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Enhancing decision-making and cognitive impulse control with transcranial direct current stimulation (tDCS) applied over the orbitofrontal cortex (OFC): A randomized and sham-controlled exploratory study

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ABSTRACT

Background: Decision-making and impulse control (both cognitive and motor) 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.
Methods: In the present study we assessed whether transcranial direct current stimulation (tDCS) applied bilaterally over the OFC is able to modulate decision-making and cognitive impulse control. More specifically, 45 healthy subjects were randomized to receive a single 30-min session of active or sham anodal tDCS (1.5 mA) applied over either the left or the right OFC (coupled with contralateral cathodal tDCS). They were also assessed pre- and post-tDCS with a battery of computerized tasks.
Results: Our results show that participants who received active anodal tDCS (irrespective of laterality), vs. those who received sham tDCS, displayed more advantageous decision-making (i.e., increased Iowa Gambling Task "net scores" [$p = 0.04$]), as well as improved cognitive impulse control (i.e., decreased "interference" in the Stroop Word-Colour Task [$p = 0.007$]). However, we did not observe tDCS-related effects on mood (assessed by visual analogue scales), attentional levels (assessed by the Continuous Performance Task) or motor impulse control (assessed by the Stop-Signal Task).
Conclusions: 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 behaviour and addiction.

Decision-making and impulse control (both cognitive and motor) are complex interrelated cognitive processes which enable humans to properly weigh the immediate and future risks and benefits of competing actions and select the appropriate behavioural response in given circumstances (Ernst and Paulus, 2005). 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 behaviour and addiction disorders (Bechara, 2005; Jollant et al., 2011). As a result, there has been an emerging interest in understanding the intricate neural mechanisms underlying the interplay between adaptive/maladaptive decision-making and impulse control (Krawczyk, 2002).

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

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regions (Krain et al., 2006; Rosenbloom et al., 2012; Wallis, 2007; Winstanley, 2007). Among them, the orbitofrontal cortex (OFC) seems to play a significant role and has thus received significant attention in recent years (Kringelbach and Rolls, 2004; Volz and von Cramon, 2009; Winstanley, 2007). 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 behaviour), and are less effective in identifying negative emotions expressed either facially or vocally (Bechara, 2004; Floden et al., 2008). Moreover, recent functional neuroimaging studies have reported that escalating risk-taking behaviour in healthy volunteers is associated with decreased activity in the ventromedial prefrontal cortex (of which the OFC is a key component) (Schonberg et al., 2012), and that the OFC is implicated in the generation of automatic negative emotions such as anger and anxiety (Dougherty et al., 1999). More broadly, this brain region (which receives inputs from all sensory systems and is thus one of the most polymodal cortical areas (Kringelbach and Rolls, 2004)) 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) (Volz and von Cramon, 2009). Thus, the OFC enables a more thorough comparison of the available behavioural responses and the selection of the optimal course of action - which should be flexible enough to change in response to fluctuations in motivational contingencies (Schoenbaum et al., 2009; Wallis, 2007).

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 (Nitsche and Paulus, 2011). 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 (Stagg and Nitsche, 2011). Because of its neural effects, tDCS has been increasingly used to gauge the functional relationship between cognitive/behavioural dimensions and putatively relevant neurocircuitry (Coffman et al., 2014; Jacobson et al., 2012). For example, anodal tDCS applied to the dorsolateral prefrontal cortex (DLPFC) of healthy volunteers has been reported to not only enhance planning abilities (Dockery et al., 2009), working memory (Zaehle et al., 2011) and attention (Stone and Tesche, 2009), but to also decrease correlates of impulsivity and risk-taking behaviour (Fecteau et al., 2007; Pripfl et al., 2013). However, despite the extensive evidence relating the activity of the OFC to decision-making and cognitive impulse control, no study to date has assessed whether non-invasive brain stimulation techniques applied over this brain region are able to modulate these two key neurocognitive dimensions.

Therefore, to investigate the potential of tDCS for modulating decision-making and cognitive impulse control by targeting the OFC, we carried out the present randomized and sham-controlled study in which 45 healthy subjects were assessed with a battery of computerized tasks before and after receiving a 30-min session of tDCS applied bilaterally over the OFC. We hypothesized that active anodal tDCS, in comparison to sham tDCS, would enhance decision-making abilities as well as cognitive impulse control owing to its putative facilitatory effects on the excitability of the OFC.

1. Materials and methods

1.1. 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 (Saghaei, 2004), to receive a single 30-min session of either (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 to either the left (n = 7) or to the right (n = 8) OFC (i.e., “sham” group).

In order to account for the possible effects of baseline depressive and anxious symptoms on participants' overall performance, the experiment started with the administration of the Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR) (Rush et al., 2003) and of two visual analogue scales (VAS, where participants had 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 battery on decision-making and impulse control (described in detail below) for a total duration of approximately 45 min. Following that, participants received a 30-min tDCS session, after which they were re-administered the computerized neurocognitive battery, the VAS as well as a brief questionnaire on study blinding.

1.2. 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.

Healthy volunteers of both genders who were naive to tDCS, to the neurocognitive tasks and to the precise nature of the experiment were recruited from the local community between April 2013 and March 2014 via advertisements. They were included if they fulfilled the following criteria: (1) age between 18 and 60 years, (2) no history of neuropsychiatric or substance-related disorders (as assessed by the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998)) as well as no clinically-significant depressive symptomatology (i.e., a score $\leq$ 5 on the QIDS-SR (Rush et al., 2003)), (3) no significant general medical condition, (4) no use of psychoactive medications or cigarette smoking, and (5) no history of brain surgery, brain tumour and/or intracranial metallic implants.

Written informed consent was obtained from all participants before study enrolment, and they were compensated with C$ 60 in addition to a smaller bonus (ranging from C$ 2 to 16) that depended on their global performance in the decision-making tasks.

1.3. tDCS procedure

tDCS was delivered by a battery-driven HDCstim® stimulator (Newronica, Italy) while participants were reclined in a chair, in resting state and with their eyes closed. Conductive-rubber electrodes of 35 cm^2 (5 × 7 cm; anode) and 55.25 cm^2 (8.5 × 6.5 cm; cathode) were placed in wet sponges saturated with saline and fixed to the scalp (using an elastic cap) over the left or the right supraorbital areas and lateral, respectively, to sites Fp1 and Fp2 of the 10/20 EEG System (Herwig et al., 2003; Merzagora et al., 2010). This corresponds to the frontal poles, which includes the OFC. A larger cathode was used to minimize its possible inhibitory cortical effects (Nozari et al., 2014).

After electrode placement, the electrical current was ramped up to 1.5 mA over the course of 30 s. In the two active tDCS groups, the current intensity was maintained at this level for 30 min, whereas in the sham tDCS group it was ramped-down after 30 s (a procedure that has been reported to be sensorily indistinguishable from active tDCS and associated with no after-effects (Ambrus et al., 2012)). Overall, active tDCS resulted in anodal and cathodal current densities of 0.04 mA/cm^2 and 0.027 mA/cm^2, respectively. Thus, current density at the cathode was likely functionally negligible, whereas at the anode it was within the accepted safety guidelines (Nitsche et al., 2003; Nitsche and Paulus, 2000).

Finally, for safety reasons, the investigator remained in the testing room (away from participants' visual field) for the duration of the experiment.

1.4. Neurocognitive tasks

The neurocognitive assessment battery contained five computerized tasks (two on decision-making, two on impulse control and one on attentional levels) and was administered in a counterbalanced sequence using Inquisit v. 4 (Millisecond Software, USA) installed on an Intel Core i32120 desktop computer and presented on a 24-inch LCD monitor with a video resolution of 1920 × 1080 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, and were given a brief practice session before starting the actual neurocognitive assessment. Importantly, instructions for the tasks were written beforehand so that all participants received the same information.

1.4.1. Decision-making

We used two tasks to tap into the decision-making construct: the Iowa Gambling Task (IGT) (Bechara et al., 1999) and the Balloon Analog Risk Task (BART) (Lejuez et al., 2002).

In the IGT (Bechara et al., 1999), 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 (Lejuez et al., 2002) 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).

1.4.2. Impulse control

Behavioural paradigms on impulse control can be broadly divided into those measuring impulsive choice (i.e., "cognitive impulsivity") or impulsive action (i.e., "motor impulsivity") (Winstanley, 2007). We used two tasks to tap into these constructs: respectively, the Stroop Colour-Word Test (SCWT) (Van der Elst et al., 2006), and the Stop-Signal Task (SST) (Logan et al., 1984).

In the SCWT (Van der Elst et al., 2006), three different types of stimuli are presented to participants: coloured rectangles (neutral stimuli), colour 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 colour 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 colour of 84 randomly presented word-colour stimuli by pressing the appropriate key on the response pad. Hence, successful performance in the SWCT requires participants to not only inhibit a planned response by disregarding distracting stimuli but to also effectively monitor the conflict between word reading vs. naming the word ink colour. The main variable of interest in the SWCT is the "interference index" which measures the difference in response latencies (in milliseconds [ms]) between incongruent vs. congruent stimuli and is thus considered a correlate of "cognitive impulsivity".

In the SST (Logan et al., 1984), 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 serve as a control variable owing to its primarily non-OFC underlying neural correlates (Aron and Poldrack, 2006; Hsu et al., 2011; Li et al., 2006).

1.4.3. Attentional levels

To assess putative between-group differences in attentional levels we used the Continuous Performance Task (CPT) (Klee and Garfinkel, 1983). In the CPT, 620 letter stimuli flash consecutively in the screen and participants are asked to press a specific key on the response pad whenever they see the letter "X" (65%), and every non-response to this letter is identified as an "omission error" (which is a correlate of inattention).

1.5. 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), while the baseline correlation

between the neurocognitive measures was assessed with Pearson's coefficients. To investigate 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 the difference in pre-post scores 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 $\leq$ 0.01, 0.02–0.06 and $\geq$ 0.14 representing small, moderate and large effect sizes, respectively (Cohen, 1988)). Furthermore, we identified and removed outliers in the variables of interest in the baseline period by using Tukey's boxplot technique (Tukey, 1977). Finally, we set statistical significance at $\alpha < 0.05$, and report uncorrected p values given the relatively small sample size and the exploratory nature of this study as well as the likelihood that Bonferroni correction may impose an excessively conservative adjustment (Perneger, 1998).

2. Results

2.1. Participants

The baseline characteristics of the healthy volunteers are summarized on Table 1. Briefly, their mean age was 25.09 ± 7.10 years, and 64.50% (n = 29) of them were females. Also, 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.

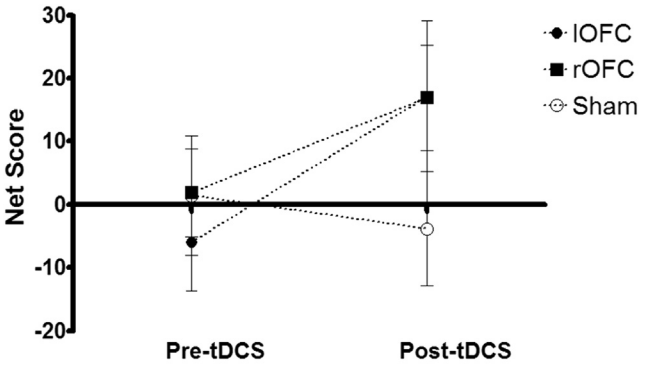
2.2. Neurocognitive tasks

2.2.1. Baseline correlations

The neurocognitive variables were not significantly correlated at baseline (i.e., the associated Pearson's coefficients and p-values ranged, respectively, from 0.02 to 0.26 and from 0.09 to 0.90).

2.2.2. Decisions-making

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



Abbreviations: lOFC = left orbitofrontal cortex; rOFC = right orbitofrontal cortex.

Fig. 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: $p = 0.52$).

Regarding the "average adjusted number of pumps" on the BART, only a trend towards a significant tDCS intervention*time interaction was found (*Wilks'* $\lambda = 0.88$, $F_{2,41} = 2.80$, $p = 0.07$) after controlling for the main effect of time (*Wilks'* $\lambda = 0.83$, $F_{1,41} = 8.65$, $p = 0.005$).

2.2.3. Impulse control

With respect to the "interference index" in the SCWT, a significant tDCS intervention*time interaction was found (*Wilks'* $\lambda = 0.78$, $F_{2,41} = 5.69$, $p = 0.007$) after controlling for the main effect of time (*Wilks'* $\lambda = 0.86$, $F_{1,41} = 6.53$, $p = 0.01$) (Fig. 2; Table 3). 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'* $\lambda = 0.75$, $F_{1,27} = 8.94$, $p = 0.006$; right OFC vs. sham: *Wilks'* $\lambda = 0.79$, $F_{1,27} = 7.23$, $p = 0.01$), representing large effect sizes (i.e., $\eta_p^2 = 0.25$ and 0.21, respectively); however, there was no difference between the two active tDCS interventions (i.e., left OFC vs. right OFC: *Wilks'* $\lambda = 0.99$, $F_{1,28} = 0.52$, $p = 0.48$). Of note, this

Table 1
Study participants: baseline characteristics.

Group	n	Gender[a]		Age in years (SD)[b]	Education in years (SD)[c]	Mean score on the QIDS-SR (SD)[d]	Depression VAS[e]	Anxiety VAS[f]
		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)

Abbreviations: OFC = Orbitofrontal cortex; QIDS-SR = Quick Inventory of Depressive Symptomatology – Self-Report; VAS = Visual analogue scale.
[a] $\chi^2(df) = 2.52(2)$, p = 0.28.
[b] $F(df) = 0.99(2,42)$, p = *0.38*.
[c] $F(df) = 0.74(2,42)$, p = 0.48.
[d] $F(df) = 0.40(2,42)$, p = 0.67.
[e] $F(df) = 1.26(2,42)$, p = 0.29.
[f] $F(df) = 1.91(2,42)$, p = 0.16.

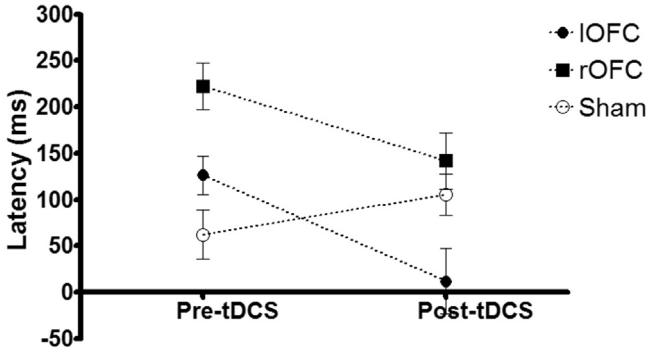
Table 2
Neurocognitive tasks on decision-making before and after active or sham tDCS.

Intervention		Iowa Gambling task (IGT) ("*net score*") (n = 43)			Balloon analog risk task (BART) ("*adjusted average number of pumps*") (n = 44)		
		Mean	SD	Omnibus test[#]	Mean	SD	Omnibus test[#]
Pre-tDCS	Left OFC	−6.00	28.79	*Wilks'* $\lambda = 0.85$, $F_{2,40} = 3.53$, $p = 0.04$[*]	25.33	10.01	*Wilks'* $\lambda = 0.88$, $F_{2,41} = 2.80$, $p = 0.07$
	Right OFC	1.87	26.00		32.84	11.94	
	Sham	1.43	35.54		27.33	11.02	
Post-tDCS	Left OFC	17.14	44.77		33.54	14.16	
	Right OFC	16.93	43.48		32.77	10.40	
	Sham	−3.86	33.91		31.96	12.96	

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

reduction in the "interference index" after active tDCS was not parallelled by higher "incongruent stimuli" error rates, as demonstrated by a non-significant tDCS intervention*time interaction (*Wilks'* $\lambda = 0.97$, $F_{2,38} = 0.58$, $p = 0.57$) after controlling for the main effect of time (*Wilks'* $\lambda = 1.00$, $F_{1,38} = 0.11$, $p = 0.74$). Overall, these results indicate that participants who received active anodal tDCS (irrespective of laterality) presented with enhanced cognitive control.

Finally, the "stop-signal reaction time" in the SST was not influenced by tDCS as demonstrated by a non-significant tDCS intervention*time interaction (*Wilks'* $\lambda = 0.98$, $F_{2,41} = 0.33$, $p = 0.72$) after controlling for the main effect of time (*Wilks'* $\lambda = 0.96$, $F_{1,41} = 1.91$, $p = 0.17$).



Abbreviations: lOFC = left orbitofrontal cortex; rOFC = right orbitofrontal cortex.

Fig. 2. "Interference index" in the Stroop Colour-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 to either the left or the right OFC, in comparison to sham tDCS, was associated with significant decreases in the "interference index" (and thus with enhanced cognitive control) (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: $p = 0.48$).

2.2.4. Attentional levels

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

2.3. Depression and anxiety symptoms

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

2.4. Integrity of blinding

The three groups did not differ in terms of the number of participants who guessed that they had received active tDCS (i.e., left OFC = 66.70%, right OFC = 60.00%, sham = 73.30%; $\chi^2 = 2.20$, $df = 4$, $p = 0.69$), thus confirming the validity of our blinding procedure.

2.5. tDCS acceptability

None of the participants experienced significant adverse effects during or after the tDCS sessions, and consequently there were no dropouts in this study.

3. Discussion

In the current randomized, single-blind and sham-controlled study we have shown that healthy participants who received 30 min of active anodal tDCS applied over either the left or the right

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

Intervention		Stroop Colour-Word task (SCWT) ("*interference index*" [*ms*]) (n = 44)			Stop-signal task (SST) ("*stop-signal reaction time*" [*ms*]) (n = 44)		
		Mean	SD	Omnibus test[#]	Mean	SD	Omnibus test[#]
Pre-tDCS	Left OFC	126.39	80.41	*Wilks'* $\lambda = 0.78$, $F_{2,41} = 5.69$, $p = 0.007$[*]	237.41	35.33	*Wilks'* $\lambda = 0.98$, $F_{2,41} = 0.33$, $p = 0.72$
	Right OFC	222.36	96.05		246.86	32.20	
	Sham	62.23	100.07		234.27	30.84	
Post-tDCS	Left OFC	11.97	137.60		218.85	47.65	
	Right OFC	141.75	117.62		238.69	50.68	
	Sham	105.22	82.47		230.01	36.99	

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

OFC (coupled with contralateral cathodal tDCS), displayed more advantageous decision-making (as indexed by increased IGT "net scores"), as well as 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. Moreover, active tDCS did not influence participants' performance on the SST - an expected finding considering that inhibitory motor control is primarily mediated by non-OFC regions (e.g., pre-supplementary motor area, inferior frontal gyrus, frontal eye fields) (Aron and Poldrack, 2006; Hsu et al., 2011; Li et al., 2006).

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 (Krain et al., 2006). Furthermore, our study highlights the important role played by the OFC on subjects' performance in the IGT (Lawrence et al., 2009; Li et al., 2010) and the SWCT (Harrison et al., 2005; Peterson et al., 1999), 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 (Noel et al., 2013), and suicidal behaviour (Courtet et al., 2011). The relevance of our findings for suicide prevention is highlighted by a recent meta-analysis (n = 2323) 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 behaviour and healthy controls, thus suggesting that deficits in decision-making and cognitive impulse control might constitute putative vulnerability markers for suicidality (Richard-Devantoy et al., 2014). 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 (Bostwick and Pankratz, 2000). 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 (Juan and Muggleton, 2012; Levasseur-Moreau and Fecteau, 2012). 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 (van 't Wout et al., 2005) and to choose higher-risk prospects (Knoch et al., 2006). Moreover, subjects who received anodal tDCS over the right DLPFC were shown to have their confidence levels boosted during risky decision-making (Minati et al., 2012), and to more frequently choose safer prospects (Fecteau et al., 2007), whereas those who received anodal tDCS over the left DLPFC were shown to more often employ sub-optimal strategic decision-making (Xue et al., 2012) despite demonstrating heightened impulse control (Jeon and Han, 2012). 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 (Beeli et al., 2008a,b), while cathodal tDCS over the right DLPFC increased both impulsiveness and electro–dermal activity related to the vegetative nervous system (Beeli et al., 2008a,b). Finally, non-DLPFC studies have shown that anodal tDCS applied to the right inferior frontal gyrus (Jacobson et al., 2011) or to the pre-supplementary motor area (Hsu et al., 2011) was associated with more efficient inhibitory control.

3.1. 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 (Gold and Shadlen, 2007; Kable and Glimcher, 2009; Rosenbloom et al., 2012; Wallis, 2007). 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 behaviour 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 (Kringelbach and Rolls, 2004). 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 (Kringelbach and Rolls, 2004). 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 (Keeser et al., 2011; Weber et al., 2014). Moreover, a recent study using functional near-infrared spectroscopy (which measures changes in cerebral concentrations of oxyhemoglobin [HbO_2]) and an electrode montage similar to ours (i.e., anode and cathode applied over the supraorbital areas and lateral, respectively, to Fp1 and Fp2) has shown that 15 min of 1 mA anodal tDCS was associated with a durable local increase of the concentration of HbO_2 (i.e., with enhanced regional cerebral blood flow) in the underlying brain tissue, while cathodal tDCS had a negligible effect (Merzagora et al., 2010).

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 (Clark et al., 2004). This could potentially explain the discrepancies observed in the effects of tDCS on the IGT (which necessitates learning), and on the BART (which does 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 behaviour according to the fluctuations in the stimulus-reward contingencies (Zald and Andreotti, 2010).

3.2. 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 behavioural changes (Stagg and Nitsche, 2011). However, we believe that this is unlikely as most investigations to date have failed to show significant cathodal

effects on subjects' cognitive performance (Jacobson et al., 2012) as well as because we have used a relatively large cathode. Furthermore, the magnitude of the behavioural changes observed in our study might have been mitigated by some of its design features (e.g., the delivery of a single 30-min session, the use of 1.5 mA, and the non-concomitant administration of tDCS with the neurocognitive battery) (Horvath et al., 2014). Yet, several previous studies which were methodologically similar to ours have been successful in eliciting significant tDCS-related cognitive changes (Coffman et al., 2014; Jacobson et al., 2012). 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 (Bornovalova et al., 2009; Sela et al., 2012), and that tDCS might preferentially improve cognitive skills in subjects who present with lower baseline performance (Tseng et al., 2012). Consequently, we anticipate that tDCS may induce more prominent behavioural effects if administered to individuals who commonly present with baseline deficits in decision-making and impulse control such as those with suicidal behaviour (Richard-Devantoy et al., 2014) or addiction disorders (Bechara, 2005). 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) (Levasseur-Moreau et al., 2013). 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. Moreover, participant fatigue is a potentially relevant issue given the repeated measures design using this battery, and may have led to an underestimation of the true effects of tDCS applied over the OFC. 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 (Zald et al., 2014)). 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 (Pelletier and Cicchetti, 2014). 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 behavioural correlates of OFC function (Bechara, 2004; Schoenbaum et al., 2009; Winstanley, 2007), (2) sham tDCS had no significant impact on task performance, and (3) active tDCS did not influence performance on the SST.

4. 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 min 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 behaviour, 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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Contributors

None.

Conflicts of interest

The authors report no conflicts of interest.

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