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# Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC)

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# ABSTRACT

Cognitive deficits that are reported in heavy marijuana users (attention, memory, affect perception, decision-making) appear to be completely reversible after a prolonged abstinence period of about 28 days. However, it remains unclear whether the reversibility of these cognitive deficits indicates that (1) chronic marijuana use is not associated with long-lasting changes in cortical networks or (2) that such changes occur but the brain adapts to and compensates for the drug-induced changes. Therefore, we examined whether chronic marijuana smokers would demonstrate a differential pattern of response in comparison to healthy volunteers on a decision-making paradigm (Risk Task) while undergoing sham or active transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). Twenty-five chronic marijuana users who were abstinent for at least 24 h were randomly assigned to receive left anodal/right cathodal tDCS of DLPFC (n = 8), right anodal/left cathodal tDCS of DLPFC (n = 9), or sham stimulation (n=8); results on Risk Task during sham/active tDCS were compared to healthy volunteers from a previously published dataset. Chronic marijuana users demonstrated more conservative (i.e. less risky) decision-making during sham stimulation. While right anodal stimulation of the DLPFC enhanced conservative decision-making in healthy volunteers, both right anodal and left anodal DLPFC stimulation increased the propensity for risk-taking in marijuana users. These findings reveal alterations in the decision-making neural networks among chronic marijuana users. Finally, we also assessed the effects of tDCS on marijuana craving and observed that right anodal/left cathodal tDCS of DLPFC is significantly associated with a diminished craving for marijuana.

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# 1. Introduction

Although marijuana is the most widely used illicit drug in the world, the long-term cognitive effects of chronic marijuana user remain poorly understood. In a study of 63 heavy marijuana users who had smoked at least 5000 times in their lives and were smoking daily at study entry, neuropsychological tests showed some impairments in cognition relative to former users and controls for up to 7 days after heavy use, but notably these impairments were virtually eliminated after 28 days of marijuana abstinence (Pope et al., 2001). Other studies support the finding that attention and memory deficits that are reported in heavy marijuana users appear to be reversible after prolonged abstinence (Harrison et al., 2002). How-

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*E-mail addresses*: boggio@mackenzie.br, psboggio@gmail.com (P.S. Boggio). <sup>1</sup> Equally contributing authors. ever, it remains unclear whether the reversibility of these cognitive deficits indicates that (1) chronic marijuana use does not alter cortical networks or (2) that such changes occur but the brain adapts to and compensates for the drug-induced changes. Indeed, functional MRI studies show changes in the functional activation of various brain areas in active and abstinent marijuana users compared to controls despite similar task and cognitive test performance (Chang et al., 2006; Gruber et al., 2009). Here we use a method of noninvasive brain stimulation to further explore the decision-making neural network response to brain stimulation among chronic marijuana users.

Methods of non-invasive brain stimulation, e.g. repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have the capacity to induce remarkable effects on real-time neuropsychological executive functioning and are valuable in studying the effect of neuromodulation on various neural networks. For example, the application of tDCS to the dorsolateral prefrontal cortex (DLFPC) can modulate the percep-

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#### Table 1 Demographic data.

	Sham tDCS	Right anodal/left cathodal	Left anodal/right cathodal	<i>p</i> -value
Marijuana subjects				
Number	8	9	8	
Sex (male)	4	5	6	0.8
Age (years $\pm$ SD)	$22.4\pm2.2$	$23.1 \pm 3.5$	$22.9 \pm 2.0$	0.6
Length of marijuana use (years $\pm$ SD)	$5.9\pm2.8$	$5.2 \pm 2.9$	$6.3 \pm 2.3$	0.7
Frequency of use (per week – mean $\pm$ SD)	$5.1\pm1.5$	$5.4\pm1.9$	$6.1\pm1.2$	0.5
Healthy subjects	12	12	12	
Number	12	12	12	
Sex (male)	4	3	4	$p > 0.17^*$
Age (years $\pm$ SD)	$21.3\pm2.1$	$19.5\pm1.0$	$20.0\pm1.4$	$p = 0.1^{**}$
General groups	Marijuana	Healthy		
Sex (male/total)	15/25	11/36		p < 0.05
Age (years $\pm$ SD)	$22.9\pm2.5$	$\textbf{20.3} \pm \textbf{1.7}$		<i>p</i> < 0.05

\* p-value when comparing marijuana subjects and healthy subjects for each subgroup (Fisher's exact test).

\*\* Values for the interaction test group × subject (healthy and marijuana).

We show measures of dispersion as standard deviation  $(\pm SD)$ .

tion of somatic (Boggio et al., 2008c) and emotional pain (Boggio et al., 2008b), alter the pattern of cravings (Fregni et al., 2008a,b; Boggio et al., 2008a) and mood (Fregni et al., 2006), and even affect learning and memory (Floel et al., 2008; Fregni et al., 2005; Boggio et al., 2009). One area of particular interest has been the effect of these neuromodulatory methods on decision-making processes and risk-taking behavior.

The Risk Task (Rogers et al., 1999) is a binary decision-making exercise that can offer a useful measure of impulse control and risk-taking behavior. In this task, subjects choose between two mutually exclusive low-risk or high-risk selections. Because the largest reward is always associated with the less likely of the two options, this gambling paradigm weighs the propensity of an individual to take risks in favor of large short-term gains at the likely expense of overall long-term losses. The decision-making system required to solve this binary choice involves a complex process that weighs converging neural inputs that assign and represent a relative preference for each of the two options (Rolls and Grabenhorst, 2008). In this process, the orbitofrontal cortex represents the expected reward value of an abstract stimulus (such as potential monetary reward) by associating these abstract stimuli with the affective value of primary reinforcers such as taste, touch, texture, and facial expression. Notably, however, a recent functional MRI study among chronic marijuana users suggests that marijuana users may process emotional information differently from those who do not use marijuana; the study demonstrated alterations in the fronto-limbic circuitry that regulates affective perception and impulse behavior (Gruber et al., 2009). This finding suggests that chronic marijuana users may also have differences in risk and decision-making neural networks.

Because it remains unknown whether chronic marijuana users process decision-making tasks differently from non-using controls, we assessed the performance of chronic marijuana users on the Risk Task while undergoing sham and active tDCS of the DLPFC. We set out to examine whether chronic marijuana smokers would demonstrate a differential pattern of response in comparison to non-marijuana smoking healthy volunteers from a previously published dataset.

## 2. Methods

#### 2.1. Study design

We conducted a single-center, doubled-blinded, randomized, and shamcontrolled trial to investigate the effect of a single-session of tDCS on marijuana craving and performance on a decision-making task (Risk Task, Rogers, 1999) in chronic marijuana users. This study conformed to the ethical standards of the Declaration of Helsinki and was approved by the institutional ethics committee from Mackenzie Presbyterian University, Brazil.

#### 2.2. Participants

Twenty-five marijuana users (15 males, 10 females; all right-handed; mean age  $22.8 \pm 2.6$  years; mean history of use  $5.8 \pm 2.7$  years; frequency  $5.5 \pm 1.9$  episodes of use/week) were recruited from Mackenzie Presbyterian University to participate in this study. Written advertisements were posted around campus and interested subjects contacted the study coordinator to enroll; the study coordinator explained the risk/benefits of the study and screened interested individuals for eligibility. Subjects were regarded as suitable to participate in this study if they fulfilled the following criteria: (1) age between 18 and 32 years, (2) right-handedness, (3) self-reported marijuana use of frequency at least 3 occasions each week for at least 3 years duration, (4) no other drug use or alcohol dependence, (5) no clinically significant neuropsychiatric disorder; (7) no use of central nervous system-effective medication, other than marijuana; and (8) no history of epilepsy, brain surgery, tumor, intracranial metal implantation, or clinically significant head trauma.

All subjects were naive to tDCS and the Risk Task. subjects were required to abstain from marijuana use for at least 24 h prior to participation in the experiments; the abstinent period was measured by self-report. All study participants provided written, informed consent. Demographic characteristics are summarized in Table 1.

#### 2.3. Transcranial direct current stimulation (tDCS)

tDCS is based on the application of a weak direct current to the scalp via two saline-soaked surface sponge electrodes (35 cm<sup>2</sup>) and delivered by a battery-driven, constant current stimulator. The device used, developed by our group, is particularly reliable for double-blind studies: a switch can be activated to interrupt the electrical current while maintaining the ON display and showing the stimulation parameters throughout the procedure to the experimenter and participant. Although there is significant shunting of current in the scalp, sufficient current penetrates the brain to modify the transmembrane neuronal potential (Miranda et al., 2006; Wagner et al., 2007), and thus, influence the level of excitability and modulate the firing rate of individual neurons. The effects on cortical excitability depend on current orientation, such that anodal stimulation generally increases cortical excitability, while cathodal stimulation decreases it (Nitsche and Paulus, 2000).

The electrodes montage was the same used in a previous study (Fecteau et al., 2007) where young, healthy, drug-naïve volunteers performed the Risk Task during prefrontal tDCS. We also followed a similar study paradigm. In this way, we became able to compare our present results to those of the previous study. Thus, participants were randomly assigned to receive left anodal/right cathodal tDCS (n = 8), right anodal/left cathodal tDCS (n=9), or sham stimulation (n=8). For left anodal/right cathodal tDCS, the anode electrode was placed over the left F3 (international EEG 10/20 system) and the cathode electrode was placed over the right F4. For stimulation right anodal/left cathodal, the polarity was reversed: the anode electrode was placed over F4 and the cathode electrode was placed over F3. For active stimulation, subjects received a constant current of 2 mA intensity with 10 s of ramp up and down. The tDCS started 5 min before the task began and was delivered during the entire course of the risk task, which lasted 10 min. The same procedure was used for sham stimulation, but current was applied only for the first 30s, a method that has been shown to be reliable for blinding subjects with respect to stimulation condition (Gandiga et al., 2006).

#### 2.4. Marijuana craving

The level of marijuana craving in each group was assessed immediately before and after the stimulation period. Participants were asked to rate their level of craving on a visual analogue scale (VAS, 0-10), where 0 represents absolutely no craving for marijuana and 10 represents the greatest craving possible.

#### 2.5. Risk task

The Risk Task was administered one time following either sham or active stimulation. In the risk task, subjects are presented with six horizontally arranged boxes colored as pink or blue. The ratio of pink and blue boxes varies from trial to trial as 5:1, 4:2, or 3:3. In each of 100 trials, the participants are asked to choose the color of the box they believe may contain the *winning token*. They are told that the token has an equal probability of being hidden in any of the six boxes. Thus, for each trial, the ratio of pink to blue boxes (referred to as *level of risk*) effectively determines the probability of finding the winning token. For instance, if the ratio of blue: pink is 5:1, this would mean that if participant chooses the blue boxes, he or she would have a 5/6 probability of finding the *winning token*. In this way, the participant's choice of pink vs. blue reflects the level of risk they are willing to endure.

Participants are rewarded with a gain of points when they correctly guess the color of the box that is hiding the winning token. However, they are punished with a loss of points when they select the wrong color. The amount of reward (or penalty) points associated with any scenario varies. The reward ratio or balance of reward is clearly indicated on the screen and varies as 90:10, 80:20, 70:30, or 60:40. Importantly, there is always an inherent conflict between level of risk and balance of reward; the largest reward is always associated with the less likely of the two outcomes (i.e. the most risky option). For example, in a trial with five blue boxes and one pink box, the winning token is more likely to be one of the blue boxes (five in six probability); however, choosing blue, in this case, would be associated with a smaller reward. However, if the participant picks the wrong color, he loses the same amount of points that he would otherwise have gained. The participants' objective is to earn as many points as possible.

In this way, the Risk Task measures the propensity for risk-taking within a decision-making task that otherwise entails little strategy and working memory. The task requires participants to weigh the immediate benefit vs. long-term cost of their choices. Participants who consistently choose the lowest risk/lowest gain option will be consistently choosing the box with the highest probability of winning but least attractive reward; such a strategy would result in small short-term gains and losses but is most likely to achieve a long-term gain. On the other hand, participants who choose the high-risk-high gain option would be demonstrating a preference for the possibility of high immediate gain at the likely detriment of large long-term losses, a disadvantageous long-term strategy.

#### 2.6. Statistical analysis

We performed a similar analysis as with our previous study in healthy drugnaïve volunteers (Fecteau et al., 2007). Thus, the outcome measures in the present study were: (1) percentage of instances in which the participant chose the highprobability/low-risk option (*percentage low-risk choice*, a binary variable, 0–100%), and (2) the amount of time it took for the participants to enter a selection (*response time*, a continuous variable, measured in milliseconds). Performance on all 100 trials of the task were analyzed except for the neutral conditions in which there were an equal number of pink and blue boxes.

Results were then combined and compared for the three tDCS groups: (1) those receiving left anodal/right cathodal tDCS of DLPFC (n = 8), (2) right anodal/left cathodal tDCS of DLPFC (n = 9), and (3) sham stimulation (n = 8). Analyses were performed using STATA (College Station, Texas, USA). We used a mixed linear model to analyze decision time difference across the groups. We modeled decision time change using the covariates of tDCS group (left anodal/right cathodal stimulation, right anodal/left cathodal stimulation, sham stimulation), balance of reward (90:10, 80:20, 70:30, 60:40), level of risk (low-risk, high-risk), and interaction terms tDCS group × balance of reward × level of risk. For the outcome considering the percentage choice of low-risk versus high-risk (binary outcome), we performed a logistic regression model in which the dependent variable was the percentage of low-risk choice [# low-risk/(#low-risk+#high-risk)] and the independent variables were group (left anodal/right cathodal stimulation, right anodal/left cathodal stimulation, sham stimulation), balance of reward (90:10, 80:20, 70:30, 60:40), and interaction tDCS group × balance of reward. As we performed multiple tests, we used Bonferroni adjustments for multiple comparisons. Finally we performed a comparison analysis with previous data from our healthy subjects study (Fecteau et al., 2007). Data from this study were combined into the full model and we assessed whether subjects group (healthy vs. marijuana subjects) was a significant variable in this model.

#### 3. Results

#### 3.1. Sample groups

There were no significant differences among the demographic data between marijuana users divided among the three groups (right anodal/left cathodal tDCS, left anodal/right anodal tDCS, sham stimulation); however when data were combined, there was a small but significant difference between the two groups (see Table 1 for statistics and absolute values). However, baseline differences in risk-taking were indeed present between healthy controls and marijuana users (see below).

#### 3.2. Adverse effects

None of the volunteers experienced adverse effects during or after tDCS. Some of the participants reported a slight itching sensation under the electrodes during approximately the first 30 s of stimulation.

#### 3.3. Low-risk choice during sham stimulation

Marijuana users randomized to sham stimulation chose the lower-risk option more frequently than healthy subjects undergoing sham stimulation. Marijuana users chose the low-risk prospect for an average of 87.3% of cases, in comparison to the healthy controls who chose the low-risk prospect 82% of the time (this difference was statistically significant (p < 0.001).

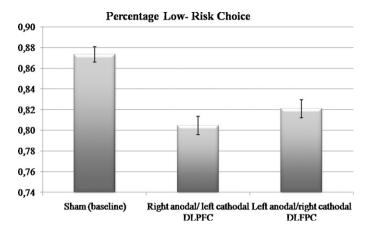
#### 3.4. Effect of transcranial stimulation on low-risk choice

Our main a-priori hypothesis based on our previous findings (Fecteau et al., 2007), was that participants receiving bifrontal tDCS (either anodal tDCS to the right DLPFC coupled with cathodal tDCS to the left DLPFC (referred as "right anodal") or anodal tDCS to the left DLPFC coupled with cathodal tDCS to the right DLPFC (referred as "left anodal")) would change risk-averse behavior on the Risk Task. To test this hypothesis, we used a specific logistic regression model using *percentage low-risk choice* as the dependent variable. Results revealed a main effect of group of stimulation (p = 0.0025). Interestingly, however, the direction of the hypothesized behavior change was opposite to the findings in healthy controls.<sup>2</sup> In fact we conducted a full model combining data from marijuana subjects with data from healthy subjects and showed a significant difference between these two groups regarding the main outcome (choice of low vs. high-risk) (p < 0.001 (z = 11.65)) for the variable subjects condition and p < 0.001 (z = 9.06) for the interaction subjects condition vs. treatment). In the marijuana group, participants receiving either condition of active stimulation (right anodal or left anodal stimulation) demonstrated a lower percentage low-risk choice; that is, both groups of active stimulation chose the high-risk prospects more often as compared to participants receiving sham stimulation. In fact, pair-wise analysis demonstrated significant differences for the comparison of anodal left vs. sham stimulation (OR = 1.29 95% CI 1.11–1.51, p=0.001) and comparison of anodal right vs. sham stimulation (OR = 1.50 95% CI 1.11–2.03, *p* = 0.008). Finally, there was no difference between anodal left and anodal right (OR = 1.11 95% CI -0.86-1.4) - (Fig. 1). Also, there was no significant difference between women and men in their choices-the term gender in the model was not significant (p > 0.05).

#### 3.5. Effect of reward ratio on low-risk choice

An important issue then is the balance of reward – whether decision-making (in this case choosing the low vs. high-risk prospect) is associated with the balance of reward (i.e. 90:10, 80:20, 70:30, or 60:40 reward ratio) (Rogers et al., 1999; Knoch et al., 2006). Results revealed a significant main effect of balance

<sup>&</sup>lt;sup>2</sup> Choice between low-risk and high-risk prospect (in percentages) from our healthy subject study during different tDCS conditions (same as in the current study in subjects users of marijuana) – note that this study has been published (Fecteau et al., 2007) are provided with the online version of this article.



**Fig. 1.** During both right anodal/left cathodal and left anodal/right cathodal tDCS of the DLPFC, the marijuana users demonstrated a significant increase in choice of the more-risky prospect. The figure shows that these subjects chose the low-risk choice with decreased frequency.

of reward (p < 0.001): Participants randomized to sham stimulation tended to choose the low-risk prospect less often when its associated reward was diminished – a similar findings as in our healthy subjects study. We then investigated whether the trends with regards to the balance of reward was similar across groups: we found a significant interaction for the term group × balance of reward (p < 0.001). However, the direction of this trend was inverted as compared to the results from our study with healthy subjects. Whereas in our previous study, healthy subjects undergoing right anodal stimulation were so conservative in their choice of the lowrisk prospect as to be nearly unaffected by the balance of reward, here, in this study, marijuana users undergoing active stimulation demonstrated a trend towards the high-risk prospect in the setting of a large balance of reward (e.g. 90:10, 80:20 reward ratio). The marijuana users demonstrate an inverted tendency during active stimulation as compared to sham to select the more superficially attractive option, the choice with the largest reward ratio (Fig. 2).

#### 3.6. Total points earned

As participants gained or lost points according to their individual decisions, we then tested whether group assignment had an interaction with the total points earned. Although there was a difference in the strategy during the trial, ANOVA showed no significant differences in the total of points earned (F(2,22) = 0.23, p = 0.79) during active and sham stimulation.

#### 3.7. Response time

We then tested whether differences in risk-taking were due to changes in decision time, a potential confounder. Our analysis showed that the main effect of *group* was not significant (p > 0.05), therefore suggesting that response time was similar across groups of stimulation. We also examined whether the decision times were longer when participants were confronted to a 4:2 vs. a 5:1 scenario, as found in Rogers et al. (1999), Knoch et al. (2006) and Fecteau et al. (2007). There was no main effect of level of risk (p > 0.05).

# 3.8. Effect of stimulation on marijuana craving

Finally, we tested the effect of stimulation on marijuana craving. ANOVA showed a significant interaction of *craving scores* (VAS, 0-10) and *time* (before/after stimulation), F(2,22) = 10.9, p = 0.0005. The results show that subjects reported significantly reduced craving for marijuana after right anodal/left cathodal DLPFC stimulation as compared to sham stimulation.

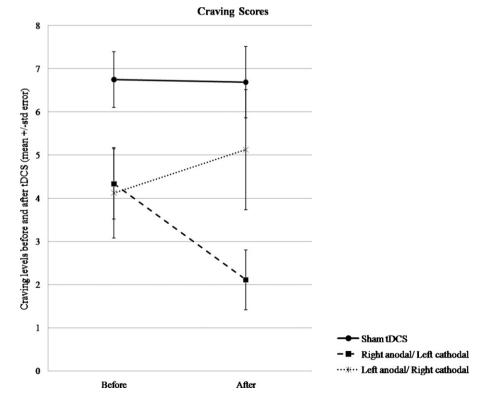


Fig. 2. Marijuana users reported a significant decrease in marijuana craving (visual analogue scale, 0–10) after right anodal/left cathodal tDCS of DLPFC (dotted line). Left anodal/right cathodal tDCS of DLPFC resulted in a non-significant increase in marijuana craving (dashed line). Sham stimulation resulted in no changes to craving scores (solid line).

# 4. Discussion

We employed the Risk Task to provide insight to the decisionmaking neural network of chronic marijuana users during sham and active transcranial stimulation. In our study, there were no significant differences in the total of points earned between groups. However, the task does offer insight to the strategies utilized by participants, particularly the propensity for risktaking.

Surprisingly, marijuana users chose the lower-risk option more frequently than healthy subjects during sham stimulation. This finding is interesting because whereas in our study marijuana users tended toward the lower-risk option, in a study by Whitlow et al. (2004) chronic marijuana users abstinent for 10-18 h displayed a propensity for more risky decisions-participants rendered decisions in the Gambling Task that led to larger immediate gains but higher overall losses. Marijuana use in that study was associated with deficits in the ability to balance rewards and punishments. Extrapolating the results from that study might have suggested that, in our study, abstinent marijuana users would have displayed a greater propensity for risk-taking at baseline, but there are a number of reasons for this difference. First of all, it should be noted that high performance on the Gambling Task requires participants to apply deductive reasoning in their on-going experience with the task to determine which deck contains advantageous vs. disadvantageous outcomes. In this respect, the Gambling Task is a more cognitively complex decision-making paradigm as compared to the Risk Task, which offers a more specific measure of propensity for risk-taking. Indeed, poor performance in the Gambling Task among marijuana users may be the result of impulsivity, an inability to learn from experience, insensitivity to gains/losses, or high levels of risk-taking.

Secondly, it is possible that chronic marijuana use may contribute to the development of compensatory mechanisms that promote more judicious risk-taking during abstinence. Lane et al. (2005) showed that acute marijuana administration among occasional users does increase selection of risky response options. However, Vadhan et al. showed that acute marijuana intoxication among highly experienced marijuana smokers does not interfere with weighing of risky options or advantageous decision-making. These results suggest that the effect of acute marijuana administration on risk-taking may differ between occasional and chronic users (Vadhan et al., 2007). Chronic marijuana use may contribute to plastic changes that alter the cognitive effects of the drug, while the same altering neural processing might persist in its absence. Changes to the distribution of endocannabanoid receptors may underlie this effect (Lichtman and Martin, 2005).

In our study, marijuana users demonstrated an increase in choice of the more-risky prospect during tDCS of the DLPFC. These results are interesting as they contrast with the result in healthy volunteers in which anodal right tDCS/cathodal left tDCS has been shown to promote conservative decision-making by upregulating the capacity of the right DLPFC to suppress superficially seductive options. Here among marijuana users, however, DLPFC stimulation renders an opposite function in that it increased the propensity for risk-taking. The result that anodal right/cathodal left tDCS method of brain stimulation had a completely opposite effect on marijuana users as compared to the pattern observed in non-marijuana using controls reveals an altered decision-making neural network among chronic marijuana users. This result is consistent with previous studies of executive functioning in marijuana users (Bolla et al., 2002), which suggest that marijuana users may recruit an alternative neural network as a compensatory mechanism during performance on tasks of executive functioning. Functional MRI studies also support the suggestion that marijuana users may shift the inter-hemispheric balance of activity across the prefrontal cortex so to overcome an underlying propensity towards sub-optimal decision-making (Eldreth et al., 2004).

An alternate aim of our study was to determine whether tDCS of the DLPFC could be used to reduce marijuana craving. Preliminary studies have shown that activation of the right DLPFC can reduce food (Uher et al., 2005), alcohol (Boggio et al.), and cocaine cravings among addicts (Camprodon et al., 2007). Moreover, activation of the left DLPFC with high-frequency TMS has been shown to reduce nicotine consumption and cigarette smoking craving (Amiaz et al., 2009; Eichhammer et al., 2003; Fregni et al., 2008a). This study shows that right anodal/left cathodal DLPFC stimulation (i.e. right DLPFC activation) reduces marijuana cravings. Indeed, subjects reported significantly reduced craving for marijuana after right anodal/left cathodal DLPFC stimulation. This study confirms the role of DLPFC as a potent target for neuromodulation of craving perception.

One limitation of this study is that chronic marijuana users were restricted from smoking marijuana for a period of only 24 h prior to the study, and this was measured only by self-report (similarly to our healthy study (no marijuana users) (Fecteau et al., 2007)). An assessment of long-term effects would best be achieved by examination of marijuana users who were abstinent for at least a 7–28 day period as verified by either hair or urine sample. Indeed, certain functional MRI changes noted in frontal and medial cerebellar regions of marijuana users have been shown to normalize with increasing duration of abstinence in the abstinent users. Even so, other fMRI changes in the right prefrontal, medial and dorsal parietal, and occipital brain regions persist in spite of long-term abstinence (Chang et al., 2006). Thus, it is indeed possible that our findings here may suggest a neuroadaptive state that is limited to active or acutely abstinent marijuana use. Further tDCS studies should investigate the role of tDCS in subjects with prolonged abstinence. Another limitation is the small sample size of this study that therefore may decrease the external validity of our findings. However the aim of this exploratory study was to generate initial data to be used in further confirmatory studies. Finally although we compared the data from this study with our previous study with healthy subjects (Fecteau et al., 2007) and showed a significant difference on the effects of tDCS across the two studies and no demographic differences between the two groups when analyzing the small subgroups; there was a small (mean difference of 2.6 years), but significant difference (as the variance was small) in age and gender between the two groups when data from subgroups are combined. Subjects in the marijuana group are slightly older and this may explain risk-taking behavior differences in baseline between these two groups of subjects. Also it needs to be considered that data comes from two different studies; therefore alternative mechanisms to explain the differences are possible.

# 5. Summary

In healthy volunteers, right anodal stimulation of the DLPFC decreases the propensity for risk-taking. Acutely abstinent marijuana users have a lower propensity for risk-taking at baseline, but this study shows that any polarity of DLPFC stimulation increases their propensity for risk-taking. The differential effect of transcranial brain stimulation reveals an altered decision-making neural network among chronic marijuana users. In addition, this study shows a role for right anodal/left cathodal DLPFC stimulation in reducing marijuana craving.

#### Role of funding source

Nothing to declare.

### Contributors

Conceived and designed the experiments: PSB ABV. Conducted the experiments: PSB ABV. Analyzed the data: SZ PSB FF SF. Interpreted the results: APL, PSB, FF. Wrote the first draft of the manuscript: SZ PSB FF. Revised and approved the manuscript: All the authors.

### **Conflict of interest**

The authors have no conflicts of interest.

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# Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drugalcdep.2010.06.019.

#### References

- Amiaz, R., Levy, D., Vainiger, D., Grunhaus, L., Zangen, A., 2009. Repeated highfrequency transcranial magnetic stimulation over the dorsolateral prefrontal cortex reduces cigarette craving and consumption. Addiction 104, 653–660.
- Boggio, P.S., Khoury, L.P., Martins, D.C., Martins, O.E., de Macedo, E.C., Fregni, F., 2009. Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. J. Neurol. Neurosurg. Psychiatry 80, 444–447.
- Boggio, P.S., Sultani, N., Fecteau, S., Merabet, L., Mecca, T., Pascual-Leone, A., Basaglia, A., Fregni, F., 2008a. Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: a double-blind, sham-controlled study. Drug Alcohol Depend. 92, 55–60.
- Boggio, P.S., Zaghi, S., Fregni, F., 2008b. Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychologia.
- Boggio, P.S., Zaghi, S., Lopes, M., Fregni, F., 2008c. Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. Eur. J. Neurol..
- Bolla, K.I., Brown, K., Eldreth, D., Tate, K., Cadet, J.L., 2002. Dose-related neurocognitive effects of marijuana use. Neurology 59, 1337–1343.
- Camprodon, J.A., Martinez-Raga, J., Alonso-Alonso, M., Shih, M.C., Pascual-Leone, A., 2007. One session of high frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduces cocaine craving. Drug Alcohol Depend. 86, 91–94.
- Chang, L., Yakupov, R., Cloak, C., Ernst, T., 2006. Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. Brain 129, 1096–1112.
- Eichhammer, P., Johann, M., Kharraz, A., Binder, H., Pittrow, D., Wodarz, N., Hajak, G., 2003. High-frequency repetitive transcranial magnetic stimulation decreases cigarette smoking. J. Clin. Psychiatry 64, 951–953.
- Eldreth, D.A., Matochik, J.A., Cadet, J.L., Bolla, K.I., 2004. Abnormal brain activity in prefrontal brain regions in abstinent marijuana users. Neuroimage 23, 914–920.
- Fecteau, S., Knoch, D., Fregni, F., Sultani, N., Boggio, P., Pascual-Leone, A., 2007. Diminishing risk-taking behavior by modulating activity in the prefrontal

cortex: a direct current stimulation study. J. Neurosci. 27 (46), 12500-12505.

- Floel, A., Rosser, N., Michka, O., Knecht, S., Breitenstein, C., 2008. Noninvasive brain stimulation improves language learning. J. Cogn. Neurosci. 20, 1415–1422.
- Fregni, F., Boggio, P.S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., Marcolin, M.A., Rigonatti, S.P., Silva, M.T., Paulus, W., Pascual-Leone, A., 2005. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp. Brain Res. 166, 23–30.
- Fregni, F., Boggio, P.S., Nitsche, M.A., Marcolin, M.A., Rigonatti, S.P., Pascual-Leone, A., 2006. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord. 8, 203–204.
- Fregni, F., Liguori, P., Fecteau, S., Nitsche, M.A., Pascual-Leone, A., Boggio, P.S., 2008a. Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving: a randomized, sham-controlled study. J. Clin. Psychiatry 69, 32–40.
- Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F.A., Nitsche, M.A., Mecca, T., Macedo, E.C., Pascual-Leone, A., Boggio, P.S., 2008b. Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. Appetite 51, 34–41.
- Gandiga, P.C., Hummel, F.C., Cohen, L.G., 2006. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin. Neurophysiol. 117, 845–850.
- Gruber, S.A., Rogowska, J., Yurgelun-Todd, D.A., 2009. Altered affective response in marijuana smokers: an FMRI study. Drug Alcohol Depend. 105, 139–153.
- Harrison Jr., G.P., Gruber, A.J., Hudson, J.I., Huestis, M.A., Yurgelun-Todd, D., 2002. Cognitive measures in long-term cannabis users. J. Clin. Pharmacol. 42, 415–475.
- Knoch, D., Gianotti, L.R., Pascual-Leone, A., Treyer, V., Regard, M., Hohmann, M., Brugger, P., 2006. Disruption of right prefrontal cortex by low-frequency repetitive transcranial magnetic stimulation induces risk-taking behavior. J. Neurosci. 26, 6469–6472.
- Lane, S.D., Cherek, D.R., Tcheremissine, O.V., Lieving, L.M., Pietras, C.J., 2005. Acute marijuana effects on human risk taking. Neuropsychopharmacology 30, 800–809.
- Lichtman, A.H., Martin, B.R., 2005. Cannabinoid tolerance and dependence. Handbook Exp. Pharmacol., 691–717.
- Miranda, P.C., Lomarev, M., Hallett, M., 2006. Modeling the current distribution during transcranial direct current stimulation. Clin. Neurophysiol. 117, 1623–1629. Nitsche. M.A., Paulus, W., 2000. Excitability changes induced in the human motor
- cortex by weak transcranial direct current stimulation. J. Physiol. 527, 633–639. Pope Jr., H.G., Gruber, A.J., Hudson, J.I., Huestis, M.A., Yurgelun-Todd, D., 2001. Neu-
- ropsychological performance in long-term cannabis users. Arch. Gen. Psychiatry 58, 909–915.
- Rogers, R.D., Everitt, B.J., Baldacchino, A., Blackshaw, A.J., Swainson, R., Wynne, K., Baker, N.B., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J.F., Sahakian, B.J., Robbins, T.W., 1999. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. Neuropsychopharmacology 20, 322–339.
- Rolls, E.T., Grabenhorst, F., 2008. The orbitofrontal cortex and beyond: from affect to decision-making. Prog. Neurobiol. 86, 216–244.
- Uher, R., Yoganathan, D., Mogg, A., Eranti, S.V., Treasure, J., Campbell, I.C., McLoughlin, D.M., Schmidt, U., 2005. Effect of left prefrontal repetitive transcranial magnetic stimulation on food craving. Biol. Psychiatry 58, 840–842.
- Vadhan, N.P., Hart, C.L., van Gorp, W.G., Gunderson, E.W., Haney, M., Foltin, R.W., 2007. Acute effects of smoked marijuana on decision making, as assessed by a modified gambling task, in experienced marijuana users. J. Clin. Exp. Neuropsychol. 29, 357–364.
- Wagner, T., Fregni, F., Fecteau, S., Grodzinsky, A., Zahn, M., Pascual-Leone, A., 2007. Transcranial direct current stimulation: a computer-based human model study. Neuroimage 35, 1113–1124.
- Whitlow, C.T., Liguori, A., Livengood, L.B., Hart, S.L., Mussat-Whitlow, B.J., Lamborn, C.M., Laurienti, P.J., Porrino, L.J., 2004. Long-term heavy marijuana users make costly decisions on a gambling task. Drug Alcohol Depend. 76, 107–111.