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Repeated stimulation of the dorsolateral-prefrontal cortex improves executive dysfunctions and craving in drug addiction: A randomized, double-blind, parallel-group study

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ABSTRACT

Background: According to the neurocognitive model of addiction, the development and maintenance of drug addiction is associated with cognitive control deficits, as well as decreased activity of prefrontal regions, especially the dorsolateral prefrontal cortex (DLPFC). This study investigated how improving executive functions (EFs) impacts methamphetamine-use disorder, which has been less explored compared to craving, but might be a central aspect for the therapeutic efficacy of DLPFC stimulation in drug addiction.

Methods: We assessed the efficacy of 10 repeated sessions of transcranial direct current stimulation (tDCS) over the DLPFC on executive dysfunctions in methamphetamine-use disorder, and its association with craving alterations. 39 of 50 initially recruited individuals with methamphetamine-use disorder who were in the abstinent-course treatment were randomly assigned to “active” and “sham” stimulation groups in a randomized, double-blind parallel-group study. They received active (2 mA, 20 min) or sham tDCS for 10 sessions over 5 weeks. Performance on major EF tasks (e.g., working memory, inhibitory control, cognitive flexibility, and risk-taking behaviour) and craving were measured before, immediately after, and 1 month following the intervention. Participants reported abstinence from drug consumption throughout the experiment, verified by regular urine tests during the course of the study up to the follow-up measurement.

Results: The group which received active DLPFC tDCS showed significantly improved task performance across all EFs immediately after and 1 month following the intervention, when compared to both pre-stimulation baseline and individuals who received sham tDCS. Similarly, a significant reduction in craving was observed immediately after and 1 month following the intervention in the active, but not sham stimulation group. A significant correlation between cognitive control improvement and craving reduction was found as well.

Abbreviations: SUD, substance use disorders; DLPFC, dorsolateral prefrontal cortex; EFs, executive functions; WM, working memory; tDCS, transcranial direct current stimulation.

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Conclusions: Improvement of cognitive control functions is closely associated with reduced craving. Repeated DLPFC stimulation in order to improve executive control could be a promising approach for therapeutic interventions in drug addiction. However, the observed findings require further confirmation by studies that measure relapse/consumption of the respective substances over longer follow-up measurements.

Introduction

With a lifetime prevalence of 0.9% worldwide and 3.5% in US-American adults [1], substance use disorder (SUD, excluding alcohol) is a major public health concern. The high rate of relapse and the need for treatments with greater efficacy require novel intervention approaches. Recent findings from the neurobiology and pathophysiology of drug addiction suggest that SUDs are associated with frontal cortex abnormalities and executive dysfunctions [2–4]. Cognitive processes such as reward processing, emotion dysregulation, and executive functions (EFs) (e.g. attention, response inhibition, risk-taking, cognitive flexibility, and working memory (WM)), are major cognitive deficits underlying drug addiction. These cognitive deficits might be more closely related to neurophysiological pathologies relevant for drug addiction, compared to currently accepted symptoms of addiction [5,6]. At the neurobiological level, interconnected cortical and subcortical circuitries (including the amygdala-striatum, prefrontal cortex, and insula) are involved in these cognitive deficits [3,7]. Moreover, the dopaminergic circuitry, which has a prominent influence on frontal brain physiology, is tightly involved in alterations of motivation, attention, habits and executive control in drug addiction [8].

The dual-process model of addiction states that addiction is the result of a dysfunctional balance between “automatic” or “impulsive” and “controlled” or “reflective” systems [9]. The automatic system involves the dopaminergic circuitry and the mesolimbic and nigrostriatal pathways [10]. It represents the automatic/implicit pursuit of pleasure which is normally reflected by impulsive behaviour, biased attention to drug cues and craving in drug addicts. The controlled system, on the other hand, involves cortical structures and higher-order cognitive functions (e.g., WM, response inhibition) that provide goal-directed actions and self-regulation processes over impulsive behaviours. The latter system is suggested to be compromised in drug addiction [7]. Modulating cortical activity in the involved brain regions by non-invasive brain stimulation may be useful in order to directly target and alter involved neurocircuits in SUD [11], and may further allow deriving causal relations between cortical brain regions and respective behaviours [12]. Neuromodulation studies that monitor treatment-relevant variables might therefore be useful for developing innovative treatments for addiction.

Among the available neuromodulatory techniques, transcranial direct current stimulation (tDCS) is increasingly used for the treatment of SUD [11,13]. TDCS is a non-invasive, painless, and well-tolerated brain stimulation technique that applies a weak direct current (typically 0.5 mA–2 mA) through surface electrodes on the scalp. It can induce acute and neuroplastic alterations of cortical excitability via subthreshold neuronal depolarization and induction of LTP-like plasticity (anodal stimulation), or hyperpolarization and LTD-like plasticity (cathodal stimulation) [14,15]. TDCS is increasingly used for studying physiological and neurocognitive functions in the healthy brain, and for clinical applications (for a detailed review see Refs. [16,17]). Importantly, it has also been used in numerous studies for exploring the physiological foundations of cognitive functions [18,19], including EFs in both healthy individuals [20–22] and patients with executive dysfunctions related to frontal abnormalities [23–26]. With respect to overall efficacy and directionality of effects, these tDCS studies have resulted in heterogeneous outcomes, with reasons that are not yet completely understood [27–29].

Previous tDCS studies focusing on methamphetamine use disorder [30,31] and other drug addictions [12,13] have targeted the dorsolateral prefrontal cortex (DLPFC) as the primary target for stimulation. The rationale for targeting this site considers that (1) DLPFC is involved in spontaneous and cue-elicited craving, (2) DLPFC is involved in EFs related to addictive behaviors (i.e., decision making, response inhibition, risk-taking, attentional bias), and (3) DLPFC stimulation may affect the reward circuitry spanning into the deeper layers of the cortex via efferents to the nucleus accumbens (NA) and ventral tegmental area (VTA) [11,32]. Specifically, stimulation of the DLPFC (both left and right) seems to be beneficial for the cognitive effects of neurostimulation in drug addiction [13,33,34]. These findings led to the hypothesis that abnormalities of the PFC are highly relevant for drug addiction and tDCS could be a feasible method to modulate PFC activity and thereby influence executive dysfunctions in methamphetamine-use disorder.

In methamphetamine-use disorder, which is the focus of the present study, recent evidence from neuroimaging studies have shown that tDCS applied bilaterally over the DLPFC increases functional connectivity of the resting-state executive control network [35]. Other tDCS studies in methamphetamine-use disorder showed that anodal right, left or bilateral DLPFC stimulation reduced drug cue-induced craving and attentional bias [30,31,35], and a case study reported improved effects of multiple tDCS sessions on both craving and cognitive impairment [36]. These studies, except for the latter case report, only examined the impact of tDCS on craving, but not other clinical parameters, and also did not systematically explore the effects of repeated tDCS over the DLPFC on executive dysfunctions in methamphetamine-use disorder. In other SUDs (e.g. cocaine, tobacco), recent studies have examined the effects of repeated tDCS sessions over the DLPFC [37–39]. All of these studies, except for Klauss et al. [37], observed increased effects of extended stimulation on reduced craving in patients, although none of them have examined executive dysfunctions.

In sum, a variety of neuroimaging studies as well as pathophysiological and cognitive models of addiction suggest that addictive behaviours may be caused by deficient cognitive control and EFs [40], and thus may qualify as important functional readouts for therapeutic interventions [4]. However, the number of studies investigating the effect of neuromodulation on the cognitive processes involved in addiction remains limited [11], precluding any firm conclusion about cognition-improving effects and clinical efficacy [11,41]. The fact that most other studies on drug addictions have targeted craving as the main outcome parameter [37,38] or applied short durations of DLPFC stimulation, which may not be clinically effective [42,43], makes it furthermore difficult to come to definite assumptions. In order to *evaluate* the potential of

tDCS in addiction, including its effects on cognitive deficits, trials with longer courses of stimulation, as suggested by recent findings [42], inclusion of objective neurophysiological and cognitive measures, and monitoring of long-term outcomes would be helpful [11]. In the present study, we therefore investigated: (1) the effects of repeated tDCS over the DLPFC on major executive dysfunctions that are involved in addictive behaviours, and (2) whether the expected improvement in cognitive control is associated with reduced craving in individuals with methamphetamine-use disorder. To our knowledge, this is the first tDCS study in methamphetamine-use disorder with a randomized parallel-group design which explores the effects of the intervention on improvement of executive dysfunctions.

Materials and methods

Participants

Fifty male individuals with methamphetamine-use disorder (18–50 years) were initially recruited from the Azadi Rehabilitation Center for Addiction in Ardabil, Iran (mean age = 34.83, $SD = 9.16$) and were randomly assigned to the active and sham stimulation groups by the block randomization method. All patients were methamphetamine-abstinent during the study for up to the 1-month follow-up, and abstinence from drug consumption was regularly checked by urine tests. Eleven subjects from both groups could not complete the whole treatment, and thus our final analysis was conducted on 39 participants (active tDCS $N = 19$, sham tDCS $N = 20$). We conducted an a-priori sample size calculation based on a small critical effect size, which is the minimum effect size we expected to detect ($f = 0.25$, $\alpha = 0.05$, power = 0.95, $N = 44$) for our study design (mixed-model ANOVA). The inclusion criteria were: (1) diagnosis of SUD according to the DSM-V diagnostic criteria including at least 1-year history of methamphetamine use (before the experiment), (2) 18–50 years old, (3) absence of other ongoing substance consumption except for tobacco smoking, as verified by a urine drug screen, (4) no previous history of neurological diseases, brain surgery, epilepsy, seizures, brain damage, head injury or metal brain implants, and (5) absence of other psychiatric disorders except for SUD, as confirmed by a structured clinical interview conducted by a professional licensed psychiatrist. All participants were native speakers and had normal or corrected-to-normal vision. The study was performed according to the Declaration of Helsinki and approved by the Ardabil University of Medical Science Ethics Committee. Participants gave their written informed consent before participation and were free to withdraw from the study at any stage. See Table 1 for demographics.

Drug consumption

Drug consumption and potential relapse were controlled by urine tests during the whole experiment up to the follow-up measurement. Abstinence was verified by the results of the respective urine tests showing no hint for drug consumption. All participants reported complete abstinence.

Tasks and measures

Executive function measures

We measured cognitive control functions with four major EF tasks. The N-back and Go/No-Go tasks were used for measuring WM and response inhibition respectively, with higher accuracy rate and shorter response times indicative of better performance. Additionally, the Wisconsin Card Sorting Task (WCST), which is the gold standard measure of executive functioning [44] and measures cognitive flexibility, planning and task-switching abilities [45,46], and the Balloon Analogue Risk Task (BART) which measures risk-taking behavior, were used. For the WSCT, more completed categories and less perseverative errors indicate better planning and higher cognitive flexibility. In the BART, lower scores of the "adjusted value", which is the average number of pumps on balloons that did not explode, and lower numbers of "pumps" per trial indicate decreased risk-taking behavior and impulsivity. These values show a more adaptive (non-punitive) form of risk-taking behavior [47]. All tasks were computerized and presented in a counterbalanced order. Full details of the task procedures and outcome variables are presented in the supplementary information (see Fig. 1).

Craving questionnaire

We measured craving with the Desires for Drug Questionnaire (DDQ) [48] before, immediately after, and 1-month following the treatment. The DDQ is a 14-item questionnaire originally designed for use in heroin addicts. We used the version adapted for methamphetamine use. It measures instant craving and consists of three subscales: "desire and intention" to use drugs, "negative reinforcement" (the relief of negative states), and "control" over drug use. The three subscales of the DDQ have good reliability, concurrent validity and a Cronbach's alpha of 0.85 [48]. Cronbach's alpha in our sample was 0.88 for the entire measure, 0.83 for the "desire" subscale, 0.78 for the "negative reinforcement" subscale, and 0.77 for the "control" subscale .

tDCS

Direct currents of 2 mA generated by an electrical stimulator (ActivaDose II Iontophoresis Delivery Unit, USA) were applied through a pair of saline-soaked sponge electrodes (7 × 5 cm) for 20 min with 15 s ramp up and 15 s ramp down. In both, active and sham conditions, anodal and cathodal electrodes were placed over the left and right DLPFC, respectively (F3–F4), according to the 10–20 EEG International System. The minimum distance between the edges of both electrodes was 6 cm to reduce the amount of shunting of current through the scalp [15]. For sham stimulation, electrical current was ramped up and down for 30 s and 15 s of short stimulation follwing the ramp-up to generate the same sensation as in the active condition and then turned off without the participants' knowledge [49]. This method of sham stimulation has been shown to be reliable [50]. The experimenter who applied tDCS was blind to the study hypotheses but not to the tDCS condition (active vs sham). Blinding efficacy (e.g. by asking the participants to guess the respective stimulation condition) was not explored. A side-effect survey was done after each tDCS session (Fig. 2).

Modeling of current flow

A 3D model of the current flow in the head was created to determine induced electrical fields in the brain for the above-mentioned tDCS protocol (2.0 mA, anodal F3 - cathodal F4). Details of the modeling procedure are summarized in Fig. 4 and supplementary information.

Procedure

All participants were drug-abstinent and stayed in the rehabilitation center during the whole course of the experiment up to the one-month follow-up. Prior to the experiment, participants completed a brief questionnaire to evaluate their suitability for brain stimulation. Both groups of participants received 10 sessions of stimulation (2 sessions weekly, 5 weeks in total) with 72 h intervals between sessions. All participants completed the EF tasks

Table 1
Demographic data.

		anodal F3 - cathodal F4 tDCS	sham tDCS	p-value*
Sample size (*n*)		19	20	
Age – Mean (SD)		34.31 (9.62)	35.35 (8.71)	0.508
Sex – Male (female)		19 (0)	20 (0)	
Marital Status – Single (married)		9 (10)	7 (13)	0.433
Length of methamphetamine use		4.73	4.35	0.261
Frequency of use per week – mean (SD)		6.21 (2.34)	5.45 (2.30)	0.694
Education	Diploma	11	10	
	BA	7	9	0.873
	MA or higher	1	1	

Note: tDCS = transcranial Direct Current Stimulation; M = Mean; SD = Standard Deviation; F3 = left DLPFC; F4 = right DLPFC; BA = Bachelor of Arts; MA = Master of Arts; * = between group differences in demographic variables were explored by Chi-square or Fisher's exact tests for categorical variables and t-tests for continuous variables.

and the DDQ before the intervention (pre-intervention), right after the end of the intervention (post-intervention) and one month following the last stimulation session (follow-up) (Fig. 2). Before each measurement, participants completed the Positive and Negative Affect Scale (PANAS) [51] in order to evaluate the stability of the affective state before measurements. Stimuli presentation in all computerized tasks was controlled by a laptop with a 15.6" screen [52], at a viewing distance of approximately 50 cm. Participants were instructed about each task before the beginning of the experiment and a detailed written instruction appeared on the screen before each task started.

Study design and statistical analysis

Our study had a double-blind, randomized parallel-group design to prevent blinding failure and carry-over effects [13]. Participants were blind to the study hypothesis and stimulation conditions. The experimenters who conducted the outcome measures were blinded to the tDCS conditions. To guarantee blinding of these investigators, tDCS was applied by other investigators [50]. Data analyses were conducted with the statistical package SPSS, version 24.0 (IBM, SPSS, Inc., Chicago, IL). The normality and homogeneity of variance of data collected at each time point were confirmed by

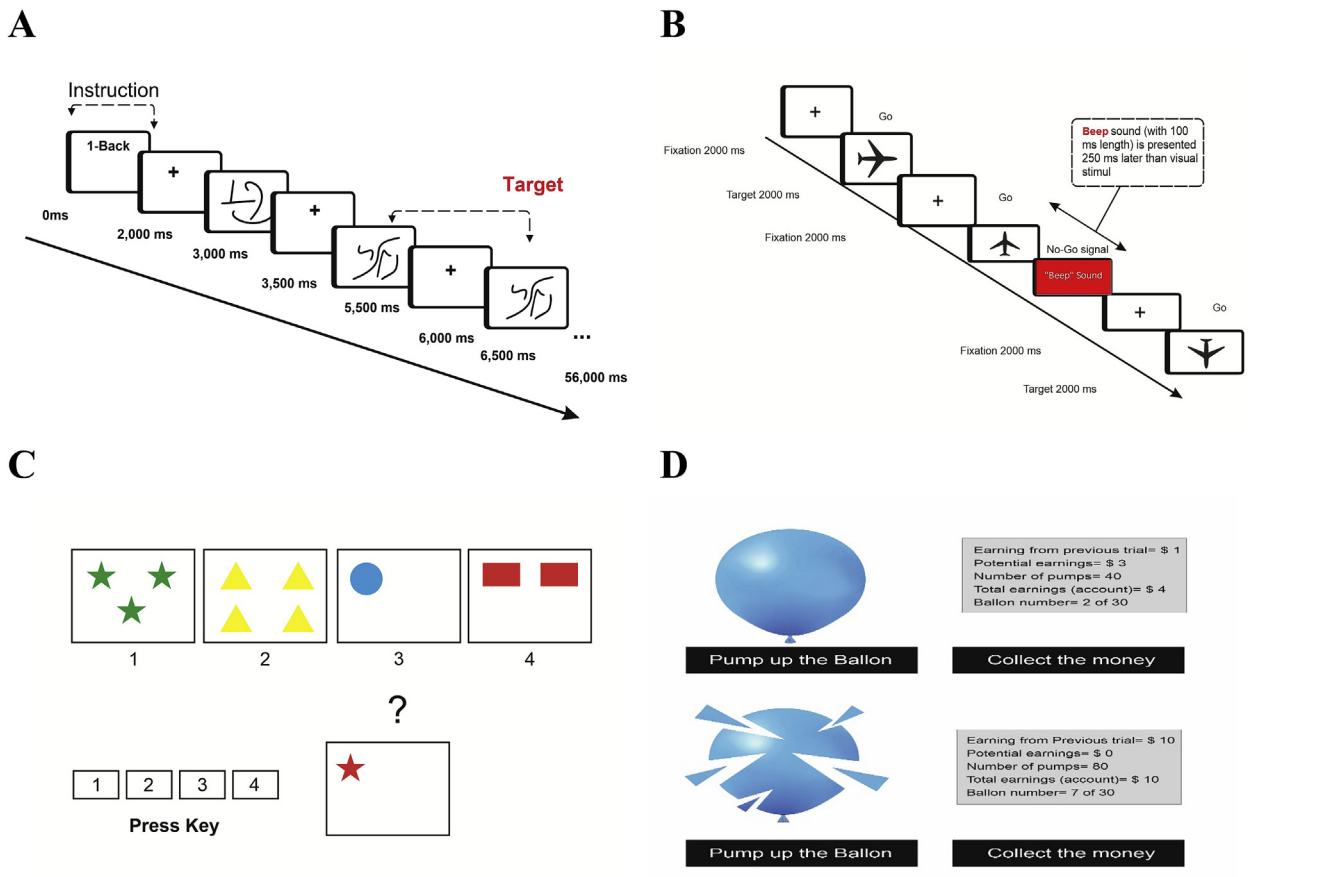

Fig. 1. Characteristics of the executive function tasks: The 1-back (A), Go/No-Go (B), WCST (C) and BART (D) tasks. More accurate response and shorter response time (RT) (in the n-back), more accurate response to Go and No-Go trials and shorter RT (in the Go/No-Go task), more completed categories and less perseverative errors (in the WCST) and smaller adjusted value and lower number of "pumps" per trial (in the BART) are indicative of better performance. *Note*: Money value was presented in local currency in the BART. All computerized tasks were presented on a 15.6″ screen in a counterbalanced order.

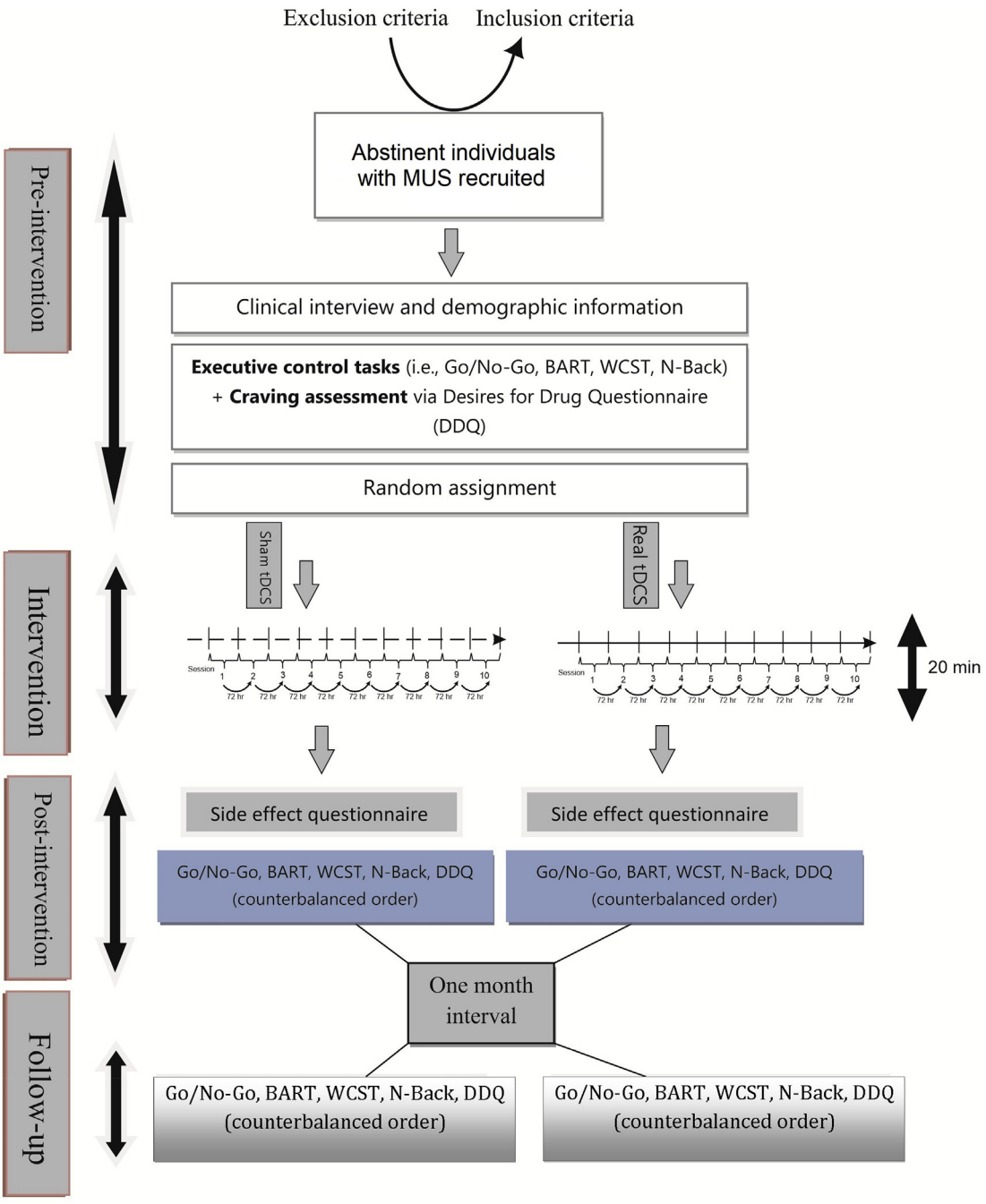

Fig. 2. Experimental procedure. The experiment was conducted in a randomized, double-blind, parallel-group design. The order of the tasks was counterbalanced across subjects.

Shapiro-Wilk and Levin tests, respectively. A 2 × 3 mixed model repeated measures ANOVA was conducted for the respective dependent variables (N-back task: accuracy and RT; Go/No-Go task: accuracy and RT; WSCT: perseverative errors and completed categories; BART: adjusted value and maximum number of pumps) with "group" (active vs sham) as the between-subject and time (pre-intervention, post-intervention, follow-up) as the within-subject factors. Mauchly's test was used to evaluate the sphericity of the data before performing the repeated measures ANOVA. In case that the assumption of sphericity was violated, the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity. Post *hoc* analyses were calculated using Bonferroni-corrected Student's t-tests. The correlation between EF task performance and craving was calculated via Pearson's correlation. A significance level of $p < 0.05$ was used for all statistical comparisons.

Results

Data overview

All participants tolerated the stimulation well and no adverse effects were reported during and after stimulation (reported side effects are summarized in the supplementary results). No

significant difference was found between the group ratings of tDCS side effects (see supplementary results, Table S1). The data overview of the dependent variables before, after and 1 month following the intervention is presented in Table 2 and Fig. 3. No significant group differences were seen for the baseline measurements (Table 1).

Attrition rate

Six participants from the active tDCS and five participants from sham stimulation group could not complete the experiment. The main reasons for attrition were: tolerability of tDCS intervention ($N = 1$, active tDCS), not completing intervention sessions ($N = 2$, active tDCS; $N = 2$, sham tDCS), and temporary or permanent leave from the rehabilitation center ($N = 3$, active tDCS; $N = 3$, sham tDCS). Clinical and neuropsychological characteristics of the excluded participants did not significantly differ from those who completed the experiment (See Supplementary Table S3).

The effect of tDCS on executive functions

In the N-back task, a significant interaction of group × time on both, accuracy ($F_{1.58} = 21.74$, $p < 0.001$, $\eta p2 = 0.37$) and RT ($F_{1.96} = 14.35$, $p < 0.001$, $\eta p2 = 0.28$) were observed, indicating a group-dependent improving effect of tDCS on WM functioning. The Bonferroni-corrected post *hoc* analysis showed a significant increase and decrease of N-back accuracy and RT, respectively, between pre-intervention and post-intervention measurements ($t = -5.45$, $p < 0.001$; $t = 7.48$, $p < 0.001$), and pre-intervention vs follow-up measurements ($t = -5.16$, $p < 0.001$; $t = 7.41$, $p < 0.001$) in the active stimulation, but not sham stimulation group. Between-group comparisons of N-back outcome measures for each time point showed no significant difference between groups in the pre-intervention measurement ($t_{accuracy} = -0.84$, $p = 0.933$; $t_{RT} = 0.53$, $p = 0.958$), but significant between-group differences in the post-intervention ($t_{accuracy} = 3.90$, $p < 0.001$; $t_{RT} = -4.05$, $p < 0.001$), and follow-up intervention ($t_{accuracy} = 4.58$, $p < 0.001$; $t_{RT} = -3.09$, $p < 0.001$) measurements. This clearly indicates that

Table 2
Means and SDs of executive functions task performance and craving before, after and 1 month following bilateral tDCS interventions.

Task	Outcome measures	Time	Group M (SD)	
			anodal F3 - cathodal F4 tDCS	sham tDCS
			M (SD)	**M (SD)**
N-back	Accuracy	Pre-intervention	72.21(8.55)	72.50(12.47)
		Post-intervention	84.15(8.05)	71.50(11.73)
		Follow-up	84.31(7.28)	71.20(10.25)
	Response time*	Pre-intervention	157.15(17.13)	156.80(24.15)
		Post-intervention	119.26(24.80)	153.20(27.28)
		Follow-up	120.94(23.00)	148.40(31.54)
Go/No-Go	Accuracy Go	Pre-intervention	83.42(20.37)	82.90(10.11)
		Post-intervention	97.42(2.34)	84.20(14.05)
		Follow-up	97.10(2.25)	82.95(14.13)
	Accuracy No-Go	Pre-intervention	71.00(11.13)	71.75(8.94)
		Post-intervention	87.10(3.71)	70.40(9.85)
		Follow-up	81.57(6.48)	71.55(6.44)
	Response time**	Pre-intervention	0.93(0.11)	0.92(0.11)
		Post-intervention	0.80(0.09)	0.91(0.11)
		Follow-up	0.82(0.08)	0.92(0.10)
WCST	Perseverative errors	Pre-intervention	17.89(4.84)	16.35(4.76)
		Post-intervention	11.00(1.91)	16.15(2.39)
		Follow-up	12.57(1.98)	15.50(1.43)
	Completed categories	Pre-intervention	1.89(0.87)	1.90(0.96)
		Post-intervention	3.73(0.56)	2.20(1.100)
		Follow-up	3.78(0.91)	2.50(1.27)
BART	Adjusted value	Pre-intervention	33.47(11.95)	34.90(13.98)
		Post-intervention	25.05(6.44)	32.70(11.98)
		Follow-up	25.36(6.02)	34.00(11.49)
	Max number of pumps	Pre-intervention	63.63(13.43)	62.35(8.70)
		Post-intervention	38.84(10.24)	60.15(10.28)
		Follow-up	42.21(10.79)	55.95(11.48)
Craving	DDQ (total score)	Pre-intervention	55.36 (12.69)	55.25 (8.71)
		Post-intervention	44.36 (10.62)	53.75 (9.27)
		Follow-up	43.68 (9.39)	54.45 (8.98)
	DDQ (desire and intention)	Pre-intervention	29.84 (7.12)	28.95(7.40)
		Post-intervention	22.63 (4.62)	29.45(7.09)
		Follow-up	23.63(4.71)	30.15(7.02)
	DDQ (negative reinforcement)	Pre-intervention	17.21 (3.83)	17.45(3.01)
		Post-intervention	15.15 (3.65)	16.40 (3.47)
		Follow-up	14.47 (3.38)	15.90 (3.56)
	DDQ (control deficit)	Pre-intervention	8.42 (4.62)	8.80 (3.86)
		Post-intervention	6.68 (4.60)	7.20 (3.99)
		Follow-up	5.82 (3.76)	8.00 (2.86)

Note: tDCS = transcranial Direct Current Stimulation; M = Mean; SD = Standard Deviation; F3 = left DLPFC; F4 = right DLPFC WCST = Wisconsin Card Sorting Test; BART = Balloon Analogue Risk Task; DDQ = Desires for Drug Questionnaire; * = Values marked by (*) are given in seconds; ** = Values marked by (*) are given in milliseconds.

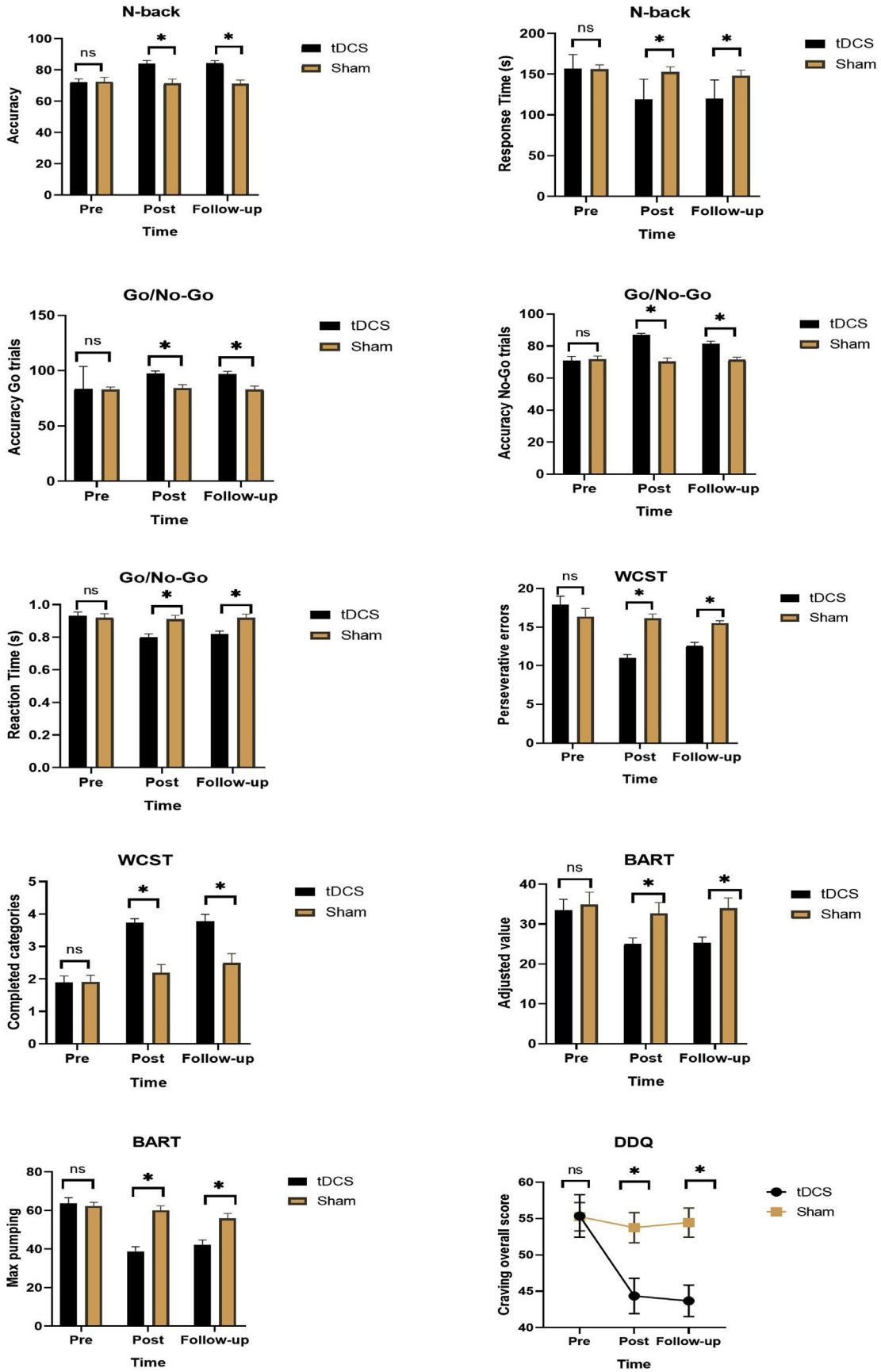

Fig. 3. EF task performance (N-back, WCST, BART and Go/No-Go) before, after intervention and 1-month following the intervention. *Note*: tDCS = active tDCS group; sham = sham tDCS group; tDCS = transcranial Direct Current Stimulation; WCST = Wisconsin Card Sorting Test; BART = Balloon Analogue Risk; DDQ = Desires for Drug Questionnaire; N-back and Go/No-Go response times are given in milliseconds; significant pair-wise comparisons are marked by (*) at $p \leq 0.05$. All error bars represent s.e.m.

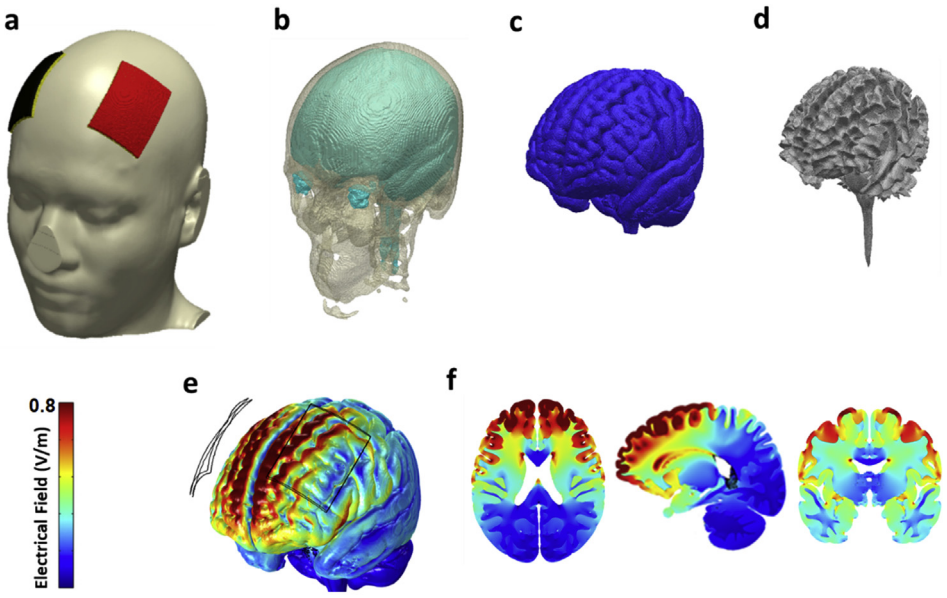

Fig 4. 3D model of the "ICBM-NY" head, including head tissue compartments (a, b, c, d). Depicted are electrical fields within cerebral tissue (e, f) for simulation of 2.0 mA with an F3 anodal-F4 cathodal montage. The anatomical head "ICBM-NY" [78] segmented into six tissue types (gray matter (GM), white matter (WM), CSF, skull, scalp, and air cavities (a, b, c, d)) via the SPM8 software package (Welcome Trust Center for Neuroimaging, London, UK). A custom MATLAB script was used to correct for segmentation errors made by SPM [79]. Then, a 3D model of the segmented images, added by the tDCS electrodes (35 cm^2) placed over F3 and F4 (based on the international 10–20 system for the electroencephalography electrode placement), was developed via the Simpleware software package version 5 (Synopsys, Mountain View, USA). Finally, the current flow distribution inside the head was calculated based on the finite element method with the COMSOL Multiphysics software package version 5.2 (COMSOL Inc., MA, USA). The conductivity values used for each tissue type are as follows (in S/m): GM: 0.276; WM: 0.126; CSF: 1.65; skull: 0.01; scalp: 0.465; air: 2.5 × 10−14; saline-soaked sponge: 1.5; electrode rubber: 29 [80,81].

improved WM performance was specific for tDCS effects. Moreover, significant main effects of group and time were found for both, N-back accuracy and RT (see Table 3). Similarly, in the Go/No-Go test, we observed a significant interaction of group × time on accuracy no-go ($F_{1.69} = 12.44$, $p < 0.001$, $\eta p2 = 0.25$), accuracy go ($F_{1.94} = 3.43$, $p < 0.037$, $\eta p2 = 0.08$), and RT ($F_{1.38} = 43.81$, $p < 0.001$, $\eta p2 = 0.54$). Post *hoc* t-tests showed increased accuracy of the No-Go and Go trials between the pre-intervention vs post-intervention (t = -5.72, $p < 0.001$; $t = -3.06$, $p < 0.007$) and pre-intervention vs follow-up measurements ($t = -3.75$, $p < 0.004$; $t = -2.86$, $p < 0.010$), and a significantly shorter RT ($t = 5.27$, $p < 0.001$; $t = 4.70$, $p < 0.001$) in the active, but not sham stimulation group. The between-group comparisons showed no significant difference in the pre-intervention measurement ($t_{Go} = -0.84$, $p = 0.933$; $t_{No\text{-}Go} = -0.23$, $p = 0.817$; $t_{RT} = 0.34$, $p = 0.733$), but significant between-group differences in the post-intervention ($t_{Go} = 4.04$, $p < 0.001$; $t_{No\text{-}Go} = 6.93$, $p < 0.001$; $t_{RT} = -3.23$, $p = 0.003$) and follow-up intervention ($t_{Go} = 4.31$, $p < 0.001$; $t_{No\text{-}Go} = 4.84$, $p < 0.001$; $t_{RT} = -3.39$, $p = 0.002$) measurements. Significant main effects of group and time were found as well (Table 3).

In the WCST, the ANOVA results showed a significant interaction of group × time on completed categories ($F_{1.74} = 7.79$, $p < 0.001$, $\eta p2 = 0.17$), and perseverative errors ($F_{1.36} = 10.98$, $p < 0.001$, $\eta p2 = 0.23$). These parameters were significantly improved in the post-intervention ($t = 6.25$, $p < 0.001$; $t = -7.91$ $p < 0.001$) and follow-up measurements ($t = 4.11$, $p < 0.001$; $t = -6.42$, $p < 0.003$) compared to the pre-intervention measurement in the active stimulation group. Between-group comparisons showed no significant differences in the pre-intervention measurement ($t = -0.02$, $p = 0.986$; $t = 1.01$, $p = 0.332$), but significant between-group differences in the post-intervention ($t = 5.85$, $p < 0.001$; $t = -7.40$, $p < 0.001$), and follow-up intervention ($t = 3.60$, $p < 0.001$; $t = -5.29$, $p < 0.001$) measurements for completed categories and perseverative errors, respectively. The main effects of group and time were also significant (Table 3). With regard to risky decision-making and impulsivity measured by the BART, no significant interaction of group × time for the *adjusted value* ($F_{1.47} = 2.83$, $p = 0.08$, $\eta p2 = 0.07$), but a significant effect of time and a marginally significant effect of group were observed (Table 3). Post *hoc* comparisons further showed a significant decrease of adjusted values at post-intervention ($t = 2.51$, $p < 0.022$) and follow-up ($t = 2.75$, $p < 0.012$) measurements in the active, but not sham stimulation group. Moreover, the interaction of group × time on maximum number of pumps ($F_{1.71} = 17.35$, $p < 0.001$, $\eta p2 = 0.32$), and the main effects of group and time were significant (Table 3). The respective post *hoc* t-tests showed a significant decrease of number of pumps in the post-intervention ($t = 7.96$, $p < 0.001$) and follow-up ($t = 5.76$, $p < 0.001$) measurements compared to the pre-intervention measurement in the active stimulation group. No significant between-group differences of the adjusted value ($t = -0.34$, $p = 0.735$) and maximum number of pumps ($t = -0.35$, $p = 0.728$) were found in the pre-intervention measurement, but significant differences were observed in the post-intervention ($t = -2.46$, $p < 0.019$; $t = -6.48$, $p < 0.001$) and follow-up intervention ($t = -2.49$, $p < 0.018$; $t = -3.85$, $p < 0.001$) measurements, indicating tDCS-specific effects on risk-taking behavior.

Craving

The ANOVA results showed a significant interaction of group × time on the total score of craving ($F_{1.77} = 16.35$, $p < 0.001$, $\eta p2 = 0.31$). Post *hoc* t-tests revealed reduced craving after the intervention ($t = 8.92$, $p < 0.001$; $M = 44.36$, $SD = 10.62$) and in the follow-up measurement ($t = 6.93$, $p < 0.001$; $M = 43.68$, $SD = 9.39$) compared to the pre-intervention measurement in the active ($M = 55.36$, $SD = 12.69$), but not sham stimulation condition. As for the cognitive effects, we found no significant between-group differences of craving ratings in the pre-intervention measurement ($t = 0.03$, $p = 0.973$), but significant between-group differences in

Table 3
Results of the Mixed model ANOVAs for effects of group (active vs sham tDCS) and time (pre-intervention, post-intervention, follow-up) on executive functions and craving in patients.

Task	Outcome measures	Source	df	Mean square	F	p-value	partial eta2
N-back	Accuracy	Time	1.58	384.33	14.80	**0.001**	0.28
		Group	1	875.46	8.59	**0.006**	0.18
		Time*group	1.58	711.39	21.74	**0.001**	0.37
	Response Time*	Time	1.96	6043.65	26.81	**0.001**	0.42
		Group	1	3767.97	8.39	**0.006**	0.18
		Time*group	1.96	3234.22	14.35	**0.001**	0.28
Go/No-Go	Accuracy Go	Time	1.94	690.44	4.19	**0.019**	0.10
		Group	1	905.62	18.78	**0.001**	0.33
		Time*group	1.94	565.21	3.43	**0.037**	0.08
	Accuracy No-Go	Time	1.69	661.74	9.21	**0.001**	0.19
		Group	1	566.03	28.01	**0.001**	0.43
		Time*group	1.69	893.83	12.44	**0.001**	0.25
	Response Time**	Time	1.38	0.080	53.72	**0.001**	0.59
		Group	1	0.064	49.25	**0.001**	0.57
		Time*group	1.38	0.066	43.81	**0.001**	0.54
WCST	Perseverative errors	Time	1.36	212.37	14.05	**0.001**	0.27
		Group	1	97.16	13.70	**0.001**	0.27
		Time*group	1.36	165.99	10.98	**0.001**	0.23
	Completed Categories	Time	1.74	17.76	20.70	**0.001**	0.35
		Group	1	8.16	24.43	**0.001**	0.39
		Time*group	1.74	6.68	7.79	**0.001**	0.17
BART	Adjusted value	Time	1.47	431.46	6.08	**0.008**	0.14
		Group	1	252.92	4.16	0.048	0.10
		Time*group	1.47	201.08	2.83	0.082	0.07
	Max pumping	Time	1.71	2854.85	32.87	**0.001**	0.47
		Group	1	1099.23	17.82	**0.008**	0.32
		Time*group	1.71	1506.49	17.35	**0.001**	0.32
Craving	DDQ (total score)	Time	1.77	560.10	30.64	**0.001**	0.45
		Group	1	456.89	18.86	**0.001**	0.33
		Time*group	1.77	337.34	16.35	**0.001**	0.31
	DDQ (desire and intention)	Time	1.64	144.02	30.16	**0.001**	0.44
		Group	1	267.53	4.28	**0.045**	0.10
		Time*group	1.64	225.74	47.28	**0.001**	0.56
	DDQ (negative reinforcement)	Time	1.88	47.75	12.02	**0.001**	0.24
		Group	1	6.86	0.95	0.334	0.02
		Time*group	1.88	3.97	1.00	0.372	0.03
	DDQ (control deficit)	Time	1.95	39.774	11.27	**0.001**	0.23
		Group	1	20.316	0.84	0.365	0.02
		Time*group	1.95	12.69	3.59	**0.032**	0.089

Note: tDCS = transcranial Direct Current Stimulation; WCST = Wisconsin Card Sorting Test; BART = Balloon Analogue Risk Task; DDQ = Desires for Drug Questionnaire; * = Values marked by (*) are given in seconds; ** = Values marked by (*) are given in milliseconds. Significant results are highlighted ($p \leq 0.05$) in **bold**.

the post-intervention ($t = -2.94$, $p < 0.006$), and follow-up ($t = -3.35$, $p < 0.002$) measurements. This indicates tDCS-specific effects on craving. The main effects of time and group were also significant (Table 3). We also analyzed DDQ subscales separately and found a significant interaction of group × time only for the "desire and intention" ($F_{1.64} = 47.28$, $p < 0.001$, $\eta p2 = 0.56$) and "control" subscales ($F_{1.95} = 3.59$, $p < 0.032$, $\eta p2 = 0.09$) but not for negative reinforcement ($F_{1.88} = 1.00$, $p = 0.372$, $\eta p2 = 0.02$) (see supplementary material for detailed results). Lastly, we calculated Pearson's correlations to see if craving scores were correlated with EF task performance, and found a significant correlation between craving and most of the executive control functions, including WM accuracy ($p < 0.003$) and RT ($p < 0.008$), accuracy Go ($p < 0.043$) and accuracy No-Go ($p < 0.005$) and RT ($p < 0.001$) in the Go/No-Go task, perseverative errors ($p < 0.030$) and completed categories ($p < 0.021$) in the WCST, and maximum number of pumps ($p < 0.019$) in the BART (supplementary results, Table S2). In all of these measures, reduced craving was associated with improved cognitive performance.

Discussion

We presented results of a randomized, double-blind study that examined the efficacy of repeated bilateral tDCS over the DLPFC on EFs and craving in individuals with methamphetamine-use disorder. We found that this intervention significantly improved major cognitive control functions involved in addictive behaviour, including WM, response inhibition, cognitive control/flexibility, and risk-taking behaviour, and that these effects were also associated with significantly reduced craving. The observed effects were specific for active tDCS stimulation. Importantly, cognitive improvement and reduced craving persisted for up to at least one month following the intervention.

Our findings support the notion that impaired executive control is central to the development and maintenance of drug addiction and its symptoms [3,8,53]. Loss of control is characteristic of drug dependence, and therefore cognitive processes involved in risky and impulsive decision-making may be central to drug addiction [4]. According to the 3-stage conceptualization of drug addiction [3], the preoccupation/anticipation (craving) stage involves neuroplastic changes in the brain reward, stress, and executive function systems. Here, PFC regions play a critical role, especially the DLPFC. Deficits in EFs in individuals with SUD are reflected by decreases in frontal cortex activity that interfere with decision-making, self-regulation, inhibitory control, and WM performance, which contribute to compulsive drug use and loss of control in addiction [3,54]. On the basis of previous studies [35,55] and the present results, we speculate that stimulation of the DLPFC with anodal

tDCS (see Fig. 4) may have increased excitability and functional connectivity in this region and other networks involved in addiction and thereby resulted in increased control of drug-seeking behavior. For example, it might have promoted cognitive control over drug use-related behavior by (1) restoring diminished inhibitory control over inappropriate impulses/behaviors, (2) reducing attentional bias to drug-related cues, (3) improving behavioral monitoring and the ability to detect errors, (4) reducing risk-taking behaviour, especially in the context of motivational salience, and (5) increasing control over negative emotions that are associated with drug withdrawal [4,56]. Such enhancing effects of tDCS over the DLPFC are in line with effects of non-invasive brain stimulation over prefrontal areas in other neuropsychiatric disorders with executive dysfunctions underlying their core symptoms (e.g., depression, obsessive-compulsive disorder, schizophrenia, ADHD) [23,25,26,57–62].

Of all EF tasks under study, only the BARTs' primary outcome measure (i.e., adjusted value) was not correlated with craving reduction. Previous studies have shown that risk-taking behaviour is only reduced by bilateral tDCS over the DLPFC (either with anodal left -cathodal right or the reverse stimulation polarity), but not unilateral stimulation [63], implying that modulation of both DLPFCs is important to modulate risk-taking behaviour. Risk-taking behavior, and specifically the BART, involve "hot" (i.e., emotional) components of EFs, and here the orbitofrontal cortex and medial PFC are relevant for value attribution , reward-anticipation, reward-gain/loss processing and fear extinction [64,65,82]. Consequently, stimulating the orbitofrontal and medial PFC simultaneously with the DLPFC might be more effective in modifying risk-taking behavior and performance in the BART, as shown in healthy populations [21].

In addition to the improvement of executive control functions, we found a significant reduction of methamphetamine craving after the intervention, which persisted for up to 1 month following the intervention. Importantly, no drug consumption or relapse occurred during this time, indicating that the observed reduction in craving cannot be explained by drug consumption. The association between improved cognitive control and craving could explain why the majority of previous neuromodulation studies targeting the DLPFC in order to reduce craving in drug and food addiction had favourable results [42]. Interestingly, results of the craving subscales showed that only "desire and intention for drug use" and "control deficit" were significantly reduced, which are both associated with cognitive and emotional control, and involve the DLPFC. But how is craving specifically associated with the executive control system?

From a neurobiological perspective, drug craving involves a widely distributed and complex prefrontal cortical-subcortical circuitry involving the DLPFC, anterior cingulate cortex, and orbitofrontal cortex, which are closely related to insular functions [3,66]. Functional imaging studies have shown that high ratings of craving positively correlate with insular activity, suggesting that craving is reflected by neural activity of the endogenous reward system [66,67]. As an indirect effect of DLPFC stimulation, modulation of insular activity could be one explanation for the observed reduction in craving, which could be accomplished by prefrontal-directed top-down modulation and cognitive down-regulation of craving [66,68,69]. Previous studies in drug addiction show that indeed cognitive inhibition and suppression of drug-related cues are associated with reduced metabolism in the insula [70] and subcortical structures, such as the ventral striatum [68]. Accordingly, the increased DLPFC activity induced by tDCS (Fig. 4), and the consequently improved executive control functions, might help to reduce cue-induced craving in drug addiction according to the neurobiology of the prefrontal-subcortical circuitry involved in craving [3]. Alternatively, the modelling results also suggest a direct effect of tDCS on the insula. As suggested by Fig. 4, electrical current generated by tDCS also reaches deep cortical regions including the insula. In sum, drug addiction is the result of increased activity of the subcortical reward system in response to drug-related cues, and decreased activity of the prefrontal-related cognitive control network [71], which are functionally related. Direct intervention targeted to respective regions with tDCS can balance and regulate this neural network and modulate drug-seeking behavior.

Finally, it is important to consider potential clinical implications of our findings. The first implication concerns the clinical efficacy of the protocol used in this study (i.e., bilateral DLPFC stimulation). While previous tDCS studies that targeted the DLPFC showed inconclusive results with modest positive effects on craving [11], most of these studies involved short courses of DLPFC stimulation. In order to establish and examine clinical efficacy, extended and repeated stimulation protocols are recommended. However, the number of such studies in drug addiction is limited [13]. Our study provides supporting evidence for the importance of *repeated* tDCS in rehabilitating drug addiction [13]. We also showed that the effect of the intervention sustains for up to at least one month following intervention. However, the optimal frequency, duration, and intervals between sessions, which can affect the efficacy of tDCS [13], need to be explored systematically in the future. Secondly, our findings suggest that cognitive control deficits might be important targets for therapeutic intervention, and especially relapse prevention. This may make sense when viewed in light of evidence proposing that better predictors of treatment outcome are those that reflect cognitive control over drug urges rather than the drug urges themselves [4,66]. Craving does not always correlate with relapse [3]. Indeed reports of craving, altough have predictive value for relapse, often prove to be poor predictors of subsequent abstinence, while cognitive and neuroimaging measures have proven to be efficacious in predicting relapse [66]. Therefore, cognitive improvement, rather than craving, may need to be prioritized in the treatment of drug addiction. Lastly, the potential importance of bilateral stimulation in the present study should not be ignored. Besides anodal tDCS over the left DLPFC, cathodal tDCS was applied over the right prefrontal cortex in our study. While standard cathodal tDCS protocols (1 mA, electrode size 35 cm^2) have excitability-diminishing effects [72], the protocol applied in the present study (2 mA for 20 min) could have had a net excitability-enhancing effect on the motor cortex as shown in previous studies conducted [73,74] or non-motor cognitive functions [75]. We therefore hypothesize that in the present study, the effect of tDCS on psychological processes might have been accomplished by bilateral excitability enhancement of the DLPFC. Since both DLPFCs are dysfunctional and have reduced cortical thickness in SUD and drug addiction [76,77], such a mechanism of action would make sense, although it should be validated directly in future studies.

Despite promising implications, some limitations of this study should be considered. First, although drug consumption (and therefore relapse) were controlled throughout the experiment and follow-up measurements by performing urine tests, we were not able to obtain such measures beyond the one month after intervention, which would be important to make assumptions about the long-term clinical efficacy of the intervention. Nevertheless, the significant correlation between craving reduction and cognitive improvement holds promise and encourages future studies that primarily target treatment-related parameters. Second, the attrition rate of 22% should is another limitation. Third, the intrinsically limited focality of tDCS resulted in a relatively diffuse stimulation. As our modeling of current flow shows, beyond the DLPFC, additional cortical and subcortical areas might also have been affected. Neuroimaging methods will help to more accurately identify the

regions directly affected by tDCS in future studies. In sum, our findings suggest that an improvement of executive dysfunctions via tDCS over the DLPFC might be a promising intervention in methamphetamine-use disorder and potentially other SUDs [34]. In addition to subjective craving, which has predictive value for relapse, neuropsychological functions, including EFs, may also predict further addictive behaviour and relapse in people with SUD [66]. Accordingly, they might evolve as an important functional target for treatment in brain stimulation studies which should be explored in future studies. Moreover, mixed cognitive effects of tDCS were also reported, which highlights the need for individualized stimulation protocols for optimal effectiveness [33]. Future studies need to focus on stimulation parameters (e.g., stimulation intensity, duration, repetition interval, etc.) to further boost the magnitude and duration of effects in studies with longer follow-up assessments.

Declaration of competing interest

MAN is a member of the Scientific Advisory Board of Neuroelectrics. All other authors declare no competing interests.

CRediT authorship contribution statement

Jaber Alizadehgoradel: Investigation, Data curation, Formal analysis, Visualization, Validation. **Vahid Nejati:** Conceptualization, Methodology. **Fariba Sadeghi Movahed:** Conceptualization, Funding acquisition, Supervision, Project administration. **Saeed Imani:** Investigation. **Mina Taherifard:** Investigation, Data curation. **Mohsen Mosayebi-Samani:** Visualization. **Carmelo M. Vicario:** Supervision, Writing - review & editing. **Michael A. Nitsche:** Supervision, Writing - review & editing. **Mohammad Ali Salehinejad:** Conceptualization, Methodology, Supervision, Writing - original draft, Writing - review & editing, Formal analysis, Visualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.12.028.

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