Enhancing Decision-Making and Cognitive Impulse Control with Transcranial Direct Current Stimulation (tDCS) Applied Over the Orbitofrontal Cortex (OFC): A Randomized and Sham-Controlled Study

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Abstract

Decision-making and impulse control are complex interrelated processes which rely on a distributed neural network that includes multiple cortical and subcortical regions. Among them, the orbitofrontal cortex (OFC) seems to be particularly relevant as demonstrated by several neuropsychological and neuroimaging investigations. In the present sham-controlled study, we assessed whether transcranial direct current stimulation (tDCS) applied bilaterally over the OFC is able to modulate decision-making and impulse control. More specifically, 45 healthy subjects were randomized into three experimental groups. The anode (excitatory electrode) was applied over the left or right OFC, while the cathode (inhibitory electrode) was applied contralaterally. Participants were assessed before and after tDCS with a battery of computerized tasks. Results show that participants who received active anodal tDCS displayed more advantageous decision-making compared to those in the sham group (i.e. increased net scores on the Iowa Gambling Task [p = 0.04]). Furthermore, there was improvement in cognitive impulse control in participants receiving active tDCS (i.e. decreased "interference" in the Stroop Word-Color Task [p = 0.007]). Both changes occurred irrespectively of whether stimulation was administered over the left or right OFC. In conclusion, our study potentially serves as a key translational step towards the development of novel non-invasive neuromodulation-based therapeutic interventions directly targeting vulnerability factors for psychiatric conditions such as suicidal behavior and addiction.

Résumé

La prise de décisions et le contrôle de l'impulsivité sont des processus complexes et interdépendants liés à un réseau étendu composé de diverses régions corticales et sous-corticales. Parmi celles-ci, le cortex orbitofrontal (COF) semble particulièrement pertinent, tel que le démontrent plusieurs études en neuropsychologie et en imagerie. Dans la présente étude contrôlée, nous avons tenté de déterminer si la stimulation transcrânienne par courant continu (STCC) peut moduler la prise de décisions et le contrôle de l'impulsivité lorsqu'elle est appliquée bilatéralement sur le COF. Plus spécifiquement, 45 sujets sains furent assignés aléatoirement à l'un des trois groupes d'intervention. L'anode (électrode excitatrice) furent posées sur le COF droits ou gauches et la cathode (électrode inhibitrice) sur le COF controlatéral. Nous avons évalués nos participants à travers une série de tests informatisés, avant et après l'intervention de STC. Nos résultats démontrent une amélioration des capacités de prise de décisions (c.-à-d. une amélioration des résultats nets sur l'Iowa Gambling Task score net [p = 0.04]) chez les participants ayant reçu l'intervention de STCC active contrairement à ceux du groupe simulé. De plus, nous avons également observé une amélioration du contrôle cognitif chez les participants des groupes actifs (c.-à-d. diminution de l'"interférence" dans le Test Stroop Couleurs-Mots [p = 0.007]). Dans les deux cas, les changements observés furent sensiblement les mêmes, et ce, indépendamment de l'hémisphère auquel appartenait le COF ciblé. En conclusion, l'expérience décrite dans cette thèse pourrait potentiellement s'avérer une étape importante dans le développement d'un traitement de neuromodulation non invasif capable de cibler les lacunes caractéristiques de problèmes psychiatriques tels que les tendances suicidaires et la dépendance.

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Preface

This dissertation is the product of an experiment on the neurocognitive effects of transcranial direct current stimulation. None of the dissertation text is taken directly from previously published or collaborative articles. I collected the data myself, and wrote this document in collaboration with my supervisor, Dr. Marcelo Berlim. The study design was the result of a collaborative effort involving my supervisors, Dr. Alexander McGirr, Dr. Frederique Van Den Eynde, Dr. Fabrice Jollant, Dr. Martin Lepage, and myself.

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Introduction

Decision-making and impulse control (both motor and cognitive) are complex interrelated cognitive processes which enable humans to properly weigh the immediate and future risks & benefits of competing actions and select the appropriate behavioral response in given circumstances [1]. Hence, it is not surprising that their impairment has been associated with deleterious personal and/or societal consequences, as well as with the development and/or chronicity of a number of pervasive psychiatric conditions including suicidal behavior and addiction disorders [2,3]. As a result, there has been emerging interest in understanding the intricate neural mechanisms underlying the interplay between adaptive/maladaptive decision-making and impulse control [4].

Growing convergent evidence strongly suggests that decision-making and impulse control are mediated by a distributed neural network that includes multiple prefrontal, limbic, and subcortical regions [5-8]. Among them, the orbitofrontal cortex (OFC) seems to play a significant role and has received significant attention in recent years [8-10]**.** This stems particularly from the fact that subjects with OFC lesions are more impulsive overall compared both to normal controls and to those with non-OFC brain damage, are usually unable to alter decisions despite negative associated outcomes (i.e. they seem to disregard the future consequences of their actions and hence to display increased risk-taking behavior), and are less effective in identifying negative emotions expressed either facially or vocally [11,12]. Moreover, recent functional neuroimaging studies have reported that escalating risk-taking behavior in healthy volunteers is associated with decreased activity in the ventromedial prefrontal cortex (of which the OFC is a key component) [13], and that the OFC is implicated in the generation of automatic negative emotions such as anger and anxiety [14]. More broadly, this brain region (which receives inputs from all sensory systems

and is thus one of the most polymodal cortical areas [9]) plays a central role in decoding the predicted reward value (or subjective expected utility) of choice options and in integrating it with non-associative information (e.g., internal state, current context, subsequent plans) [10]. Thus, the OFC enables a more thorough comparison of the available behavioral responses and the selection of the optimal course of action, which should be flexible enough to change in response to fluctuations in motivational contingencies [5,15].

Transcranial direct current stimulation (tDCS) is a safe method for non-invasively modulating cortical excitability through the use of weak electrical currents (usually of 1-2 mA) circulating between two scalp electrodes (i.e., an anode and a cathode) placed over the target cortical regions [16]. The effects of tDCS on brain activity are polarity-dependent, such that anodal stimulation generally enhances cortical excitability by depolarizing cell membranes and increasing neuronal firing rates, while cathodal stimulation generally results in the opposite effect [17]. Because of its neural effects, tDCS has been increasingly used to gauge the functional relationship between cognitive/behavioral dimensions and putatively relevant neurocircuitry [18,19]. For example, anodal tDCS applied over the dorsolateral prefrontal cortex (DLPFC) of healthy volunteers has been reported to not only enhance planning abilities [20], working memory [21], and attention [22], but to also to decrease correlates of impulsivity and risk-taking behavior [23,24].

To our knowledge, no study to date has assessed the neurocognitive effects of non-invasive brain stimulation of the OFC, despite mounting evidence of its potential with regards to cognitive enhancement and of the role this brain region plays in mediating impulse control and decision-making. Therefore, we carried out the present randomized and sham-controlled study in which 45 healthy subjects were evaluated using a battery of computerized tasks before and after a 30-minute session of tDCS applied bilaterally over the OFC. We hypothesized that active anodal

tDCS would enhance decision-making abilities as well as cognitive impulse control in comparison to sham tDCS, owing to its putative facilitatory effects on the excitability of the OFC.

Materials and Methods

Design

We conducted a single-blind (i.e. subjects were kept unaware of the type of tDCS intervention received), three-arm, randomized, and sham-controlled study. Participants were randomly assigned in a 1:1:1 ratio, using their order of entrance and a computer-generated randomization list [25]. Each group received 30 minutes of one of three possible tDCS interventions: (1) active anodal left OFC/cathodal right OFC (i.e. "left OFC" group; n = 15), (2) active anodal right OFC/cathodal left OFC (i.e. "right OFC" group; n = 15) or (3) sham anodal/cathodal tDCS randomly applied over the left (n = 7) or to the right (n = 8) OFC (i.e. "sham" group).

In order to account for the possible effects of depressive and anxious symptoms on overall performance, the experiment began with the administration of the Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR)[26] and of two visual analogue scales (VAS; which required participants to indicate, on a horizontal 10 cm line, whether they felt "depressed" or "anxious" at that moment, ranging from "0" ["not at all"] to "10" ["extremely"]). Subsequently, they were administered a computerized neurocognitive test battery (see page 12-16) on decision-making and impulse control that took approximately 45 minutes to complete. Following this, participants received a 30-minute session of tDCS before being re-submitted to the computerized neurocognitive battery, the VAS, as well as a brief questionnaire on study blinding.

Participants

The present study was registered at www.clinicaltrials.gov (identifier # NCT01805401) and was approved by the Douglas Mental Health University Institute's Research Ethics Board. We recruited healthy male and female volunteers from the local community through advertisements between April 2013 and March 2014. They were naive to tDCS, as well as to the neurocognitive tasks and the nature of our experiment. Their inclusion was conditional on meeting the following criteria: (1) being aged between 18 and 60 years; (2) having no history of neuropsychiatric or substance-related disorders (as assessed by the Mini-International Neuropsychiatric Interview[27]) as well as no clinically-significant depressive symptomatology (i.e. a score ≤ 5 on the QIDS-SR [26]); (3) being free of major medical conditions; (4) not using any psychoactive medications or smoking cigarettes; and (5) not having a history of brain surgery, brain tumor, and/or intracranial metallic implants.

We obtained written informed consent from all participants before enrolment, and they were compensated with C$ 60 and a smaller (C$ 2 to 16) bonus based on their performance on the decision-making tasks.

tDCS Procedure

tDCS was delivered by a battery-driven HDCstim® stimulator (Newronica, Italy) while participants resting in a reclining chair with their eyes closed. Two conductive-rubber electrodes of 45 cm^2 (anode) and 85 cm^2 (cathode) were encased in wet sponges saturated with saline and fixed to the scalp (using an elastic cap)above the left and the right supraorbital ridges (i.e. Fp1 and Fp2 positions of the 10/20 EEG System, respectively)[28]. A larger cathode was used to minimize its possible inhibitory cortical effects [29].

Following the electrode placement, the electrical current was progressively ramped up to 1.5 mA over the course of 30 seconds. In the two active tDCS groups, the current intensity was maintained at this level for 30 minutes, while in the sham group it was ramped-down after 30 seconds (a procedure that has been shown to be sensorily indistinguishable from active tDCS and associated with no after-effects [30]). The overall current density under the electrodes was of 0.04 mA/cm² under the anode and of 0.018 mA/cm² under the cathode. Thus, current density at the cathode was likely functionally insignificant, whereas it fell within the accepted safety guidelines at the anode [31,32].

Finally, the investigator remained in the testing room for the duration of the experiment to ensure the participants' safety.

Neurocognitive Tasks

The neurocognitive assessment battery was composed of three decision-making and three impulse control tasks which were administered in a counterbalanced sequence using Inquisit v. 4 (Millisecond Software, USA). The Inquisit software ran on an Intel Core i32120 desktop computer and was presented on a 24-inch LCD monitor with a video resolution of 1,920 X 1,080 pixels. Data were collected through a response pad (model RB-540, Cedrus, USA), which offers a high reaction time resolution (i.e. 2-3 ms). Participants sat approximately 70 cm from the screen, which was positioned at the eye level.

Decision-making

Decision-making tasks can be broadly divided, depending on the explicitness of the rules for gains and losses, into those involving risk, and those involving both risk and ambiguity [33]. Decisions involving risk reflect situations in which outcome probabilities can be reasoned easily

(or are known in advance), whereas decisions involving both risk and ambiguity reflect situations in which choices have unknown probabilities that can only be estimated through trial and error. We used three tasks to tap into these two constructs: the Iowa Gambling Task (IGT) [34], the Balloon Analog Risk Task (BART) [35] and the Game of Dice Task (GofD) [36].

In the IGT [34], the most popular measure of ambiguous decision-making, participants are asked to draw cards from four different decks with the goal of earning as much virtual money as possible. However, they are unaware that this task involves a total of 100 card draws, and that two of the decks (A and B) are disadvantageous in that they yield significant immediate gains but even greater long-term losses, whereas the two remaining decks (C and D) yield relatively small immediate and long-term gains. Successful performance in the IGT thus requires participants to implicitly and explicitly learn its underlying rules on frequencies and magnitude of wins and losses and to develop a long-term profitable monetary strategy involving choosing progressively less disadvantageous card choices. The main variable of interest in the IGT is its "net score", which is the number of cards drawn from the advantageous decks minus the number of cards drawn from the disadvantageous decks.

The BART [35], also a measure of ambiguous decision-making, requires participants to inflate 30 virtual balloons by repeatedly pressing a key on the response pad. Each balloon is programmed to pop between 1 and 128 pumps, with an average breakpoint of 64 pumps. Specific information regarding the balloon breakpoint is not provided to participants, and every pump gives them C$ 0.05, which is gradually added to a "temporary bank". At any point during each trial, participants can stop pumping the balloon and click the "Collect $$$" button, which transfers the money accumulated from that trial into a "permanent bank" and produces a slot machine payoff sound. In contrast, when a balloon explodes, a "pop" sound is heard, the balloon

disappears from the screen, the money in the "temporary bank" is lost, and the next trial begins. Hence, contrary to the IGT, the BART does not involve an explicit learning process as each balloon trial has a random outcome. The variable of interest in this task is the "average adjusted number of pumps" (i.e. the average number of pumps on each balloon prior to money collection).

Finally, the GofD [36], a measure of risky decision-making, requires participants to bet on either one or a combination of up to four numbers before throwing 18 virtual dices. They win or lose virtual money depending on whether their chosen number (or numbers) includes the outcome of the throw or not. They are given all the necessary information to understand that choosing a larger combination of numbers will increase their chances of having a winning bet but decrease the monetary sum earned. Thus, contrary to the IGT but similar to the BART, the GoD does not involve an explicit learning process. The variable of interest in this task is the "number of risky choices" (i.e. those associated with winning probabilities of less than 50%).

Impulse Control

Behavioral paradigms of impulse control can be broadly divided into those measuring impulsive choice (i.e. "cognitive impulsivity") or impulsive action (i.e. "motor impulsivity") [8]. We used three tasks to tap into these two categories: the Stroop Color-Word Test (SCWT) [37], the Continuous Performance Task (CPT)[38], and the Stop-Signal Task (SST) [39].

In the SCWT [37], three different types of stimuli are presented to participants: coloured rectangles (neutral stimuli), colored words written in the same ink as their meaning (e.g., the word "red" displayed in red ink; also known as congruent stimuli) as well as colored words written in a discrepant ink relative to their meaning (e.g., the word "red" displayed in blue ink; also known as incongruent stimuli). They are asked to identify, as quickly and accurately as

possible, the ink color of 84 randomly presented word-color stimuli by pressing the appropriate key on the response pad. Hence, successful performance in the SWCT requires participants not only to inhibit a planned response by disregarding distracting stimuli, but also to effectively monitor the conflict between word reading and naming the word ink color. The main variable of interest in the SWCT is the "interference index" which measures the difference in response latencies (in milliseconds [ms]) between incongruent and congruent stimuli. This is considered a correlate of "cognitive impulsivity".

In the CPT [38], 620 letter stimuli flash consecutively the computer screen. Participants are asked to press a specific key on the response pad whenever they see the letter "X" (65%). Every response to a letter other than "X" (35%) is identified as a "commission error" (which is indicative of "motor impulsivity"), and will serve as a "control" variable considering that inhibitory motor regulation is primarily mediated by non-OFC regions [40-42]. Furthermore, every non-response to a letter "X" is identified as an "omission error" (which is a correlate of inattention), and will be used to assess putative between-group differences in attentional levels.

Finally, in the SST [39], a measure of "motor impulsivity", participants are presented with both "go" and "stop" trials. On "go" trials, they are shown 192 "go" stimuli (i.e. consecutive arrows randomly pointing left or right) and are required to press the matching key on the response pad (e.g. left arrow = left key). On "stop" trials, the "go" stimulus is immediately followed by a stop-signal sound (750 Hz, 75 ms), which indicates to participants that they must refrain from responding. Initially, the stop signal delay (SSD) is set at 250 ms after the presentation of the "go" stimulus, but afterwards it varies in a step-wise manner dependent on the previous response (i.e. it is decreased or increased by 50 ms after a successful or an unsuccessful "stop" trial, respectively). In total, there are 48 "stop" trials and 144 "go" trials, presented

intermixed and counterbalanced for left and right arrows, in three separate blocks. The main variable of interest in the SST is the "stop-signal reaction time" (SSRT), which is estimated by subtracting the mean "go" reaction time from the mean SSD, and thus reflects the amount of time required by participants to prevent a planned motor response. The SSRT will also serve as a "control" variable owing to its primarily non-OFC underlying neural correlates [40-42].

Statistical Analyses

Statistical analyses were conducted with SPSS v. 20 (IBM, USA). Baseline continuous (i.e. age, education, and QIDS-SR and VAS scores), and categorical (i.e. gender) variables were compared between groups, respectively, with one-way analysis of variance (ANOVA) and chi-square (χ^2). To assess the effects of tDCS on decision-making and impulse control we employed repeated measures ANOVA with time (i.e. pre-tDCS, post-tDCS) as the independent within-subjects variable, tDCS intervention (i.e. active anodal left OFC, active anodal right OFC, sham) as the independent between-subjects variable, and score on the neurocognitive tasks as the dependent variable. If the omnibus test for the tDCS intervention*time interaction was statistically significant, we then carried out planned comparisons (using the least significant difference) to examine the nature of the differences, and also calculated partial eta squared (η_p^2) estimates (with values ≤ 0.01, 0.02-0.06 and ≥ 0.14 representing small, moderate and large effect sizes, respectively [43]). Furthermore, we identified and removed outliers for the variables of interest in the baseline period by using Tukey's boxplot technique [44]. Finally, statistical significance was set at $\alpha < 0.05$.

Results

Participants

The baseline characteristics of healthy volunteers are summarized on **Table 1**. Their mean age was 25.09 ± 7.10 years, and 64.50% (n = 29) of them were females. They had 16.89 ± 2.41 years of education as well as mean scores on the QIDS-SR, "depression" VAS and "anxiety" VAS of 3.16 ± 1.03, 1.14 ± 1.63, and 2.50 ± 2.20, respectively. Overall, there were no significant differences between the three groups in terms of age, gender, education or baseline QIDS-SR and VAS scores (all with $p > 0.10$), thus suggesting the validity of the randomization process.

Table 1. Study participants: baseline characteristics.

Group	n	Gender[1]		Age in years (SD)[2]	Education in years (SD)[3]	Mean score on the QIDS-SR (SD)[4]	Depression VAS[5]	Anxiety VAS[6]
		Males	*Females*					
Left OFC	15	3	12	24.07 (3.59)	16.80 (2.57)	3.20 (1.32)	1.57 (1.91)	3.38 (2.44)
Right OFC	15	6	9	27.20 (11.19)	16.40 (2.59)	2.80 (2.07)	0.64 (1.03)	1.96 (2.01)
Sham	15	7	8	24.00 (3.62)	17.47 (2.10)	3.47 (1.13)	1.21 (1.79)	2.15 (1.98)

[1] $\chi^2(df) = 2.52(2)$, p = 0.28; [2] $F(df) = 0.99(2,42)$, p = *0.38*; [3] $F(df) = 0.74(2,42)$, p = 0.48; [4] $F(df) = 0.40(2,42)$, p = 0.67; [5] $F(df) = 1.26(2,42)$, p = 0.29; [6] $F(df) = 1.91(2,42)$, p = 0.16.
Abbreviations: OFC = orbitofrontal cortex; QIDS-SR = Quick Inventory of Depressive Symptomatology – Self-Report; VAS = Visual analogue scale.

Neurocognitive Tasks

Decision-Making

Table 2. Neurocognitive tasks on decision-making before and after active or sham tDCS.

Intervention	Iowa Gambling Task (IGT) ("*net score*") (n = 43)	Balloon Analogue Risk Task (BART) ("*adjusted average number of pumps"*) (n = 44)	Game of Dice Task (GofD) ("*number of risky choices*") (n = 42)

		Mean	***SD***	***Omnibus test*[#]**	***Mean***	***SD***	***Omnibus test*[#]**	***Mean***	***SD***	***Omnibus test*[#]**
Pre-tDCS	***left OFC***	-6.00	28.79	*Wilks' λ* = 0.85, $F_{2,40}$ = 3.53, p = 0.04*	25.33	10.01	*Wilks' λ* = 0.88, $F_{2,41}$ = 2.80, p = 0.07	2.93	2.71	*Wilks' λ* = 0.97, $F_{2,39}$ = 0.56, p = 0.57
	right OFC	1.87	26.00		32.84	11.94		2.00	3.46	
	sham	1.43	35.54		27.33	11.02		2.73	3.30	
Post-tDCS	***left OFC***	17.14	44.77		33.54	14.16		2.73	3.22	
	right OFC	16.93	43.48		32.77	10.40		0.58	0.90	
	sham	-3.86	33.91		31.96	12.96		2.20	3.36	

[#] for the tDCS intervention*time interaction.
[*] Statistically significant.
Abbreviation: OFC = orbitofrontal cortex; tDCS = transcranial direct current stimulation.

A significant tDCS intervention*time interaction was found for the IGT net score (*Wilks' λ* = 0.85, $F_{2,40}$ = 3.53, p = 0.04) after controlling for the main effect of time (*Wilks' λ* = 0.87, $F_{1,40}$ = 6.05, p = 0.02) (**Figure 1**). Planned comparisons revealed that active tDCS applied over either the left or the right OFC, in comparison to sham tDCS, were associated with significant increases in the IGT "net score" (i.e. left OFC vs. sham: *Wilks' λ* = 0.80, $F_{1,26}$ = 6.50, p = 0.02; right OFC vs. sham: *Wilks' λ* = 0.84, $F_{1,27}$ = 4.98, p = 0.03), representing large effect sizes (i.e. η_p^2 = 0.20 and 0.16, respectively); however, there was no difference between the two active tDCS interventions (i.e. left OFC vs. right OFC: *Wilks' λ* = 0.98, $F_{1,27}$ = 0.43, p = 0.52). Overall, these results indicate that participants who received active anodal tDCS (irrespective of laterality) presented with more advantageous decision-making.

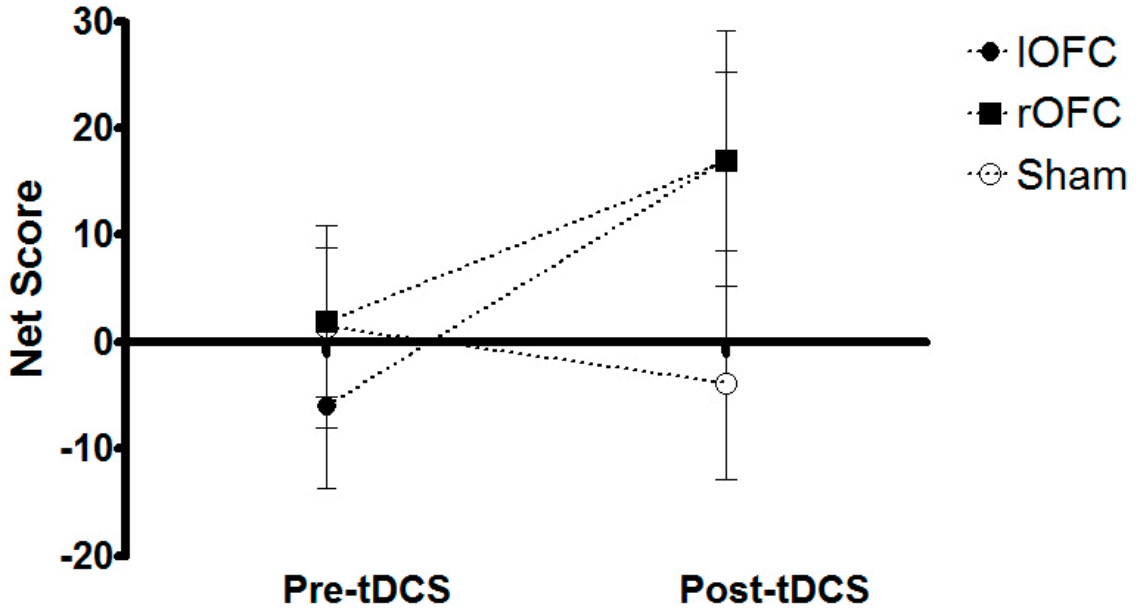

Figure 1. *Net score in the Iowa Gambling Task before and after active or sham tDCS.*
A significant tDCS intervention*time interaction was found (p = 0.04) after controlling for the main effect of time (p = 0.02). Planned comparisons revealed that active tDCS applied to either the left or the right OFC, in comparison to sham tDCS, was associated with significant increases in the IGT net score (and thus with more advantageous and decision-making) (i.e. left OFC vs. sham: p = 0.02; right OFC vs. sham: p = 0.03), although there was no difference between the two active tDCS interventions (i.e. left OFC vs. right OFC: p = 0.52).
Abbreviations: lOFC = left orbitofrontal cortex; rOFC = right orbitofrontal cortex

Regarding the "average adjusted number of pumps" on the BART, only a trend towards a significant tDCS intervention*time interaction was found (*Wilks'* λ = 0.88, $F_{2,41}$ = 2.80, p = 0.07) after controlling for the main effect of time (*Wilks'* λ = 0.83, $F_{1,41}$ = 8.65, p = 0.005). Finally, the "number of risky choices" in the GofD was not affected by tDCS as demonstrated by a non-significant tDCS intervention*time interaction (*Wilks'* λ = 0.97, $F_{2,39}$ = 0.56, p = 0.57) after controlling for the main effect of time (*Wilks'* λ =0.94, $F_{1,39}$ = 2.33, p = 0.13).

Impulse Control

Table 3. Neurocognitive tasks on impulse control before and after active or sham tDCS.

Intervention		**Stroop Color-Word Task (SCWT)** (*"interference index"* [*ms*]) (n = 44)			**Continuous Performance Task (CPT)** (*number of "commission errors"*) (n = 44)			**Stop-Signal Task (SST)** ("*stop-signal reaction time*" [*ms*]) (n = 44)		
		Mean	***SD***	***Omnibus test*[#]**	***Mean***	***SD***	***Omnibus test*[#]**	***Mean***	***SD***	***Omnibus test*[#]**
Pre-tDCS	***left OFC***	126.39	80.41	*Wilks' λ* = 0.78, $F_{2,41}$ = 5.69, p = 0.007*	1.33	1.23	*Wilks' λ* = 0.89, $F_{2,41}$ = 2.56, p = 0.09	237.41	35.33	*Wilks' λ* = 0.98, $F_{2,41}$ = 0.33, p = 0.72
	right OFC	222.36	96.05		1.60	1.64		246.86	32.20	
	sham	62.23	100.07		2.57	1.65		234.27	30.84	
Post-tDCS	***left OFC***	11.97	137.60		0.80	0.94		218.85	47.65	
	right OFC	141.75	117.62		1.93	2.31		238.69	50.68	
	sham	105.22	82.47		1.33	1.23		230.01	36.99	

[#] for the tDCS intervention*time interaction.
* Statistically significant.
Abbreviation: OFC = orbitofrontal cortex; tDCS = transcranial direct current stimulation.

With respect to the "interference index" in the SCWT, a significant tDCS intervention*time interaction was found (*Wilks' λ* = 0.78, $F_{2,41}$ = 5.69, p = 0.007) after controlling for the main effect of time (*Wilks' λ* = 0.86, $F_{1,41}$ = 6.53, p = 0.01) (**Figure 2**). Planned comparisons revealed that active tDCS applied over either the left or the right OFC, in comparison to sham tDCS, were associated with significant decreases in the "interference index" (i.e. left OFC vs. sham: *Wilks' λ* = 0.75, $F_{1,27}$ = 8.94, p = 0.006; right OFC vs. sham: *Wilks' λ* = 0.79, $F_{1,27}$ = 7.23, p = 0.01), representing large effect sizes (i.e. η_p^2 = 0.25 and 0.21, respectively); however, there was no difference between the two active tDCS interventions (i.e. left OFC vs. right OFC: *Wilks' λ* = 0.99, $F_{1,28}$ = 0.52, p = 0.48). Of note, this reduction in the "interference index" after active tDCS was not paralleled by higher "incongruent stimuli" error rates, as demonstrated by a non-significant tDCS intervention*time interaction (*Wilks' λ* = 0.97, $F_{2,38}$ =

0.58, p = 0.57) after controlling for the main effect of time (*Wilks'* λ = 1.00, $F_{1,38}$ = 0.11, p = 0.74). Overall, these results indicate that participants who received active anodal tDCS (irrespective of laterality) presented with enhanced cognitive control.

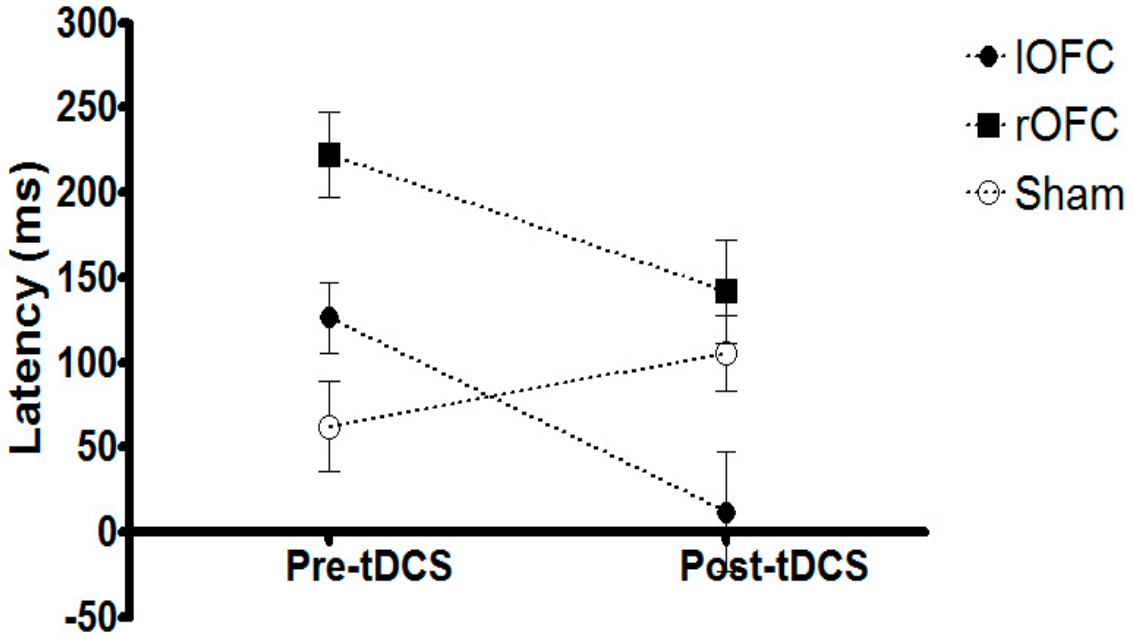

Figure 2. *"Interference index" in the Stroop Color-Word Task before and after active or sham tDCS.*
A significant tDCS intervention*time interaction was found (p = 0.007) after controlling for the main effect of time (p = 0.01). Planned comparisons revealed that active tDCS applied over the left or right OFC was associated with significant decreases in Stroop (interference),and thus enhanced cognitive control relative to sham tDCS (i.e. left OFC vs. sham: p = 0.006; right OFC vs. sham: p = 0.01), although there was no difference between the two active tDCS interventions (i.e. left OFC vs. right OFC: p = 0.48).
Abbreviations: lOFC = left orbitofrontal cortex; rOFC = right orbitofrontal cortex.

The number of "commission errors" in the CPT was not affected by tDCS as demonstrated by a non-significant tDCS intervention*time interaction (*Wilks'* λ = 0.89, $F_{2,41}$ = 2.56, p = 0.09) after controlling for the main effect of time (*Wilks'* λ = 0.94, $F_{1,41}$ = 2.69, p = 0.11). Finally, the "stop-signal reaction time" in the SST was likewise not influenced by tDCS as demonstrated by a non-significant tDCS intervention*time interaction (*Wilks'* λ = 0.98, $F_{2,41}$ = 0.33, p = 0.72) after controlling for the main effect of time (*Wilks'* λ = 0.96, $F_{1,41}$ = 1.91, p = 0.17).

Attentional Levels

tDCS did not affect the number of "omission errors" in the CPT (i.e. non-significant tDCS intervention*time interaction [*Wilks'* λ = 0.95, $F_{2,40}$ = 1.14, p = 0.33] after controlling for the main effect of time [*Wilks'* λ = 0.92, $F_{1,40}$ = 3.48, p = 0.07]). This suggests that differential attentional levels cannot explain the neurocognitive changes observed after tDCS.

Depression and Anxiety Symptoms

VAS scores on "depression" and "anxiety" were associated with non-significant tDCS intervention*time interactions (depression VAS: *Wilks'* λ = 0.98, $F_{2,39}$ = 0.39, p = 0.68; anxiety VAS: *Wilks'* λ = 0.98, $F_{2,42}$ = 0.45, p = 0.64) after controlling for the main effect of time (depression VAS: *Wilks'* λ = 0.94, $F_{1,39}$ = 2.30, p = 0.14; anxiety VAS: *Wilks'* λ = 0.85, $F_{1,42}$ = 7.56, p = 0.009). This suggests that tDCS had no mood-related effects.

Integrity of Blinding

The three groups did not differ in terms of the number of participants who guessed whether they had received active vs. sham tDCS (χ^2 = 5.11, df = 4, p = 0.28), thus confirming the validity of our blinding procedure.

tDCS Acceptability

None of the participants suffered from significant adverse effects during or after the tDCS sessions. Consequently, there were no dropouts in this study.

Discussion

In the current randomized, single-blind and sham-controlled study we have shown that healthy participants who received 30 minutes of active anodal tDCS applied over either the left or the right OFC (coupled with contralateral cathodal tDCS), displayed more advantageous decision-making (as indexed by increased IGT "net scores"), in addition to improved ability to inhibit inappropriate responses (as indicated by decreased "interference" in the SWCT) than those who received sham tDCS. Of note, neither attentional levels nor mood-related variables seem to explain these changes, and the blinding procedure seems to have been effective. Overall, our results are in line with data from functional neuroimaging studies in healthy participants that reported a strong association between bilateral OFC activity and both risky and ambiguous decision-making [7]. Furthermore, our study highlights the important role played by the OFC on subjects' performance in the IGT [45,46] and the SWCT [47,48], and identifies this brain region as a potential therapeutic target for disorders characterized by impulsivity and poor decision-making.

To our knowledge, this is the first study demonstrating that non-invasive neuromodulation applied over the OFC can enhance both decision-making and cognitive impulse control - two key neurocognitive traits whose deficits have been implicated in the development of a number of pervasive psychiatric conditions such as addiction disorders [49], and suicidal behavior [50]. The relevance of our findings for suicide prevention is highlighted by a recent meta-analysis (n = 2,323) which reported that patients with a history of suicide attempts have poorer performance on the IGT and the SWCT relative to both patients without previous suicidal behavior and healthy controls, thus suggesting that deficits in decision-making and cognitive impulse control might constitute putative vulnerability markers for suicidality [51]. Consequently, we hypothesize that anodal tDCS applied over the OFC may hold promise as an emerging therapeutic intervention for

suicide prevention in at-risk clinical populations such as depressed individuals [52]. Yet, further studies are clearly needed to investigate this intriguing possibility.

It is difficult to compare our findings with those of previous non-invasive neuromodulation studies on decision-making and impulse control as, to our knowledge, none of them have primarily targeted the OFC [53,54]. Nevertheless, current evidence shows that inhibitory low frequency repetitive transcranial magnetic stimulation (rTMS) applied to the right DLPFC seems to lead participants to more often accept unfair offers [55] and to choose higher-risk prospects [56]. Moreover, subjects who received anodal tDCS over the right DLPFC were shown to have their confidence levels boosted during risky decision-making [57], and to more frequently choose safer prospects [23], whereas those who received anodal tDCS over the left DLPFC were shown to more often employ suboptimal strategic decision-making [58] despite demonstrating heightened impulse control [59]. Additional investigations have reported that anodal tDCS applied to either the left or the right DLPFC was associated with a more careful driving style in virtual scenarios [60], while cathodal tDCS over the right DLPFC increased both impulsiveness and electro-dermal activity related to the vegetative nervous system [61]. Finally, non-DLPFC studies have shown that anodal tDCS applied to the right inferior frontal gyrus [62] or to the pre-supplementary motor area [42] was associated with more efficient inhibitory control.

Neurocognitive Effects of tDCS Applied over the OFC: Putative Mechanism of Action

Growing evidence suggests that the neural processes underlying decision-making and impulse control are mediated by the interaction between a "limbic loop" (affective/motivational), mainly encompassing the OFC, the amygdala and the ventral striatum, and a "cognitive loop" (executive/motor), mainly encompassing the DLPFC, the anterior cingulate cortex (ACC) and the

dorsal striatum [5,6,63,64]. More specifically, the "limbic loop" seems to be involved in the immediate decoding and response to potential rewards, losses or threats (i.e. impulse regulation) as well as in emotional control (i.e. in adjusting behavior to changing contingencies), whereas the "cognitive loop" seems to be mostly involved in long-term reward prediction, action representation and goal maintenance, as well as in monitoring conflicting (or ambiguous) choices (i.e. top-down cognitive control).

Based on the model described above, we propose that the neurocognitive changes observed in our study after anodal tDCS might have resulted from its direct facilitatory effects on the activity of the OFC coupled with the indirect modulation of other relevant frontal regions such as the DLPFC and the ACC via their dense anatomic connections [9]. Also, the strong bidirectional links between the OFC and the hippocampus, the amygdala, and the nucleus accumbens might have contributed to tDCS' mechanism of action [9]. Importantly, this hypothesis is supported by recent functional neuroimaging studies reporting that tDCS is not only able to enhance cortical excitability underneath the anode but to also influence the resting-state connectivity and neural activity in both neighbouring and more distal sites [65,66]. In addition, from a neurocognitive standpoint, we suggest that active anodal tDCS applied over the OFC might have enhanced (or accelerated) participants ability to decode the motivationally salient information inherent to the IGT (i.e. its reward and punishment contingencies), thus enabling a more advantageous decision-making strategy [67]. This could potentially explain the discrepancies observed in the effects of tDCS on the IGT (which necessitates learning), and on the BART and the GofD (which do not involve explicit learning processes). Furthermore, this positive shift in decision-making might have been facilitated by the parallel improvement in cognitive control (demonstrated by lower "interference" in the SWCT) which allowed participants to more

effectively suppress distracting/irrelevant information, and ultimately to better adapt their choice behavior according to the fluctuations in the stimulus-reward contingencies [68].

Limitations

Despite its encouraging results, our study has a number of potential limitations. For example, it is possible that the inhibitory effects of the cathode applied over the contralateral OFC might have contributed to the observed behavioral changes[17]. However, this is unlikely as most investigations to date have failed to show significant cathodal effects on subjects' cognitive performance [19] as well as because we have used a relatively large cathode. Furthermore, the magnitude of the behavioral changes observed in our study might have been mitigated by some of its design features (e.g., the delivery of a single 30-minute session, the use of 1.5 mA, and the non-concomitant administration of tDCS with the neurocognitive battery) [69]. Yet, several previous studies which were methodologically similar to ours have been successful in eliciting significant tDCS-related cognitive changes [18,19]. Moreover, it is possible that some of our nearly significant findings might have resulted from intrinsic task-related "ceiling/floor" or time-dependent effects that limited the detection of post-tDCS changes. Indeed, previous studies have shown that healthy participants performing the BART tend to exhibit a risk-averse response style that often leads to suboptimal results [70,71], and that tDCS might preferentially improve cognitive skills in subjects who present with lower baseline performance [72]. Consequently, we anticipate that tDCS may induce more prominent behavioral effects if administered to individuals who commonly present with baseline deficits in decision-making and impulse control such as those with suicidal behavior [51] or addiction disorders [2]. A related issue that remains unresolved is whether the statistically significant neurocognitive changes observed after tDCS are indeed

meaningful in "real-life" (e.g., in terms of their magnitude and duration) [73]. Additionally, although the neurocognitive battery employed in this study is well established in clinical research, none of the individual tasks allows for a detailed dissection of their underlying component processes/computations. Additionally, although the neurocognitive battery employed in this study is well established in clinical research, none of the individual tasks allows for a detailed dissection of their underlying component processes/computations. Finally, as we did not employ pre-post functional neuroimaging, we cannot determine whether anodal tDCS might have differentially influenced the activity of OFC sub-regions which are thought to be functionally distinct (e.g., medial vs. lateral OFC [74]). Also, for the same reason, our attempt to causally connect the putative facilitatory effects of anodal tDCS on OFC cortical excitability with the observed neurocognitive changes in decision-making and cognitive impulse control remains tentative. Hence, whether the chosen electrode setup effectively modulated the OFC cannot be directly confirmed by our study, and one might suggest that other prefrontal areas (e.g., DLPFC) could have also been affected by the induced electrical field considering tDCS' possible long-range effects and unknown plasticity of neural circuitry [75]. Nevertheless, we believe that there are at least three relatively strong indicators that the OFC was indeed primarily modulated by our tDCS montage: (1) the neurocognitive changes observed after active tDCS are compatible with the behavioral correlates of OFC function [8,11,15], (2) sham tDCS had no significant impact on task performance, and (3) active tDCS did not influence performance on the SST or the rate of "commission errors" in the CPT – both expected findings considering that inhibitory motor control is primarily mediated by non-OFC regions including the pre-supplementary motor area, the inferior frontal gyrus, and the frontal eye fields [40-42].

Conclusion

Our study demonstrates that tDCS - a safe, inexpensive and easy to use technique, can putatively shift decision-making towards less risky choices as well as enhance cognitive impulse control when applied for 30 minutes over the OFC of healthy participants. Overall, our results support the notion that the OFC plays a central role in mediating these two neurocognitive processes, and also potentially serve as a key translational step towards the development of novel non-invasive neuromodulation-based therapeutic interventions specifically targeting vulnerability factors for a number of psychiatric conditions such as suicidal behavior, attention deficit hyperactivity disorder, and addiction disorders.

Finally, future investigations in healthy volunteers and in individuals with psychiatric conditions should aim at replicating and extending our findings (e.g., by using tasks with more clearly dissectible cognitive components), investigating the neural basis of tDCS applied over the OFC with functional neuroimaging and/or electrophysiological, measures as well as exploring novel strategies for optimizing both the magnitude and duration of the neurocognitive effects associated with this promising non-invasive neuromodulation technique.

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