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Research paper

Improved decision-making in patients with mood disorders following Transcranial Direct Current Stimulation (tDCS) applied to the left orbitofrontal cortex: A proof-of-concept study

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ABSTRACT

Deficits in decision-making is found in several mental disorders, including anorexia nervosa, addiction, mood disorders, and suicidal behavior. Improving decision-making is a relevant therapeutic objective to reduce vulnerability and risky behaviors. Transcranial Direct Current Stimulation (tDCS) is a simple and non-invasive technique that allows for the stimulation of a cortical area of interest. Previous studies have shown that tDCS of the orbitofrontal cortex (OFC) in healthy volunteers improves decision-making in the short-term. We aimed to demonstrate this short-term effect in patients with a mood disorder. This was a prospective, single-center, interventional, randomized controlled trial (ClinicalTrial.gov NCT06110559) with two parallel arms (active vs sham stimulation) in a single-blind design. tDCS was applied during 30 min over the left OFC (anode Fp1/cathode Fp2). The primary outcome was a change in the net score on the Iowa Gambling Task (IGT) measured immediately before and after stimulation. Sixty-two patients were randomized to receive active ($N = 30$) or sham ($N = 32$) stimulation. We observed a significant improvement in IGT net score in the active vs sham arm (time*arm interaction $\chi^2 = 4.10$; $p = .043$). No significant change at other cognitive tasks (d2, Go/No-Go, Emotional Stroop) or self-rating perceived emotion questionnaires (PANAS, STAI-Y-A) was found. Patients did not correctly guess the treatment arm. These preliminary findings support the use of tDCS over the OFC to improve decision-making in patients with mood disorders. Future studies should assess the best strategies for sustained improvement, and the naturalistic consequences in terms of real-life decision-making and functioning.

1. Introduction

Decision-making is a cognitive function by which an individual selects among available options in a given context. It can be conceptualized in five stages — representation, valuation, action selection, outcome evaluation, and learning — modulated by risk, uncertainty, and temporal delay (Rangel et al., 2008). This function can be assessed using various tasks; notably, the Iowa Gambling Task (IGT) differentiates between impaired or risky decision-making — where risky choices yield attractive short-term rewards but long-term disadvantageous outcomes — and adequate or prudent decision-making, characterized by selections that optimize long-term gains (Bechara et al., 1994, 1999).

Adequate decision-making is crucial for everyday life. Deficits in decision-making is found in numerous mental disorders in a "trans-nosographic" way. Impairments in this cognitive function are notably found in anorexia nervosa, addictions, and mood disorders (Clark and Robbins, 2002; Smith et al., 2018). Risky decision-making is observed in all three phases of bipolar disorder suggesting a vulnerability trait (Adida et al., 2011). While data in depressed individuals are heterogeneous, risky decision-making is robustly found in the subgroup of patients with a history of suicide attempts (Jollant et al., 2005; Perrain et al., 2021). It is particularly found in individuals with a history of violent suicide attempts, a subgroup clinically close to those who die by suicide (Perrain et al., 2021). Furthermore, decision-making impairment

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is found in healthy biological relatives of patients who died by suicide, therefore representing the only known cognitive endophenotype of suicidal behavior to date (Courtet et al., 2011; Ding et al., 2017; Hoehne et al., 2015). During a suicidal crisis, the patient may choose the immediate relief of intense mental pain through the choice of a suicidal act (and the means to achieve this goal) in spite of the vital risk. Importantly, 16 % of people who have attempted suicide will reattempt in the following twelve months (Carroll et al., 2014). Improving decision-making may allow to reduce this risk by reducing the suicidal vulnerability.

Decision-making is a complex function involving numerous brain regions such as the ventromedial prefrontal cortex and the orbitofrontal cortex (OFC) (Lawrence et al., 2009). The OFC allows for value attribution to guide choices (Rangel et al., 2008; Rolls, 2023; Wang et al., 2023; Zha et al., 2022). Lesions of the OFC result in risky decision-making (Bechara, 2004). Moreover, OFC dysfunction has been associated with risky decision-making in suicide attempters and their healthy relatives (Alacreu-Crespo et al., 2020; Ding et al., 2017; Jollant et al., 2010; Olié et al., 2015). Impairment in OFC functioning or structure has also been associated with risky decision-making in depression, eating disorders, obsessive-compulsive disorder, attention deficit disorder and addictions (Bodell et al., 2014; Hüpen et al., 2023; Perkes et al., 2022; Yang et al., 2019; Zhang et al., 2024).

Therapies aiming at improving decision-making are currently lacking. Preliminary studies suggest potential benefits of some drugs such as lithium (Adida et al., 2015) or behavioral psychotherapy (Oldershaw et al., 2012). One promising technique is neurostimulation of specific brain regions. Transcranial Direct Current Stimulation (tDCS) is a brain stimulation method that targets a specific brain area by altering the neuronal excitability of the cortex under the electrodes and associated brain networks (Brevet-Aeby et al., 2016). It induces immediate and transient elastic effects followed by long-term and lasting plastic effects through the secretion of growth factors (Stagg and Nitsche, 2011). It is a simple, painless, portable, relatively inexpensive, and non-invasive technique (Meron et al., 2015).

Previous research has suggested that tDCS could impact decision-making. In 45 healthy volunteers randomized into two stimulation groups and a sham stimulation group, Ouellet et al. (Ouellet et al., 2015) showed that a single anodal tDCS session targeting the OFC (whether on the left or right side) was effective in improving decision-making measured by the IGT with a large effect size. Similarly, in 42 healthy subjects, Moro et al. (Moro et al., 2023) showed that stimulation of the OFC by anodal tDCS was associated with a decrease in delay discounting. These data suggest that anodal tDCS applied to the OFC could improve decision-making performance. The potential mechanisms underlying this effect may involve a direct facilitatory effect on OFC activity, as well as indirect modulation of other relevant frontal regions such as the dorsolateral prefrontal cortex and anterior cingulate cortex, and subcortical regions including the hippocampus, amygdala, and nucleus accumbens (Ouellet et al., 2015).

The effect of OFC stimulation on other cognitive functions and emotions, as well as the impact of this potential effect on decision-making, should be considered and assessed. Indeed, OFC underlies inhibitory control (Szatkowska et al., 2007) and the stimulation of the OFC has been associated with improved cognitive impulsive control (Ouellet et al., 2015). However, not all decision-making deficits seem to be related to cognitive control deficits (Richard-Devantoy et al., 2013; Toplak et al., 2010). For instance, deficits in the capacity to give an adequate values to options have been postulated in the case of suicidal behavior (Richard-Devantoy et al., 2013).

In this study, we tried to replicate Ouellet's results in a clinical population. The main objective was to demonstrate the possibility of a significant short-term improvement in decision-making performance, measured by the IGT, through active anodal tDCS applied to the OFC compared to sham stimulation in patients with a personal history of major depressive episode. We hypothesized that participants receiving active stimulation would show higher IGT performance than those receiving sham stimulation. This study, therefore, represents a first step toward the development of therapies targeting decision-making in patients with mental disorders.

Secondary objectives were to assess potential mechanisms of changes, notably whether induced changes in decision-making under tDCS were associated with changes in other cognitive functions including inhibition, or self-rated emotions.

2. Methods

2.1. Design, randomization and blinding

This was a prospective, single-center, interventional controlled randomized study comparing active treatment to placebo (sham tDCS) in two parallel groups.

Centralized randomization was implemented through the REDCap software platform using a 1:1 allocation ratio (active stimulation vs. sham stimulation) (Harris et al., 2019). Randomization was stratified by baseline mood state (euthymia vs. current depressive episode) and used randomly permuted blocks of variable sizes to minimize allocation predictability. The block-balanced randomization list, with randomly varying block sizes, was generated by a biostatistician using R software and integrated into the e-CRF within the REDCap software platform (Harris et al., 2019). The investigators had no access to this list and it was strictly impossible for them to predict the randomization group. This approach ensured balanced group assignment while maintaining allocation concealment. This study was single-blind, meaning the patients were unaware of their randomization group, but neither the investigators nor the raters were blinded. The analyses were also conducted blindly, meaning the data analyst was unaware of the randomization group.

This study was approved by the regional ethic committee (Comité de Protection des Personnes Île-de-France) on December 3, 2020 and registered on ClinicalTrials.gov (registration number: NCT06110559).

Recruitment took place between April 16, 2021 and July 19, 2024 at one single location at Clinique des Maladies Mentales et de l'Encéphale (CMME), Sainte-Anne Hospital, Paris, France.

Registration on Clinicaltrials.gov (NCT06110559) was done on October 25, 2023, therefore with delays after the first inclusion due to a non-intentional omission. However, the description of the Randomized Controlled Trial is strictly identical to the protocol approved by the local Institutional Review Board on December 3, 2020, which can be provided on request.

All data have been pseudonymized and directly collected in the coded e-CRF on the REDCap software platform (Harris et al., 2019). The clinical research and investigation department of the GHU Paris ensures the quality control of the study.

2.2. Inclusion and non-inclusion criteria

Inclusion criteria were: male and female out- or inpatients; aged between 18 and 65 years; suffering from a unipolar depressive or bipolar disorder with a current or partially/fully remitted mild to moderate depressive episode, according to DSM-5 criteria; have signed informed consent; with a social security insurance. Non-inclusion criteria were: refusal to participate; insufficient French speaking ability; deprivation of freedom; pregnant or breastfeeding women; current hypomanic, manic, or mixed episode according to DSM-5 criteria; electroconvulsive therapy (ECT) within the last six months; cardiac pacemaker; intracranial electrodes; implantable cardioverter-defibrillator; known epilepsy.

2.3. Procedure and assessment

The pre-inclusion visit involved checking inclusion criteria and giving a clear, fair, and appropriate information with the provision of an

information sheet. A 24-h period was respected before obtaining informed consent.

The inclusion visit took place on day 1 and included signing of consent, a socio-demographic assessment, collection of medical data, psychiatric assessment by an experienced clinician (MD), self-questionnaires, and neuropsychological evaluation. The psychiatric assessment included: Mini International Neuropsychiatric Interview 7.0.0 (MINI-7.0) (Sheehan et al., 1998), Hamilton Rating Scale for Depression (HDRS) (Hamilton, 1960), Hamilton Rating Scale for Anxiety (HARS) (Hamilton, 1959), Young Mania Rating Scale (YMRS), and Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011). Self-questionnaires comprised the Beck Depression Inventory II (BDI-II) (Beck et al., 1961), State-Trait Anxiety Inventory - form Y - trait subscale (STAI-Y-B) (Gauthier and Bouchard, 1993), State-Trait Anger Expression Inventory 2 (STAXI-2) (Spielberger, 1999), Psychological and Physical Pain Visual Analog Scale (PPP-VAS) (Jollant et al., 2019), and Barrat Impulsivity Scale (BIS-11) (Patton et al., 1995). The baseline neuropsychological evaluation included National Adult Reading Test (NART) (Mackinnon and Mulligan, 2005), lexical and categorical fluency tests, and N-back (Sweet, 2011).

The stimulation visit took place on day 2 and included three parts: i) pre-stimulation neuropsychological evaluation; ii) tDCS session; iii) post-stimulation neuropsychological evaluation, and a group guessing test. Pre- and post-stimulation evaluations were strictly identical and included the IGT (Bechara et al., 1994, 1999), Emotional Stroop Test (interference test in emotional context, specifically negative words and death-related words) (Ben-Haim et al., 2016), Go/No-Go (cognitive inhibition test) (Iverson, 2011), d2-Test (attention test) (Gorwood et al., 2014; Zillmer and Brickenkamp, 1998), State-Trait Anxiety Inventory - form Y - state subscale (STAI-Y-A) (Gauthier and Bouchard, 1993), and Positive And Negative Affect Schedule (PANAS) (Watson et al., 1988).

The stimulation visit always took place in the same office, on weekdays during standard working hours. The lighting was the usual ambient lighting of the room (which included both a window and an overhead light). Adjacent offices were soundproofed and used for low-noise consultations, and the window overlooked a quiet and infrequently used pedestrian walkway. No one was present in the room besides the patient and the investigator. The stimulation visit lasted approximately 180 min and was conducted without interruption, either in the morning or in the afternoon. The pre-stimulation assessment lasted approximately 70 min, followed by a 10-min tDCS setup, then a tDCS session lasting exactly 30 min and 30 s, and finally a post-stimulation assessment of approximately 70 min, carried out immediately after the end of the tDCS session. The order of assessments was always the same: IGT, followed by the Emotional Stroop Test, the Go/No-Go task, the d2 Test, the STAI-Y-A, the PANAS, and finally the group guessing test (administered only post-stimulation).

Here, sex (male or female) refers to their official sexual status, not gender.

2.4. Intervention

The tDCS session followed the same procedures as the original study (Ouellet et al., 2015). We used the HDCstim device from Newronika and placed the electrodes according to the EEG 10/20 system (Tu et al., 2021). We chose the left OFC as the target region as previous studies found no side difference (Ouellet et al., 2015) while we aimed at reducing the number of groups. To perform stimulation of the left OFC, the anode was placed over the left supraorbital region at site Fp1, and the cathode was placed over the right supraorbital region at site Fp2. The electrodes were inserted into sponges soaked in saline solution to reduce impedance. We used a small activating anode of 50 × 50 × 1.3 mm (sponge size 60 × 75 × 4 mm), equivalent to 0.04 mA/cm2, which corresponds to a safe current density in accordance with safety recommendations (Ouellet et al., 2015). We used a large inhibitory cathode of 60 × 85 × 1.3 mm (sponge size 85 × 100 × 4 mm) to minimize inhibitory effects on the cortex underneath, which amounts to 0.02 mA/cm2 and is functionally negligible (Ouellet et al., 2015). Stimulation lasted for 30 min, during which a continuous current of 1.5 mA was delivered. An initial current ramp-up preceded the stimulation and lasted for 30 s, during which tingling and itching sensations were most intense. There was no final current ramp-down: the current automatically and abruptly stops, with no gradual decrease, as this is the only possible termination mode of the device and cannot be modified by the investigator.

For patients randomized into the control group, a sham stimulation consisting only of the initial 30-s current ramp-up was administered, followed by 36 s of stimulation, then 29 min and 24 s without stimulation (Ambrus et al., 2012). For reproducibility purposes, patients were instructed to sit still with their eyes closed for the 30-min stimulation period, following the same procedure as the original study. To ensure that the patient does not fall asleep, we talked to them every 5 min, asking if everything was okay, if they were not experiencing any discomfort, and informing them of the remaining time (Ouellet et al., 2015). We finally assessed the quality of blinding using a guessing group assignment-test, which involved a computerized question presented at the end of the study.

To illustrate the distribution of the induced electric field (E-field), we performed a computational simulation using SimNIBS software (Thielscher et al., 2015). We used the “ernie” head model, a standardized anatomical template derived from high-resolution MRI data of a healthy adult male, commonly employed as a realistic and reproducible reference for cranio-cerebral anatomy. The model includes realistic segmentation of five tissue compartments – gray matter, white matter, cerebrospinal fluid, skull, and scalp – with standard isotropic conductivity values assigned to each (Gomez et al., 2021). It also features a detailed tetrahedral cortical mesh that preserves individual gyral and sulcal anatomy, allowing for precise simulation of current flow. Exact implementation of stimulation parameters – including current intensity, electrode placement, and electrode and sponge sizes – yields the simulated E-field distribution presented in Fig. 1.

2.5. Principal outcome: change in decision-making performance

The IGT is a neuropsychological test used to measure decision-making (Bechara et al., 1994, 1999). Four decks of cards are presented on a computer screen. The patient's goal is to earn virtual money by drawing cards from the decks of their choice. The patient is unaware that they will draw 100 cards and that two decks are disadvantageous because they yield large immediate gains but also larger occasional losses, resulting in a long-term loss of money. The other two decks are advantageous, yielding small immediate gains but also smaller occasional losses, resulting in a long-term profit. The patient is naive to these contingencies and must therefore learn through trial-and-errors to avoid the risky decks. The net score is the number of draws from advantageous decks minus the number of draws from disadvantageous decks over the 100 trials.

The primary outcome was the change in pre- vs post-stimulation IGT net score in both arms.

This computerized test was administered using the PEBL software (Mueller and Piper, 2014).

2.6. Number of subjects

Calculating the necessary number of subjects has been complicated by the absence of a similar previous study involving patients. Therefore, for the sample size calculation, we referred to the study by Ouellet et al. conducted in healthy volunteers (Ouellet et al., 2015). It showed a mean change in net score after stimulation of 17.14 ($\sigma = 44.77$) in the experimental left OFC arm compared to −3.86 ($\sigma = 33.91$) in the sham arm. Since the number of subjects was only 15 per arm and the variability of the results was significant, the assumption of normality was

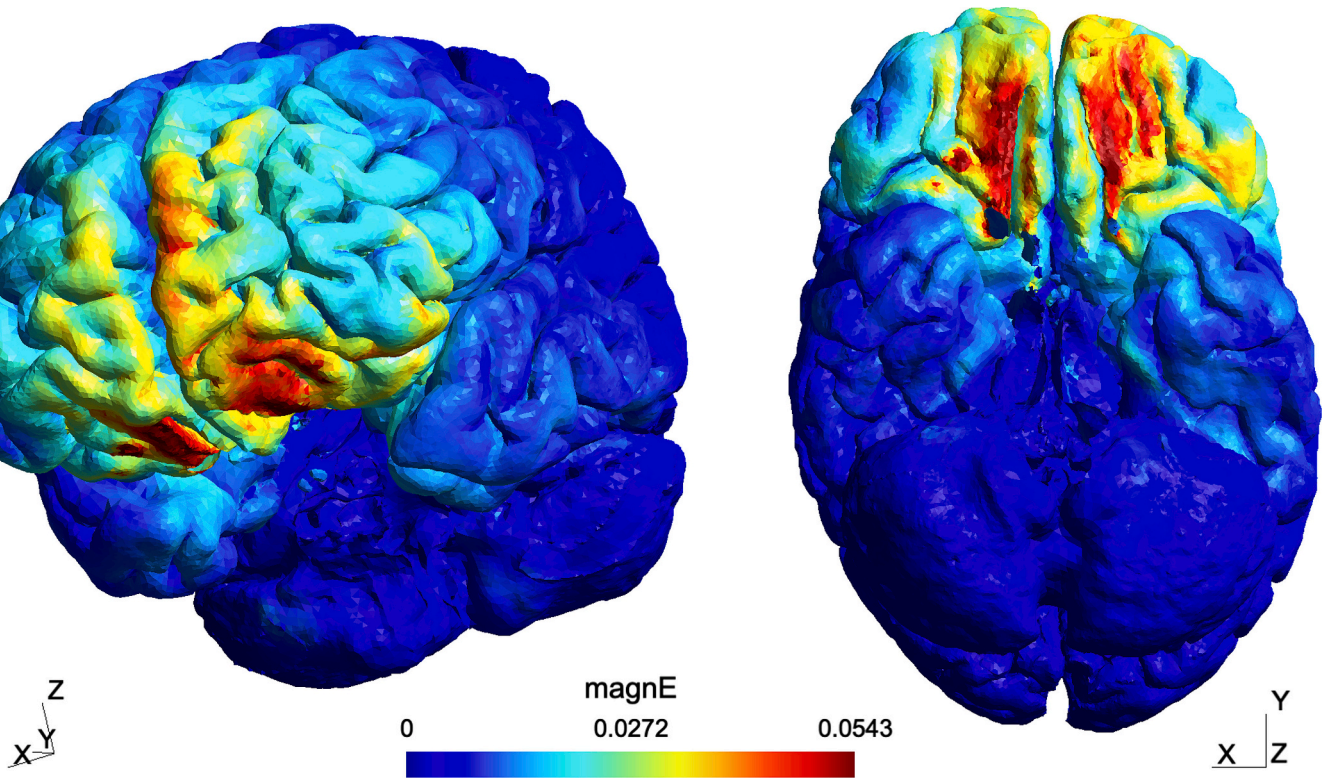

Fig. 1. Title: Current distribution simulation based on SimNIBS. Legend: Simulated electric field induced by the tDCS montage used in the study, computed with SimNIBS using the "ernie" template head model. The anode was placed at Fp1 (according to the EEG 10/20 system) and measured 50 × 50 × 1.3 mm (sponge size: 60 × 75 × 4 mm); the cathode was placed at Fp2 and measured 60 × 85 × 1.3 mm (sponge size: 85 × 100 × 4 mm). Stimulation intensity was 1.5 mA for 30 min. The color scale represents the magnitude of the electric field (magnE) on the cortical surface, expressed in V/m (volts per meter).

considered uncertain. Therefore, a non-parametric Mann-Whitney & Wilcoxon test was used for sample size estimation. Taking a bilateral alpha risk of 5 % and a power of 80 %, and assuming that the same difference between the means of the two experimental arms is achieved at the end of the study, 62 patients per arm were required.

Given the innovative nature of the technique used, an interim analysis was a priori planned when at least 50 % of the planned patients were recruited. After intermediate blind analyses were conducted, the independent data monitoring committee proposed stopping the study before the end of the study due to significant between-arm differences.

2.7. Analysis

Data analyses were conducted blindly regarding the treatment arm, using the Neyman-Pearson hypothesis testing approach with a null hypothesis of no difference. All tests were two-tailed. The alpha risk was set at 5 %, and the beta risk was set at 20 %. The analysis for the primary objective was conducted on an intention-to-treat basis to prevent attrition bias. *t*-tests were used to compare variables between groups. We also employed a linear regression on the variation of the IGT net score with adjustment for the initial IGT net score. To address the main objective, we used a mixed model with the IGT net score as the dependent variable, arm (stimulation or sham) as a fixed between-subjects factor, time (pre- or post-stimulation) as a fixed within-subjects factor, subject as a random factor, and the interaction term "time*arm" reflecting the effect of stimulation on the evolution of the IGT. Fixed effects were evaluated using likelihood ratio tests. We then used the same models on the other variables.

The primary outcome is defined as the test of the null hypothesis for the interaction term "time*arm" of the mixed model with the IGT net score as the dependent variable.

The partial eta squared (ηp^2) for the time*arm interaction was furthermore estimated based on the F statistic obtained using the Kenward-Roger correction. This effect size is an approximation based on the F-distribution, and while not formally defined for mixed models, it is commonly used as a practical and interpretable estimate for fixed effects in such contexts (Lakens, 2013; Ouellet et al., 2015). It was also used in the previous study by Ouellet et al. (Ouellet et al., 2015). We therefore computed it for comparison purposes.

Analyses were performed using the SPSS software (IBM Corp. Released 2019. IBM SPSS Statistics for Macintosh, Version 26.0. Armonk, NY: IBM Corp.).

3. Results

3.1. Population

Details on participant inclusion and exclusion are provided in the flow diagram (Supplementary Fig. 1).

Sixty-two patients were included, randomized for 30 in the active stimulation arm (Stim) and for 32 in the placebo stimulation arm (Sham). Randomization yielded comparable groups as shown in Table 1. The patients were on average 36.8 (Stim) and 40.7 (Sham) years old; 63.3 % and 68.8 %, respectively, were females. 66.7 % and 68.8 % of the patients were currently depressed, 26.7 % and 28.1 % had bipolar disorders, and 3.3 % and 12.5 % had a personal history of suicide attempt.

3.2. Primary objective: IGT net score

The absolute variation in the IGT net score (pre-post tDCS) was significantly greater in the Stim compared to the Sham group ($t = 2.04$; $p = .045$) (Fig. 2). The linear regression on the variation of the IGT net score with adjustment for the pre-stimulation IGT net score showed a significant effect of the treatment arm on the improvement of the IGT

Table 1
Baseline sociodemographic, clinical and neuropsychological description of the two groups randomized for active or sham tDCS arms.

	Stim (n = 30)	Sham (*n* = 32)
	μ (σ)	μ (σ)
Age	36.80 (14.30)	40.70 (15.60)
HDRS	13.62 (7.98)	15.69 (8.67)
HARS	13.17 (9.10)	14.38 (7.40)
BDI-II	27.50 (11.83)	29.22 (13.51)
PANAS positive score	26.72 (7.33)	24.94 (7.97)
PANAS negative score	17.67 (7.59)	17.19 (8.72)
STAI-Y-A state score	43.03 (13.51)	43.50 (13.53)
STAI-Y-B trait score	56.67 (9.27)	52.88 (12.31)
STAXI-2 state score	21.00 (8.36)	20.56 (8.58)
STAXI-2 trait score	22.23 (6.10)	21.00 (7.44)
BIS-11	63.80 (11.50)	65.20 (15.30)
PPP-VAS psychache mean	62.47 (24.13)	66.81 (25.50)
PPP-VAS suicidal mean	26.10 (24.87)	39.94 (33.23)
National Adult Reading Test	27.43 (4.24)	26.22 (5.88)
Categorial fluency	19.70 (3.67)	19.19 (5.80)
Lexical fluency	11.17 (5.19)	12.00 (3.97)
N-back 1-back performance	5.20 (1.77)	5.41 (1.76)
N-back 2-back performance	3.77 (1.92)	3.84 (1.92)
N-back 3-back performance	2.63 (1.67)	2.25 (1.50)
N-back 1-back accuracy	0.88 (0.17)	0.91 (0.16)
N-back 2-back accuracy	0.69 (0.29)	0.71 (0.26)
N-back 3-back accuracy	0.63 (0.27)	0.62 (0.28)
d2-Test omission error (F1)	17.33 (13.45)	19.61 (18.22)
d2-Test commission error (F2)	3.74 (7.26)	3.77 (4.39)
d2-Test total error (F)	18.97 (14.97)	22.66 (18.74)
d2-Test total signs correctly marked (BR)	168.37 (53.54)	172.90 (50.25)
d2-Test quantitative performance (GZ)	444.79 (114.23)	442.73 (115.16)
d2-Test error rate (F%)	5.28 (4.32)	5.41 (4.21)
d2-Test global performance (GZ-F)	423.04 (109.23)	419.90 (119.30)
Go/No-Go reaction time	106.29 (39.00)	127.31 (53.03)
Go/No-Go commission error	7.33 (5.98)	5.84 (4.64)
Go/No-Go inverted contingency reaction time	105.22 (34.53)	117.00 (56.07)
Go/No-Go inverted contingency commission error	7.07 (6.69)	6.13 (6.03)
Emotional stroop depression index	−44.90 (680)	110.20 (899)
Emotional stroop suicide index	−463.90 (788)	−455.50 (1117)
Emotional stroop positive index	−97.17 (509.89)	−13.22 (1396.75)
IGT net score	11.50 (26.20)	9.30 (28.80)
	n (%)	n (%)
Female	19 (63.3)	22 (68.8)
Unemployed	16 (53.3)	14 (43.8)
Single	16 (53.3)	17 (53.1)
Currently hospitalized	26 (86.7)	29 (90.6)
Current depressive episode	20 (66.7)	22 (68.8)
Bipolar disorder	8 (26.7)	9 (28.1)
History of suicide attempt	1 (3.3)	4 (12.5)
Social phobia	9 (30.0)	2 (6.3)
Panic disorder	5 (16.6)	3 (9.4)
Agoraphobia	0 (0.0)	1 (3.1)
Generalized anxiety disorder	6 (20.0)	7 (21.9)
Obsessive compulsive disorder	0 (0.0)	1 (3.1)
Post-traumatic stress disorder	3 (10.0)	6 (18.8)
Attention deficit disorder	1 (3.3)	2 (6.3)
Anorexia nervosa	3 (10.0)	4 (12.5)
Bulimia nervosa	5 (16.7)	5 (15.6)
Alcool use disorder	7 (23.3)	5 (15.6)
Substance use disorder	5 (16.6)	6 (18.8)
Psychotic disorder	0 (0.0)	0 (0.0)
Antidepressant	23 (76.7)	26 (81.3)
Antipsychotic	21 (70.0)	24 (75.0)
Anticonvulsant	8 (26.7)	8 (25.0)
Lithium	5 (16.7)	6 (18.8)
Anxiolytic	12 (40.0)	10 (31.3)

Legend: μ: mean; σ: standard deviation; BIS: Barratt impulsiveness scale; BDI: Beck depression inventory; HARS: Hamilton anxiety rating scale; HDRS: Hamilton depression rating scale; IGT: Iowa gambling task; n: number; PANAS: Positive and negative affective schedule; PPP-VAS: Physical and psychological pain – visual analog scale; Sham: Sham tDCS; STAI-Y-A: State-trait anxiety inventory – form Y – state subscore; STAI-Y-B: State-trait anxiety inventory – form Y – trait subscore; STAXI-2: State-trait anger expression inventory; Stim: Active tDCS; tDCS: Transcranial direct current stimulation.

net score ($t = 2.09$; $p = .041$) in favor of active stimulation. The mixed model on the IGT net score showed a significant time*arm interaction ($\chi^2 = 4.10$; $p = .043$) in favor of active stimulation, with a moderate approximated effect size ($\eta p^2 = 0.065$) (Table 2).

3.3. Secondary objectives

No significant change in performance was found for the d2-Test, the Go/No-Go and the Emotional Stroop test. Similarly, no significant change in scores was found for the PANAS and the STAI-Y-A (Table 2).

3.4. Quality of blinding

No significant difference was observed between the two groups regarding the guessing group assignment-test ($\chi^2 = 0.99$; $p = .319$).

3.5. Neuropsychological correlations

After Bonferroni correction (p-value threshold = 0.003), significant correlations were only found between the IGT net score and Go/No-Go reaction time under normal contingency before ($r = -0.41$; $p = .001$) and after ($r = -0.42$; p = .001) the stimulation (Table 3).

4. Discussion

In this study, we found that one session of tDCS applied to the left OFC in patients with a mood disorder improves decision-making performance as measured by the IGT in the short-term. Our study, therefore, replicates in patients a previous study in healthy people (Ouellet et al., 2015). Although our approximated effect size is smaller than the one reported by Ouellet et al., it still indicates a moderate effect in a clinical population, and supports its potential clinical relevance (Ouellet et al., 2015). Moreover, this improvement appears to be independent of changes in other cognitive functions - including attention, working memory and cognitive control - or perceived emotions. These findings represent a promising first step toward the use of brain stimulation to improve an important endophenotype and vulnerability neurocognitive trait of many mental disorders.

In addition to the initial study (Ouellet et al., 2015), several studies have investigated the effect of OFC stimulation on decision-making. Moro et al. showed that activating tDCS over the OFC (anode at Fp1) was associated with a decrease in delay discounting (Moro et al., 2023). Two studies further demonstrated that continuous theta burst stimulation (cTBS), an inhibitory stimulation of the OFC, impaired value attribution and decision-making (Howard et al., 2020; Wang et al., 2020). Yu et al. observed that activating tDCS of the OFC (anode at Fp1) decreased regret regarding outcomes after decision-making (Yu et al., 2021), while Van't Wout et al. observed that inhibitory tDCS of the OFC (cathode at Fp1) decreased relief regarding outcomes after decision-making (van't Wout and Silverman, 2017). These data suggest that activating stimulation of the OFC may improve decision-making performance, through various mechanisms comprising value attribution, emotional evaluation of outcomes, or the modulation of values over time.

Findings from our study shed some additional lights on potential mechanisms. First, we did not find any improvement in attention, working memory and cognitive inhibition following tDCS of the left OFC, suggesting that observed improvement in IGT decision-making in our patients was not related to changes in these processes. Indeed, both the complex IGT and the OFC have previously been associated with

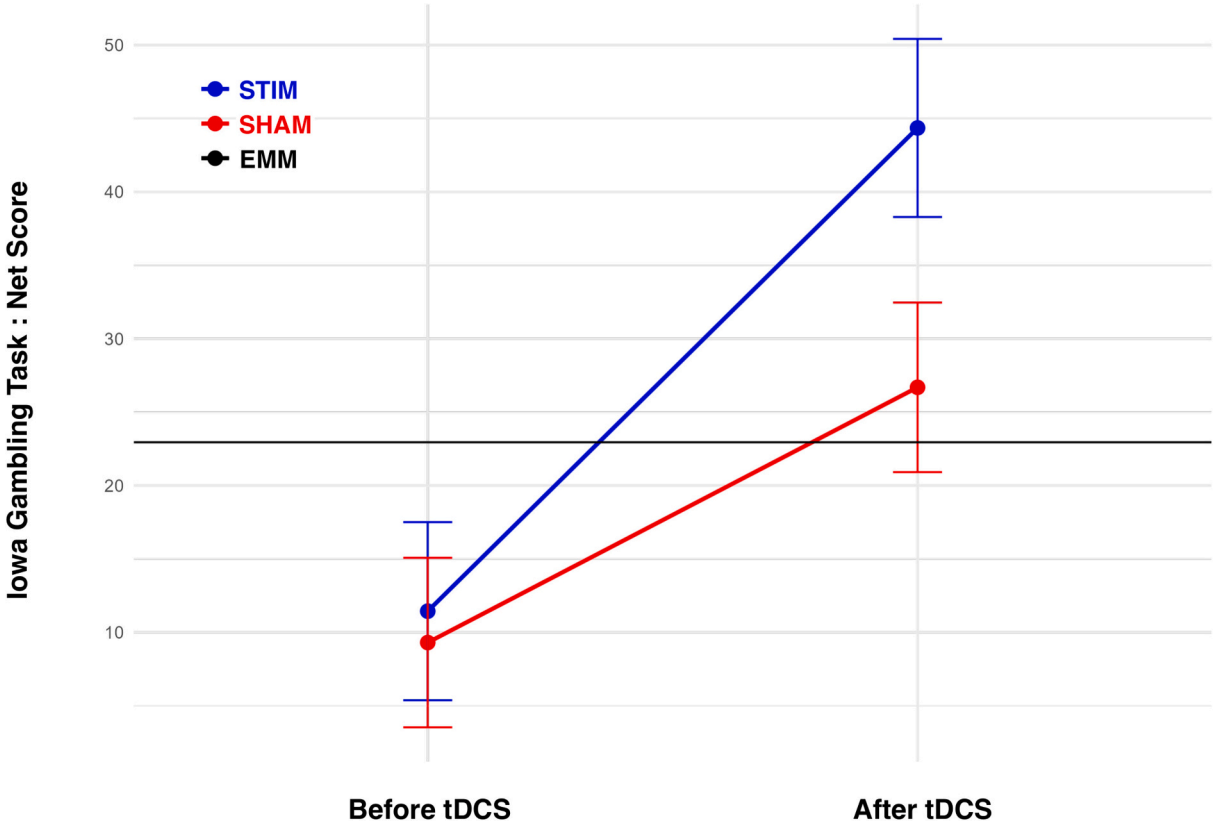

Fig. 2. Title: Iowa Gambling task (IGT) net scores before and after active or sham transcranial Direct Current Stimulation (tDCS) over the left orbitofrontal cortex. Legend: EMM: Estimated marginal means; SHAM: Sham tDCS stimulation; STIM: Active tDCS stimulation.

attention, inhibitory control, and working memory. Damage to the OFC has been associated with deficits in working memory, but only in non-pure tasks involving other executive functions (Barbey et al., 2011). OFC lesions have also been linked to impaired inhibitory control (Szatkowska et al., 2007). In rats, OFC lesions have been associated with impaired Go/No-Go performance, but only in contingency reversal tasks (Schoenbaum et al., 2002). In humans, tDCS of the OFC has been linked to improvements in cognitive but not motor control (Ouellet et al., 2015). Beyond simple inhibition, the OFC may play a role in supporting one action over another and in latent inhibition, which aligns more closely with decision-making (Bryden and Roesch, 2015; Costa et al., 2021). Bechara et al. observed independent processing of working memory by the dorsolateral prefrontal cortex and decision-making by the ventromedial prefrontal cortex, but these results were based on a small sample size (Bechara et al., 1998). Moreover, if anterior OFC damage impairs decision-making without affecting working memory, posterior OFC damage impairs both cognitive functions (Bechara et al., 1998). However, Toplak et al.'s review suggests that the IGT is largely independent of other executive functions (Toplak et al., 2010). In 260 suicide attempters, Richard-Devantoy et al. (Richard-Devantoy et al., 2013) also observed that impaired performance in IGT was largely independent of working memory, attention, and inhibition. Regarding inhibition, Toplak et al. showed that the vast majority of studies found no significant correlation between the IGT and inhibition (Toplak et al., 2010). Additionally, Richard-Devantoy et al. reported only a weak correlation between the IGT and the Hayling test penalties score, while no significant correlation was found between the IGT and either the Hayling test reaction time or the Stroop color test (Richard-Devantoy et al., 2013). In our sample, we only observed a correlation between the IGT and the Go/No-Go reaction time before and after stimulation but not under reversed contingencies. In sum, changes in IGT performance following tDCS do not seem to be explained by changes in attention, working memory or cognitive control.

Finally, we tested the possibility that improvement in emotion perception would improve decision-making. Indeed, Vinckier et al. (Vinckier et al., 2018) have shown that inducing sadness alters decision-making using a precision challenge task. In our study, we did not find any variation in emotions associated with tDCS of the left OFC, suggesting that in our sample, improvement in risky decision-making performance was not related to changes in emotion perception.

Following these findings, one hypothesis could be that stimulation of the OFC improves the implicit valuation of the risk attributed to each option. It has indeed been proposed that the OFC allows for the attribution of values to guide choices and the modulation of this value by risk, ambiguity and delay (Rangel et al., 2008; Zha et al., 2022). More specifically, Zha et al. have recently shown that the OFC represents advantageous choice and that IGT performance was correlated with advantageous choice representation in the OFC (Zha et al., 2022). OFC stimulation would enable patients to favor advantageous choices, resulting in an improvement of the IGT net score. The OFC is also involved in choice and value coding, and its stimulation has also been associated with a decrease in delay discounting (Moro et al., 2023; Zha et al., 2022). OFC stimulation by tDCS could improve the IGT net score by allowing patients to attribute adequate values to risk level (here, the comparison between short-term and long-term reward and punishments) and choose with a better appreciation of long-term outcomes.

Several limitations have to be underlined. First, tDCS is imprecise. While we targeted the OFC, tDCS also affects the medial part of the anterior frontopolar cortex, a region that could be responsible for the most complex and abstract cognitive functions. This region is not activated in simple cognitive tasks that exclusively involve working memory or divided attention but seems to mediate the ability to keep primary goals in mind while exploring and executing secondary objectives (Koechlin et al., 1999). These skills are essential for associative

Table 2
Comparison of pre- vs post-tDCS variations in measured variables between the randomization arms (sham or stim tDCS).

	Variation comparison+		Linear regression adjusted on baseline score++		Mixed model+++	
	t	p	t	p	χ^2	p
IGT net score	2.04	**0.045***	2.09	**0.041***	4.10	**0.043***
d2-Test omission error (F1)	−0.78	0.440	−0.84	0.405	0.41	0.520
d2-Test commission error (F2)	1.53	0.134	0.21	0.836	2.22	0.137
d2-Test total error (F)	−1.59	0.116	−0.67	0.508	2.55	0.110
d2-Test total signs correctly marked (BR)	−0.99	0.328	−0.06	0.949	0.00	0.976
d2-Test quantitative performance (GZ)	−1.00	0.323	−0.21	0.838	0.00	0.945
d2-Test error rate (F %)	−1.49	0.144	−0.92	0.360	2.38	0.123
d2-Test global performance (GZ-F)	−0.65	0.516	0.91	0.365	0.41	0.521
Emotional stroop depression index	0.61	0.548	−0.04	0.966	0.34	0.557
Emotional stroop suicide index	1.16	0.251	−1.18	0.244	1.53	0.217
Emotional stroop positive index	0.06	0.954	0.07	0.942	0.02	0.885
Go/No-Go reaction time	1.08	0.286	−0.31	0.754	1.14	0.286
Go/No-Go commission error	1.66	0.102	−1.56	0.123	2.68	0.101
Go/No-Go inverted contingency reaction time	−0.45	0.657	0.83	0.412	0.19	0.659
Go/No-Go inverted contingency commission error	0.58	0.565	−0.76	0.447	0.33	0.564
PANAS negative score	0.03	0.979	−0.13	0.893	0.00	0.964
PANAS positive score	−0.01	0.989	−0.18	0.860	0.01	0.936
STAI-Y-A state score	0.71	0.483	−0.59	0.561	0.33	0.568

Legend: *: statistically significant at $p < .05$; +: Variation comparison between the two arms; ++: Variation comparison between the two arms adjusted on baseline score; +++: Null hypothesis test of the arm*time interaction factor in the mixed model; χ^2: Chi-square score; p: *p* value; PANAS: Positive and negative affective schedule; STAI-YA: State-trait anxiety inventory state score; t: t test.

Table 3
Correlations between the IGT net score and other neuropsychological measures.

	Pre tDCS		Post tDCS	
IGT net score	r	p	r	p
d2-Test omission error (F1)	0.10	0.445	0	0.988
d2-Test commission error (F2)	−0.04	0.781	−0.12	0.376
d2-Test total error (F)	0.04	0.735	−0.06	0.624
d2-Test total signs correctly marked (BR)	0.09	0.529	0.21	0.114
d2-Test quantitative performance (GZ)	0.08	0.560	0.20	0.129
d2-Test error rate (F%)	0.10	0.445	0	0.361
d2-Test global performance (GZ-F)	−0.03	0.821	0.05	0.685
Emotional stroop depression index	0.28	0.027	−0.11	0.395
Emotional stroop suicide index	0.20	0.129	−0.07	0.608
Emotional stroop positive index	0.14	0.271	−0.19	0.138
Go/No-Go reaction time	−0.41	**0.001***	−0.42	**0.001***
Go/No-Go commission error	−0.01	0.942	−0.02	0.899
Go/No-Go inverted contingency reaction time	−0.29	0.021	−0.36	0.004
Go/No-Go inverted contingency commission error	−0.01	0.926	−0.09	0.500
PANAS negative score	0.06	0.645	−0.33	0.008
PANAS positive score	−0.38	0.003	0.14	0.295
STAI-Y-A state score	−0.29	0.025	−0.33	0.010

Legend: *: statistically significant at $p < .003$ after Bonferroni correction; p: p value; PANAS: Positive and negative affective schedule; r: Pearson correlation coefficient; STAI-YA: State-trait anxiety inventory state score.

combination, creativity, reasoning, planning, and problem-solving. Therefore, stimulating this region is unlikely to alter the simple cognitive functions explored in this study, but its impact on decision-making is hard to predict. Domenech and Koechlin (Domenech and Koechlin, 2015) proposed that the frontopolar region plays a role in the central decision-making system involved in arbitrating between the exploitation/adjustment of previously learned behavioral sets and the exploration/creation of new ones for effective adaptive behavior. This function could be useful in decision-making under conditions of ambiguity/uncertainty and may contribute to improved net scores at the IGT. Finally, our intervention could potentially enhance participants' creativity and planning, thereby improving their problem-solving abilities and possibly protecting them from a suicidal crisis according to Beck's cognitive-behavioral model (Beck et al., 1975). Interestingly, it is worth noting that our stimulation seems to target more the medial OFC than the lateral OFC, a region specifically associated with the representation of advantageous choices (Zha et al., 2022). This observation is important because, during depression, the altered connectivity of the medial OFC and its low sensitivity to reward have been associated with anhedonia, in contrast to the lateral OFC, whose high connectivity and high sensitivity to punishment have been associated with negative bias (Zhang et al., 2024). Of note, the electric field intensity observed in our simulation within the OFC (about 0.05 V/m) is consistent with previous studies employing similar tDCS configurations and simulation methodologies (Herrojo Ruiz et al., 2021). This low intensity is attributable to the anatomical depth and ventral positioning of the OFC, which inherently attenuates the electric field compared to more superficial cortical targets. Moreover, it is important to note that the threshold for effective neuromodulation in tDCS remains to be definitively established (Esmaeilpour et al., 2018).

A second limitation of our study is that it did not assess the persistence of the effect. This proof-of-concept study mainly aimed to verify the possibility of improving decision-making after a single session of tDCS over the OFC. Repeated tDCS sessions could yield significant and stable delayed plastic effects (Agboada et al., 2020; Au et al., 2017). Thus, evaluating the persistence of the effect will have to be considered in a protocol involving multiple stimulation sessions for each patient. Furthermore, the duration of the immediate effects of a single session of anodal tDCS varies depending on the stimulation parameters and across studies. Some teams have reported cortical excitability enhancements lasting up to 90 min (Nitsche and Paulus, 2001), while others observed effects lasting only 30 min (Agboada et al., 2020). Given that the average duration of the post-stimulation assessment was 70 min, it is possible that, during the tasks and evaluations occurring toward the end of this period, the effect of the stimulation might have diminished or even dissipated. This could increase the risk of a Type II error. To mitigate this potential issue, we fixed the order of the assessments so that the IGT was always administered first, ensuring that all patients completed the IGT entirely within the first 30 min following stimulation. While this approach allows for an accurate evaluation of the effect of our intervention on the primary outcome, the results for secondary outcomes – assessed later – might be biased due to the waning of the stimulation effect. Further studies specifically targeting these secondary outcomes are warranted.

A third limitation of this study is the absence of a standardized cognitive task during stimulation. Cognitive activity during stimulation influences the effects of tDCS on post-stimulation performance (Bikson and Rahman, 2013; Gill et al., 2015). Not controlling this activity impacts reproducibility, and the lack of a neutral cognitive task during stimulation in our protocol is therefore a potential source of noise and variability in the results, leading to an increased risk of Type II error and decreased power. Nevertheless, the neurocognitive impact of using such a task during stimulation is hard to predict and could influence our results, thus complicating their interpretation. Moreover, our study requires the patient to remain still and close their eyes during stimulation, which reduces variability in brain activity, and these stimulation

modalities have been effective in demonstrating a difference compared to the sham group in the original study (Ouellet et al., 2015).

A fourth limitation of this study is the single-blind design, which introduces three risks of classification bias: follow-up bias, detection bias, and performance bias. Nevertheless, using an objective, consensual, valid, reproducible, and quantifiable primary outcome measure like the IGT net score helps limit detection and performance biases. Moreover, all primary and secondary outcomes relied on computerized standardized tasks that did not involve raters, thereby limiting those biases. More anecdotally, the variable size of randomization blocks helps limit follow-up classification bias. Replicating this study with a double-blind design will be necessary. Of note, the guessing group assignment test did not show any difference between the two groups. Also, as with any single-center study, a selection bias of the center effect type is potentially present, and replicating this study in a multicenter format could be relevant. In our sample, the proportions of patients with bipolar disorder, eating disorders, and substance use disorders were higher than those reported by other research teams (Wu et al., 2024). These differences may be explained by the fact that the recruitment site includes several specialized units dedicated to the treatment of bipolar disorder, eating disorders, and substance use disorders. This overrepresentation should be taken into account when considering the generalizability of our findings. Replication in other diagnostic groups is therefore needed.

Finally, several sham tDCS modalities have been proposed to evaluate the effectiveness of tDCS (Ambrus et al., 2012; Palm et al., 2013). We chose to use the same modalities as the original study within the limits imposed by our device manufacturer (namely 6 additional seconds of effective stimulation for the sham group) (Ouellet et al., 2015).

In conclusion, this pilot study supports the use of tDCS to improve decision-making measured by the IGT in patients with mood disorders. Future studies should explore the best strategies to have sustained enhancing effects on a crucial endophenotype and vulnerability trait. In the long term, the results of this study and subsequent ones could lead to a substantial modification of our practices. tDCS aiming at improving decision-making could be used in clinical practice in an individualized fashion. It may benefit many individuals suffering from severe neuropsychiatric conditions associated with decision-making deficits, but also those with a personal history of a violent suicide attempt or a family history of suicide, or childhood abuse histories, thereby offering additional therapeutic options to caregivers and patients.

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CRediT authorship contribution statement

M. Danon: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **R. Perrain:** Writing – review & editing, Conceptualization. **Ph. Gorwood:** Writing – review & editing. **F. Jollant:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Philip Gorwood reports a relationship with Angelini that includes: board membership, consulting or advisory, and speaking and lecture fees. Philip Gorwood reports a relationship with Janssen that includes: board membership, consulting or advisory, and speaking and lecture fees. Philip Gorwood reports a relationship with Lundbeck that includes: board membership, consulting or advisory, and speaking and lecture fees. Philip Gorwood reports a relationship with Otsuka that includes: board membership, consulting or advisory, and speaking and lecture fees. Philip Gorwood reports a relationship with Viatris that includes: board membership, consulting or advisory, and speaking and lecture fees. Rebecca Perrain reports a relationship with Janssen that includes: travel reimbursement. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data are available from the corresponding author upon reasonable request.

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