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ARTICLE

State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving

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Abstract

Transcranial direct current stimulation (tDCS) has been shown to modulate subjective craving ratings in drug dependents by modification of cortical excitability in dorsolateral prefrontal cortex (DLPFC). Given the mechanism of craving in methamphetamine (meth) users, we aimed to test whether tDCS of DLPFC could also alter self-reported craving in abstinent meth users while being exposed to meth cues. In this double-blinded, crossover, sham-controlled study, thirty two right-handed abstinent male meth users were recruited. We applied 20 min 'anodal' tDCS (2 mA) or 'sham' tDCS over right DLPFC in a random sequence while subjects performed a computerized cue-induced craving task (CICT) starting after 10 min of stimulation. Immediate craving was assessed before the stimulation, after 10 min of tDCS, and after tDCS termination by visual analog scale (VAS) of 0 to 100. Anodal tDCS of rDLPFC altered craving ratings significantly. We found a significant reduction of craving at rest in real tDCS relative to the sham condition ($p=0.016$) after 10 min of stimulation. On the other hand, cue-induced VAS craving was rated significantly higher in the real condition in comparison with sham stimulation ($p=0.012$). Our findings showed a state dependent effect of tDCS: while active prefrontal tDCS acutely reduced craving at rest in the abstinent meth users, it increased craving during meth-related cue exposure. These findings reflect the important role of the prefrontal cortex in both cue saliency evaluation and urge to meth consumption.

Research highlights: DLPFC plays an important role in the modulation of meth craving; anodal tDCS on the right DLPFC decreases immediate craving at rest after 10 min; cue-induced meth craving rating increases under the active online stimulation of the right DLPFC; TDCS has a state dependent effect on craving in meth users.

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Introduction

According to the world drug report, after cannabis, amphetamine-type stimulants (ATS) are the world's most widely used drugs. ATS has become an international public health problem with an estimation of 13.7 to 56.4 million users worldwide (United Nations Office on Drugs and Crime, 2011). Methamphetamine (meth) is an extremely potent psycho-stimulant and highly addictive drug, accompanied by cheap price, ease of synthesis and long lasting effects (Henry et al., 2005; Shoptaw et al., 2008; Weber et al., 2012).

Relapse to drug use is a common phenomenon in the treatment of addiction that can occur after prolonged abstinence, and is often precipitated by the exposure to drug-associated cues that provoke drug craving

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(Pickens et al., 2011). Drug craving is one of the most important factors in addiction that can lead to drug-seeking behaviour during abstinence. It represents a complex condition that includes emotional and cognitive aspects along with behavioural and physiological states. Emerging evidence suggests that craving induced by meth cues can be reliably measured in meth-dependent individuals and cue-induced craving is a strong predictor of subsequent meth use (Culbertson et al., 2010). Accordingly, cue-elicited meth craving should be viewed as a clinically important phenomenon and one of the primary behavioural symptoms of meth dependence.

According to several neuroimaging studies, the prefrontal cortex, especially the dorsolateral prefrontal cortex (DLPFC), plays an important role in drug craving (Brody et al., 2002; Due et al., 2002; Wilson et al., 2004; McBride et al., 2006). DLPFC dysfunction has been reported frequently among meth-dependent subjects (Paulus et al., 2002; Payer et al., 2008; Salo et al., 2009). Additionally, modulation of DLPFC activity using repetitive transcranial magnetic stimulation (rTMS), which is a non-invasive brain stimulation technique, has shown significant effects on nicotine (Eichhammer et al., 2003; Li et al., 2013a), cocaine (Camprodon et al., 2007) and meth (Li et al., 2013b) craving.

Previous studies and the preliminarily collected evidence from novel non-pharmacological methods support the potential role of prefrontal cortex in meth-dependents' craving state. Hence, we aimed to test the effects of prefrontal cortex modulation using a technique that has been shown to induce significant behavioural effects and can interact with current neural processes to enhance neuroplasticity – transcranial direct current stimulation (tDCS). TDCS is a method of non-invasive brain stimulation which has recently demonstrated promising neuro-rehabilitative effects in different types of neuropsychiatric disorders (Demirtas-Tatlidede et al., 2013) such as major depression (Nitsche et al., 2009), pain (Fregni et al., 2006; Lefaucheur et al., 2008; Mcfadden et al., 2011) Alzheimer's disease (Boggio et al., 2011, 2012; Nardone et al., 2012), schizophrenia (Vercammen et al., 2011; Brunelin and Mondino, 2012), and stroke (Kandel et al., 2012; O'Shea et al., 2014). TDCS delivers a weak and continuous current to the cortex through an electrode connection with the subject's scalp, and either inhibits or enhances neuronal firing in an area related to the location of the electrode. The interesting advantage of tDCS is its interactive effect with the ongoing neural process; thus it is an attractive technique to be used in combination with behavioural stimulation.

Recently several tDCS-related studies have shown that anodal stimulation of right DLPFC reduced craving for cigarettes (Fregni et al., 2008; Boggio et al., 2009) alcohol (Boggio et al., 2008), marijuana (Boggio et al., 2010), and food (Goldman et al., 2011). A main drawback of these studies is the possible confounding effect of bilateral protocols, in the sense that excitatory effects of the anodal electrode are not distinguishable from inhibitory effects of the cathodal electrode. We therefore assessed the effects of unilateral stimulation of the right DLPFC on the immediate and cue-induced craving in abstinent meth-dependent subjects. We used a cue reactivity paradigm, which has been demonstrated to be a validated method for craving induction and thus, given the mechanism of tDCS, appropriate to be combined with tDCS of the prefrontal cortex. We chose the right DLPFC as we hypothesized that increasing ongoing activity of this area, would have an inhibitory effect on craving behaviour.

Methods and materials

Participants

Subjects were recruited from meth-dependent patients who were admitted to Vardij Abstinence-Based Residential Centre which is specialized for ATS dependence. This centre is located at Vardij, a rural area near Tehran, and is a part of the therapeutic network belonging to Rebirth Society Organization (RSO), a non-profit charity. The setting was ideal for this study as the population was relatively homogeneous and given the large numbers of meth users in this facility, it also provided an adequate external validity. Thirty two right-handed male subjects were initially enrolled, although only 30 completed the whole procedure of the study. Subjects were between the ages of 20 and 45 (mean = 29.90) with no previous participation in a tDCS study and were chosen according to the following criteria: a history of at least 12 months of meth dependence based on DSM-IV criteria before receiving treatment, and also abstinence from any drugs except cigarettes, for at least a week prior to the experiment, confirmed by urine analysis inside the residential centre. All the subjects had used meth at least 6 d a week in the last month before entering the treatment and the most common route of administration was smoking among all subjects. We tested subjects' cue-reactivity in the recruitment process based on their subjective reports of craving feelings after exposure to two pictorial meth-related cues, which were not included in the main craving task. Subjects were excluded if their self-reported mean craving was below 20 out of 100.

We also excluded individuals with any current or past major clinical neurologic disorders, central nervous system-effective medication intake, history of epilepsy, brain surgery, tumor, intracranial metal implantation, clinically significant head trauma, or any major clinical psychiatric disorders (in axis I, except substance-related disorders). Subjects meeting exclusion/inclusion criteria were considered eligible to participate in this study.

The experimental protocol was designed and carried out according to the Declaration of Helsinki principle. This study was also approved by Independent Ethics Committee (IEC) of Tehran University of Medical Sciences. Since exposing patients to meth cues may

increase the possibility of relapse, similarly to studies using cue-reactivity paradigms, we carefully addressed this important ethical concern by using images instead of real substance and paraphernalia and subjects received IEC-approved psychological interventions to manage potential drug craving after being exposed to drug cues. As the subjects were already admitted to a caring facility they were closely monitored through the following week for any sign of relapse. This study was registered in Iranian Registry of Clinical Trials (IRCT) in 2012 with the code IRCT2012102311234N1. All subjects signed a written informed consent form.

Study design

This study was a randomized, double-blinded, sham-controlled, crossover study. Participants and the evaluating investigators (except the technician that applied tDCS) were blinded to the intervention type. The procedure consisted of three separate sessions, a recruitment session followed by two intervention sessions. At the beginning of the recruitment session, all aspects of the experiment were explained completely to each individual, and then, in the case of full consent for participation, each individual was asked to sign the consent form.

Basic demographic information, drug abuse and treatment history, and high risk behaviours of each subject were recorded during a structured interview by an expert drug counsellor.

The next two intervention sessions consisted of an active and a sham stimulation session, the sequence of which was randomly chosen. All subjects were asked to abstain for cigarettes 1 h prior to intervention sessions to control for potential nicotine effect. At the beginning of the sessions, the subject was seated on a comfortable chair and was asked to complete the Persian version of Positive and Negative Affect Scale (PANAS) in order to control for his affective status before each session. Then, subject's immediate craving was assessed three times by Visual Analog Scale (VAS), at the beginning (VAS-A), middle (VAS-B) and end (VAS-C) of the 20 min stimulation, in which the subject was asked to rate his meth craving (at that exact moment) using VAS on a 10 cm ruler graded 0–100 at the back. Eventually, we assessed any possible side effects using a tDCS side-effect checklist at the end of the intervention sessions (Fig. 1).

In both interventional sessions, the exact same procedure was followed, except for the type of the stimulation and task version. The sequence of stimulation and task type was randomized with permuted-block method. The same investigators carried out stimulation sessions, at the same time of the day and the same room.

Computerized cue-induced craving assessment task (CICT)

The task was developed with MATLAB software (v. 7.10.0.499 R2010a) on a Windows 7 operating system

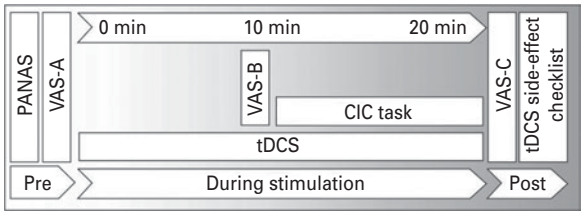

Fig. 1. Intervention procedure. Before the stimulation started, subject completed Positive and Negative Affect Scale (PANAS) and immediate craving self-report (VAS-A). VAS-B was performed in the middle of the stimulation (in the 10th minute) after which Cue Induced Craving Task (CICT) was started. After completion of the stimulation, VAS-C and tDCS side-effect checklists were filled out.

and consisted of 25 trials. Duration of each trial was 24 s in which a visual cue (an image) accompanied by a computerized Visual Analog Scale (cVAS) were shown in a fixed and predefined order on the screen of a 14 in laptop and the subject was asked to rate his cue-induced craving on a scale of 0 to 100. The total duration of the task was exactly 10 min, which contained twenty drug-related and five neutral cues (Fig. 2).

This task was carried out in two equivalent versions with two different sets of images, CICT1 and CICT2 to avoid memory interference and training effects. Two versions were performed randomly for each subject during two intervention sessions, meaning that if CICT1 had been used in the first session, then CICT2 would be used in the second one and vice versa. CICT1 and CICT2 images were previously validated as craving inducing cues. The two series of images were counterbalanced for two equivalent versions based on their mean craving induction power, which was assessed in a previous study by Ekhtiari et al. (2009).

Transcranial direct current stimulation

Direct current was delivered from a battery-driven, constant current stimulator (ActivaDose®II. Iontophoresis Delivery Unit, USA) and transferred by a pair of 5 × 7 cm (35 cm^2) electrodes. Electrodes were standard carbonic, covered with a normal saline soaked sponge cases. Subjects were randomized to receive sham or anodal tDCS. The anode was placed over F4 (EEG 10/20 system) to target the right dorsolateral prefrontal cortex (rDLPFC) and the cathode over the contralateral supraorbital area. During anodal tDCS, a 2 mA current was applied for 20 min. For the sham stimulation, the same montage was used, but the stimulator was turned off after gradually ramping up to 2 mA and down to 0 mA which took 1 min. The electrodes were on the scalp for the remaining 19 min and subjects were not informed that the device was turned off. Wash-out period between two sessions of intervention was at least 72 h to avoid any potential carry-over effects.

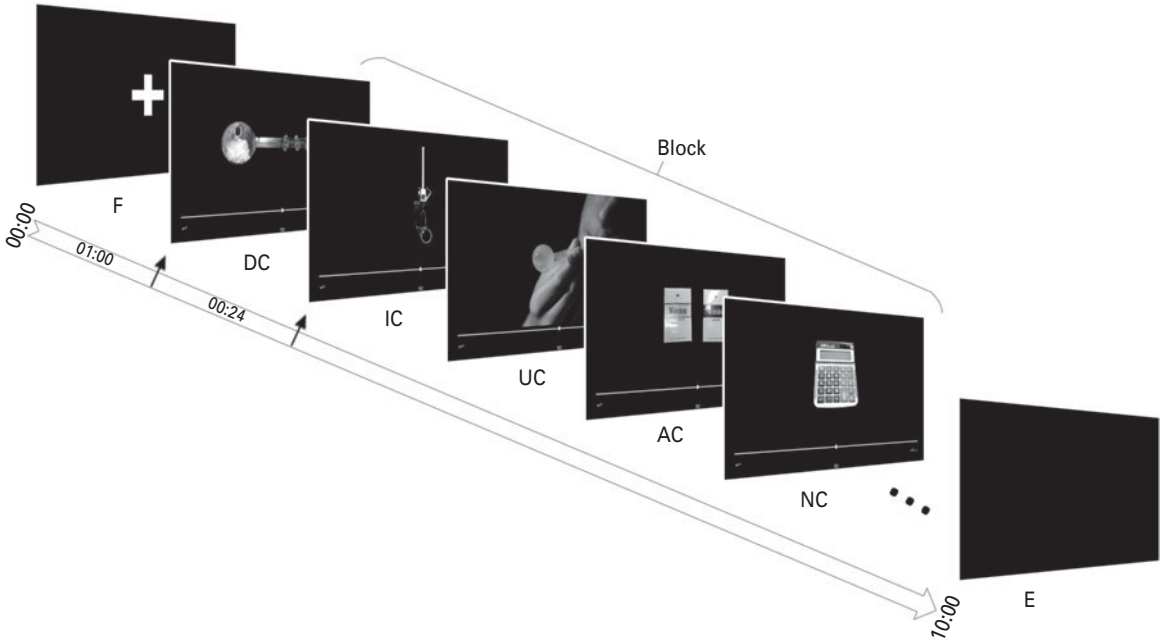

Fig. 2. Computerized Cue-Induced Craving Assessment Task (CICT). Each block of the task started with a fixation point which lasted for 1 m followed by images of Drug Cues (DC), Instrument Cues (IC), Usage Cues (UC), Associated Cues (AC), and Neutral Cues (NC) each of which was displayed for 24 s. Every subject completed five blocks of current task containing different stimuli from each cue group with the same sequence of the cues in each block. The task was completed in 10 min during which the craving elicited by each stimulus was rated 0–100 by the subject using a cVAS located under each image.

Statistical analysis

All data are presented as mean (±S.E.M.) or frequency unless mentioned otherwise. Statistical analysis was performed by R v.2.15.2 (Wickham, 2009) using a linear mixed model, following a *post-hoc* paired *t*-test. Multiple comparison error was corrected by the Bonferroni method. Pearson's correlation coefficient was computed to test for bivariate correlation among potential confounder variables such as age, duration of abstinence, duration of addiction and marital status and explanatory variables. An α level of less than 0.05 was considered significant.

Results

A total of 32 subjects initially entered the study, but two of them withdrew from the study. As this was a cross-over study, statistical analysis was performed on 30 subjects. Demographic and drug-related variables are summarized in Table 1.

Baseline variables of age, duration of meth abstinence, duration of meth dependence, and marital status had no significant correlation with tDCS effect on craving. Mean positive and negative affect (PANAS) measured at the beginning of each session was not significantly different between sham and active conditions (p=0.11 and 0.93, respectively).

Effects of tDCS on craving at rest

To assess the effect of tDCS on craving at rest in three time points, a 3 (pre-tDCS, during tDCS, post-tDCS)×2 (real *vs.* sham) mixed model was fitted. Participants' intercepts were entered into the model as random effects at level 1. A significant effect of time ($F_{1,147}$=9.53, p=0.002) and tDCS condition ($F_{1,147}$=4.50, p-value=0.0357) on craving measured by VAS was observed. Also the results showed a marginal interaction effect of time and tDCS condition. ($F_{1,147}$=3.44, p=0.0657). *Post-hoc* analysis

Table 1. Demographic and substance abuse characteristics

	Descriptive statistics
Gender (men)	30/30
Age	29.90±1.04
Education (years)	11.90±0.39
Duration of meth abstinence (d)	73.33±9.64
Duration of meth dependence (months)	58±5.75
Marital status (married)	30/12
Number of subjects with a history of opium abuse	30/19
Number of subjects with a history of heroin abuse	30/2
Number of subjects with a history of crystalline heroin abuse	30/6
Number of subjects with a history of alcohol abuse	30/17
Number of subjects with a history of hashish abuse	30/22
Number of subjects with a history of cocaine abuse	30/3
Number of subjects with a history of cigarette smoking	30/29

Note: Values are reported as mean±S.E.M.

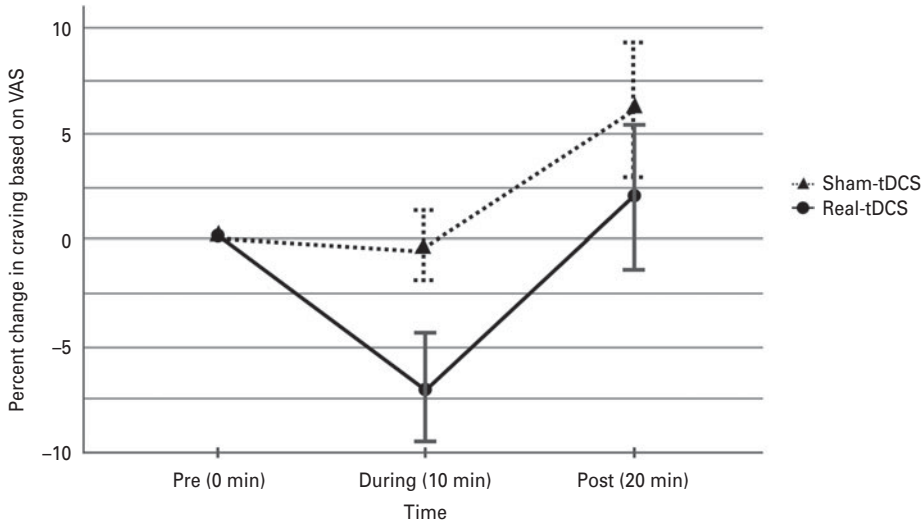

Fig. 3. Mean percent change in craving for sham and real tDCS as reported in VAS. After 10 min of stimulation, immediate craving ratings significantly decreased ($p<0.05$) only in real tDCS (solid line) condition where it stayed almost unchanged in sham condition (dotted line). Note: error bars represent mean ± S.E.M.

revealed VAS craving from pre- to during-tDCS reduced significantly more in the real condition (−6.97% (±2.535) reduction) compared to sham (−0.29% (±1.61%) reduction), ($t_{29}=2.266$, $p=0.016$). Percent change in craving for real and sham tDCS are shown in Fig. 3.

Effects of tDCS on craving during cue exposure

A comparison between mean self-reported CICT score of each participant in sham *vs.* anodal stimulation demonstrated that the ratings increased significantly in the active condition in comparison with sham stimulation ($t_{29}=-2.67$, p-value=0.012). For further investigation paired t-test was used to compare variation of induced craving among four groups of stimuli which were presented in both sham and active conditions. Results showed that the drug cues and associated cues induced highest and lowest craving, respectively. Detailed results are presented in Table 2. It appears that some stimuli induced more craving than others; therefore pictures with a median rating of over 30 were grouped as more provocative. As illustrated in Fig. 4, the more provocative cues induced significantly more craving in the active condition in comparison to the sham condition.

Side effects of tDCS

All participants tolerated tDCS without any major complications. Side effects occurring during active session were headache ($n=3$), vertigo ($n=6$), tingling ($n=25$) itching ($n=16$), dizziness ($n=10$), drowsiness ($n=21$), and nausea ($n=1$). As for sham session, side effects were headache ($n=4$), vertigo ($n=3$), tingling ($n=13$) itching ($n=12$), dizziness ($n=7$), and drowsiness ($n=16$). Results were compared between sham and active; itching ($p=0.02$) and tingling ($p=0.006$) were reported significantly more in the active condition. According to Fisher's exact test, other side effects including headache, vertigo, drowsiness, dizziness and nausea, were not significantly different between two conditions. The most common side effects were drowsiness, itching and tingling. All side effects were temporary and mostly from mild to moderate in intensity.

Table 2. Cue-Induced Craving Task (CICT) scores during sham and real conditions based on cue type

	Real-tDCS Mean (±S.E.M)	Sham-tDCS Mean (±S.E.M)	T (p-value)
Drug	50.76 (±2.94)	32.68 (±2.66)	−4.98 (<0.0001)
Instruments	18.24 (±1.94)	11.67 (±1.53)	−2.90 (0.004)
Drug usage procedure	38.57 (±1.97)	25.88 (±1.65)	−5.44 (<0.0001)
Associated cues	10.34 (±1.79)	11.09 (±2.12)	0.33 (0.75)

Discussion

The purpose of this study was to investigate the effects of anodal stimulation of right DLPFC on the immediate and online cue-induced meth craving. The results showed a clear state dependent effect of tDCS: while active tDCS in comparison with sham stimulation led to a larger decrease of self-reported craving at rest, active stimulation of the right DLPFC compared to sham stimulation induced larger craving ratings during cue exposure.

The first important finding to discuss is the decrease of craving at rest after 10 min of anodal stimulation on the right DLPFC of abstinent subjects. This change was observed before exposure to meth-related cues. This

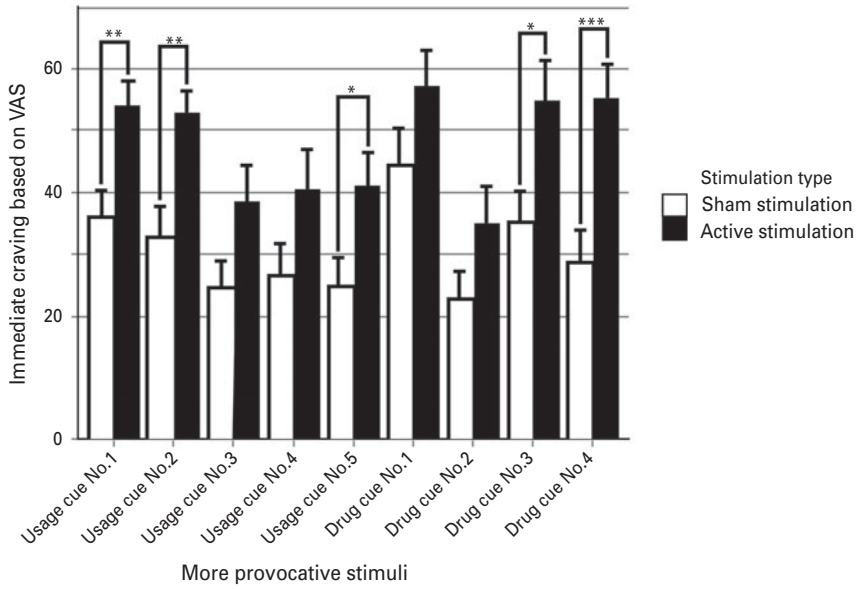

Fig. 4. Induced craving ratings for real and sham tDCS with more provocative stimuli. Columns and error bars represent based on mean±S.E.M. for each provocative image. Asterisks represent significant differences between sham and active stimulations (*$p<0.05$, **$p<0.01$, ***$p<0.001$).

result is therefore consistent with previous findings from studies using tDCS to modulate other types of craving. Fregni et al. (2008) showed that anodal stimulation of both left and right DLPFC with active, but not sham, tDCS reduced smoking craving compared to baseline. Furthermore Boggio et al. (2008) found that both anodal left/cathodal right and anodal right/cathodal left tDCS significantly decreased alcohol craving compared to sham stimulation. Finally, this effect was also found for marijuana craving. Boggio et al. (2010) observed that right anodal/left cathodal tDCS of DLPFC reduced craving for marijuana. Although effects on craving are similar across these studies, mechanisms may not be necessarily the same, as these studies used some variations in the assessments and parameters of stimulation. In spite of no direct measurement of neurophysiological parameters such as cortical excitability, these tDCS studies had targeted the DLPFC area as a common location for stimulation. It is well published that the DLPFC is critically involved in processing of drug craving (Garavan, 2000; George et al., 2001; Myrick et al., 2004; McBride et al., 2006; Brody et al., 2007). Furthermore, drug-dependent individuals exhibit lower resting and metabolic activity in the prefrontal cortex (Botelho et al., 2006; Jiang et al., 2011; Li et al., 2013b). The DLPFC integrates cognitive and motivationally relevant information about decision making, reward, motivation, and internal state and uses this information to regulate drug seeking and drug avoiding behaviours (Goldstein and Volkow, 2002; Bechara, 2005; McBride et al., 2006). According to these findings, and considering mechanisms of anodal tDCS in facilitating spontaneous neuronal activity and reinforcing local plasticity, we conjecture that anodal stimulation enhances DLPFC activity, which may inhibit drug seeking behaviour.

The second important finding of our study was the small increase in craving ratings during cue exposure under anodal stimulation compared to sham. To date, few studies have investigated effects of online tDCS on induced craving. In fact, our results are inconsistent with the previous study conducted by Goldman et al. (2011) which showed that active prefrontal tDCS acutely and significantly decreased food craving ratings for sweet foods and carbohydrates more than sham tDCS. The increased cue-induced craving observed in our study could be due to an increase in the effective processing of drug cue saliency through enhancement of sustained attention under anodal stimulation of DLPFC. Nelson et al. (2014) indicated the enhancement of sustained attention during tDCS of the prefrontal cortex. Here, one provocative speculation is that enhancing the processing of a drug-related cue without the reward associated with the drug may in fact decrease the conditioning effect of the drug and result in a late decrease in relapse. Such a hypothesis needs to be tested in future studies.

Although we have shown that 10 min of anodal tDCS stimulation on the right DLPFC can acutely reduce the immediate meth craving, the results of this study do not imply necessarily that this type of stimulation can lead to clinical applications for meth abstinence. It should be noted that this reduced craving might be transient. Although it is possible that repeated stimulation could enhance and prolong the effect of tDCS on clinical applications, as shown previously (Boggio et al., 2009), this still needs to be tested. As there is no clinically approved pharmacologic intervention to reduce meth craving and

abstinence, further clinical trials with daily repeated tDCS sessions should be explored. Furthermore, our study was focused on abstinent and treatment-seeking patients, who have different patterns of brain activity from active drug users who do not seek treatment. Therefore single session tDCS studies could target non-treatment seekers, gender effects and other cognitive processing involved in continued drug use, including lack of insight, attentional bias towards drug cues and impaired motor control or even craving self-reports with other possible electrode montages over PFC.

Our findings showed that active prefrontal tDCS reduces craving at rest in the abstinent meth users while it may increase craving during cue exposure. This may reflect the role of the prefrontal cortex in both cue saliency evaluation and top-down craving modulation. These results offer preliminary promising data to support further studies investigating tDCS as a clinical application for craving control among meth-dependent subjects.

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Statement of Interest

None.

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