Title: tDCS Targeting the DLPFC for Reducing Cigarette Craving and Risky Decision Making: A Protocol Study

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Abstract

Background: Cigarette smoking is a prevalent addictive behavior. Despite the well-known health risks, many individuals are unable to quit. One of the key factors contributing to the failure of smoking cessation efforts is the presence of craving and the tendency toward risk-taking behaviors. Noninvasive brain stimulation techniques have recently emerged as potential treatments for addiction. The present study is a pilot trial to examine the impact of tDCS targeting DLPFC on risk-taking, EEG frequency power, and their relationship with the cue-induced nicotine craving in smokers.

Methods: In this double-blind study, which is part of a larger randomized clinical trial, sixty-three cigarette smokers who met the ICD-10 criteria for tobacco addiction were enrolled. tDCS sham, left anodal/right cathodal, and right anodal/left cathodal tDCS will be applied to three participant groups. Participants were required to refrain from smoking for two hours prior to the study visit. The effects of tDCS on cue-triggered nicotine craving, certain risky decision-making tasks, and some resting-state EEG frequency power analyses were evaluated both before and after periods of tDCS (2 mA for 20 minutes) applied to the dorsolateral prefrontal cortex on five consecutive days.

Discussion: Although several studies have reported that tDCS may have beneficial effects on drug abuse by suppressing the degrees of cravings, impulsivity, and risk decision making.

However, to date, no study has evaluated the impact of tDCS on the DLPFC and its relationship with EEG frequency power characteristics. The results of this study are anticipated to represent a significant step toward improving smoking cessation efforts. The findings from this randomized controlled trial will explore the therapeutic potential of transcranial direct current stimulation (tDCS) in treating nicotine addiction among smokers.

Keywords: Transcranial direct current stimulation; Dorsolateral prefrontal cortex; Risky decision-making behavior; Brain wave pattern; Nicotine; Craving.

Trial registration

This trial was registered with the Iranian Registry of Clinical Trials (IRCT) on 14 November 2023 under the identifier IRCT20230806059051N1.

Introduction

Background

Nicotine is the main psychoactive component of cigarette smoke and plays a major role in the global burden of diseases. Cigarette smoking, a prevalent form of tobacco use, is a significant public health risk, and it is projected that the number of smokers will increase to 1.7 billion by 202 (1, 2). It is estimated that in 2030, the number of deaths caused by smoking will reach 8 million annually. Additionally, smokers often exhibit behaviors such as risky decision-making (3). Currently, many approaches are used to prevent and manage tobacco addiction. Despite numerous available interventions, including cognitive-behavioral therapy and pharmaceutical treatments, smoking relapse remains a major challenge (4, 5). Thus, novel strategies such as brain stimulation have been proposed to reduce tobacco cravings and support smoking cessation. Transcranial direct current stimulation (tDCS) is a widely used non-invasive technique for modulating brain function, particularly in individuals with central nervous system (CNS) disorders (6). Numerous studies have verified that tDCS can modulate excitability in both superficial and deep brain structures. During tDCS, anodal stimulation increases cortical excitability through neural depolarization, whereas cathodal stimulation reduces it via hyperpolarization(7, 8). Since alterations in the activity of prefrontal regions such as the DLPFC are associated with drug craving, studies suggest that anodal tDCS may enhance DLPFC activity and thereby reduce craving (9, 10). Loss of control over drug-seeking is a well-recognized feature of drug addiction, which is defined as a compulsive drive to seek drugs for acute rewards despite the risk of aversive consequences.

In this manner, dysfunctions within prefrontal cortical circuits, the DLPFC, contribute to impaired decision-making and cognitive evaluation of consequences, which which play a key role play a key role in compulsive drug-seeking behavior. In addition, several human studies emphasized that

drug addiction leads to significant behavioral impairments in tasks related to making risky decisions(11-13). From this perspective, evidence suggests that tDCS applied to frontal regions such as the DLPFC can influence risk-taking behavior. For instance, Gorini et al. demonstrated that anodal stimulation of the DLPFC modulated risky choices in abstinent, cocaine-dependent individuals. Moreover, to date, few studies have investigated the effects of non-invasive brain stimulation on EEG frequency power changes in cigarette smokers. In a study using repetitive transcranial magnetic stimulation (rTMS), Pripfl et al.(14) found that rTMS applied to the left DLPFC reduced nicotine craving and decreased EEG delta power in cigarette smokers. It seems that a delta power decrease has been linked to increased activity of the dopaminergic mesolimbic system. Nevertheless, from a neuropsychological perspective, risk-taking and addictive behaviors share several features that influence brain electrical activity. Taken together, this study aims to evaluate and compare the effects of the left and right-sided tDCS over the DLPFC on performance in two risk-taking tasks and EEG frequency power changes in nicotine smokers and control participants.

Objectives

The aim of this study is to evaluate the effectiveness of transcranial direct current stimulation (tDCS) on the dorsolateral prefrontal cortex(DLPFC) in reducing craving, risky decision-making, and altering EEG power spectra in cigarette smokers. We hypothesize that tDCS can alter EEG frequency power in the DLPFC, thereby decreasing craving and risky decision-making, and ultimately leading to reduced cigarette consumption among smokers.

Specific Objectives

To assess the effect of (tDCS) on nicotine craving in cigarette smokers using the Tobacco Craving Questionnaire (TCQ).

To compare the differential effects of left- versus right-sided DLPFC stimulation on craving intensity.

To examine the effects of left- and right-sided tDCS on risky decision-making behavior using the Iowa Gambling Task (IGT) and the Balloon Analogue Risk Task (BART).

To analyze shifts in the power spectra of the electroencephalogram (EEG) (alpha, beta, theta, delta, and gamma bands) after stimulation of the left and right DLPFC Comparing relative power and dominant brainwave profiles after tDCS in both conditions.

Trial design

This randomized clinical trial includes three parallel arms: an intervention group, a control group, and a sham group. The study aims to evaluate the effects of electrical stimulation on the DLPFC on risky decision-making and brain wave patterns, craving induction in cigarette smokers. Participants will be randomly assigned to one of the three groups to ensure balanced allocation across study arms. Specific outcome measures will include decision-making tasks and EEG recordings to assess brain wave patterns associated with craving and risk-related behavior. This structured approach enables a comprehensive evaluation of the effectiveness of electrical stimulation in enhancing decision-making compared to sham treatment. Ethical approval for this study was granted by the Ethics Committee of Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1402.17548), and the trial was registered with the Iranian Registry of Clinical Trials (IRCT) under code 72660.

Methods: participants, interventions and outcomes

Study setting

The study will be conducted at Mazandaran University of Medical Sciences, located in Mazandaran, Iran. The research sample will include individuals from the target population who meet the predefined eligibility criteria. Participants will be recruited via a public announcement targeting interested and eligible individuals. Individuals who express interest and meet the eligibility criteria will be enrolled in the study. Based on Krejcie and Morgan's sample size determination table, 63 participants are required for this study, assuming unknown population variance and a 50% response probability (Fig.1)(15). It should be mentioned that in addition to obtaining written informed consent from all participants, the study protocol will incorporate continuous monitoring for any adverse psychological effects during and after each stimulation session. Participants will be specifically observed for signs of increased anxiety, emotional instability, or discomfort. A licensed clinical psychologist will be present on-site throughout the intervention period to provide immediate evaluation and support if needed. Moreover, participants will be clearly informed of their right to withdraw from the study at any point without any consequences. These measures are intended to ensure the psychological safety and well-being of all participants throughout the entire course of the experiment.

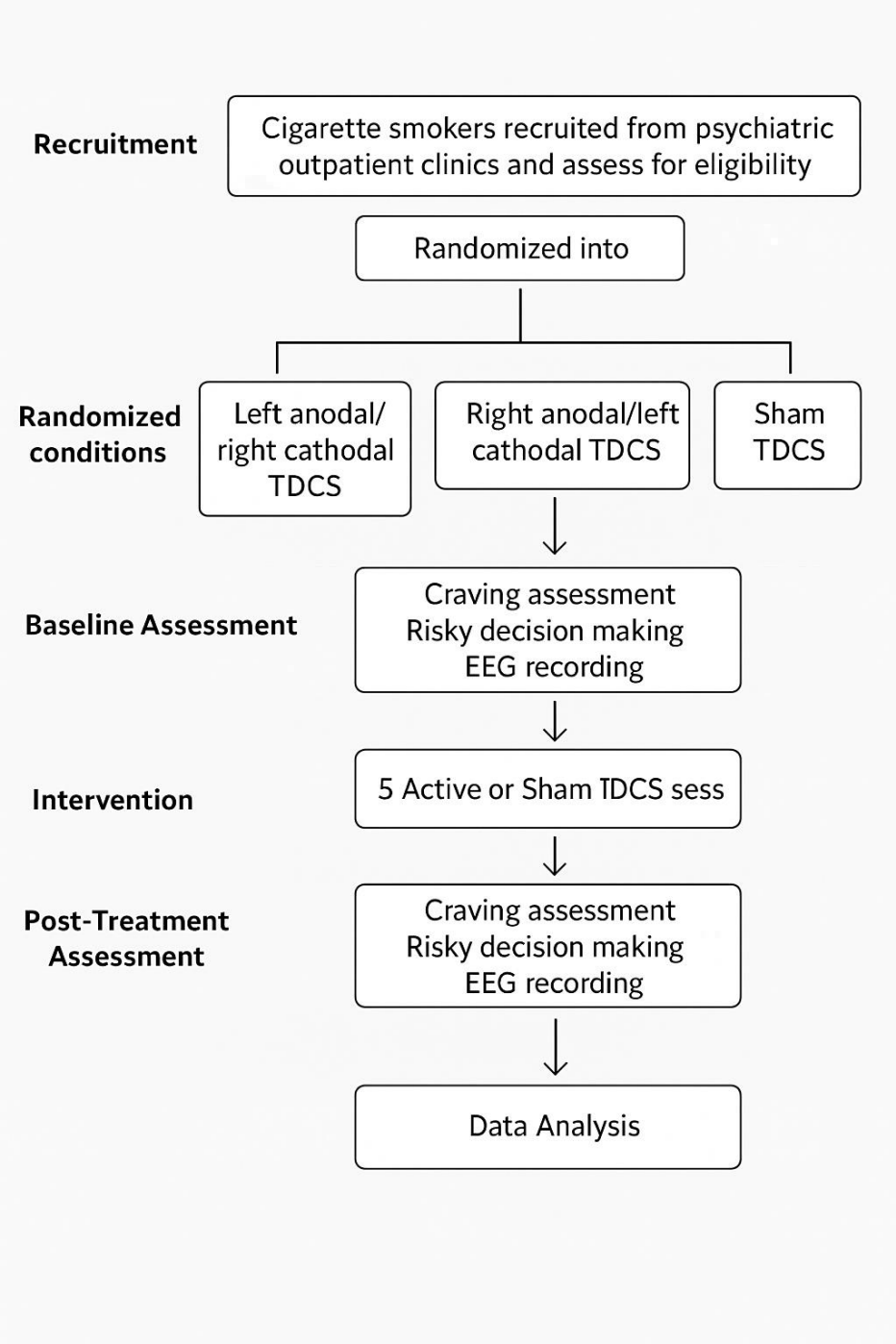

Figure1. Overview of the study design. Participants will be randomly assigned to one of three tDCS conditions (active left, active right, or sham). Craving, risky decision-making, and EEG will be assessed before and after five stimulation sessions. tDCS: transcranial direct current stimulation, EEG: Electroencephalography.

Inclusion and Exclusion Criteria:

Eligible participants will be male cigarette smokers between the ages of 18 and 45 who provide informed consent and are proficient in Persian, including the Mazandarani dialect. Participants must have a history of daily smoking (at least 10 cigarettes per day) for a minimum of two years. They must not have any history of head trauma, brain injury, or neurological disorders such as epilepsy, seizures, stroke, or brain/spinal cord tumors. Individuals with metallic implants in the head, visual impairments, or current enrollment in other research studies will be excluded. Participants must also have no current or past psychiatric disorders according to DSM-5 criteria. The decision to include only male participants was based on practical, cultural, and scientific considerations. Prior tDCS studies in addiction research have predominantly focused on males, and cultural sensitivities in Iran, along with limited female volunteerism, pose significant challenges to recruiting a gender-balanced sample. Furthermore, sex differences in craving, risk-taking, and neural responses may introduce variability in EEG measures; thus, limiting the sample to males improves internal validity. Nonetheless, future studies will aim to include female participants to explore gender-specific effects. Participants will be excluded if they report uncomfortable physical symptoms during testing, have a history of chronic physical illnesses (e.g., multiple sclerosis, diabetes, cardiovascular, pulmonary, hepatic, or renal diseases), psychiatric illness, seizures (regardless of cause), or recent use (within the past three months) of psychiatric or anticonvulsant medications. Additionally, individuals with any substance or alcohol abuse history, sleep deprivation the night before testing, or consumption of tea or caffeine within three hours prior to cognitive testing will be excluded.(16, 17).

Who will get informed consent?

Participants will be consented by the investigator prior to participation in the study. Subjects must understand before signing whether they could be harmed or might benefit from the study. Subjects will be told that their participation is completely voluntary and they have the right to withdraw consent at any time without penalty.

A study information sheet clearly worded using non-specialist language will be given to aid participants with differing levels of literacy.

Intervention

A total of 63 participants who meet the eligibility criteria will be enrolled in the study. Prior to randomization, demographic and descriptive data will be collected as previously described.The Fagerström Test for Nicotine Dependence will be used to assess the degree of nicotine dependence among participants(18, 19). The scale includes six items reflecting: time to first cigarette, number of cigarettes per day, the cigarette considered to be most important to the respondent, cigarettes per day smoked, smoking during illness, and smoking in forbidden areas. The scores vary from 0 to 10, with 0–4 referring to low dependence, 5–7 moderate dependence and 8–10 high dependence.

Cue-Induced Craving Measures

In the subsequent stage, participants will be presented with smoking-related pictures to provoke cue-induced craving. Cravings will be rated by the TCQ following exposure. Afterward, participants will undertake the IGT and the BART before performing EEG recordings.

Brain Mapping Procedure

A trained technician, who is blind to the study aims and group allocations, will perform the EEG recordings. After acclimatization, EEG will be measured under resting conditions.

Participants will be asked to avoid drinking coffee or tea within at least 3 h and smoking for 1 h prior to EEG recording.

EEG collection will be performed with a 21-electrode system of MITSAR. Electrodes: We will adhere to the 10–20 system, with an electrocap, 500 Hz sample rate, impedance less than 5 kΩ, 0.3 Hz low-pass filter and 45–55 Hz notch filter.

Collected EEG data will be processed using Python-based tools to eliminate motion and visual artifacts. Data collected will be analyzed through Python software to remove motion and visual artifacts.

Balloon Analogue Risk Task *(BART)*

- The BART is a computerized risk task based on real-world risky behavior. Participants are incentivized to take risk, though too much of the risk is not for the best.
- This method allows for the assessment of the risk-prone decision-making style of an individual, as well as the way (s)he exaggerates the risk-taking approach in real-life conditions. Low 'adjusted values' (average number of balloon pumps before an explosion) and few 'pumps' on the part of the participant in the BART reflect low risk taking behavior and impulsivity
- (20-22).
- ***Iowa gambling task (IGT)***
- The IGT uses cards to mimic real-life decision-making and consists of four decks of cards (A, B, C, and D): two decks (C and D) offering long-term advantages and the remaining two (A and B) generating losses.
- This activity requires subjects to make judgments by comparing navigation of the risk/reward of atleast one deck to all others.

- Randomization and Blinding(23) (Fig2).

Randomization and Blinding

Randomization through block randomization and random allocation software will be stratified. This approach is called block random allocation and is a way of creating blocks of subject allocations regrouping three basic interventions (treatment, control and placebo) in a random fashion, led by another colleague ignorant of the nature of the interventions.

Both participants and assessors will remain blinded to minimize bias regarding the effects of transcranial stimulation .

Participants will be randomized using block randomization and random allocation software.

Intervention Groups

The experimental group consisted of three subgroups:

Group 1: Smokers will receive transcranial direct current stimulation (tDCS) for 20 minutes at an intensity of 2 mA, which targeted the left dorsolateral prefrontal cortex (DLPFC), with the cathode electrode placed on the right side.

Group 2: consisted of smokers receiving the same duration of tDCS at intensity of 2 mA to the right DLPFC.

Group 3 (sham): Stimulation electrodes are located on the DLPFC for 30 s without active stimulation.

The participants will undergo five sessions lasting 20 minutes each using the Neurostim device with electrodes covered by salt-absorbing sponges, scheduled every other day at a power of 2 mA.

To limit any possible bias, and to precisely assess the real effects of tDCS, we used a sham stimulation group. This method follows standard strategies used in the growing body of research on tDCS and maintains proper blinding while controlling for placebo bias.

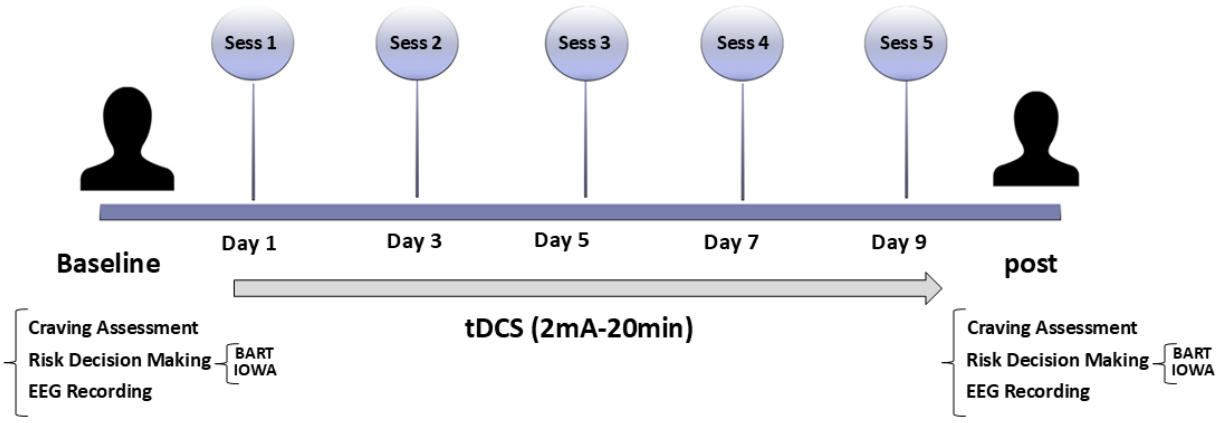

Fig. 2. tDCS procedure: The figure illustrates the timeline of the study, which includes five sessions of tDCS administered over a 9-day period (Days 1, 3, 5, 7, and 9), each lasting 20 minutes with an intensity of 2 mA. Craving assessment, risk-based decision-making tasks (including BART and IGT), and EEG recordings are conducted at both baseline (Day 1) and post-intervention (Day 9). The aim is to evaluate the acute effects of repeated tDCS targeting the DLPFC on craving, impulsivity, and neural activity. tDCS: transcranial direct current stimulation, BART: Balloon Analogue Risk Task, IGT: Iowa Gambling Task, EEG: electroencephalography

Outcomes:

Baseline assessments

Diagnostic Interview

Diagnoses will be confirmed via a semistructured psychiatric diagnostic assessment based on the validated Structured Clinical Interview for DSM Mental Disorders, which will be conducted by an experienced psychiatrist according to the DSM-V criteria.

Demographic Data

Basic demographic information, including age, sex, years of education, place of birth, marital status, number of children, financial condition, family history of affective disorders, and household income, will be collected at study entry. Medical comorbidities will be evaluated using the Cumulative Illness Rating Scale. Psychiatric history data, age at onset of the first depressive episode, number of relapse and current medication and dosage will also be collected.

Primary Outcomes

Craving reduction

*The primary outcome will be the difference scores in craving levels (as measured by TCQ)between pre- and post-*intervention*. We postulate that tDCS of left and right DLPFC significantly decreases the craving scores in smokers of tobacco.*

Cigarette Consumption

The second outcome will be the decrease in number of cigarettes smoked per day. This will be measured at baseline, post intervention*, and at follow ups (eg., 2 and 4 weeks post treatment).*

Secondary Outcomes

1. ***Risky decision-making***

   The effects of tDCS on risky decision-making will be evaluated via the IGT and the BART. Performance metrics such as total points earned in the IGT and adjusted values in the BART will be analyzed before and after the intervention.

2. **Cognitive Functioning**

   Global cognitive status will be measured using MoCA, which is expected to reflect post-intervention changes in cognitive function.

3. **EEG frequency power changes**

   Frequency powers (alpha, beta, theta, delta, and gamma) will be examined by EEG recordings. It is our hypothesis that tDCS will modulate these frequency bands in the DLPFC area, reflecting that alterations in coupling (changes in excitability) of the underlying cortex are related to craving reduction.

4. ***Subjective assessments***

   Craving intensity and subjective mental fatigue will be assessed from a subjective measure of craving and a visual analogue scale (VAS) (before and after each session) to estimate perceived change in craving intensity and mental fatigue.

Acceptability and tolerability

The acceptability of tDCS as an intervention will be measured through participant feedback collected via the VAS regarding their levels of tension, stress, and anxiety before and after each

session. Treatment tolerability will also be assessed by recording any discomfort experienced during the sessions.

Sample size

The sample size for this study was estimated via G*Power 3.1, which is based on previous research indicating the effectiveness of transcranial direct current stimulation (tDCS) in reducing cravings and improving decision-makingFor the present study, 63 participants are required (21 each group). Considering a 20% dropout rate, we will aim to recruit 75 participants in total (25 per group). Recruitment.

Recruitment

The recruitment process begins after approval is obtained from the Institutional Review Board at Mazandaran University of Medical Sciences. Participants will be recruited through advertisements targeting cigarette smokers who meet the eligibility criteria. Interested individuals will undergo screening to confirm their eligibility on the basis of the inclusion and exclusion criteria outlined in the study protocol.

Assignment of Interventions: Allocation

Sequence Generation

Block randomization will be used to assign participants to one of three intervention groups: left anodal/right cathodal tDCS, right anodal/left cathodal tDCS, and sham tDCS. Each block will consist of eight participants to ensure balanced allocation across groups.

Concealing mechanism

An independent team member not involved in recruitment or assessment will conduct the randomization process and maintain the allocation sequence confidentiality by sealing it in opaque envelopes.

Implementation

The participants will be informed about the study's purpose and procedures by trained investigators who are not involved in data collection or analysis. After providing informed consent, the participants will be randomized to their respective groups.

Assignment of Interventions: Blinding

Who Will Be Blinded

This study uses a double-blind design in which both participants and assessors are unaware of group assignments to reduce bias in data collection and analysis .

Procedure for unblinding if needed

If unblinding is necessary due to medical emergencies, the principal investigator will make the final decision regarding unblinding procedures.

Data collection and management

Plans for the assessment and collection of outcomes

A trained clinician investigator who is not involved in the intervention or randomization procedure will perform assessments at baseline and immediately postintervention.

participant retention

To prevent drop outs, they will be reminded by short message service (SMS) or phone prior to the appointment and paid for travel costs for attending the assessment.

Data Management

Information on demographics and health will be maintained securely on a Clinical Management System (CMS) with the data entered being able to be checked by trained individuals to help minimise the inaccuracy of responses."

Confidentiality

Participant details will be confidentialized with ID numbers assigned so that privacy is protected.State stored securely so that only authorized individuals have access.

Plans for collection, laboratory evaluation, and storage of biomarkers for genetic or molecular analysis in this trial/future use

N/A. No biological samples were collected in this study.

Statistical methods

Statistical methods for primary *and secondary outcomes*

The primary outcome measurement will be the change in craving levels assessed via the TCQ. A significant reduction in TCQ scores postintervention will indicate the effectiveness of the tDCS intervention. The secondary outcomes are described as changes in cigarette consumption; changes in risky decision-making, as measured by IGT and BART; and changes in EEG frequency power.

Statistical Analysis

A two-way, 2 × 2, repeated-measures ANOVA will be conducted to check the effect of group allocation (active tDCS vs. sham tDCS) time (pre- vs. post-intervention) upon the set of primary and secondary outcome variables.Post hoc analyses using Bonferroni correction will be undertaken to correct for multiple comparisons with the significance level set at $p < 0.05$ for primary outcomes and $p < 0.0125$ for secondary outcomes.

Interim Analyses

Interim analyses will be conducted once approximately half of the participants have been recruited. The study team will review data for any serious adverse effects reported during the intervention or significant deterioration in participants' mental or physical health. An early termination of the trial would have to be decided upon by the principal investigator in company with the Ethics Committee.

Additional Statistical Analyses

Subgroup analyses may be conducted according to demographic variables such as age, smoking history, etc., to see if the effects of tDCS differ regarding craving and decision-making outcomes.

Methods of Analysis to Handle Protocol Non-Adherence and Missing Data

The analyses will be conducted on an intention-to-treat basis; therefore, for missing data, a carry-forward method will be used, possibly last observation carried forward. Where patterns of missing data are found to be random, multiple imputation techniques will be used to allow for more robust statistical analyses.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

The full study protocol will be made available through the Iranian Registry of Clinical Trials. Anonymized participant-level data and statistical code can be requested from the principal investigator upon completion of the study.

Oversight and Monitoring

Composition of the Coordinating Centre *and Trial Steering Committee*

The trial will be overseen by a research management group comprising the principal investigator and coinvestigators, including psychiatrists and neuroscientists from Mazandaran University of Medical Sciences. This group will meet monthly to discuss progress and ensure compliance with ethical standards.

Composition of the Data Monitoring Committee, Role, and Reporting Structure

For the purpose of data monitoring, an independent committee will be composed of a psychiatrist, a methodologist, a statistician, and a data manager. This committee oversees the processes of data collection, ensuring they comply with the research protocols and reporting any issues to the principal investigator directly.

Adverse Event Reporting and Harms

A checklist of potential adverse effects associated with tDCS administration will be developed on the basis of literature. The participants will be informed about possible side effects during the consent process. Any adverse effects reported during the study will be documented in the CMS, and participants experiencing significant discomfort will be monitored closely by the principal investigator until resolution. Serious adverse events occurring during treatment sessions will mandate the immediate notification of local healthcare professionals, and emergency protocols

will be implemented. Any serious adverse events will be reviewed by the principal investigator to be reported to the Ethics Committee.

Frequency and Plans for Auditing Trial Conduct

On-site monitoring of the conduct of the trial will take place on a monthly basis by designated clinical coordinators affiliated with Mazandaran University of Medical Sciences in order to guarantee the safety of participants and conformance to the protocol.

Plans for communicating important protocol amendments

Significant amendments to the protocol (such as changes in eligibility criteria or outcome measures) will be discussed by the investigators and submitted to the Ethics Committee for approval before being implemented.

Dissemination Plans

The results of this trial will be disseminated among healthcare professionals, researchers, and policymakers through conferences and publication in peer-reviewed journals. The participants will then be given a summary of their results in layman's terms with visual aids to help them understand.

3-Discussion

tDCS is a rising method that uses soft electric signals to change how certain parts of the brain work, which may make nerve connections stronger(24). It offers a new way to deal with being too impulsive, different from usual drug treatments. It is safe and easy to use in cases of drug misuse. Recent works showed that tDCS changes how we think by three main ways: turning on the right

brain area with electric flow, changing key brain chemicals, and making the blood flow and oxygen in the brain better(25, 26).

Recent human neuroimaging and neurophysiological studies have advanced our understanding of how tDCS modulates brain function in addiction-related behaviors. For example, Kalu et al. (27)demonstrated that anodal tDCS over the DLPFC enhances cortical excitability and connectivity within executive control networks, which are crucial for regulating craving and impulsivity. Furthermore, a study by Dittert et al. (28)using combined tDCS and EEG showed modulation of frontal midline theta oscillations, correlating with improved inhibitory control and reduced risk-taking behavior. These findings underscore the role of tDCS in reshaping neural circuits that govern decision-making and craving, supporting the neurobiological rationale for its use in tobacco addiction. Integrating these human-based mechanistic insights with behavioral data enriches the interpretation of tDCS effects and guides optimization of stimulation

tDCS alters synaptic plasticity by influencing N-methyl-D-aspartate (NMDA) receptors and modulating the gamma-aminobutyric acid (GABA) and dopaminergic systems (29). It immediately affects regional cerebral blood flow, with anodic stimulation increasing blood flow by approximately 17.1% and cathodic stimulation by 5.6%. After the stimulation session, blood flow returns to baseline levels. Moreover, stimulating the DLPFC with an electrical current of 1–2 mA increases blood flow in related areas, suggesting a role in enhancing awareness and cognitive functions(30). The DLPFC plays a critical role in risky decision-making by influencing how probabilities are weighted and the subjective valuation of rewards. Downregulating the left DLPFC decreases the likelihood of choosing options with higher expected values, whereas TMS increases distorted probability weighting, suggesting that the left DLPFC weights probabilities more objectively. The DLPFC integrates reward magnitude and probability to assess option value;

disrupting it leads to distorted probability weighting and altered perceptions of expected value and risk. In short, the DLPFC looks at chances. The left side of the DLPFC helps with not wanting to take risks when there is a chance to gain, and the right side leans towards taking risks when there could be a loss, putting together how big the reward could be and how likely it is to decide on risky choices. As far as we know, this work is the first try of its kind to check how tDCS can change craving and risk-taking acts in people who smoke.The findings will contribute to new treatment concepts for smoking cessation and enhance our understanding of the neural mechanisms involved, providing better insights into the cortical brain areas associated with craving and subsequent risky behavior through a combination of EEG and behavioral measures. The point that needs to be considered is that despite the promising therapeutic potential of tDCS, it will be essential to consider possible psychological side effects, such as transient increases in anxiety, mood fluctuations, or mental fatigue that may arise during or after stimulation sessions. In this study, continuous monitoring protocols will be implemented to promptly detect any adverse psychological reactions. Participants will be regularly assessed for discomfort or changes in affective state using standardized self-report scales and clinical interviews. Any participant exhibiting significant distress will be provided with immediate psychological support, and stimulation sessions will be adjusted or discontinued if necessary to ensure participant safety. These precautions will underscore our commitment to minimizing potential harm and safeguarding mental well-being throughout the intervention.

However, one notable limitation of the present study is the exclusion of female participants, which restricts the generalizability of our findings to the broader population of smokers. This decision was primarily driven by practical and cultural barriers in recruiting female smokers in Iran, especially in studies involving brain stimulation. Furthermore, sex-related hormonal fluctuations may influence neural responses to tDCS and EEG, introducing additional variability. By limiting the sample to males, we aimed to enhance internal validity in this pilot phase. Nevertheless, future studies should aim to include both genders to explore

potential sex-specific effects and improve the external validity of the findings. Moreover, We acknowledge that the absence of a follow-up phase represents a significant limitation of the current protocol. Given that this study is designed as an initial pilot protocol, the primary focus was on assessing the immediate, acute effects of tDCS on craving and risky decision-making. However, to fully understand the durability and clinical relevance of these effects, longitudinal follow-up assessments are essential. We have now explicitly addressed this limitation in the manuscript's limitations section and indicated that future studies will incorporate follow-up phases to evaluate the long-term sustainability and potential clinical benefits of the intervention.

Trial status

Protocol version: February 2, 2024.

Recruitment begins: January 1, 2025.

Estimated recruitment completion: January 2026.

Expected completion of recruitment: June 2026 (Fig. 3)

https://irct.behdasht.gov.ir/trial/72660

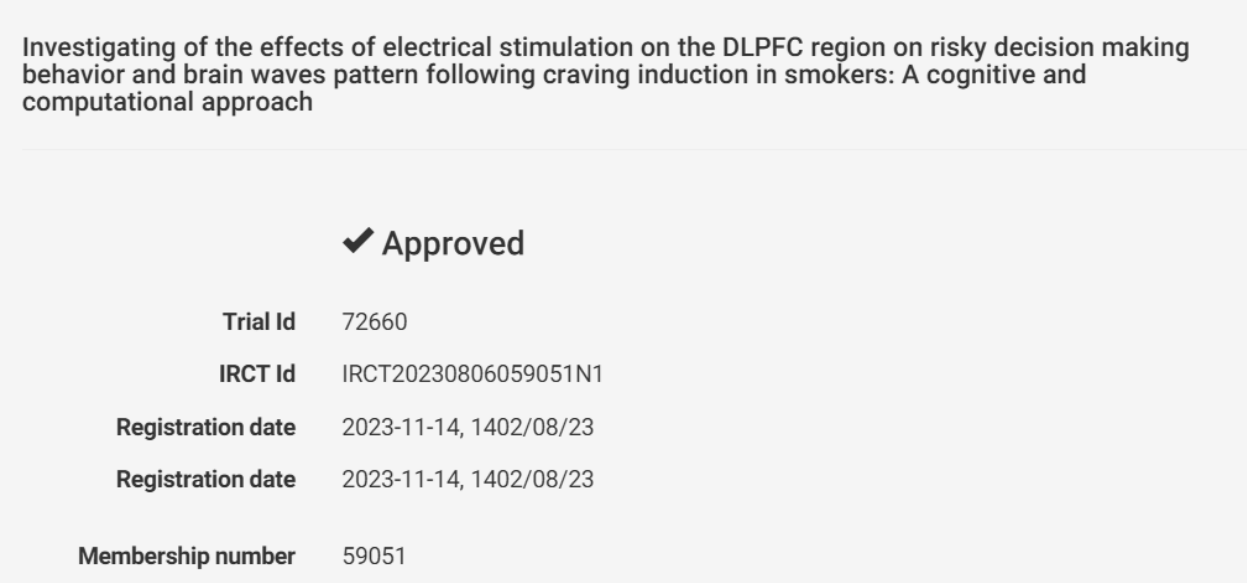

Fig.3. Trial Status

Abbreviations

tDCS: Transcranial direct current stimulation; EEG: electroencephalography; ICD-10: International Classification of Disease-10; DLPFC: Dorsolateral prefrontal cortex; IRCT: Iranian Registry of Clinical Trials; CNS: Central nervous system; rTMS: Repetitive transcranial magnetic stimulation; DSM-5: Diagnostic and statistical manual of mental disorders, five edition; IGT: Iowa gambling task; BART: Balloon analogue risk task; TCQ: Tobacco craving questionnaire; MoCA: Montreal cognitive assessment; VAS: Visual analog scale ; CMS: Clinical management system; NMDA: N-methyl-D-aspartate; GABA: Gamma-aminobutyric acid

Acknowledgments

Not applicable.

Authors' contributions

H.GH. and S.N. developed and wrote the protocol. All authors contributed to the protocol design and manuscript revision. The authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

The Ethics Committee of Mazandaran University of Medical Sciences approved the study. All participants will provide written informed consent before participation. The ethics approval number is IR.MAZUMS.REC.1402.17548, and the trial is registered with the Iranian Registry of Clinical Trials (IRCT), under code 72660.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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