


# The effect of anodal transcranial direct current stimulation on affective impulsivity in methamphetamine users: A randomized experimental study

Xiaoyu Jiang<sup>1,2</sup>  | Jiaqi Liu<sup>1</sup> | Jiemin Yang<sup>1</sup> | Yufang Gao<sup>3</sup> | Peng Shuai<sup>4</sup> | Jiajin Yuan<sup>1,5</sup> 

<sup>1</sup>The Affect Cognition and Regulation Laboratory (ACRLab), Institute of Brain and Psychological Sciences, Sichuan Normal University, Chengdu, China

<sup>2</sup>School of Business and Management, Shanghai International Studies University, Shanghai, China

<sup>3</sup>Sichuan Ziyang Drug Rehabilitation Center, Ziyang, China

<sup>4</sup>Sichuan Yaan Drug Rehabilitation Center, Yaan, China

<sup>5</sup>Sichuan Key Laboratory of Psychology and Behavior of Discipline Inspection and Supervision, Sichuan Normal University, Chengdu, China

## Correspondence

Jiajin Yuan, The Affect Cognition and Regulation Laboratory (ACRLab), Institute of Brain and Psychological Sciences, Sichuan Normal University, Chengdu 610066, China. Email: [yuanjiajin168@126.com](mailto:yuanjiajin168@126.com)

## Funding information

The study was funded by the National Natural Science Foundation of China (NSFC31971018 to J.Y.) and by the Science Fund for Distinguished Young Scholars of Sichuan Province (2023NSFSC1938 to J.Y.). The funders had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## Abstract

**Background and Aims:** Methamphetamine use disorder (MUD) is associated with significant impairments in impulsivity control, contributing to relapse and poor treatment outcomes. Transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex (DLPFC) may be helpful in modulating these symptoms. This study aimed at [1] investigating the differential effects of anodal and cathodal tDCS on craving, affective impulsivity, and motor impulsivity; and [2] exploring the correlations between changes in affective impulsivity & drug craving, and alterations in resting-state electroencephalography (Rs-EEG) microstate parameters following tDCS interventions.

**Design:** A randomized, parallel, double-blind experimental study.

**Setting:** Two drug rehabilitation centers in China, from June 2022 to June 2023.

**Participants:** One hundred male participants (ages  $33.7 \pm 6.26$  years) during rehabilitation for MUD.

**Intervention:** Participants were randomly assigned to anodal ( $n = 33$ ), cathodal ( $n = 31$ ), or sham ( $n = 36$ ) tDCS conditions. tDCS was delivered at 2 mA (anodal and cathodal) or 0 mA (sham) for 20 minutes, twice daily for ten consecutive days. The central electrode was placed on the left dorsolateral prefrontal cortex.

**Measurements:** Primary and secondary outcomes were assessed at four time points: baseline (before intervention), post-intervention 1 (after two sessions), post-intervention 2 (after 20 sessions, primary time-point), and one-month follow-up (post-intervention 3). Primary outcomes were affective impulsivity and motor impulsivity. Secondary outcomes included drug craving, Rs-EEG microstates, and adverse effects.

**Findings:** Anodal tDCS statistically significantly improved affective impulsivity control after 20 sessions (estimate =  $-36.23$ , 95% confidence interval [CI]  $[-59.72, -12.73]$ ,  $p < 0.01$ ) but not motor impulsivity control. Both anodal and cathodal tDCS statistically significantly reduced drug craving after 20 sessions (anodal: estimate =  $3.36$ , 95% CI  $[1.15, 5.57]$ ,  $p < 0.01$ ; cathodal: estimate =  $2.62$ , 95% CI  $[0.34, 4.9]$ ,  $p = 0.02$ ). Changes in affective impulsivity were statistically significantly correlated with alterations in Rs-EEG microstate parameters, such as microstate B coverage ( $r = 0.29$ ,  $p < 0.01$ ,  $n = 100$ );

however, there is a lack of clear evidence for correlations between changes in craving and microstate parameters.

**Conclusions:** Among methamphetamine users in rehabilitation, anodal transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex appears to improve affective impulsivity control, but not motor impulsivity control, and both anodal and cathodal tDCS reduce drug craving.

#### KEYWORDS

dorsolateral prefrontal cortex, impulsivity, methamphetamine use disorder, microstate, resting-state electroencephalography, transcranial direct current stimulation

## INTRODUCTION

Methamphetamine use disorder (MUD) is a global health concern, imposing significant burdens on individuals and society [1]. A core feature of MUD is impaired impulsivity control, which drives compulsive drug-seeking and relapse, even after prolonged abstinence [2, 3]. Impulsivity is a multi-faceted construct, encompassing three distinct dimensions: impulsive choice, impulsive action and impulsive traits [4, 5]. Impulsive choice, also referred to as affective impulsivity, is commonly assessed using the Iowa gambling task (IGT), which reflect a difficulty in regulating impulsive responses driven by immediate emotional rewards [6, 7]. Impulsive action, or motor impulsivity, is typically evaluated with task such as the two-choice oddball task (TCOT) or go/no-go task, which assess the difficulty in suppressing pre-planned or habitual actions [5, 8]. Impulsive traits, captured through self-report questionnaires like the Barratt Impulsiveness Scale [9], represent an individual's general propensity toward acting without forethought [5]. These facets of impulsivity may play distinct roles in MUD. For example, impaired affective impulsivity control can lead to prioritizing immediate drug gratification over long-term health goal [6], while exaggerated motor impulsivity may manifest as difficulty inhibiting drug-seeking behaviors. Impulsive traits could heighten vulnerability to relapse [10]. Therefore, reducing impulsivity is critical for the effective treatment of MUD.

Although traditional treatments for MUD, including cognitive-behavioral therapy (CBT) and pharmacotherapy, have demonstrated some efficacy, they often fall short in directly addressing the core issue of impulsivity [11]. Furthermore, studies suggest that the effects of these methods on impulsivity may be short-lived [4]. CBT can be time-consuming and requires substantial patient engagement, with variable outcomes [11]. Pharmacological options for MUD are limited, because they do not specifically target the multi-faceted nature of impulsivity [12]. These limitations highlight the urgent need for novel therapeutic strategies that can specifically target and modify the underlying neural mechanisms of, impulsivity in MUD.

Transcranial direct current stimulation (tDCS) has emerged as a promising non-invasive neuromodulation technique with the potential to address this need. By delivering a weak electrical current to the scalp, tDCS can modulate neuronal activity in targeted brain regions, thereby influencing cognitive and behavioral processes [13]. It has been applied in various psychiatric disorders because of its ease to

use and safe [14]. Given the critical role of the prefrontal cortex, particularly the dorsolateral prefrontal cortex (DLPFC) [15], in impulse control, it becomes a logical target for tDCS interventions in MUD. Alizadehgoradel *et al.* [16, 17] have applied tDCS to treat youths with MUD, demonstrating that repeated tDCS sessions (2 mA, 20 minutes) over the DLPFC can reduce craving and improve performance on the go/no-go task in this population. This effect may be related to tDCS-induced alterations in the brain networks of individuals with addiction [13]. This raises the possibility that tDCS could directly modulate the neural circuitry underlying impulsivity in MUD, leading to improved treatment outcomes. However, the precise mechanisms by which tDCS exerts its effects on the brain, and how these effects translate into changes in impulsivity control, remain unclear.

Anodal tDCS is generally believed to enhance cortical excitability by depolarizing neuronal membranes, while cathodal tDCS decreases excitability by hyperpolarizing them [18]. These opposing effects raise a crucial question: do anodal and cathodal tDCS differentially impact affective impulsivity and motor impulsivity in MUD patients? Surprisingly, few studies have directly compared these two stimulation modalities in the context of MUD, particularly regarding their effects on impulsivity control. Meta-analyses of sham-controlled trials have shown various protocols, including bilateral (e.g. right anodal and left cathodal) and unilateral (e.g. left cathodal) over the DLPFC, and can be used to intervene in addictive symptoms [19]. However, not all studies have demonstrated a positive effect of tDCS in MUD, possibly because of the heterogeneity of methods used across studies [19, 20]. For example, Jiang *et al.* [20] found that individuals with MUD exhibited increased motor impulsivity, as measured by TCOT, after bilateral DLPFC stimulation. In summary, the differential effects of anodal and cathodal tDCS, which exert opposing influences on neuronal excitability, warrant further investigation, particularly in the context of impulsivity control.

To gain a deeper understanding of the neural mechanisms underlying tDCS effects, this study used resting-state electroencephalography (Rs-EEG) microstate analysis. Rs-EEG, a non-invasive measure of spontaneous brain activity, can be broken down into a series of quasi-stable topographies called microstates [21]. These microstates, typically labeled A, B, C and D, are thought to represent the fundamental building blocks of large-scale brain network activity and are associated with distinct cognitive and affective processes [22]. Microstates A, B, C and D are considered relevant to the auditory, visual, saliency and

attention networks, respectively [23]. Emerging evidence suggests that individuals with psychiatric disorders, including substance use disorders, exhibit altered microstate parameters, such as changes in duration, occurrence and global explained variance (GEV) of specific microstates [24, 25]. It is plausible that MUD patients also exhibit aberrant microstate dynamics, reflecting the underlying neural dysregulation associated with impulsivity and other clinical symptoms. Indeed, some studies have shown changes in brain dynamics of methamphetamine users [26]. The current study examines whether tDCS, by modulating cortical excitability, could normalize these aberrant microstate patterns, leading to improvements in impulsivity control.

To identify the differential effects of tDCS on multi-dimensional impulsivity, we designed a randomized experimental study to investigate the effect of anodal or cathodal tDCS over the left DLPFC on two distinct aspects of impulsivity (motor and affective) in individuals with MUD. Additionally, we examine whether these behavioral changes are associated with alterations in Rs-EEG microstate parameters. We hypothesized that:

**H1.** Anodal and cathodal tDCS would exert differential effects on motor impulsivity, affective impulsivity and craving in MUD.

**H1a.** Anodal tDCS, because of its excitatory effects, would reduce craving and impulsivity.

**H1b.** The effects of cathodal tDCS on impulsivity are less clear, and we will explore these effects without specifying a hypothesis.

**H2.** Changes in impulsivities and craving will be correlated with alterations in Rs-EEG microstate parameters.

## METHODS

### Study design

This randomized, parallel, double-blind experimental study was conducted at two drug rehabilitation centers, Zi Yang Drug Rehabilitation Centre (Ziyang, China) and Ya An Drug Rehabilitation Centre (Yaan, China), between June 2022 and June 2023. The study protocol (Data S1) was approved by the Ethics Committee of the Institute of Brain and Psychological Sciences at Sichuan Normal University and registered at the Chinese Clinical Trial Registry (ChiCTR2100046112). This study adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines [27].

### Participants

Participants were recruited based on the following eligibility criteria: (1) meeting the Diagnostic and Statistical Manual of Mental Disorders

(DSM-5) criteria for stimulant use disorder [28], according to clinical records provided by rehabilitation centers before study enrollment; (2) reporting no history of illicit drug use other than methamphetamine; (3) age under 50 years; and (4) having a rehabilitation period of less than 365 days. Exclusion criteria included (1) current use of methamphetamine or other psychiatry medications; (2) a history of major neurological disorders, significant unstable medical conditions or severe lifetime psychiatric disorders (excluding MUD); (3) presence of metal implants in the body; and (4) a history of brain stimulation interventions.

Of the 815 individuals screened for eligibility, all were mandated by law enforcement to 2 years of compulsory residential detoxification at two male-only rehabilitation centers following their last drug use. These centers offer interventions (e.g. CBT, group therapy and motivational interviewing) to address the psychological and social aspects of the disorder. Staff at these centers informed eligible patients ( $n = 176$ ) about the study. Of those, 100 expressed interest and were referred to the research team for further screening and enrollment (Figure 1). All participants provided written informed consent before the intervention.

## Procedures

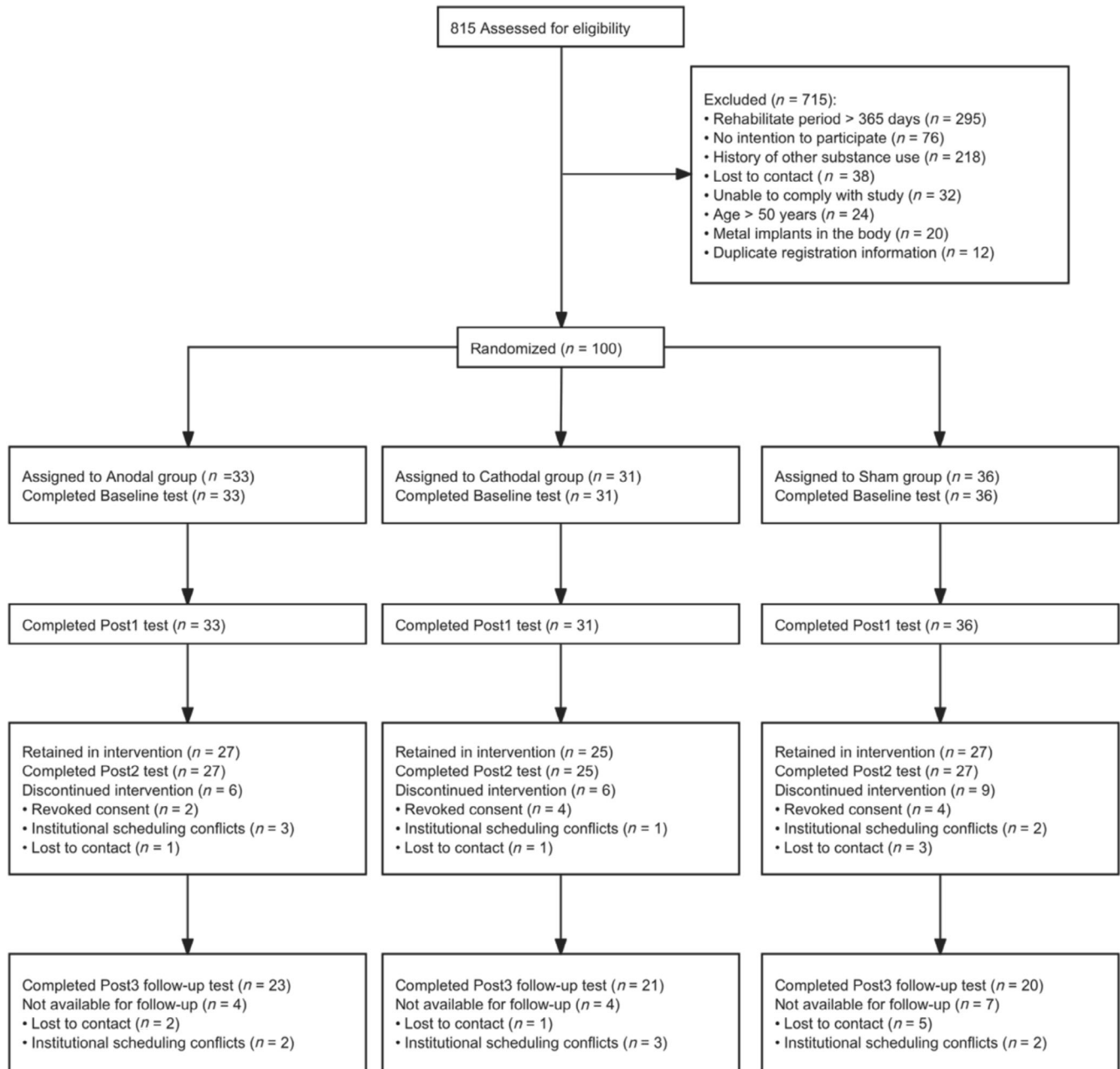
### Study procedures

This study comprised four assessments and two phases [Figure 2(a)]. Baseline assessment preceded phase 1, which consisted of two intervention sessions and post-intervention 1 (Post1) assessment on day 1. Phase 2 involved nine subsequent days of interventions (two daily) with post-intervention 2 (Post2) assessment immediately following. Post-intervention 3 (Post3) assessment was conducted 1 month later for follow-up. Baseline assessments included a personal characteristics questionnaire (age, education level, etc.) and primary and secondary outcome measures. Primary and secondary outcome measures were also collected at Post1, Post2 and Post3. An adverse effect questionnaire was administered after each intervention day. All assessments were conducted in quiet, comfortable rooms within the rehabilitation center, ensuring environmental consistency.

Following baseline assessment, participants were randomly assigned to anodal, cathodal or sham tDCS groups using a computer-generated randomization sequence. This randomization was conducted by researchers blinded to the study purpose and intervention conditions and who had no further involvement in the experiment.

### Interventions

High-definition (HD) tDCS was delivered using a multi-channel wireless transcranial electrical stimulation system (Neuracle NeuStim NSS18). Five Ag/AgCl electrodes, with conductive gel, were positioned via an HD cap according to the extended 10–20 system. The center F3 electrode (left DLPFC) was surrounded by the return electrodes at Fp1, Fz, C3 and F7 [Figure 2 (d)]. The center electrode was anodal or cathodal depending on the group.



**FIGURE 1** Study flowchart.

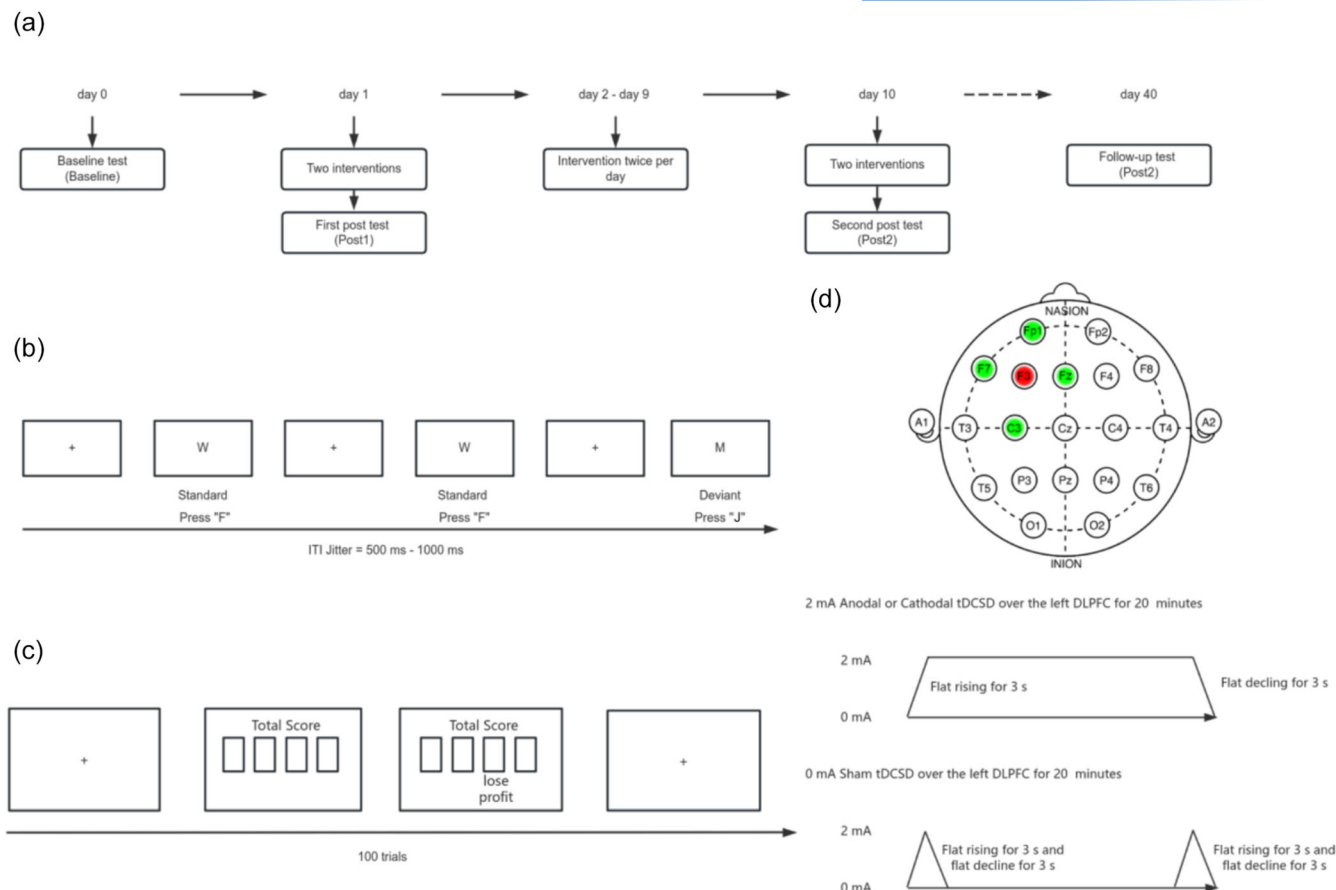
Consistent with previous studies demonstrating effective neuromodulation effects of 2 mA tDCS over the DLPFC in individuals with substance use disorders [19], the intensity of tDCS was set to 2 mA for anodal and cathodal groups and to 0 mA for the sham group. For both anodal and cathodal groups, the current intensity increased linearly to 2 mA over 3 seconds at stimulation onset and linearly decreased to 0 mA over the final 3 seconds. In the sham group, two brief current pulses were delivered at the start and end to mimic real intervention: a 3-second linear ramp-up to 2 mA followed by a 3-second drop to 0 mA (onset), and a 3-second ramp-up to 2 mA followed by a 3-second linear fade-out (offset) [Figure 2(d)]. To maximize the therapeutic effect of tDCS, multi-session interventions (20 minutes twice daily for 10 consecutive days) were used. Meta-

analyses have shown that multi-session interventions are more effective than single-session approaches for craving and consumption reduction in people with drug dependence [29].

## Measurements

### Primary outcomes

The primary outcomes were impulsivity, including motor and affective impulsivity. The primary comparison time point was immediately after the end of the intervention (Post2), to focus on the direct effects of the stimulation protocol.



**FIGURE 2** Schematic diagrams (a) schematic diagram of experimental flow, (b) schematic diagram of experimental paradigm of two-choice oddball task (TCOT), the ratio of standard to deviation trial is 80%: 20%. (c) Iowa gambling task (IGT) diagram, starting from the left, the first two cards are ‘advantageous’ cards and the last two are ‘disadvantageous’ cards. (d) Electrode placement position and current release schematic diagram, red indicates the center electrode, green indicates the return electrodes.

Motor impulsivity was assessed using the TCOT [8]. Participants respond to standard (‘W’; 80% of trials) or deviant (‘M’; 20% of trials) stimuli, yielding two indicators of motor impulsivity: accuracy cost (ACC cost) and reaction time (RT) delay. ACC cost, defined as the decrease in accuracy for deviant trials compared to standard trials, indicates increased motor impulsivity. RT delay, defined as the increase in response time for accurate deviant trials compared to standard trials, was also analyzed [8] [see Figure 2(b)].

Affective impulsivity was assessed using the IGT, a measure that simulates real-life decision-making by requiring participants to balance immediate rewards against long-term consequences [6]. Affective impulsivity was quantified using the net IGT score, calculated as the difference between advantageous and disadvantageous card selections [30]. Lower net scores indicate higher affective impulsivity [see Figure 2(c)].

Secondary outcomes

Secondary outcomes included drug use craving, adverse effects and Rs-EEG microstates.

The Obsessive-Compulsive Drug Use Scale (OCDUS) was used to measure the self-reported drug use craving in methamphetamine users. The OCDUS is a 13-item self-report scale that assesses various aspects of craving, including thoughts about drug use, desire to use drugs and resistance to drug use. Higher scores indicate greater craving [31]. It has demonstrated good reliability (Cronbach’s  $\alpha = 0.89$ ) [31].

Rs- EEG data were recorded using a Cognionics Quick-30 wireless dry-electrode EEG device. Rs-EEG consists of two conditions: 5 minutes with eyes open and 5 minutes with eyes closed. This device used 30 EEG channels, adhering to the enhanced international 10-20 system, with a 500 Hz sampling rate, a 0.01 to 100 Hz band-pass filter and impedances maintained below 50 k $\Omega$  [32]. Horizontal and vertical electrooculography electrodes were used to monitor eye movements for artifact correction. Rs-EEG data processing and microstate feature extraction are detailed in Data S1.

Adverse effects and tolerability were assessed using a self-reported questionnaire (0-4 Likert-type) administered after each intervention day. This questionnaire rated the intensity of 10 somatic and affective symptoms: headache, scalp pain, etc.

## Other measures

Demographic information and psychological status were recorded at baseline, including age, years of addiction, days of abstinence, Self-Rating Anxiety Scale (SAS) [33], Self-Rating Depression Scale (SDS) [34] and Barrett Impulsive Behavior Scale (BIS-11) [9]. Years since first repeated use of methamphetamine (YRU) were defined as the number of years from the onset of repeated use to the year of assessment.

## Sample size

A priori power analysis using G\*Power indicated that 63 participants (21 per group) were needed for 0.95 power ( $\alpha = 0.05$ ) at the primary end-point (post 2) [35]. The effect size, Cohen's  $f = 0.228$ , was based on previous meta-analysis of tDCS for drug addiction craving reduction [29]. Allowing for 30% potential dropout, 100 participants were recruited at baseline, with the following allocations: 33 anodal, 31 cathodal and 36 sham. Group allocation randomization ensured balance despite unequal final numbers.

## Statistical analysis

Analyses were conducted following the intention-to-treat (ITT) principle, including all participants who received at least two intervention sessions. All  $P$ -values were two-tailed tests, with the significance threshold set at 0.05. Bonferroni correction was applied to adjust for multiple comparisons in these *post hoc* tests. Effect sizes were reported as partial  $\eta$ -squared ( $\eta^2_p$ ). In response to peer review, new statistical analyses were performed using R version 4.4.1 [36]. Missing data, assumed missing at random (MAR), were imputed using the *mice* package (20 imputations, predictive mean matching, maximum iterations = 100) [37]. Linear mixed-effects models (LMMs) were fitted using the *lme4* package [38].

## Primary outcomes

Primary outcomes, including IGT score (affective impulsivity), TCOT RT delay and TCOT ACC cost (motor impulsivity), were analyzed. To explore baseline predictors of improvement in impulsivity control from baseline to Post2, binary logistic regression models were fitted. The dependent variable was a binary indicator of improvement (1 = yes, 0 = no), defined by the change score from baseline to Post2. Predictors included standardized baseline variables: age, education level, YRU, rehabilitation days, BIS, SAS, SDS and group (sham reference). The full model was reported.

LMMs were used to analyze data from baseline, Post1 and Post2. The LMMs included fixed effects for group (between-subject), session (within-subject) and their interaction (group  $\times$  session). YRU was included as a covariate, given its significant main effect on the primary outcomes. Participant ID was a random intercept. Type III analysis of variance

assessed fixed effects, and *post hoc* tests explored changes/differences if interaction/main effects approached significance ( $P < 0.10$ ).

The maintenance of treatment effects was assessed by comparing Post3 and Post2 scores within each group using paired  $t$ -tests for each primary outcome.

## Secondary outcomes

Secondary outcomes included OCDUS scores and microstate metrics (A, B, C, D: average duration, frequency of occurrence, coverage and GEV). The same logistic regression models as used for primary outcomes were used to explore baseline predictors of OCDUS score improvement. LMMs, *post hoc* comparisons and correction methods were applied to each secondary outcome, analyzing data from baseline, Post1 to Post2, with YRU as a covariate. Maintenance of effects on OCDUS scores were assessed using the same methods as for primary outcomes.

## Correlation analyses

Two correlational analyses were conducted. First, Pearson correlation explored associations between baseline measures of primary and secondary outcome, and other variables across all groups. Second, Pearson correlation assessed correlations between the change values (Post2-baseline) for primary and secondary outcomes.

# RESULTS

## Sample characteristics

One hundred males with MUD (33 anodal, 31 cathodal and 36 sham) were enrolled and received at least one tDCS session. Post2 assessments were completed by 79 participants (27 anodal, 25 cathodal and 27 sham), with a 21.0% attrition rate. Post3 assessments were completed by 64 participants (23 anodal, 21 cathodal and 20 sham), with a 36% attrition rate. Attrition rates did not differ significantly between groups at Post2 [ $\chi^2(2) = 0.56, P = 0.757$ ] or Post3 [ $\chi^2(2) = 1.77, P = 0.413$ ]. Participant attrition across time points is detailed in Figure 1.

The enrolled participants ( $n = 100$ ) were all males with MUD, with a mean age of 33.7 years ( $SD = 6.26$ ). Most participants (73%) reported had 10 or fewer years of education. The mean YRU was 8.3 years ( $SD = 4.47$ ), and participants averaged 212 days in rehabilitation ( $SD = 136.18$ ). Baseline scores indicated moderate impulsivity trait and low levels of anxiety and depression. Demographic and questionnaire characteristics are presented in Table 1.

## Primary outcomes

Intervention group significantly predicted IGT improvement, with the anodal group showing a significantly higher likelihood of improvement

**TABLE 1** Participant characteristics.

	Anodal (n = 33)	Cathodal (n = 31)	Sham (n = 36)	All (n = 100)
Age in y, mean (SD)	32.8 (6.16)	34.6 (7.12)	33.8 (5.60)	33.7 (6.26)
Male, n (%)	33 (100)	31 (100)	36 (100)	100 (100)
Highest level of education				
Year 10 or below, n (%)	24 (73)	26 (84)	23 (67)	73 (73)
Year 12, n (%)	6 (19)	3 (10)	11 (31)	20 (20)
University degree, n (%)	3 (9)	2 (7)	2 (6)	7 (7)
Smoking	1.85 (0.972)	1.93 (0.868)	2.29 (0.957)	2.03 (0.94)
YRU, mean (SD)	6.67 (3.28)	7.81 (4.54)	10.2 (4.73)	8.30 (4.47)
Rehabilitate days, mean (SD)	188.52 (135.35)	238.19 (128.85)	211.14 (142.66)	212.06 (136.18)
BIS total, mean (SD)	79.3 (17.7)	81.7 (14.2)	78.8 (19.6)	79.67 (17.16)
SAS score, mean (SD)	34.1 (7.40)	31.8 (6.58)	34.9 (6.62)	33.51 (6.97)
SDS score, mean (SD)	40.3 (8.83)	39.7 (8.91)	40.3 (8.92)	39.90 (8.85)
Adverse events, mean (SD) <sup>a</sup>	4.03 (4.22)	5.4 (4.7)	3.5 (3.5)	4.26 (4.17)

Notes: Values are mean (SD) or count.

Abbreviations: BIS, Barrett Impulsive Behavior Scale; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; YRU, years since first repeated use of methamphetamine.

<sup>a</sup>Adverse event scales assessed after tDCS intervention on the first day were selected for analysis.

**TABLE 2** Prediction model for improvement from baseline to Post2.

	IGT scores OR (CI), P	TCOT ACC delay OR (CI), P	TCOT ACC cost OR (CI), P	OCDUS scores OR (CI), P
(Intercept)	0.85 (0.39–1.80), 0.67	3.29 (1.44–8.40), 0.08	0.49 (0.22–1.03), 0.07	0.71 (0.34–1.46), 0.36
Age	0.84 (0.53–1.31), 0.44	1.11 (0.66–1.88), 0.7	1.18 (0.76–1.86), 0.46	0.85 (0.55–1.30), 0.44
Education	0.94 (0.55–1.63), 0.84	0.65 (0.39–1.06), 0.09	0.82 (0.51–1.27), 0.38	1.00 (0.65–1.53), 0.99
YRU	1.11 (0.99–1.25), 0.09	0.64 (0.36–1.12), 0.12	0.79 (0.46–1.30), 0.36	1.01 (0.62–1.66), 0.98
Rehabilitation days	1.00 (1.00–1.01), 0.35	0.87 (0.47–1.57), 0.65	1.01 (0.60–1.75), 0.96	0.91 (0.54–1.50), 0.71
BIS total	1.02 (0.99–1.05), 0.14	0.64 (0.36–1.08), 0.1	0.88 (0.53–1.44), 0.62	1.31 (0.82–2.13), 0.26
SAS total	1.00 (0.92–1.09), 0.97	1.05 (0.54–2.08), 0.89	0.78 (0.42–1.42), 0.43	1.02 (0.58–1.81), 0.94
SDS total	1.03 (0.96–1.11), 0.43	0.70 (0.32–1.44), 0.34	1.46 (0.77–2.89), 0.26	0.65 (0.34–1.18), 0.16
Type anodal	6.03 (1.86–22.15), 0.004*	0.97 (0.28–3.38), 0.96	0.60 (0.18–1.89), 0.39	2.46 (0.86–7.30), 0.1
Type cathodal	1.97 (0.63–6.45), 0.25	1.10 (0.30–4.10), 0.88	1.28 (0.42–3.93), 0.67	2.62 (0.88–8.19), 0.09

Notes: OR with 95% CI were derived from logistic regression models for each predictor variable.

Abbreviations: BIS, Barrett Impulsive Behavior Scale; IGT, Iowa gambling task; OCDUS, Obsessive-Compulsive Drug Use Scale; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; TCOT ACC cost, accuracy cost for standard trials minus deviant trials; TCOT RT delay, two-choice oddball task response time delay (deviant minus standard); YRU, years since first repeated use of methamphetamine;

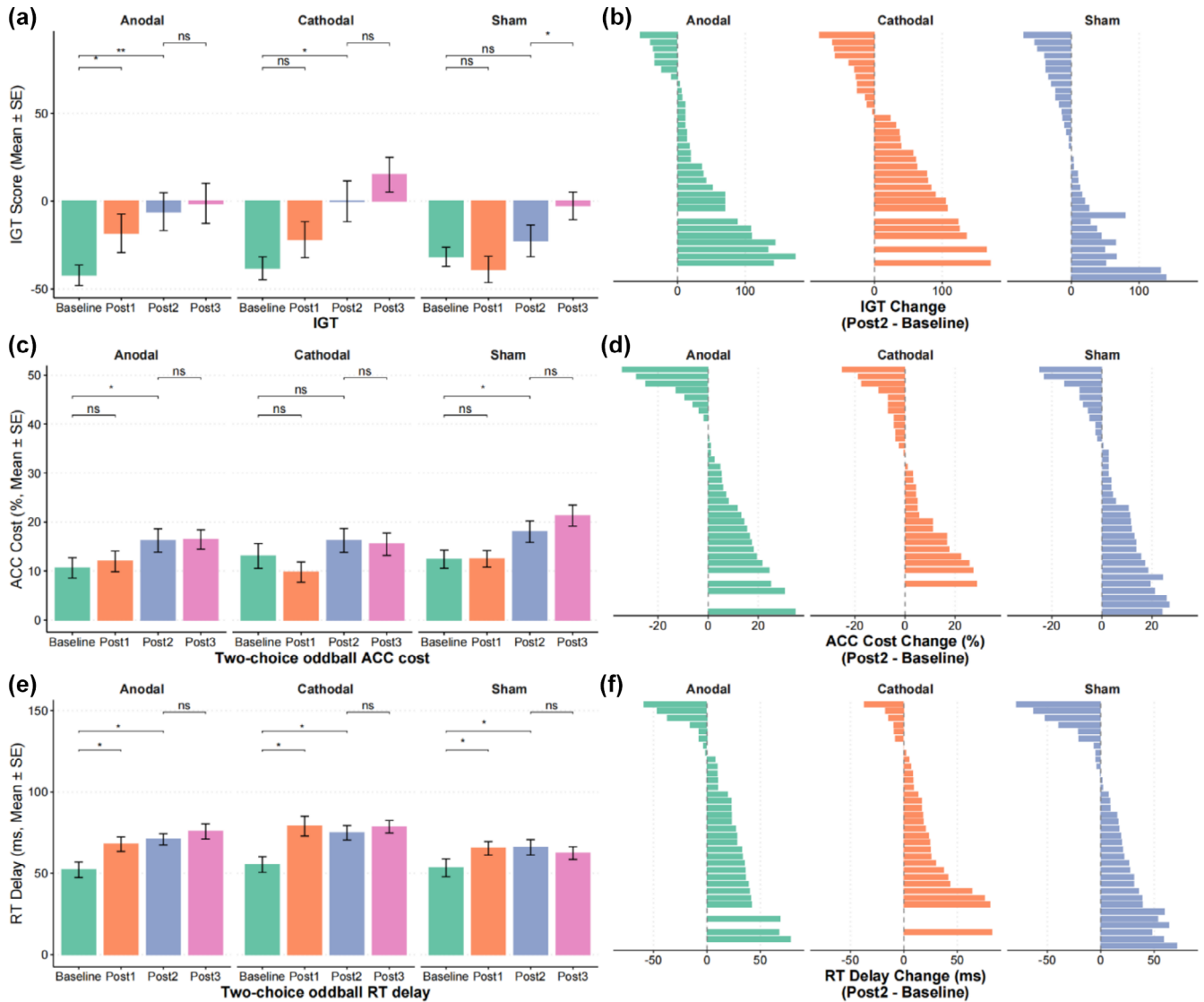
\* $P < 0.05$ . Non-significant  $P$ -values are unmarked.

compared to sham (OR = 6.03) (Table 2). IGT improvement percentages significantly varied across groups [ $\chi^2$  (2) = 6.18,  $P = 0.046$ ]: anodal 78.8%, cathodal 61.3% and sham 50% [Figure 3(b)].

LMM analysis, with YRU as a covariate, of IGT scores showed a significant session effect [ $\chi^2$  (2) = 14.33,  $P = 0.001$ ] and near-significant group  $\times$  session interaction [ $\chi^2$  (4) = 8.08,  $P = 0.089$ ]. *Post hoc* tests revealed significant within-group changes in the anodal group (baseline vs. Post1/Post2) and cathodal group (baseline vs. Post2), but not sham. Between-group comparisons at

each time point did not reveal any significant differences [Table 3, Figure 3(a)].

Regression models for TCOT RT delay and ACC cost found no significant predictors [Table 2, Figures 3(d), (f)]. LMMs, also including YRU as a covariate, also did not reveal a significant interaction effect for group by session on TCOT measures [RT delay:  $\chi^2$  (4) = 3.05,  $P = 0.549$ ; ACC cost:  $\chi^2$  (4) = 2.32,  $P = 0.678$ ], despite a significant session effects on the RT delay [ $\chi^2$  (2) = 14.72,  $P = 0.001$ ] and ACC cost [ $\chi^2$  (2) = 6.80,  $P = 0.033$ ] [Table 3, Figure 3(c), (e)].



**FIGURE 3** Primary outcomes. This figure shows mean ( $\pm$  SE) values for (a) Iowa gambling task (IGT), (c) reaction time (RT) delay and (e) accuracy (ACC) cost at four time points during two-choice oddball, along with individual change (Post2-baseline) for (b) IGT, (d) ACC cost and (f) RT delay. Statistical significances: *post hoc* tests following linear mixed models (baseline, Post1 and Post2) or paired *t*-tests (Post2 vs. Post3). \* $P < 0.05$ ; ns, not significant.

For tDCS effect maintenance, Post2-Post3 comparisons showed only a significant IGT increase in the sham group [Table 3, Figure 3(a)]. No significant Post2-Post3 changes were found for TCOT RT delay or ACC cost in any group [Table 3, Figures 3(c),(e)].

## Secondary outcomes

### OCDUS score

Logistic regression models for OCDUS approached significance for intervention type, with anodal (OR = 2.46) (Table 2) and cathodal (OR = 2.62) (Table 2) groups. Improvement percentages were 63.6% (anodal), 64.5% (cathodal) and 41.7% (sham) [Figure 4(b)].

However, LMMs showed a significant interaction between tDCS group and session for OCDUS scores [ $\chi^2(4) = 9.68, P = 0.046$ ]. *Post*

*hoc* comparisons indicated significant differences within the anodal group between baseline and Post1 (Table 2) and between baseline and Post2 (Table 2). Within the cathodal group, significant differences were also observed between baseline and Post1 (Table 2) and between baseline and Post2 (Table 2). No significant differences were found between time points in the sham group. Between-group comparisons at each time point did not reveal any significant differences [-Figure 4(a)]. No significant within-group changes were observed from Post2 to Post3 in any group.

### Rs-EEG microstates

The frequency of occurrence of microstate B showed a significant session and group interaction [ $\chi^2(4) = 19.22, P < 0.001$ ]. *Post hoc* tests revealed significant within-group changes from baseline to Post1

**TABLE 3** Impulsivity and craving variable comparisons.

	Baseline values, mean (CI)	Baseline-Post1 <sup>a</sup> Difference (CI), P	Baseline-Post2 <sup>a</sup> Difference (CI), P	Post2-Post3 <sup>b</sup> Difference (CI), P
The net scores of Iowa gambling task				
Anodal	-42.24 (-54.21 to -30.27)	-23.89 (-47.39 to -0.4), 0.04*	-36.23 (-59.72 to -12.73), <0.01*	-4.66 (-26.52 to 17.19), 0.67
Cathodal	-38.23 (-51.55 to -24.92)	-16.3 (-40.54 to 7.94), 0.32	-38.12 (-62.36 to -13.87), <0.01*	-15.2 (-37.43 to 7.03), 0.17
Sham	-31.71 (-42.92 to -20.49)	7.16 (-15.33 to 29.66), 1	-9.05 (-31.55 to 13.45), 1	-20 (-36.86 to -3.14), 0.02*
RT delay of two-choice oddball task (ms)				
Anodal	52.29 (42.48, 61.96)	-15.72 (-28.37 to -3.08), 0.01*	-18.69 (-31.33 to -6.04), <0.01*	-4.75 (-11.65 to 2.16), 0.17
Cathodal	55.30 (45.62, 64.97)	-23.66 (-36.7 to -10.61), <0.01*	-19.55 (-32.6 to -6.51), <0.01*	-3.75 (-11.96 to 4.47), 0.36
Sham	53.32 (42.14, 64.49)	-11.99 (-24.10 to 0.12), 0.05*	-12.58 (-24.69 to -0.47), 0.04*	3.50 (-6.77 to 13.77), 0.49
ACC cost of two-choice oddball task (%)				
Anodal	10.67 (6.4-14.94)	-1.33 (-6.72 to 4.06), 1	-5.57 (-10.97 to -0.18), 0.04*	-0.23 (-4.75 to 4.29), 0.92
Cathodal	13.09 (7.97-18.2)	3.31 (-2.26 to 8.87), 0.46	-3.17 (-8.73 to 2.4), 0.51	0.75 (-2.92 to 4.42), 0.68
Sham	12.45 (8.69-16.22)	-0.07 (-5.24 to 5.09), 1	-5.6 (-10.76 to -0.43), 0.03*	-3.28 (-7.98 to 1.42), 0.17
The scores of obsessive-compulsive drug use scale				
Anodal	29.56 (27.94-31.18)	3.03 (0.82-5.25), <0.01*	3.36 (1.15-5.57), <0.01*	-2.16 (-4.68 to 0.36), 0.09
Cathodal	29.65 (27.34-31.96)	2.39 (0.1-4.67), 0.04*	2.62 (0.34-4.9), 0.02*	-1.91 (-4.17 to 0.35), 0.1
Sham	28.61 (26.61-30.62)	-0.06 (-2.17 to 2.06), 1	0 (-2.12 to 2.12), 1	-0.36 (-2.02 to 1.3), 0.66

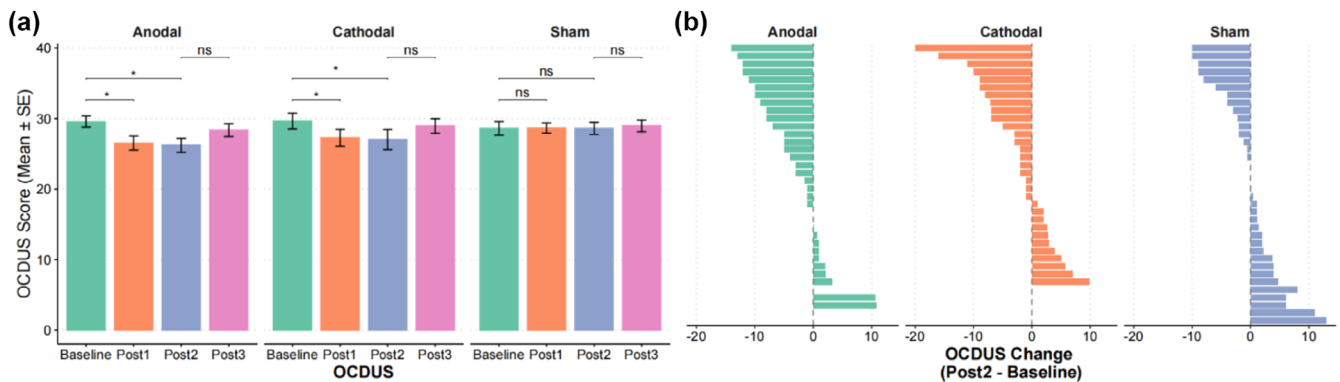
Notes: Means and differences (with 95% CIs).

Abbreviations: ACC cost, accuracy cost (standard minus deviant); RT delay, response time delay (deviant minus standard).

<sup>a</sup>Post hoc tests following linear mixed model (for baseline, Post1 and Post2 comparisons).

<sup>b</sup>Paired-samples t-tests (for Post2 vs. Post3 comparisons).

\*P < 0.05. Non-significant P-values are unmarked.



**FIGURE 4** Craving variable [Obsessive-Compulsive Drug Use Scale (OCDUS)]. This figure shows (a) mean (± SE) values and (b) individual change (Post2-baseline) for the OCDUS scores. Statistical significances: *post hoc* tests following linear mixed models (baseline, Post1 and Post2) or paired t-tests (Post2 vs. Post3). \*P < 0.05; ns, not significant.

**TABLE 4** Rs-EEG microstate parameters comparisons.

	Baseline values, mean (CI)	Baseline-Post1 Difference (CI), <i>P</i>	Baseline-Post2 Difference (CI), <i>P</i>	Post1-Post2 Difference (CI), <i>P</i>
The frequency of occurrence of microstate B (Hz)				
Anodal	3.35 (3.17–3.52)	0.28 (0.07–0.48), <0.01*	−0.02 (−0.22 to 0.19), 1.00	−0.3 (−0.5 to −0.09), <0.00*
Cathodal	2.98 (2.79–3.17)	0.16 (−0.05 to 0.37), 0.19	−0.22 (−0.43 to −0.01), 0.04*	−0.39 (−0.6 to −0.17), <0.01*
Sham	3.31 (3.19–3.43)	0.1 (−0.09, 0.3), 0.61	0.16 (−0.03 to 0.36), 0.13	0.06 (−0.14 to 0.26), 1
The coverage of microstate A (%)				
Anodal	24.27 (21.94–26.59)	−1.14 (−3.75 to 1.46), 0.87	0.82 (−1.79 to 3.43), 1	1.96 (−0.64 to 4.57), 0.21
Cathodal	26.2 (24.4–27.99)	−1.41 (−4.1 to 1.28), 0.62	2.58 (−0.1 to 5.27), 0.06*	3.99 (1.3–6.68), <0.01*
Sham	24.72 (22.85–26.58)	−0.76 (−3.26 to 1.73), 1	−1.21 (−3.7 to 1.29), 0.73	−0.45 (−2.94 to 2.05), 1
The coverage of microstate B (%)				
Anodal	25.95 (23.56–28.34)	2.88 (0.55–5.2), 0.01*	−0.4 (−2.72 to 1.93), 1	−3.27 (−5.6 to −0.95), <0.01*
Cathodal	21.47 (19.88–23.05)	0.87 (−1.53 to 3.27), 1	−3.66 (−6.06 to −1.27), <0.01*	−4.53 (−6.93 to −2.14), <0.01*
Sham	24.65 (23.03–26.28)	1.12 (−1.1 to 3.34), 0.68	1.11 (−1.12 to 3.33), 0.69	−0.01 (−2.24 to 2.21), 1
The coverage of microstate D (%)				
Anodal	25.04 (21.24–28.84)	−1.05 (−4.39 to 2.3), 1	0.65 (−2.69 to 3.99), 1	1.7 (−1.65 to 5.04), 0.67
Cathodal	30.65 (27.8–33.49)	0.31 (−3.14 to 3.75), 1	5.95 (2.51–9.4), <0.01*	5.65 (2.2–9.1), <0.01*
Sham	27.06 (24.5, 29.62)	0 (−3.2 to 3.2), 1	1.2 (−2 to 4.41), 1	1.21 (−1.99 to 4.41), 1
The global explained variance of microstate A (%)				
Anodal	10.88 (9.2–12.56)	−1.89 (−3.79 to 0), 0.05*	1.45 (−0.45 to 3.34), 0.20	3.34 (1.44–5.23), <0.01*
Cathodal	13.62 (11.96–15.29)	−0.89 (−2.85 to 1.06), 0.81	3.42 (1.46–5.37), <0.01*	4.31 (2.36–6.27), <0.01*
Sham	11.28 (9.96–12.6)	−1.16 (−2.98 to 0.66), 0.37	−0.66 (−2.47 to 1.16), 1	0.5 (−1.31 to 2.32), 1
The global explained variance of microstate B (%)				
Anodal	13.88 (12.2–15.57)	2.96 (1.15–4.76), <0.01*	−0.11 (−1.91 to 1.7), 1	−3.07 (−4.87 to −1.26), <0.01*
Cathodal	10.22 (8.91–11.53)	0.86 (−1 to 2.73), 0.79	−1.46 (−3.32 to 0.4), 0.18	−2.33 (−4.19 to −0.46), 0.01*
Sham	13.07 (11.85–14.3)	0.84 (−0.89 to 2.56), 0.73	1.21 (−0.52 to 2.93), 0.28	0.37 (−1.36 to 2.1), 1

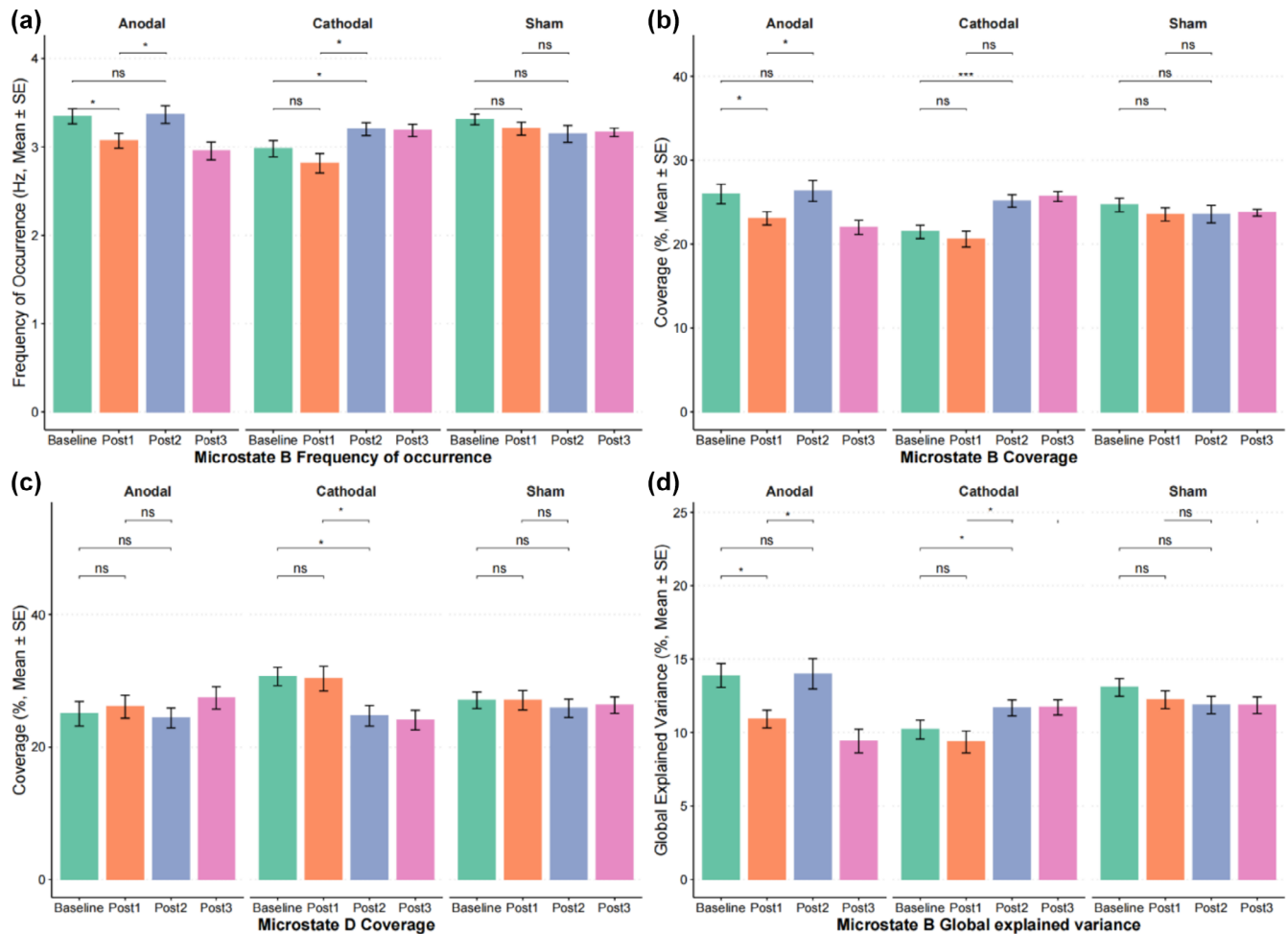
Notes: Means and differences (with 95% CIs) were derived from *post hoc* tests following linear mixed model (for baseline, Post1 and Post2 comparisons).

Abbreviations: EEG, electroencephalography.

\**P* < 0.05. Non-significant *P*-values are unmarked.

and from Post1 to Post2 across both anodal and cathodal groups (Table 4). The coverage of microstate B showed a significant group by session interaction [ $\chi^2(4) = 18.31, P = 0.001$ ]. *Post hoc* tests revealed significant within-group changes from baseline to Post1 and from Post1 to Post2 in the anodal group, as well as from Post1 to Post2 in the cathodal group (Table 4). The coverage of microstate D

also exhibited a significant group  $\times$  session interaction [ $\chi^2(4) = 10.11, P = 0.039$ ], with significant within-group changes observed from baseline to Post2 in the cathodal group (Table 4). Finally, GEV showed significant group  $\times$  session interaction effects for microstates A and B [A:  $\chi^2(4) = 18.43, P = 0.001$ ; B:  $\chi^2(4) = 16.07, P = 0.003$ ] (see Figure 5).



**FIGURE 5** Microstate parameters. This figure illustrates the mean values ( $\pm$  SE) for resting-state electroencephalography (EEG) microstate parameters that showed significant interaction effects across three-time points: baseline, Post1 and Post2. Statistical significance was determined using *post hoc* tests following linear mixed models (baseline, Post1 and Post2) for comparisons between these time points. \* $P < 0.05$ ; ns, not significant.

## Correlations

At baseline, IGT scores were significantly positively correlated with microstate D average duration ( $r = 0.20$ ,  $P = 0.046$ ,  $n = 100$ ). OCDUS scores were significantly positively correlated with TCOT RT delay ( $r = 0.21$ ,  $P = 0.039$ ,  $n = 100$ ) and days of abstinence ( $r = 0.21$ ,  $P = 0.038$ ,  $n = 100$ ). BIS total score was positively correlated with TCOT RT delay ( $r = 0.22$ ,  $P = 0.03$ ,  $n = 1000$ ).

Additionally, changes (Post2-baseline) in IGT scores of overall individuals were significantly correlated with alterations in microstate B coverage and GEV, with microstate A average duration and frequency of occurrence across groups (Table 5). No significant correlations were found between changes in OCDUS scores and alterations in microstate parameters.

## Adverse effects and safety

No serious adverse effects were reported. Furthermore, there is no significant differences in adverse effect across the three tDCS groups on the first day ( $F_{2,96} = 1.796$ ;  $\eta^2_p = 0.037$ ;  $P = 0.172$ ).

## DISCUSSION

This study aimed to investigate the effects of tDCS over the left DLPFC on impulsivity in individuals with MUD. Key findings revealed that tDCS exerted distinct intervention effects on different dimensions of impulsivity. Specifically, anodal tDCS significantly reduced affective impulsivity, as evidenced by improvement in the IGT. However, no significant effects were observed on motor impulsivity. Additionally, both anodal and cathodal tDCS showed efficacy in modulating craving, suggesting a broader impact on craving-related behaviors. Furthermore, this study also identified significant effects of tDCS on Rs-EEG microstates. Significant correlations were observed between changes in affective impulsivity measures and alterations in Rs-EEG microstate parameters, but not between changes in craving measures and microstate parameters. These results demonstrate the distinct effects of tDCS on impulsivity and provide evidence to inform the development of tDCS protocol for the rehabilitation of MUD, targeting both craving and impulsivity control.

According to the dual-systems theory of substance addiction, addiction results from an imbalance between dynamically interacting

**TABLE 5** Correlations in changes.

Group	A		B	
	Average duration	Frequency of occurrence	GEV	Coverage
Overall (n = 100)	-0.23*	-0.209*	0.229*	0.29*
Anodal (n = 33)	-0.041	0.103	0.358*	0.314
Cathodal (n = 31)	-0.368*	-0.607*	0.022	0.183
Sham (n = 36)	-0.171	-0.08	0.125	0.275

Notes: The Pearson correlation coefficients (*r*) between changes in IGT scores and alterations in resting-state EEG microstate parameters for the overall group and subgroups (anodal, cathodal and sham). Only display the coefficients when overall group showed significant correlations.

Abbreviations: EEG, electroencephalography; GEV, global explained variance; IGT, Iowa gambling task.

\**P* < 0.05.

reward and inhibitory systems, characterized by excessive activation of the reward system and weakened inhibitory control system [12]. In this study, affective impulsivity, as measured by the IGT, is likely closely associated with reward evaluation and decision-making processes [39]. The reward system is predominantly driven by dopamine-mediated mesolimbic circuits, including dopamine projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) and prefrontal cortex (PFC) [12]. Studies have shown that individuals with MUD exhibit increased dopamine release from the NAcc on exposure to drug cues, with the magnitude of release positively correlated with self-reported craving scores [30]. Furthermore, diminished DLPFC activity has been observed in individuals with addiction, and activation of the DLPFC can modulate dopamine release or inhibit excessive responses to reward signals, thereby reducing addiction-related cravings and affective impulsivity [19, 40].

Additionally, this study found that both anodal and cathodal tDCS yielded positive effects on the IGT and the OCDUS. Intuitively, this seem inconsistent with the conventional understanding of tDCS, where anodal stimulation increases the excitability of the targeted brain region, and cathodal stimulation decreases it. However, according to the dual-systems theory, substance addiction results from an imbalance between two dynamically coupled systems. Both anodal and cathodal tDCS may restore system equilibrium through distinct neuromodulator pathways. Anodal tDCS may enhance the excitability of DLPFC via depolarization, facilitating its top-down inhibition of dopamine release in the NAcc [7, 12]. Cathodal stimulation, while temporarily suppressing DLPFC activation through hyperpolarization, may also disinhibit abnormal regulation of inhibitory networks [7]. For instance, it could suppress the activation of brain regions exhibiting functional hyperactivity, but reduced efficacy because of long-term compensation, thereby reactivating neural plasticity [17]. This effect, however, may depend on multiple sessions of stimulation, as multi-dose cathodal stimulation can overcome the neural adaptation threshold [17]. This study also provides behavioral and neural-level support for previous research using bilateral DLPFC stimulation for addiction treatment [41, 42]. In summary, the improvements in affective impulsivity and craving observed with both cathodal and anodal tDCS may reflect multi-target dynamic compensation of the imbalanced systems, rather than the modulation of a single pathway. This inference is

further supported by the significant correlations between the changes of IGT scores and EEG microstate alterations across tDCS protocols, such as those of microstate B coverage and GEV that are thought to reflect reorganization of brain network dynamics and visual-attentional function [23, 24].

In contrast, this study did not find a significant effect of tDCS on motor impulsivity, assessed by the TCOT, with either anodal or cathodal tDCS. This differential effect of tDCS on affective and motor impulsivity may arise from the distinct neural circuits underlying these behavioral dimensions. Motor impulsivity involves motor inhibition and response control, potentially reflecting the functionality of the inhibitory system, which involves DLPFC, anterior cingulate cortex, orbitofrontal cortex and other brain regions [12, 39]. Although both systems involve the DLPFC, their underlying neural circuits and mechanisms differ. The DLPFC may primarily participate in impulse monitoring and rule maintenance, rather than directly executing inhibitory actions [17]. Neuroplasticity may prompt other brain regions to compensate for impaired DLPFC function, therefore, masking the stimulation effect. Previous studies have also reported limited effects of tDCS over the DLPFC on motor impulsivity across various task metrics in addiction populations [43]. Conversely, tDCS studies directly targeting the motor cortex have demonstrated significant effects on motor impulsivity, supporting the notion of circuit-specific neuromodulation [44].

## Strengths and limitations

To our knowledge, this is the first study to examine the effect of tDCS on multi-dimensional impulsivity control in individuals with MUD during rehabilitation. Furthermore, this study included a 1-month follow-up assessment after the intervention to evaluate the long-term effects of tDCS treatment. The double-blind approach, multiple-center participant recruitment and the combined use of behavioral tasks and Rs-EEG minimized the risk of bias and enhanced the robustness of the results.

However, several limitations should be acknowledged. First, because of the challenges associated with participant recruitment, we imposed restrictions on participant eligibility, including male

individuals under 50 years of age without comorbid physical or psychiatric illnesses (excluding MUD). Consequently, the potential influence of variables such as age on impulsivity could not be explored, which may limit the generalizability of our findings to a broader population. Future studies could expand the participant population to investigate the therapeutic effects of tDCS on MUD in a more diverse cohort.

Second, the intensive tDCS protocol, consisting of two sessions per day for 10 consecutive days, was implemented to maximize intervention efficacy within safe stimulation parameters. However, this protocol may have placed a significant burden on participants, potentially affecting adherence. In clinical practice, it may be advisable to consider increasing the intervals between intervention sessions. Future studies should systematically compare the effects of varying tDCS protocols on treatment outcomes and participant tolerability to optimize therapeutic efficacy while minimizing patient burden.

Finally, this study used Rs-EEG to explore the relationship between resting-state brain activity patterns and behavioral changes in individuals with MUD. However, Rs-EEG does not directly capture brain activity during the occurrence of impulsive behaviors or performing impulsivity control. Therefore, future research could use task-based EEG methods to examine the neuroplastic changes associated with impulsivity control interventions in methamphetamine users.

## CONCLUSIONS

This study demonstrates that tDCS over the left DLPFC differentially modulates affective and motor impulsivity in individuals with MUD. Specifically, anodal tDCS significantly improved affective impulsivity control, as evidenced by enhanced performance on the IGT, but not motor impulsivity control. Both anodal and cathodal tDCS effectively reduced craving, suggesting a broader impact on addiction-related behaviors. Furthermore, changes in affective impulsivity correlated with alterations in Rs-EEG microstate parameters, highlighting the potential of neurophysiological biomarkers to track treatment response. These findings provide insights into the neural mechanisms underlying tDCS effects in MUD and support its potential as a therapeutic intervention for impulsivity and craving.

## AUTHOR CONTRIBUTIONS

**Xiaoyu Jiang:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); validation (equal); visualization (equal); writing—original draft (equal); writing—review and editing (equal). **Jiaqi Liu:** Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing—original draft (equal). **Jiemin Yang:** Conceptualization (equal); methodology (equal); supervision (equal); validation (equal); writing—original draft (equal); writing—review and editing (equal). **Yufang Gao:** Data curation (equal); investigation (equal); project administration (equal); resources (equal); writing—original draft (equal); writing—review and editing (equal). **Peng Shuai:** Data curation (equal); investigation (equal);

project administration (equal); resources (equal); writing—original draft (equal); writing—review and editing (equal). **Jiajin Yuan:** Conceptualization (lead); funding acquisition (lead); methodology (lead); project administration (equal); resources (equal); supervision (lead); validation (equal); writing—original draft (equal); writing—review and editing (lead).

## ACKNOWLEDGEMENTS

We thank Ti-Fei Yuan (Shanghai Mental Health Center) for study design assistance and Rufang Wang, Jingzhen He (Chengdu University of Traditional Chinese Medicine), Ting Luo, Changwei Zhou (Sichuan Ziyang Drug Rehabilitation Centre), Zhiwei Hong and Qinglin Chen (Sichuan Normal University) for data collection support. We also acknowledge the contributions of the staff at Ziyang Drug Rehabilitation Centre and Yaan Drug Rehabilitation Centre for their assistance with data collection.

## DECLARATION OF INTERESTS

None.

## DATA AVAILABILITY STATEMENT

Data available: Yes.

Data types: Data dictionary.

How to access data: Dr. Jiajin Yuan, E-mail: [yuanjiajin168@126.com](mailto:yuanjiajin168@126.com)

When available: With publication.

Document types: None.

Who can access the data: researchers whose proposed use of the data has been approved.

Types of analyses: for meta-analysis, etc.

Mechanisms of data availability: with a signed data access agreement.

## CLINICAL TRIAL REGISTRATION

ChiCTR2100046112 in [chictr.org.cn](http://chictr.org.cn)

## ORCID

Xiaoyu Jiang  <https://orcid.org/0009-0000-8626-5250>

Jiajin Yuan  <https://orcid.org/0000-0001-5670-4531>

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Jiang X, Liu J, Yang J, Gao Y, Shuai P, Yuan J. The effect of anodal transcranial direct current stimulation on affective impulsivity in methamphetamine users: A randomized experimental study. *Addiction.* 2026; 121(3):655–69. <https://doi.org/10.1111/add.70259>