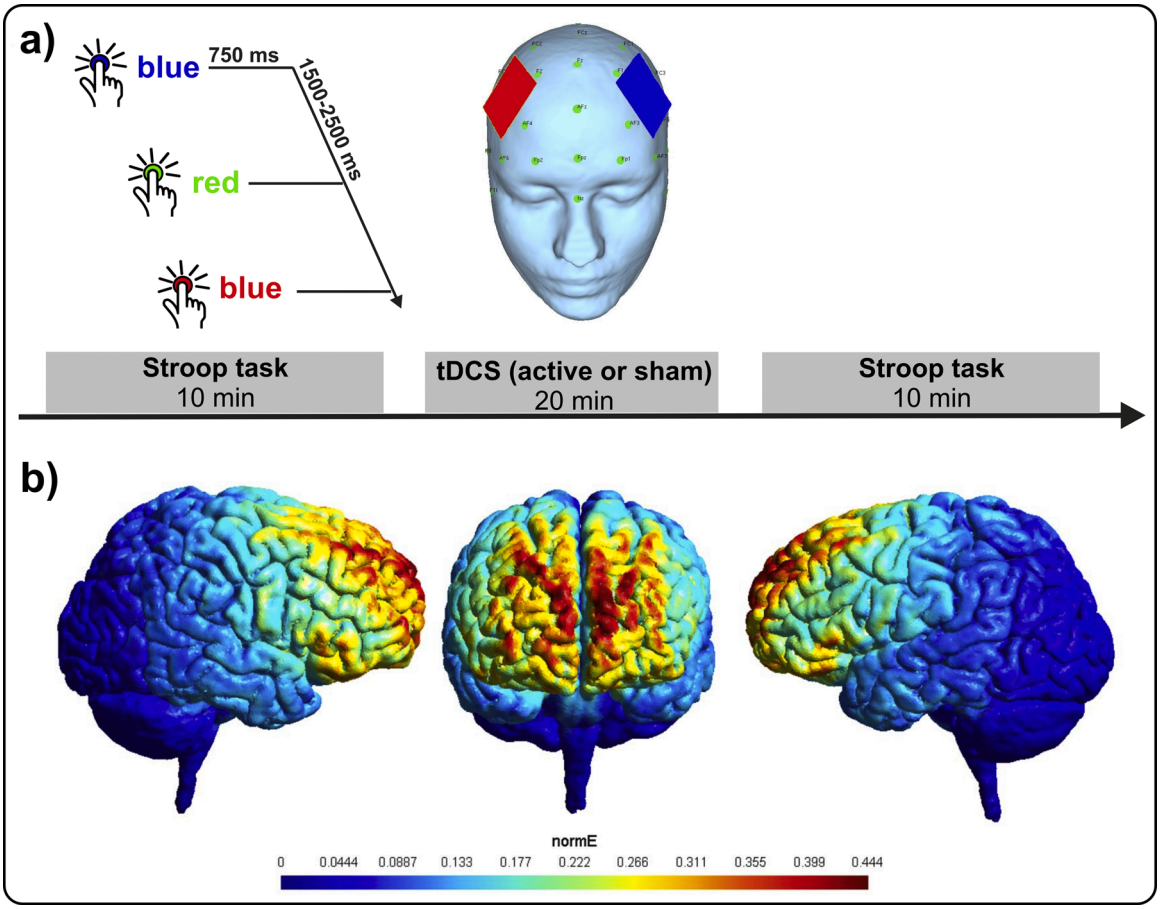

Fig. 3. Experiment 3: a) schematic representation of the Stroop task. Bilateral montage with 25 cm^2 electrodes was adopted for the tDCS stimulation of the dorsolateral prefrontal cortex. Red = anode; blue = cathode b). Electric field modeling performed with SimNIBS 3.2.

the right and the left DLPFC respectively [66]. For the active stimulation, the current intensity was gradually increased for 10 s at the beginning of the stimulation session (ramp up), delivered at 2.0 mA for 20 min, and decreased for 10 s at the end of the session (ramp down) to diminish its perception. In the sham stimulation, the ramp up was delivered for 10 s until reaching 2.0 mA, the current was transferred for 7 s, and it was followed by a ramp down lasting 10 s. Then, after 20 min of no-stimulation, the ramp up-ramp down cycle was repeated at the end of the session.

4.2.4. Behavioral data

The following measures were considered for the Stroop task: individual median RT and percentage of errors (ERR) for congruent, neutral and incongruent trials. Further, the RT of each category were used to calculate the main effects of the Stroop task as follows: Facilitation (Neutral minus Congruent), Interference (Incongruent minus Neutral), inhibition (Incongruent minus Congruent).

4.2.5. Data analysis

Statistical analyses were carried out with Statistica 6.1 (StatSoft, Inc. 2004[83]). For analysis of the RTs and Errors, data were submitted to 2 × 2 ANOVA with Group (Anodal vs Sham) and Session (Pre vs Post) as factors, repeated for each category (incongruent, congruent, neutral) and effect (interference, inhibition, facilitation) of the Stroop test. The

overall alpha level was fixed at 0.05, the post-hoc comparisons were carried out using Bonferroni correction, and the effect sizes were calculated as partial eta squared (ηp^2). According to Cohen [67], $\eta p^2 \geq 0.01$ were interpreted as small effects, ≥ 0.06 as moderate effects and ≥ 0.14 as large effects.

4.3. Results

No significant effects emerged from the statistical analysis on the Stroop effects and RTs in all conditions, as well as for Error rates of the congruent and neutral stimuli (all $p_s > 0.05$). At the opposite, ANOVA on the Error rates of the incongruent stimuli revealed a significant Group by Session interaction ($F_{1,15} = 4.66$, $p < 0.05$; $\eta p^2 = 0.23$), and post-hoc indicated that anodic stimulation reduced the errors from pre-stimulation to post-stimulation ($p < 0.05$). No differences emerged in the sham group from pre- to post-stimulation ($p > 0.05$), as well as between groups before stimulation ($p > 0.05$). Behavioral data of the Stroop task are reported in Table 4 for the anodal and the sham group.

4.4. Discussion

The bilateral stimulation of the dorsolateral prefrontal cortex produced a significant reduction of errors for the incongruent stimuli of the Stroop test. Compared to experiments 1 and 2, two main differences were introduced in the present experiment: a between-subjects approach was adopted, and the dorsolateral portion of the PFC was stimulated bilaterally with the anode over the right hemisphere.

Present findings would corroborate the extensive clinical literature about the key-role of the rDLPFC in behavioral inhibition (e.g., Ref. [57]). This is probably because stimulation of the DLPFC recruited more executive control or other functions other than the pure motor inhibition as the rIFG is supposed to do. Also, it is possible to suppose that the higher excitability of the rDLPFC increased the level of sustained attention, which is known to be processed in this cortical area [47,56]. This interpretation is consistent with the assumption of the attentional inhibitory control model (AIC [11]), predicting that an increase in sustained attention would be paralleled by an increase in proactive inhibition.

Results of the present experiment were probably driven by the anodal stimulation of the right DLPFC, such as by the cathodal stimulation of the left DLPFC or by the interaction of right anodal/left cathodal effects. In fact, the Stroop test requires linguistic processing, and the cathodal stimulation of the left frontal lobe could have worsened reading processes which in turn made easier the Stroop performance [68,69]. Future studies could test directly the hypothesis of left cathodal effects and also verify if the present montage may interfere with the sequence effect in the Stroop task, as reported by previous investigations (e.g., Ref. [20]).

Table 4
Behavioral data of the Stroop task for the sham and the anodal group of participants. Mean (± SD) are reported. *p < 0.05.

	Sham		Anodal	
	Pre	Post	Pre	Post
RT Congruent	681 (107)	669 (83.61)	718 (128)	663 (105)
RT Incongruent	722 (88.08)	713 (61.76	783 (169)	718 (150)
RT Neutral	706 (150)	651 (71.06)	722 (117)	657 (100)
ERR Congruent	1.82 (1.73)	1.82 (2.34)	0.92 (1.51)	0.92 (1.51)
ERR Incongruent	2.60 (3.47)	2.60 (1.84)	**4.85 (3.45)**	**1.85* (1.62)**
ERR Neutral	1.82 (2.34)	1.04 (1.11)	2.54 (2.71)	0.46 (0.91)
Facilitation	24.95 (49.77)	−18.35 (35.81)	4.3 (38.45)	−6.50 (45.79)
Inhibition	41.16 (62.87)	43.49 (79.76)	64.75 (90.48)	54.90 (100)
Interference	16.20 (109)	61.85 (86.07)	60.44 (106)	61.41 (76.82)

5. General discussion

We failed to confirm our hypotheses in experiments 1 and 2: the negative results were probably due to different factors. First, in both protocols we employed a within-subjects design that could have facilitated a learning effect, regardless of the task (Go/no-go or combined Stroop and N-back). Second, the selected stimulated area, corresponding to the scalp location of the rIFG, was probably not the best for enhancing accuracy and inhibition. At the opposite, in experiment 3 we found a significant effect of stimulation on the error rates for the incongruent stimuli of the Stroop task. Differently from the previous experiments, we assigned participants to the anodal or sham group in a between-subject design: this choice was motivated mainly by the need to reduce the learning effect, although it cannot be excluded that it emerged in such a design as well. Further, unlike the experiment 1 and 2, the active electrode was placed over the rDLPFC, and not over the rIFG. However, in order to directly compare the extension of the electric field produced by the different setups, the stimulated cortical areas have been highlighted and superimposed in Fig. 4 (simulation performed with SimNIBS 3.2).

Electric field modeling suggested that current flow of experiment 1 was bilaterally distributed over the middle and inferior frontal gyrus, while setup of experiment 2 stimulated similar portions of the right hemisphere but to a greater extent, and only a restricted area of the orbitofrontal cortex was involved on the left hemisphere. These results are consistent with our initial hypothesis of stimulating the same areas of the right hemisphere, but with a large extension (because of the larger electrodes) and leaving the contralateral hemisphere unaffected (because of the supra-orbital reference). On the other hand, tDCS montage of experiment 3 produced a bilateral and wider stimulation of cortical areas corresponding mainly to the middle and superior frontal gyrus. Of course, tDCS is a low spatial resolution technique, and findings from this modeling must be taken with caution as it reflects a simulation of the electric field distribution and not a real measure of cortical excitability. Nevertheless, it is also interesting to note that present observations are consistent with studies that combined neuroimaging measures to detect the neurofunctional effects of similar PFC stimulations (e.g., Refs. [70,71]).

According to our hypothesis of experiment 3 and to modeling of electric field, the recruitment of the DLPFC might explain the effect on the accuracy performance, probably because of the involvement of the rDLPFC in the sustained attention [56]. In fact, neuropsychological evidence from human [56,15,72,73] and animal [74] studies revealed a causal relation between the lesions of the dorsal portion of the PFC and the poor sustained attention. Moreover, a research on patients with lesions of the lateral rPFC revealed an increase of Stroop errors (but not a difference in response speed) when compared to controls [47]: the authors interpreted the reduced inhibition as an effect of the impaired sustained attention. This evidence is in line with the prediction of the AIC model [11], which proposes a unitary view of inhibitory functions by identifying the relationship between subcomponents of attention and inhibition, and, in particular, between the sustained attention and the so-called proactive inhibition. In fact, even if not closely associated to inhibition like the IFG, it is noteworthy that the involvement of the DLPFC in the inhibitory network has been documented by different studies (e.g., Refs. [43,75]), including a robust clinical literature which validates the use of the tDCS to help people refrain from undesired behaviors (for a meta-analysis see Jensen et al., 2013[81]). It is also crucial to acknowledge the important role of this cortical area in adjusting cognitive control on a trial-by-trial basis [20], such as in maintaining and updating the task rules [76,77], as also demonstrated by the opposite effects of anodal [43] and cathodal [17] stimulation of the rDLPFC in the Stop signal task. In other words, we suggest that stimulation of the DLPFC might increase the level of sustained attention and modulate the activity of other PFC areas in a top-down fashion, according to the internal goals.

As for the lack of effects in experiments 1 and 2, the role of the rIFG

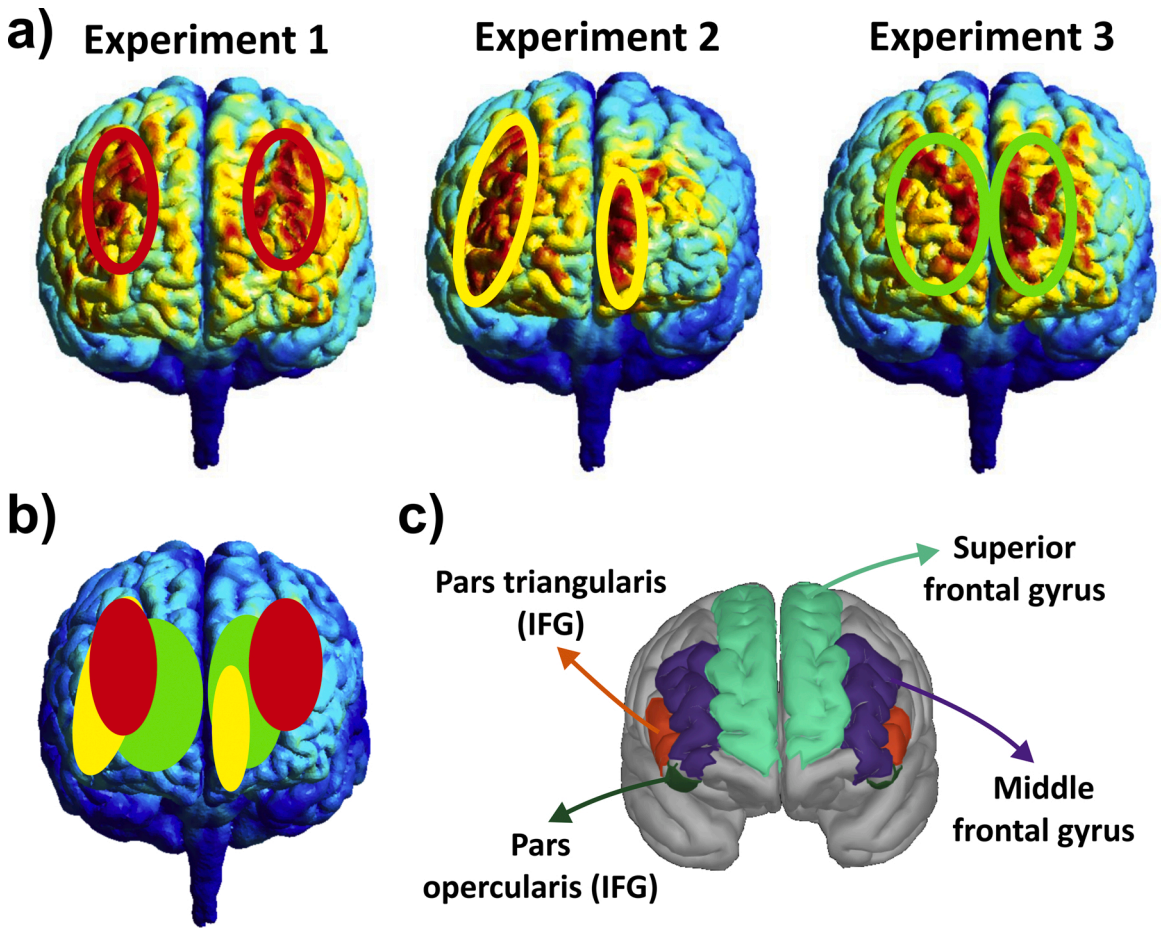

Fig. 4. a) Electric field modeling resulting from the tDCS setup of the three experiments (frontal view) and b) Overlapping of the frontal areas theoretically stimulated in the different experiments. c) labeling of the frontal gyri from the Mindboggle atlas [80]. IFG: inferior frontal gyrus.

as a inhibitory target area of stimulation is questioned. In fact, it is noteworthy that also a very recent investigation with a focus on response inhibition revealed that anodal tDCS over the IFG failed to enhance inhibitory control [19]. Authors positioned the reference electrode posterior to the anodal one, hypothesizing that the reduced distance between electrodes would lead to a more selective stimulation of the IFG. On the other side, the reduced widespread of current distribution to the DLPFC could explain the lack of experimental effects, in line with the results of our third experiment. In fact, the electrode montage needs to be evaluated in line with tDCS mechanisms. Even though anodal and cathodal tDCS are characterized by inverse current polarization, both typologies use two types of electrodes. From this point of view, for instance, in anodal stimulation the cathodal electrode could provoke a hyperpolarization in the cortical region under the reference electrode. This detail could be a further factor that influenced the lack of significant results in the second experiment, where the right unilateral stimulation was provided. In other terms, given the position of the reference electrodes above the left supra-orbital cortex, we could hypothesize a lack of effect caused by the absence of the left hemisphere stimulation. Similarly, as the Stroop test requires the ability to inhibit the word-reading, this function could become easier with the cathodal electrode placed over the left frontal areas, as in our third experiment. However, the role of lDLPFC in the Stroop test should be further investigated to corroborate this hypothesis, since several studies revealed effects of the tDCS stimulation on frontal regions during verbal processing, in particular with semantic interference [20,68,69].

In order to confirm present findings, future studies recruiting larger samples of subjects are needed as a limitation of the present experiments might consist in the rather small number of participants. Likewise, it is important to note that the three experiments adopted different tasks and we cannot be sure that the different results are entirely dependent on the stimulation sites: in other terms, further investigations will be needed to eliminate confounding effects of different protocols and stimulation montages.

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CRediT authorship contribution statement

Davide Perrotta: Conceptualization, Methodology, Software, Writing - original draft. **Valentina Bianco:** Writing - review & editing. **Marika Berchicci:** Writing - review & editing. **Federico Quinzi:** Writing - review & editing. **Rinaldo Livio Perri:** Conceptualization, Methodology, Software, Writing - original draft.

Declaration of Competing Interest

The authors report no declarations of interest.

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