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ARTICLE

Cognitive related electrophysiological changes induced by non-invasive cortical electrical stimulation in crack-cocaine addiction

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Abstract

Prefrontal dysfunction is a hallmark in drug addiction, yet interventions exploring modulation of prefrontal cortex function in drug addiction have not been fully investigated with regard to physiological alterations. We tested the hypothesis that non-invasive prefrontal stimulation would change neural activity in crack-cocaine addiction, investigating the effects of transcranial Direct Current Stimulation (tDCS) of Dorsolateral Prefrontal Cortex (DLPFC) induced cortical excitability modulation on the visual P3 Event Related Potentials (ERP) component under neutral and drug cue exposition in crack-cocaine addicts. Thirteen crack-cocaine users were randomly distributed to receive five applications (once a day, every other day) of bilateral (left cathodal/right anodal) tDCS (20 min, 2 mA, 35 cm^2) or sham tDCS over the DLPFC. Brain activity was measured under crack-related or neutral visual-cued ERPs. There were significant differences in P3-related parameters when comparing group of stimulation (active *vs.* sham tDCS) and number of sessions (single *vs.* repetitive tDCS). After a single session of tDCS, P3 current intensity in the left DLPFC increased during neutral cues and decreased during crack-related cues. This effect was opposite to what was observed in the sham-tDCS group. In contrast, repetitive tDCS increased current density not only in the DLPFC, but also in a wider array of prefrontal areas, including presumably the frontopolar cortex (FPC) orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), when subjects were visualizing crack-related cues. Thus, single and repetitive application of tDCS can impact cognitive processing of neutral and especially crack-related visual cues in prefrontal areas, which may be of importance for treatment of crack-cocaine addiction.

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Introduction

Prefrontal cortex (PFC) areas are involved in drug-related processes and are activated when drug addicts are exposed to either the drug or drug-cues (Grant et al., 1996; Volkow et al., 1999; Garavan et al., 2000; Sell et al., 2000; Daglish and Nutt, 2003; Tapert et al., 2003; Wilson et al., 2004; McBride et al., 2006). Volkow et al. (2002) postulated that this enhanced PFC activity could contribute to compulsive self-administration and the lack of control (impaired inhibition) in addicted subjects and also contribute to disruptive cognitive operations that impair judgment and favor relapse to drug use (Volkow et al., 2002).

Experimental investigations of addictive phenomena by use of a cue-reactivity paradigm have been performed extensively (Carter and Tiffany, 1999; Modesto-Lowe and Kranzler, 1999; Hester et al., 2006; Sokhadze et al., 2008) and a growing amount of evidence suggests that electroencephalographic activity of fronto-central areas increases when cocaine users are exposed to pictures of cocaine compared to neutral images (Bauer and Kranzler, 1994; van de Laar et al., 2004; Dunning et al., 2011).

One of the most studied endogenous event-related potential (ERP) components is the P3 wave, which is the largest positive peak occurring within a time window of 250–600 ms after stimulus presentation. The P3 wave is typically observed in more anterior brain areas (Katayama and Polich, 1998) and is sensitive to general and specific arousal, contributing to attention and

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information processing (Polich, 2007). An association between the P3 amplitude and cue-reactivity has been described in volunteers with a history of cocaine use (Grant et al., 1996; Franken et al., 2004) and other drugs (Namkoong et al., 2004; Littel and Franken, 2007). These studies report increased craving after the presentation of drug-related cues, as well as an increased P3 amplitude.

The dorsolateral PFC (DLPFC) has an important role in executive functions (Fuster, 2000; Hartley and Speer, 2000; Ko et al., 2008; Metuki et al., 2012; Enriquez-Geppert et al., 2013), and it has increasingly been associated with 'top-down' cognitive control when complexity or integration demands during action control increase (Miller and Cohen, 2001; Cieslik et al., 2013). Thus, its modulation may constitute a promising target as an ancillary treatment of drug addiction, notably as a cognitive control component.

In this context, a non-invasive brain stimulation technique – transcranial Direct Current Stimulation (tDCS) – which induces polarity-dependent alterations of cortical excitability due to modulation of neuronal resting membrane potentials (Nitsche et al., 2003a, b, 2008) is a desirable method to be explored. Briefly, cathodal tDCS decreases cortical excitability, while anodal stimulation increases it, as shown for motor and visual cortex models in healthy humans (Nitsche and Paulus, 2000; Antal et al., 2004), and suggested by functional effects of tDCS of prefrontal regions (Kuo and Nitsche, 2012). Sufficiently long stimulation results in identically directed neuroplastic after-effects of the stimulation (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2002; Wassermann and Grafman, 2005) which may induce stable neural connective changes, translating thus in behavioral improvements.

Considering the limited data with regard to studies focusing on cognitive changes with potential control of craving in drug addiction, we hypothesized that cortical stimulation with tDCS would alter prefrontal cortex activity and thus possibly change an important neural signature of crack addiction: the cognitive-event-related potential P3 during crack-cocaine-related stimulus presentation, which may be of clinical importance for drug dependence treatment. We decided to elect the neurophysiological P3 parameter as the main outcome as clinical changes would not be immediately observable and also to understand further the mechanisms of tDCS in modulating dorsolateral prefrontal activity. Thus, this study aimed to investigate the effects of DLPFC modulation by single and repetitive tDCS on the prefrontal visual ERP components under neutral and drug cue exposition in crack-cocaine addicted subjects.

Method

Subjects

Crack-cocaine addicted subjects, as defined by the DSM-IV, were consecutively recruited from the Center for Psychosocial Care for treatment of abuse and dependence of psychoactive substances disorders in Espírito Santo, Brazil. All participants had normal or corrected-to-normal vision.

The inclusion criteria for this study were: (1) patients between the age of 18 and 60 years; (2) met criteria for crack-cocaine dependence according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), as determined by clinical evaluation; (3) no more than 31 d of abstinence; (4) in stable clinical condition with no need for inpatient care; and (5) able to read, write, and speak Portuguese. Conversely, exclusion criteria included: (1) a diagnosis of epilepsy, convulsions, or history of severe brain injury; (2) any contraindication for electrical brain stimulation procedures such as electronic implants or metal implants; (3) suspected pregnancy for female participants; and (4) cardiac pacemaker.

Treatment and data collection were conducted according to the ethical principles of the Declaration of Helsinki, which are equivalent to those established by the Ethics Committee for Research at the Center of Health Sciences, Federal University of Espírito Santo, Brazil, where this study was conducted. Ethical approval for this study was provided by the Brazilian Institutional Review Board of the Federal University of Espírito Santo (registration 296/10), Brazil. We are presenting results from the study registered at the ClinicalTrials.gov Protocol Registration System under identifier NCT01337297.

General procedures

Subjects were fully informed about the experimental protocol and voluntarily signed an informed consent form. They were randomly assigned to receive real brain stimulation (tDCS group) or sham simulation of this procedure (sham-tDCS group) (Fig. 1). The experimental protocol consisted of global physical and clinical examination, and electrophysiological recording of brain activity during random visual presentation of three drug-related images and three neutral images before and after a single session or after five sessions (every other day) of bilateral tDCS (left cathodal/right anodal) or sham tDCS over the Dorsolateral Prefrontal Cortex (DLPFC) (Fig. 1).

Event-related potentials (ERPs)

EEG recording

Electrophysiological recording was obtained through a 32-channel system (QuickAmp40, BrainProducts Ltd, Germany) using active electrodes with an integrated impedance converter for noise subtraction circuits (actiCAP BP; BrainProducts Ltd, Germany) placed on the scalp according to the International 10/20 EEG system. Data were recorded with a sampling rate of 1000 Hz, and analog filtered between 0.016 and 1000 Hz with common average reference.

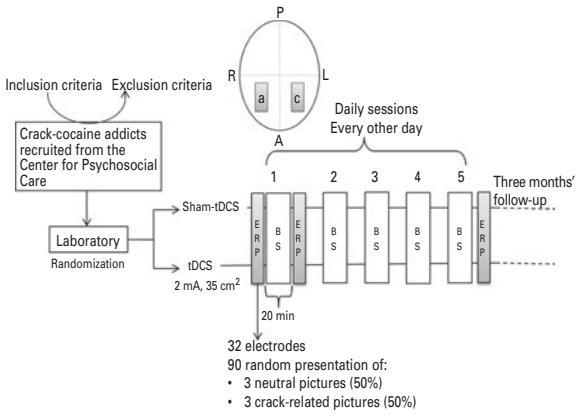

Fig. 1. General Procedures. After subjects were fully informed about the experimental protocol and voluntarily signed an informed consent form, crack-cocaine addicts were randomly assigned to receive five applications (daily sessions every other day) of real brain stimulation (BS) by bilateral (left (L) cathodal (c)/right (R) anodal (a)) transcranial Direct Current Stimulation (tDCS group, 2 mA, 35 cm^2, for 20 min) over the Dorsolateral Prefrontal Cortex (DLPFC) or to receive a simulation of this procedure (sham-tDCS group). Event Related Potentials (ERPs) were registered before and after a single session and after five sessions via random presentation of neutral or crack-related pictures as visual cues. Craving for drug use was scored before and after ERP procedures. Subjects were followed up to three months after the end of the tDCS treatment.

Experimental design and task

We adapted a cue-reactivity paradigm (LaRowe et al., 2007) following standard cue-reactivity paradigms well established for pictures (Prisciandaro et al., 2012) and videos (Volkow et al., 2011). During picture presentation the subjects were asked to press a button whenever the crack-related pictures were presented, and to withhold the response when the neutral pictures were presented (each 50% of the stimuli). This allowed us to assert that patients were aware about picture presentation. Besides, these responses were registered and constitute a parameter of performance.

Stimuli

Three pictures related to the consumption of crack-cocaine (i.e. crack-related cues) such as crack rocks, pipes or paraphernalia used for substance use, and someone inhaling the substance constituted the target visual stimuli. Additionally, three neutral pictures that were unrelated to the consumption of crack (i.e. neutral cues) such as a landscape with a small road, a field of flowers, and a butterfly constituted the non-target visual stimuli.

The trial consisted of a randomized sequence of 90 visual presentations (15 times for each picture) approximately presented at eye level, using a 17-in. monitor (1280 × 1024 × 32-bit color, 60 Hz refresh rate). Each picture was presented for 1000 ms, at intervals of 2000 ms, the entire procedure lasted 4.5 min.. The default screen consisted of a black background at all times. All pictures were presented by Presentation 10.0 software (Presentation, Neurobehavioral Systems, Inc, USA).

Data processing

All EEG data were processed using BrainVision Analyzer 2.0 Professional (BrainProducts Ltd, Germany). Data were offline-filtered from 1 to 10 Hz. After ocular correction by independent component analysis and visual inspection for artifact removal, all datasets were segmented into epochs from −200 to 800 ms relative to picture onset and averaged. All epochs were retained. Baseline correction was performed using the prestimulus interval (i.e. −200 to 0 ms). Low-resolution brain electromagnetic tomography (LORETA) was applied to estimate the three-dimensional intracerebral current density distribution ($\mu A/mm^2$). Together with the high temporal resolution of ERP, these functional images of electric neuronal activity have been validated by comparisons with Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) findings (Pascual-Marqui et al., 1999; Anderer et al., 2000; Worrell et al., 2000; Pascual-Marqui et al., 2002). Because we were mostly interested in frontal activity in crack-cocaine users and tDCS was applied in the DLPFC, we focused our analysis on PFC areas as regions of interest (ROI) and the mean absolute P3 (350 to 600 ms) values after stimulus presentation were analyzed. Anatomically, the chosen ROI included the rostral middle frontal gyrus, including Brodmann areas 9 and 46 as DLPFC. We also included analysis of area 10 corresponding to the frontopolar cortex (FPC), area 11 to the orbitofrontal cortex (OFC), and areas 24, 32 and 33 to the anterior cingulate cortex (ACC).

Urge for crack-cocaine use after ERP

A version of the Brief Cocaine Craving Questionnaire (Sussner et al., 2006) translated into Portuguese and adapted for assessing crack-cocaine craving (Araujo et al., 2010) was used to examine the compulsion to the use of crack-cocaine in patients before and after each ERP recording. This questionnaire uses a grading scale of seven points between 'strongly disagree' to 'strongly agree'. The total score was obtained by summing the scores of each question.

Brain stimulation

Direct currents were transferred via a pair of carbonated-silicone electrodes (35 cm^2) with a thick layer of high conductive EEG-electrode gel underneath them accordingly to our previous study (Nakamura-Palacios et al., 2012). The electric current was delivered by an electric stimulator (Striat, Ibramed Indústria Brasileira de Equipamentos Médicos Ltd, Brazil).

For bilateral tDCS, the cathode electrode was placed over F3 (left DLPFC) and the anode over F4 (right DLPFC) (left cathodal/right anodal tDCS) according to the 10–20 international system for EEG electrode placement. The currents flowed continuously for 20 min with an intensity of 2.0 mA. For sham tDCS, the electrodes were placed at the same positions for each polarity, but the stimulator was turned off after 20 s (gradually from 2 to 1 mA and then switched off), thus that the subjects felt the initial itching sensation at the beginning, but received no current for the rest of the stimulation period. This procedure allowed keeping subjects blinded for the respective stimulation condition (Gandiga et al., 2006; Russo et al., 2013).

Statistical analyses

Data are presented as mean and S.D. The effect of tDCS on the P3 component in the DLPFC was analyzed via a non-parametric paired test, the Wilcoxon signed rank test, because activity (current density) and percent (%) of changes from baseline after the first and the fifth tDCS application were not normally distributed. For the pre- and post-analysis in the first session, differences of DLPFC activity in the P3 segment were adjusted for baseline (pre) and compared using analysis of covariance. A p-value of 0.05 or less was considered to indicate statistical significance. To ensure that our analysis considered the complete two randomized groups, we conducted an intention to treat (ITT) analysis only for the clinical data using the method of worst case scenario, considering dropouts as relapses. GraphPad Prism 5.0 (GraphPad Software Inc, USA) was employed for statistical analysis and graphic presentations.

It has to be mentioned that in this study, the team that was running the ERP procedures was not informed to which group the patients belonged, and more importantly the individual who processed all statistical analysis was not involved with both the tDCS application and ERP procedures.

Results

Of approximately 70 eligible crack-cocaine users from the outpatient service invited to this trial, 20 (28.6%) met the inclusion criteria and accepted to participate in this study, but only 13 (18.6%) started the trial. The remaining seven subjects never came to our laboratory for the first study session, thus they were not included in the randomization and analysis of this trial.

From these 13 crack-cocaine users, seven (aging 32 y ± 8 S.D., 6 males) (Table 1) were randomly assigned to receive the real bilateral tDCS whereas the other six (aging 27.5 y ± 5.3 S.D., 5 males) were assigned to the sham-tDCS group (Fig. 2). The two groups were similar regarding socio-demographic characteristics and pattern of drug use (Table 1), showing that randomization was effective in matching them for the important baseline characteristics. The only small baseline difference was days of abstinence before treatment. The average was slightly larger in the tDCS group because of one outlier in this group – a subject who was abstinent for 90 d. However, when considering the remaining six subjects from this group, the minimum abstinence before treatment was three and the maximum was 20 d, whereas it was four and 30 d for the sham-tDCS group.

Three subjects from the sham-tDCS and one from the tDCS group dropped out during the treatment (Fig. 2); but all of them received the first tDCS session; thus completing an important endpoint. Therefore, only three subjects (50%) from the sham-tDCS group, whereas six subjects (85.7%) from the tDCS group reached the end of the five sessions of brain stimulation (over 12 d). Data analyzed with ITT showed no statistically significant difference considering relapses between groups during the treatment period ($p=0.27$, Fisher test). By the end of three months of follow-up, only one subject (16.6%) from the sham-tDCS group, but five subjects (71.4%) from the real tDCS maintained abstinence from crack-cocaine. Although suggestive of favorable effects of the real tDCS treatment, data analyzed with ITT for relapses after three months showed only a trend for significance ($p=0.1$, Fisher test).

In general, crack-cocaine users were very accurate in task performance (cue-response) in the ERP procedure. The number of errors (false or missing responses) was zero or 1 (out of 90 visual presentations in each trial). Craving (Brief Cocaine Craving Questionnaire) was not significantly changed after the exposition to visual cues related to the use of crack-cocaine in the ERP procedure. The technique of direct current (DC) stimulation proved to be safe as no major adverse events were reported. The only minor adverse effects that was reported was itching sensation at the beginning of sessions, which was similar in both sham-tDCS and tDCS groups.

Neurophysiological data

Analysis of single session of bilateral tDCS: sham vs. *active tDCS*

Changes of DLPFC activity, represented by the current density, in the P3 component (time window between 350 and 600 ms) after neutral or crack-related cue presentation, before and after a single session of the bilateral tDCS are shown in Fig. 3.

In the sham-tDCS group, when compared to the respective baseline values (pre-treatment activity), the DLPFC activity in the P3 segment was decreased ($p<0.0001$) under neutral cues (Fig. 3*a*) and increased ($p<0.0001$) under crack-related cues (Fig. 3*b*) bilaterally. In the active tDCS group, on the other hand, when compared to baseline, in the neutral cues condition, activity was slightly increased ($p<0.001$) on the left side and

Table 1. Socio-demographic characteristics and patterns of crack-cocaine use from this drug addicts submitted to repetitive (five applications) bilateral (left cathodal/right anodal) transcranial Direct Current Stimulation (tDCS) or sham-tDCS over the Dorsolateral Prefrontal Cortex (DLPFC)

	Sham (n=6)	tDCS (n=7)		p value
Age (*mean*±S.D.)	27.5±5.3	32.0±8.0	$t_{(11)}=-1.17$	0.27
Gender n (%)				
Female	1 (16.6%)	1 (14.3%)	Fisher=1.0	0.73
Male	5 (83.4%)	6 (85.7%)		
Years of education n (%)				
0–4 yr	0 (0%)	0 (0%)	$t_{(11)}=-1.02$	0.33
5–8 yr	3 (50%)	2 (28.6%)		
9–12 yr	3 (50%)	4 (57.1%)		
>13 yr	0 (0%)	1 (14.3%)		
Employment n (%)				
Formal job	3 (50%)	2 (28.6%)	$X_2=2.14$	0.34
Retired	0 (0%)	0 (0%)		
Informal job	0 (0%)	2 (28.6%)		
Unemployed	3 (50%)	3 (42.8%)		
Marital state n (%)				
Single	3 (50%)	3 (42.8%)	$X_2=1.60$	0.45
Married	2 (33.3%)	4 (57.2%)		
Divorced	1 (16.7%)	0 (0%)		
Crack-cocaine use				
Age at onset of crack use (*mean*±S.D.)	21.0±5.5	26.7±8.0	$t_{(11)}=-1.47$	0.17
Amount of crack used (rocks/wk) (*mean*±S.D.)	115.8±133.0	125.0±104.4	$t_{(11)}=-0.14$	0.89
Days of abstinence before the study (*mean*±S.D.)	9.2±10.2	22.1±30.5	$t_{(11)}=-0.99$	0.34
Previous treatment n (%)				
Yes	3 (50%)	5 (71.4%)	Fisher=0.6	0.41
No	3 (50%)	2 (28.6%)		
Tobacco use n (%)				
Yes	5 (83.3%)	5 (71.4%)	Fisher=1.0	0.56
No	1 (16.7%)	2 (28.6%)		

was unchanged on the right side (Fig. 3*a*); and during the crack-related cues, it was increased (p<0.001) on the right side but slightly decreased (p<0.05) on the left side (Fig. 3*b*).

Additionally, for topographical distribution of the difference (post minus pre-treatment) current source density (CSD) (Fig. 3*c*), a larger change of brain activation in the tDCS group under neutral cues, and by contrast, a smaller change of brain activation for crack-related cues in this group, as compared to the sham-tDCS group, was identified.

Analysis controlling for hemisphere and visual cue showed that P3 DLPFC activity remained significantly different between groups. In fact, further analysis confirmed that, for the left hemisphere, changes occurred in opposite directions between groups under neutral cues [F(1,497)=6.94, p<0.01] and also under crack-related cues [F(1,497)=371.13, p<0.0001] (Fig. 3). For the right-hemispheric PFC, P3 amplitudes also changed in opposite directions for neutral cues [F(1,497)=180.65, p<0.0001], and in the same direction, but to a lesser extent in the tDCS group under crack-related cues [F(1,497)=240.88, p<0.0001] in the right DLPFC (Fig. 3).

Analysis of repetitive bilateral tDCS: baseline vs. *final*

ERP waveforms evoked by neutral and crack-related cues in the frontal site (Fz) in the first recording (initial) and after the end of the five brain stimulation sessions (final) are illustrated in the inbox of Fig. 4. Although changes in latencies and amplitudes of ERP components, especially of the P3 component, were present, they were not considered for statistical analysis due to the low power of this analysis given the dropout rate after the single session. The specific activation, i.e. current density, in defined regions of interest, was preferred as main parameter for this analysis of pre *vs.* post.

There were significant increases (p<0.0001) in the P3 DLPFC activity under both neutral cues (Fig. 4*a*) and crack-related cues (Fig. 4*b*) in both sides of the brain after the end of the five applications of bilateral tDCS

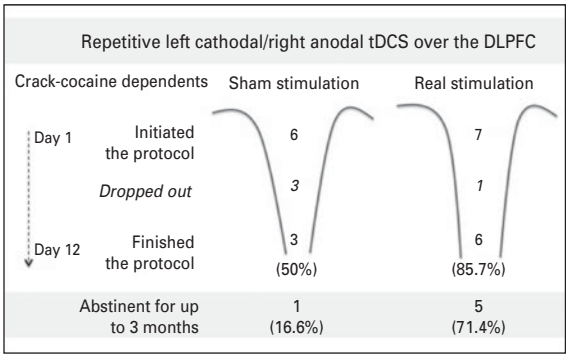

Fig. 2. Diagram of study development showing the poor adherence of crack-cocaine subjects enrolled to the sham procedure and the higher percentage of abstinence observed up to three months in crack-cocaine addicts that underwent real brain stimulation with bilateral (left cathodal/right anodal) repetitive (five applications, once a day, every other day) transcranial Direct Current Stimulation (tDCS, 2 mA, 35 cm^2, for 20 min) over the Dorsolateral Prefrontal Cortex (DLPFC).

when compared to the activity observed before the start of the treatment.

Analysis of single vs. *repetitive bilateral tDCS*

ERPs evoked by neutral and crack-related cues in the frontal site (Fz) after the first and after the fifth tDCS application are shown in the inbox of Fig. 5.

Analyses were performed for the percentage (%) of changes of current density from baseline (ERP before tDCS application) obtained after the first and the last (fifth) session of tDCS under neutral and crack-related cues (Fig. 5*a*, *b*, respectively).

Current density alterations were decreased ($p<0.0001$) in the FPC and even reversed in the OFC and ACC, but unchanged in the DLPFC under neutral cues (Fig. 5*a*), whereas they were significantly increased ($p<0.0001$) in all prefrontal areas (FPC, OFC, ACC and DLPFC) under crack-related cues (Fig. 5*b*).

Discussion

In crack-cocaine addicts that underwent repetitive bilateral (left cathodal/right anodal) tDCS over the DLPFC the P3 current intensity in the DLPFC after a single dose of bilateral tDCS was increased when subjects were visualizing neutral cues but decreased when they were visualizing and responding to crack-related cues in the left side of the brain, whereas in the sham-tDCS group opposite changes were obtained. In the right hemisphere, alterations did not differ between groups. In contrast, the P3 DLPFC current density after five applications of bilateral tDCS was increased in both hemispheres for neutral and crack-related cues, as compared with baseline values. However, when compared to the effects of a single dose, repetitive tDCS increased current density not only in the DLPFC, but also in the FPC, OFC and ACC, when subjects were visualizing crack-related cues, but decreased or reversed it in these prefrontal areas, except in the DLPFC, when subjects were visualizing neutral cues.

This study brings novel data as we explored the effects of tDCS on drug-visualization-related ERP, specifically the P3 component, in crack-cocaine addicts. This electrophysiological paradigm might be suited as an objective outcome measure for studying cognitive control processes in addiction considering that ERPs capture different stages of sensorial stimuli, cognitive and motor response processing.

Considering that the DLPFC has an important role in executive functions, which is usually impaired in drug addicts, we initially hypothesized that any intervention that could improve its activity would have beneficial effects in drug dependence treatment. The P3 and also P3-related Late Positive Potential (LPP) have been related to enhanced motivated attention for the presented stimuli (Schupp et al., 2000; Olofsson et al., 2008; Hajcak et al., 2010). It is assumed that the enlargement of these late ERP components in substance users reflects their motivated and elaborated attention for drug-related stimuli. A meta-analytic investigation by Field et al. (2009) shows that attentional bias and craving are related phenomena, i.e. in most studies of drug addiction, P3 and LPP amplitudes are positively correlated with subjective craving (Field et al., 2009).

In the present study, the analysis of current densities during P3 time window (350–600 ms) in the DLPFC of the brain are clearly suggestive of different changes of cortical activity in this PFC area under the presentation of neutral or crack-related visual cue after DC stimulation.

It seems that a single application of left cathodal/right anodal tDCS was able to reverse the decrease and the increase of neural activation triggered by neutral and crack-related cues, respectively, in the left DLPFC as indexed by P3 ERP as compared to the sham-tDCS group. More specifically, cathodal stimulation over the left DLPFC reversed the changes observed in the left side of the respective sham group, suggesting an inhibitory effect of cathodal tDCS, similar to what has been described for other cortical areas (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2002; Wassermann and Grafman, 2005).

The inhibitory effect on P3 drug-cued cortical activation produced by a single dose of bilateral tDCS shifted toward increases after repetitive (five) dosing of bilateral tDCS, notably when crack-cocaine addicts were visualizing crack-related cues in the DLPFC, but more expressively in other prefrontal areas such as FPC and OFC and milder in ACC. On the contrary, P3 activation under neutral cues visualization was decreased in these prefrontal areas, but not in the DLPFC. Although apparently contradictory, this shift of PFC activation may

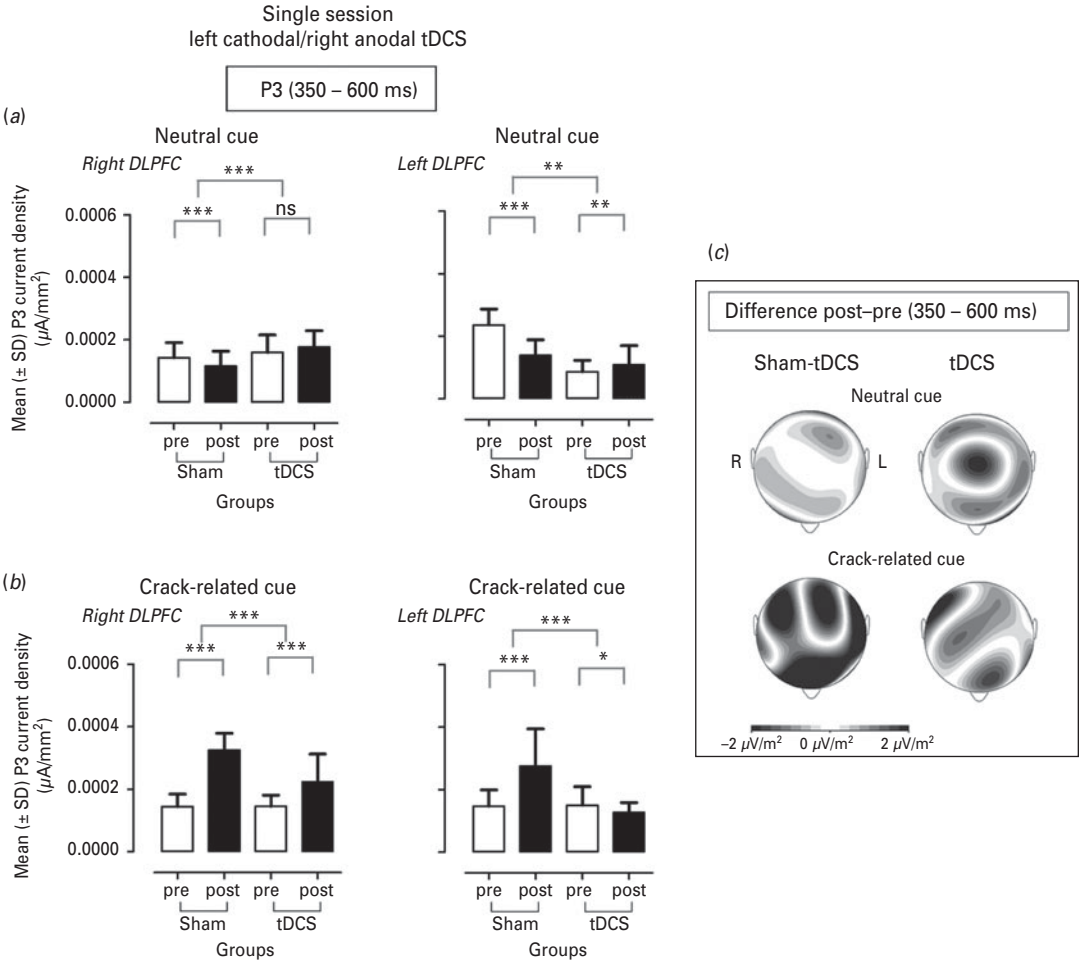

Fig. 3. Current density in the P3 segment (350–600 ms) elicited by neutral (*a*) or crack-related (*b*) cue presentation in the right and left Dorsolateral Prefrontal Cortex (DLPFC) before (pre) and after (post) a single session of bilateral (left cathodal/right anodal) transcranial Direct Current Stimulation (tDCS, 2 mA, 35 cm^2, for 20 min, $n=7$) or sham stimulation ($n=6$) over the DLPFC of crack-cocaine addicts. Right inbox (*c*): Topographical distribution of the difference (post minus pre) of the current source density (CSD) over the P3 segment (R: right side; L: left side). *$p<0.05$, **$p<0.001$, ***$p<0.0001$ (Wilcoxon signed rank test when comparing pre *vs.* post in each group; analysis of covariance (ANCOVA) when comparing between sham *vs.* tDCS).

represent a reversion of cortical activity that may be impaired as a result of successive use of crack-cocaine added by interpolated periods of abstinence before treatment. In fact, repeated exposure to crack-cocaine leads to changes of activity in some subcortical structures such as nucleus accumbens, thalamus and basal ganglia, resulting also in a decrease of cortical prefrontal processing which may sustain addiction and impair cognition, hallmark characteristics of this condition (Di Sclafani et al., 2002; De Oliveira et al., 2009). In this context, tDCS may rescue at least cortical prefrontal processing of environmental stimuli.

Phan et al. (2005) examined the neural substrates involved in the voluntary suppression of negative affect and observed that suppression of emotional experience to highly aversive pictures using a cognitive control strategy reduced the self-reported intensity of negative affect in response to the picture and increased activity within PFC areas. They showed that increased activity within the dorsal ACC, DLPFC, and ventrolateral PFC was not only associated with voluntary suppression of affect but was also correlated with decreased intensity of negative affect. They suggest that increased recruitment of this cognitive circuit could reflect increasing effectiveness in emotion regulation.

Dysfunctional PFC activity during the exposure of drug-related cues may be specifically related to addiction and associated with the desire for the drug (Goldstein and Volkow, 2011b). Thus, the increased activity of PFC areas involved in drug-related processes, including emotional responses (medial OFC and ventromedial PFC possibly related to craving), automatic behaviors (OFC in drug expectation and ACC in attention bias) and also higher-order executive responses involved in drug-related working memory (DLPFC) (Goldstein and Volkow, 2011a), may represent the rescuing of high order cognitive network function, and be a hint for increased effectiveness of cognitive control over

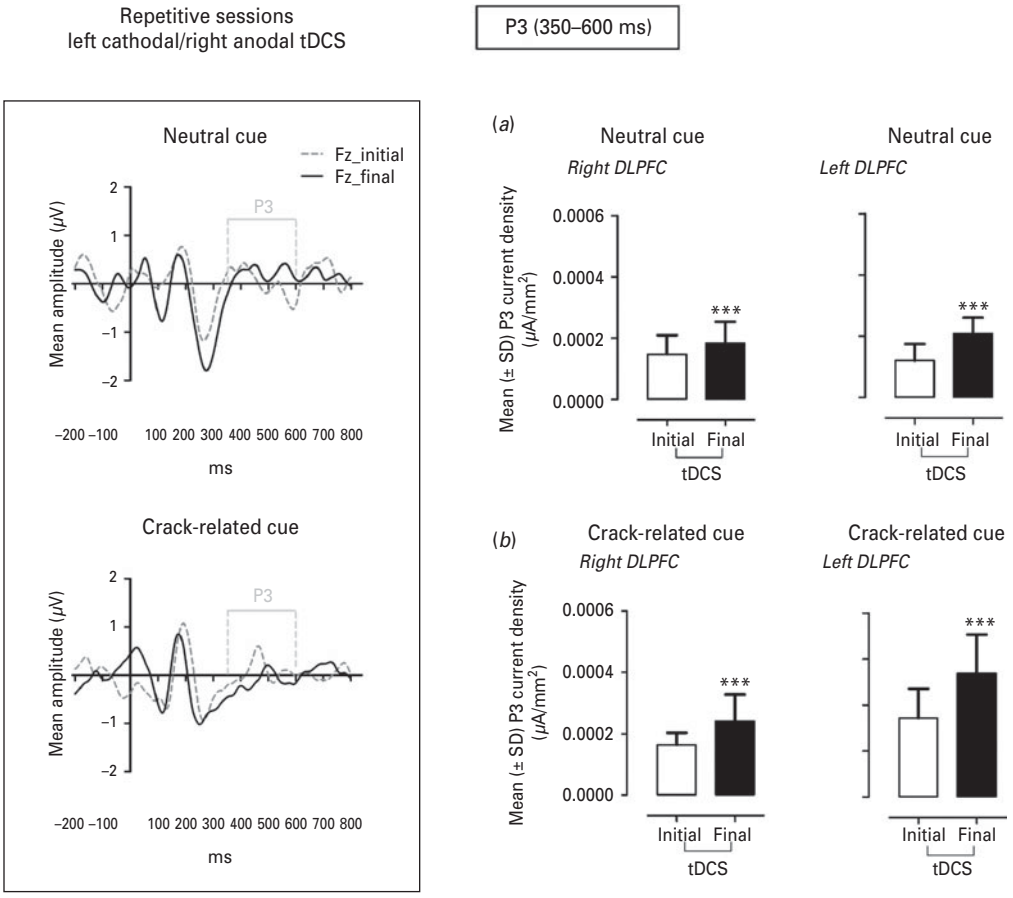

Fig. 4. Left inbox: Event Related Potentials (ERPs) evoked by neutral or crack-related visual stimuli at baseline (initial) and after five (final) applications of bilateral (left cathodal/right anodal) transcranial Direct Current Stimulation (tDCS, 2 mA, 35 cm^2, for 20 min) in crack-cocaine addicts at frontal site (Fz) Fz (according to 10–20 EEG international system). Current density in the P3 segment (350–600 ms) elicited by neutral (*a*) or crack-related (*b*) cue presentation in the right and left Dorsolateral Prefrontal Cortex (DLPFC) at the baseline (initial) and at the end of five sessions (final) of bilateral tDCS (n=6) over the DLPFC ***p<0.0001 (Wilcoxon signed rank test when comparing initial *vs.* final).

automatic behavior toward drug use, which match with the lesser dropouts and relapses in crack-cocaine addicts treated with repetitive bilateral tDCS showing greater P3 drug-cued activation in prefrontal areas after the end of treatment.

In fact, according to Volkow et al. (2010) 'The frontal mediation of a neural circuit involved in the craving response provides a target for top-down cognitive interventions that may be therapeutically beneficial. Interventions that strengthen a weakened but still functional fronto-accumbal circuit may increase the ability of cocaine abusers to block or reduce the drug craving response' (Volkow et al., 2010).

An important limitation of this study is the small number of subjects in each group. Crack-cocaine is one of the highest addictive drugs, extremely difficult to treat and manage, with very low adherence of drug addicts to standard biopsychosocial approaches offered by public outpatient services, and consequently, with high proportions of dropouts. Because of these features, although a high number of eligible crack-cocaine users were invited to participate in our trials, very few subjects really came to our research center even after they had agreed to participate in the study. However, the evidence for a significant change on PFC activity after a single and repetitive dosing of bilateral tDCS, which suggests a potential modulation on control of addictive processes with low risk of adverse events, is important as a starting point for more robust trials involving larger number of subjects. Regarding the effectiveness of blinding in this study, we were not able to receive systematic information from most of the participants, mostly because of the high amount of dropouts, as the participants should have been asked when returning to the outpatient service after the end of the tDCS procedures. However, blindness effectiveness has already been well established in similar studies, and thus should not have been compromised (Russo et al., 2013; Brunoni et al., 2014). Another limitation is the poor spatial resolution of electroencephalographic data, which prevents a clear determination of the specific contribution or interdependence of other prefrontal areas, such as ACC, OFC, FPC in the tDCS effects

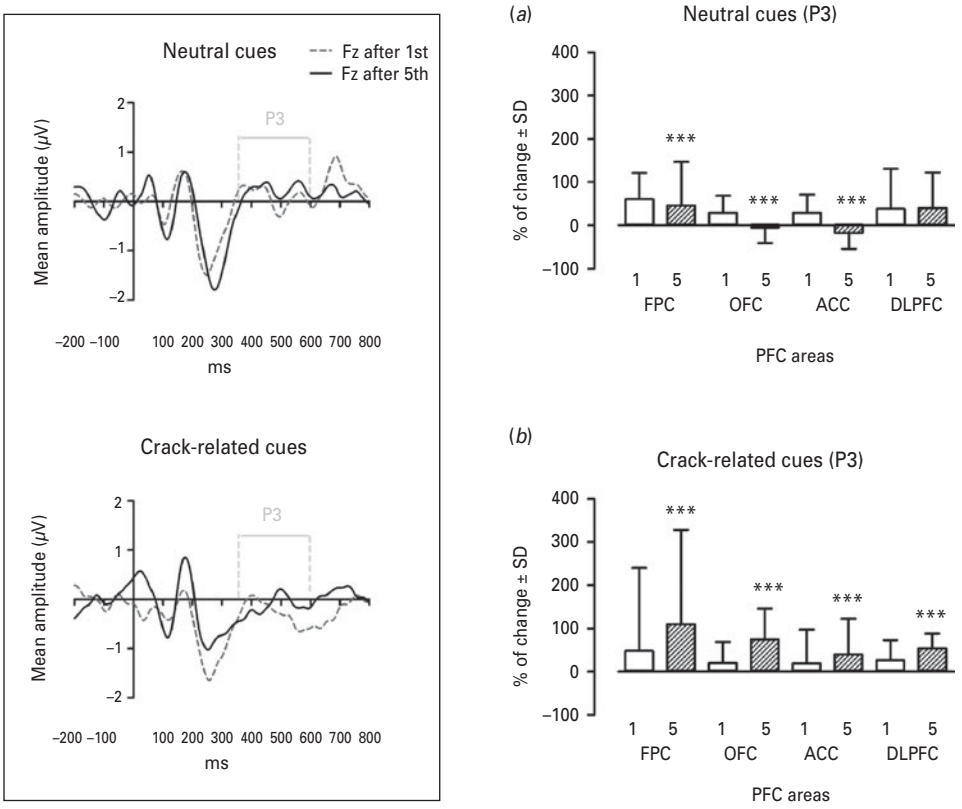

Fig. 5. Left inbox: Event Related Potentials (ERPs) evoked by neutral or crack-related visual stimuli after the first and after the fifth applications of bilateral (left cathodal/right anodal) transcranial Direct Current Stimulation (tDCS, 2 mA, 35 cm^2, for 20 min) in crack-cocaine addicts at frontal site (Fz) (according to 10–20 EEG international system). Percentage (%) of changes of current density in the P3 segment (350–600 ms) elicited by neutral (*a*) or crack-related (*b*) cue presentation in the Frontopolar Cortex (FPC), Orbitofrontal Cortex (OFC), Anterior Cingulate Cortex (ACC) and Dorsolateral Prefrontal Cortex (DLPFC) after the first (1) and after the fifth (5) sessions of bilateral tDCS ($n=6$) over the DLPFC ***$p<0.0001$ (Wilcoxon signed rank test when comparing P3 after the first *vs.* fifth sessions).

over the DLPFC activity. Future studies with high resolution neuroimaging techniques may be helpful to clarify these open questions. Finally, concerning the basic physiological effects of anodal and cathodal tDCS on prefrontal cortex activity, and excitability, it cannot be excluded completely that these differed in the present study from those obtained in others, exploring motor, and visual cortex excitability in healthy humans (Nitsche and Paulus, 2001; Nitsche et al., 2003b; Antal et al., 2004), since the direction of the effects of tDCS depends largely, and in a non-linear fashion not only on stimulation parameters (Batsikadze et al., 2013; Monte-Silva et al., 2013), but also on the activity state of neuromodulators such as dopamine, and adrenaline (Nitsche et al., 2004; Kuo et al., 2008; Monte-Silva et al., 2010), which might relevantly differ between healthy humans and drug addicts. Thus, the next step towards a development of a novel strategy focusing on cognitive control and using an approach of neuromodulation in drug addicts is to define ideal parameters of stimulation and to investigate neurophysiological parameters associated with long-lasting clinical changes.

In summary, we induced changes of P3 visual cue-reactivity in the DLPFC with a probable extension to FPC, OFC and ACC, notably present for drug-related stimuli, by repetitive bilateral (left cathodal/right anodal) tDCS over the DLPFC. These effects may reflect rescuing of prefrontal cognitive control that might be of clinical importance as adjunctive treatment of crack-cocaine addiction.

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Statement of Interest

Authors have no financial interests to disclose.

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