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Transcranial direct current stimulation combined with cognitive training improves decision making and executive functions in opioid use disorder: a triple-blind sham-controlled pilot study

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ABSTRACT

Background: Opioid use disorder (OUD) is a chronic disorder with a considerable amount of morbidity and mortality. Despite remarkable improvement achieved by maintenance programs, an array of treatment goals were still unmet. Mounting evidence suggests that transcranial Direct Current Stimulation (tDCS) improves decision making and cognitive functions in addictive disorders. tDCS paired with a decision making task was depicted to diminish impulsivity as well.

Objectives: The present study aimed to assess the effect of tDCS combined with cognitive training (CT) in OUD for the first time.

Methods: In this triple-blind randomized sham-controlled pilot study, 38 individuals with OUD from the Buprenorphine-Naloxone Maintenance Therapy program were administered 20-minutes of 2 mA active/sham tDCS over the dorsolateral prefrontal cortex with concomitant cognitive training. A selected test battery evaluating decision making under risk and ambiguity as well as executive functions, verbal fluency and working memory was utilized before and after the intervention.

Results: Greater improvements were observed in decision making under ambiguity ($p = 0.016$), set shifting ability and alternating fluency while no improvements were observed in decision making under risk in the active group, compared to sham.

Conclusions: Deficits of decision making and executive functions have a pivotal role in the perpetuation and the relapse of the OUD. Alleviation of these impairments brought tDCS/CT forth as an expedient neuroscientifically-grounded treatment option that merits further exploration in OUD, Trial registration: NCT05568251.

Introduction

Opioid Use Disorder (OUD) is an urgent public health concern and one of the crucial causes of drug-related deaths with disconcertingly increasing prevalence rates irrespective of what policies are put in place.[1,2] A substantial amount of increase in the rate of treatment-seeking was observed in OUD after the utilization of opioid agonist maintenance programs as a mainstay in the last decades and buprenorphine treatment resulted in better outcomes than other treatment options.[3] Nevertheless, relapse rates up to 73% in six-months,[4] and numerous other unmet treatment goals still abide.[5] Thus, the employment of multiple concomitant strategies like non-pharmacological treatments is suggested to reduce harm reduction at the utmost.[2]

Similar to other addictive disorders,[6–9] cognitive dysfunction and decision making deficits on account of both premorbid factors and deleterious

drug-related effects have frequently been observed in individuals with OUD[10–12] and have been associated with a lower probability of remission and successful social interaction.[10,13] Thus far there is scanty evidence on whether these deficits renovate throughout the treatment in OUD.[11] Contrarily, these deficits seem to be irrespective of the current phase of the treatment as no difference in decision making deficits between short and long-term abstinent opioid users were observed[14] and substance use parameters have not been associated with decision making deficits.[15] Apart from these, there has also been no difference between active opioid users and individuals in the methadone maintenance therapy in deficits of response inhibition[16] which have also been associated with drug use.[17] Indeed, the duration of the drug exposure might be the principal factor underlying decision making[18] and executive function deficits.[19] Consistently, a meta-analysis also reported that the length of abstinence has not been associated with decision making deficits.[20] Additionally, both current or previous heroin users showed relatively lower activation in the right dorsolateral prefrontal cortex (DLPFC) during decision making.[21] In this context, the degree of gray matter deficits and resting-state abnormalities in the right DLPFC that have been built over time have been considered to be the outstanding cause of these deficits.[22] Overall, accumulating evidence revealed the need for novel treatments particularly targeting decision making deficits in OUD. To this end, neuromodulatory treatments have been suggested with regard to a conceptual neurocognitive framework in addictive disorders[23,24] and OUD.[25]

Transcranial Direct Current Stimulation (tDCS) is a noninvasive brain stimulation technique that has distinguishing features such as remarkable safety, tolerability and easy applicability.[26] Similar to multitudinous encouraging results of tDCS over the DLPFC in individuals with addictive disorders in both clinical[23,27] and cognitive[28] outcomes, preliminary results of tDCS in OUD have been reported to decrease subjective craving,[29–31] craving induced by heroin cues,[32] depression,[31,33] anxiety,[29,31,33] impulsivity,[34] slow brain waves[35] and to increase serum Brain Derived Neurotrophic Factor levels.[29] On the other hand, there is a dearth of research regarding the effect of tDCS on cognitive functions in individuals with OUD.[36] Besides, cognitive training (CT) is another neuroplasticity-based modality to improve both cognitive and clinical outcomes[37,38] though only a few studies utilized CT in OUD, with thriving improvements in cognitive functions and decision making.[13,39,40]

Current research in the field of cognitive neuroscience also focused on the combination of tDCS with CT approaches[27] to achieve a synergistic effect on cognitive functions. Regarding the concomitant use of tDCS with CT, a pioneering study adopted a more direct approach focusing on decision making.[41] The authors reported improved decision making after tDCS paired with a Risk Task in a clinically impulsive sample of war veterans.[41] Bearing these in mind, concomitant use of tDCS with CT focusing on decision making might be beneficial to rewire the addicted brain though it has not been tested in OUD yet. We aim to assess the effect of bilateral tDCS over the DLPFC concurrent with the Game of Dice Task (GDT) on frontal functions. The GDT was adopted as it is an objective risky decision making task with explicit rules and sturdy links with working memory and executive functions,[42] and individuals with OUD had shortfalls in both these domains and decision making.[43] We hypothesized that tDCS over the DLPFC concurrent with CT might improve cognitive functions in individuals with OUD.

Methods

Participants

The present study sample consisted of 38 individuals diagnosed as having moderate or severe Opioid Use Disorder (OUD) in compliance with DSM-5.[44] Participants were recruited from the Buprenorphine Naloxane Maintenance Therapy (BNMT) program of the AMATEM Clinic (Alcohol and Drug Research, Treatment and Training Center), Bakirköy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery if they met the following criteria: Being aged between 18–65 years, being in the maintenance phase of the OUD treatment, naivety to tDCS, at least 5 years of education. Participants were discarded if they had a current diagnosis of major depressive disorder, current diagnosis or

history of bipolar disorders, psychotic disorders, neurocognitive disorders, pervasive developmental disorders, mental retardation, severe neurological disorders, or common tDCS contraindications.

The present study was in accordance with the Declaration of Helsinki. Ethical approval was obtained for the present study (Approving body: İstanbul Bakırköy Dr. Sadi Konuk Research and Training Hospital, Clinical Research Ethical Committee, Approving body: İstanbul Bakırköy Dr. Sadi Konuk Research and Training Hospital, Approval number: Decision number: 2019/03/14 (File number 2019/66)). Trial registration was performed in Clinicaltrials.gov website (NCT05568251). All participants provided written informed consent. The primary outcome measures of the study were the changes in the measures of decision making under risk and ambiguity. Secondary outcome measures included the changes in response inhibition, executive functions, working memory, and verbal fluency.

Procedures

CONSORT Flow Diagram of the study is illustrated in Figure 1. Participants were allocated into active and sham groups (1:1 ratio) to receive active or sham tDCS concurrent with CT. Assessments of selected cognitive functions were performed before and immediately after the intervention protocol. Assessors were blinded and not involved in the recruitment, tDCS administration, and statistical analysis phases.

Baseline clinical evaluation

Duration of the OUD, duration of the individuals in the BNMT program, current dose of the buprenorphine-naloxone, and maximum dose of the buprenorphine-naloxone during the BNMT program were questioned. The Penn Drug Craving Scale (adapted from the Penn Alcohol Craving Scale) was administered to assess the degree of
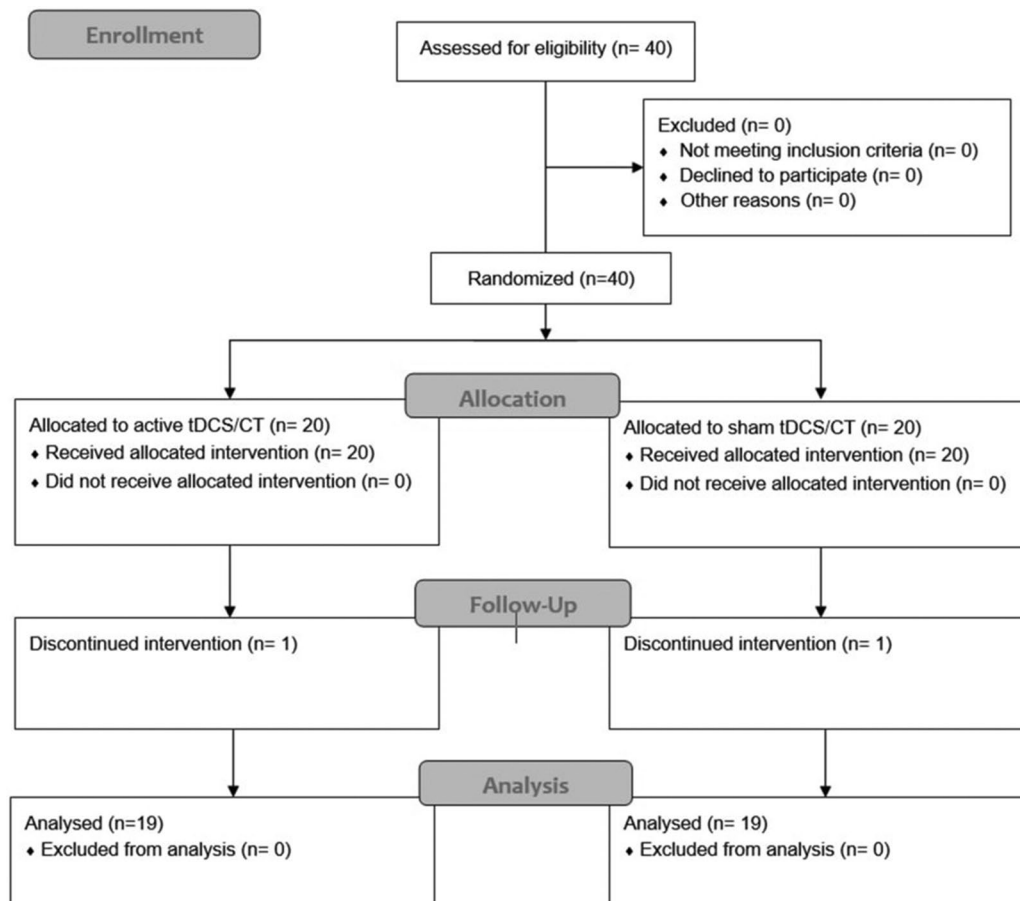

Figure 1. Flow diagram of the study.

current heroin craving.[45] The Beck Depression Inventory (BDI)[46] and the Beck Anxiety Scale (BAS)[47] were administered to determine depression and anxiety levels.

Neurocognitive evaluation

A selected neurocognitive battery was used to assess decision making under risk and ambiguity, attention, executive functions, response inhibition, working memory and verbal fluency. Decision making under ambiguity was assessed with the Iowa Gambling Task (IGT) Net score[48] while decision making under risk was assessed with the Adjusted Number of Pumps in the Balloon Analogue Risk Task (BART).[49] Response inhibition was assessed with the Stop Signal Reaction Time in the Stop-Signal Task. Stroop Test Interference Time was used to assess cognitive inhibition and executive functions.[50] Digit span forward and backward subtests and Letter Number Sequencing (LNS) subtests of the Wechsler Adult Intelligence Scale[51] were used to assess short-term memory and working memory. Phonemic (K-A-S letters), semantic (animal), and alternating (name-fruit pairs) fluency tests were used to assess verbal fluency. Trail Making Test (TMT) A and B Times were used to assess attention and executive functions.

Transcranial direct current stimulation

A single 20-minute 2 mA session of right anodal/left cathodal tDCS over the DLPFC with a 30 s ramp-up and ramp-down of current using two 5×7 cm electrodes was administered using a Neuroconn DC Stimulator Plus (Neuroconn Group, Ilmenau, Germany) device. The electrode montage selection was made regarding bilateral tDCS studies depicting improved decision making in healthy individuals[52] and individuals with gambling disorder.[53] Imitation of the sensations during active tDCS was achieved via a 30 s ramp-up and ramp-down in the sham tDCS protocol. Blinding of the investigator and the participant was accomplished by using pre-programmed codes of the Neuroconn stimulator.

During tDCS, participants were sitting on a comfortable chair and completed CT protocol on a 15" laptop screen. Adverse events during tDCS were questioned to compare between-group differences.

Cognitive training protocol

GDT[42] was administered three times (18*3 trials) consecutively during the tDCS session after the initial three minutes. In every trial of the task, a single dice was thrown and participants were asked to predict the value of the dice. Participants were allowed to select 1–4 numbers as the value of the dice and the selection of a single number meant the highest degree of bet (the riskiest option) while the selection of 4 numbers meant the lowest degree of bet. For instance, when the participant selected the numbers "1-3-5-6", the participant won the bet but earned the minimum prize when the value of the dice was one of these numbers.

Statistical analysis

All statistical analyses were conducted in SPSS for Windows 25.0 (IBM SPSS Statistics, Armonk, NY, USA). The normality of the variables was tested using the Shapiro-Wilk tests. Non-parametric versions of the statistical tests were utilized for non-normal variables. Between-group comparisons at baseline were performed using Independent Samples T-tests and Mann-Whitney U tests. Fisher's exact tests were used to compare categorical variables between groups. Levene tests were used to assess the homogeneity of variance. Mauchsley's sphericity tests were used to assess the assumption of sphericity and Greenhouse-Geisser correction was used when appropriate. A p-value of 0.05 was set for the significance level. Two-way repeated measures Analysis of Variance (Rm ANOVA) tests were performed with time as the independent within-subjects variable, tDCS intervention group as the independent between-subjects variable, and the neuropsychological performance variables as the dependent variables. For non-normal longitudinal outcome variables, Wilcoxon signed-rank tests were utilized to determine the changes after active/sham tDCS.

Results

Baseline demographic and clinical differences between intervention groups

Among 40 recruited individuals, one participant in the active group and one participant in the sham group did not complete all assessments due to personal reasons. Hence, baseline and longitudinal data analyses were performed for 38 individuals. Regarding tolerability, no significant adverse effects were found. No statistically significant demographic, clinical and neurocognitive differences were found at baseline between active and sham groups (Table 1). Repeated measures analysis of variance (Rm ANOVA) tests' results

are shown in Table 2. Wilcoxon signed-rank tests' results regarding time effects observed in each groups are shown in Table 3.

TDCS effects on primary outcomes

Regarding decision making under ambiguity, Rm ANOVA indicated no effect of Time but a significant Time*Group interaction in the IGT net scores (Table 2 and Figure 2) ([$F(1,36) = 6.357$; $p = 0.016$; $1 - \beta = 0.689$; $\eta p^2 = 0.150$]). Regarding decision making under risk, no significant differences were found in Wilcoxon signed-rank tests in both active and sham groups (Table 3 and Figure 3).

Table 1. Baseline characteristics of the study sample.

	Active group (n = 19)	Sham group (n = 19)	Total (n = 38)	P-values
Gender ratio (Males/Females)	18/1	18/1	36/2	0.757
Age (Years)	34.00 (13.00)	30.00 (13.00)	30.00 (12.50)	0.311
Education (Years)	8.00 (7.00)	8.00 (4.00)	8.00 (4.00)	0.644
Clinical features				
Duration of OUD (Years)	7.00 (8.00)	8.00 (8.00)	7.00 (7.00)	0.624
Duration of the BNMT (Months)	20.00 (51.00)	12.00 (32.00)	16.50 (31.25)	0.212
Penn Drug Craving Scale	5.00 (4.00)	9.00 (12.00)	8.00 (10.00)	0.223
Current dose of BN (mg)	8.00 (2.00)	8.00 (6.00)	8.00 (3.5)	0.284
Maximum dose of BN (mg)	10.00 (4.00)	8.00 (4.00)	8.00 (12.00)	0.506
Cognitive Measures				
Iowa Gambling Test (Net Score)	−7.95 (16.71)	−0.95 (18.00)	−4.45 (17.49)	0.222*
BART Net Score	38.79 (20.25)	45.35 (28.60)	43.36 (22.47)	0.111
Stroop Test	40.26 (18.19)	48.77 (36.80)	44.40 (28.70)	0.375*
TMT A duration (sec)	31.00 (17.00)	33.00 (12.00)	33.00 (12.00)	1.000
TMT B duration (sec)	85.00 (36.50)	97.00 (48.00)	93.50 (48.25)	0.247
Digit span forward	6.00 (1.50)	6.00 (2.00)	6.00 (2.00)	0.931
Digit span backwards	4.00 (1.00)	4.00 (1.00)	4.00 (1.00)	0.624
Letter-Number Sequencing	8.00 (4.50)	7.00 (3.00)	7.96 (3.00)	0.552
Stop Signal Reaction Time (msec)	277.27 (98.57)	312.07 (91.30)	294.67 (95.29)	0.280*
Semantic fluency	19.15 (4.77)	18.15 (3.94)	18.65 (4.35)	0.486*
Phonemic fluency	30.00 (18.50)	34.00 (9.00)	33.00 (9.25)	0.644
Alternating fluency	9.00 (4.50)	8.00 (2.00)	8.00 (2.75)	0.385
Psychiatric measures				
Beck Depression Inventory	20.68 (10.25)	23.26 (11.78)	21.97 (10.97)	0.476*
Beck Anxiety Inventory	16.68 (14.92)	19.84 (10.79)	18.26 (12.94)	0.460*

BART: Balloon Analogue Risk Test; BN: Buprenorphine-Naloxone; BNMT: Buprenorphine-Naloxone Maintenance Therapy; mg: milligrams; OUD: Opioid Use Disorder; TMT: Trail Making Test; sec: seconds; msec: milliseconds. Means (Standard Deviations) are shown for normally-distributed variables. Medians (Interquartile Ranges) were shown for non-normally distributed variables. P-values obtained from the Fisher's exact test (gender ratio), Mann-Whitney U tests and Independent Samples T Tests (*) are shown.

Table 2. Changes in the outcome measures (Repeated Measures Analysis of Variance Tests).

Measures	Active group (n = 19) Baseline	Active group (n = 19) Post	Sham group (n = 19) Baseline	Sham group (n = 19) Post	P-values Time	P-values Time*Group
Iowa Gambling Test Net Score	−7.95 (16.71)	2.31 (26.02)	−0.95 (18.00)	−6.73 (24.57)	0.487	**0.016**
Stroop Interference Time (sec)	40.26 (18.19)	26.26 (10.67)	48.77 (36.80)	35.05 (27.68)	**<0.001**	0.955
Semantic fluency	19.15 (4.77)	20.15 (5.73)	18.15 (3.94)	18.26 (3.52)	0.475	0.563
SSRT (msec)	277.27 (98.57)	229.71 (100.60)	312.07 (91.30)	282.91 (108.63)	**0.015**	0.541

Sec: seconds; SSRT: Stop Signal Reaction Time, msec: milliseconds. Means (Standard Deviations) are shown. Baseline columns show the values before the administrations. Post columns show the values after the administrations. Time column shows the time p-values of the repeated measures ANOVA test. Time*Group column shows the Time*Group interaction p-values of the repeated measures analysis of variance tests.

Table 3. **Changes in the outcome measures (Wilcoxon signed-rank tests).**

Measures	Active group (n = 19)			
	Baseline	Post	Z	P-values
BART Adjusted Number of Pumps	38.79 (20.25)	38.18 (14.38)	−1.198	0.231
Digit span forward	6.00 (1.50)	6.00 (2.00)	−0.061	0.951
Digit span backward	4.00 (1.00)	4.00 (2.00)	−0.351	0.726
TMT A Time	31.00 (17.00)	25.00 (11.00)	−3.305	**0.001**
TMT B Time	85.00 (36.50)	80.00 (43.50)	−2.512	**0.002**
Phonemic fluency	36.38 (18.50)	35.00 (22.50)	−1.303	0.193
Alternating fluency	9.00 (4.50)	10.00 (13.00)	−3.019	**0.003**
LNS	8.00 (4.50)	8.00 (4.00)	−0.216	0.829
	Sham group (n = 19)			
	Baseline	Post	Z	P-values
BART Adjusted Number of Pumps	45.35 (28.60)	47.35 (39.74)	−1.127	0.260
Digit span forward	6.00 (2.00)	6.00 (2.00)	−0.411	0.681
Digit span backward	4.00 (1.00)	4.00 (1.00)	−1.072	0.284
TMT A Time	33.00 (12.00)	28.00 (10.00)	−2.960	**0.003**
TMT B Time	97.00 (48.00)	67.00 (35.00)	−1.821	0.069
Phonemic fluency	34.00 (9.00)	37.00 (14.00)	−3.161	**0.002**
Alternating fluency	8.00 (2.00)	9.00 (3.00)	−1.240	0.215
LNS	7.00 (3.00)	8.00 (3.00)	−0.686	0.493

BART: Balloon Analogue Risk Task; TMT: Trail Making Test; LNS: Letter-Number Sequencing. Medians (Interquartile Ranges) are shown. Baseline columns show the values before the administrations. Post columns show the values after the administrations. *P*-values below 0.05 are bold.
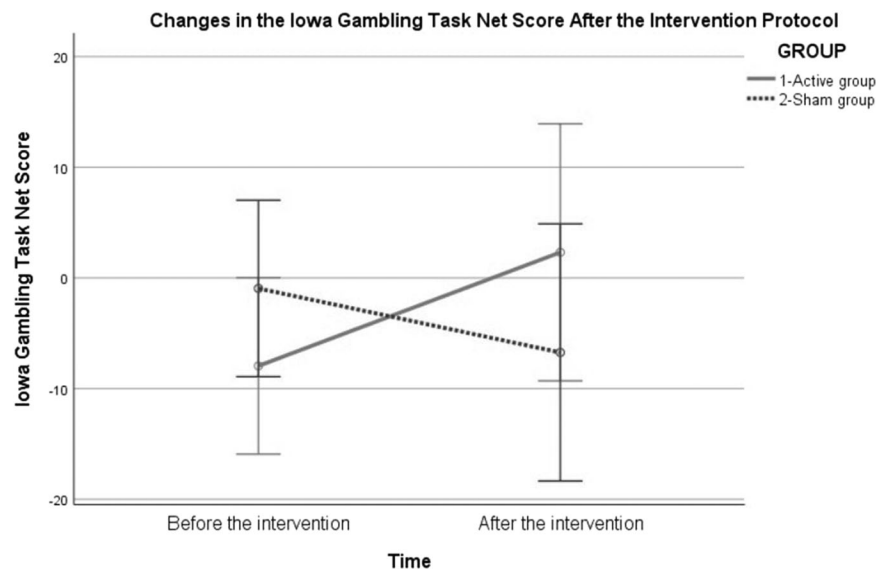

Figure 2. Changes in the Iowa Gambling Task net score after the intervention protocol. Flat line shows the active group. Dashed line shows the sham group. Error bars represent the standard error of the mean.

TDCS effects on secondary outcomes

A significant effect of Time was found for Stroop Interference Time ([$F(1,36)$ =32.451; $p < 0.001$; $1 − β = 1.000$; $ηp2 = 0.481$]) and Stop Signal Reaction Time ([$F(1,36) = 6.620$; $p = 0.015$; $1 − β = 0.705$; $ηp2 = 0.163$]) in Rm ANOVA tests (Table 2). None of the Time*Group interactions in Rm ANOVA tests were significant in secondary longitudinal outcome variables (Table 2).

Wilcoxon signed-rank tests indicated significant differences in TMT A Time in both active ($Z= -3.305$; $p = 0.001$) and sham ($Z= -2.960$; $p = 0.003$) groups. A significant difference was found in phonemic fluency in the sham group (-3.161; $p = 0.002$). Significant differences were found in TMT B Time ($Z= -2.512$; $p = 0.012$) and alternating fluency ($Z= -3.019$; $p = 0.003$) in the active group. There were no significant differences in the remaining variables in both groups.

Discussion

The present triple-blind randomized sham-controlled study was a pilot study that assessed the effect of tDCS combined with CT in OUD for the first time. Our results propound
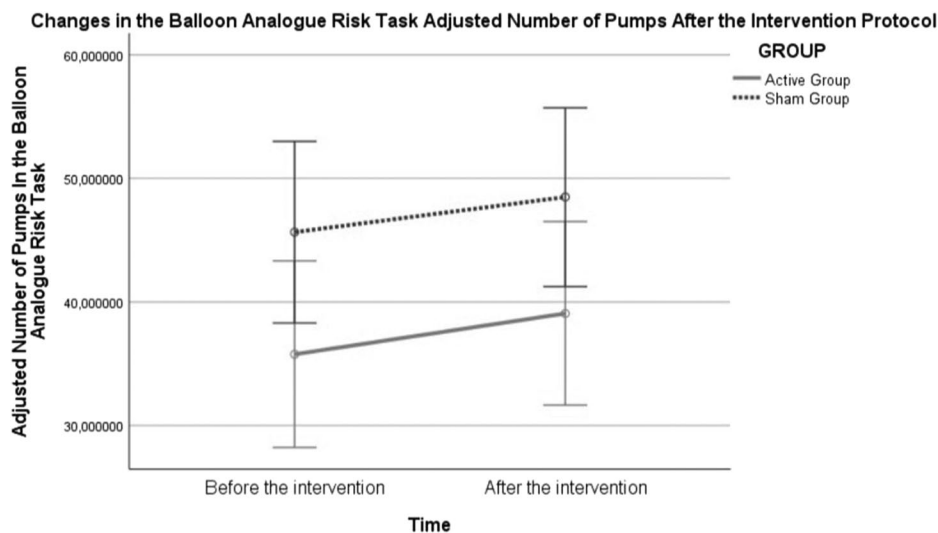
Changes in the Balloon Analogue Risk Task Adjusted Number of Pumps After the Intervention Protocol

Figure 3. Changes in the Iowa Gambling Task net score after the intervention protocol. Flat line shows the active group. Dashed line shows the sham group. Error bars represent the standard error of the mean.

that a tDCS/CT protocol selectively focusing on decision making resulted in improved TMT B performance and verbal fluency. Moreover, active tDCS concurrent with CT exerted higher decision making and alternating fluency performances.

Primary hypotheses were partially met, namely more improvements after active tDCS in decision making under ambiguity were observed while decision making under risk remained unchanged in both active and sham groups. The conspicuous improvement of decision making under ambiguity after tDCS/CT is concordant with the previous tDCS literature[23,53] and is a clinically worthwhile finding as individuals with OUD manifest considerable deficits in decision making under ambiguity, largely irrespective of the treatment phase or duration.[20] Of particular importance, a previous study found no effect of tDCS on relapse rates in OUD.[33] Since decision making deficits have been associated with relapse rates in OUD[54] and other addictive disorders,[9] and showing regard to the observed decision making improvement, further studies using tDCS/CT assessing relapse rates warrant consideration.

Mounting evidence suggests that the DLPFC and anterior cingulate cortex activity has been increased during the GDT.[55] The utilized tDCS/CT protocol using the GDT relied on evidence that neuroplasticity-related effects of tDCS had been more apparent when tDCS had been administered over an already engaged brain region.[56]

The facilitation of engagement to the task during CT through increased prefrontal cortex activity by tDCS might expound the observed effect on the IGT performance. Accordingly, lesion studies revealed the relationship between the IGT performance and the DLPFC/ventromedial frontal cortex.[57] A recent cathodal Theta Burst Stimulation study also reported a causal link between the right DLPFC and the IGT performance.[58]

Somewhat contrary to our expectations, no further improvements in decision making under risk were observed in the active tDCS group. Likewise, a recent meta-analysis also found no effect of bilateral tDCS on risk-taking.[59] This result was, in fact, not inexplicable and might be due to the resultant effect of discrete factors. Even though right anodal/left cathodal tDCS over the DLPFC was shown to improve decision making under risk in healthy individuals[52] and in dependent cocaine users,[60] contrasting results were also reported in healthy older individuals[61] and in chronic marijuana users,[62,63] possibly due to alterations or differences in neural circuitry. Similarly, the degree and type of dysfunction in the frontostriatal circuitry might also be more complex than previously thought in OUD. Moreover, a recent meta-analysis reported that decision making under ambiguity specifically recruited the DLPFC which has not been observed after decision making under risk.[64] Concerning that the intensity of the tDCS current is chiefly

over the DLPFC, a single session of tDCS/CT might be inadequate to improve decision making under risk in individuals with OUD.

The present study also depicted more improvements in the TMT B performance and alternating fluency in the active group. Both TMT B and verbal fluency are commonly used to assess executive functions.[65] Deficits of executive functions have been depicted to be still substantially evident during the chronic abstinence period in OUD.[10] Verbal fluency has also been found to be robustly impaired in a meta-analysis in individuals with OUD[12] which might provide room for improvement with neuromodulatory treatments.

On the basis of the long-established relationship between the GDT performance and executive functions,[66] it might be presumed that decision making improvements were at least partially due to improvements in executive functions. Of note, executive functions and working memory have been observed to moderate the performance of the GDT.[67] Further, this relationship was also indicated in individuals with OUD.[43] Thus, cognitive training conducted using the GDT might also trigger improvement in executive functions. However, the lack of TMT B and alternating fluency improvements in the sham group were contrary to this notion. Moreover, there is still controversy concerning the relationship between decision making and executive functions.[68,69] Alternatively, tDCS over the DLPFC itself might directly exert an improvement in executive functions.[28] Besides, improvement in executive functions might also contribute to the improvement in decision making under ambiguity as the IGT performance has been associated with executive functions.[57] Nonetheless, it should be emphasized that the relationship between executive functions and decision making has been mainly observed in risky decision making tasks,[66,69,70] instead of the IGT.[69,71] Eventually, improvement in general cognition and executive functions might contribute to treatment outcomes by decreasing relapse rates and increasing treatment adherence.[9]

In line with the inconsistent results of tDCS over the DLPFC,[72] the present study was not able to find an improvement in response inhibition. As a result, it might be contemplated that improvements in decision making might not be associated with response inhibition. This relationship is still not clear as there are both studies linking inhibitory control improvements to decision making improvements and studies reporting decision making deficits without disrupted response inhibition.[73] Correspondingly, future alcohol use has been predicted by the IGT performance but not by the Stop Signal Task performance in a study.[8] Respecting some studies proposed the relationship of risky decision making but not decision making under ambiguity in individuals with neuropsychiatric disorders,[74,75] decision making under ambiguity might be a more dissociating construct of cognitive functions with partial links to response inhibition. Besides, cognitive and motor response inhibition deficits might only be observed due to drug-related cues in individuals with OUD.[76,77] Thus, well-designed studies are warranted to parse the cognitive processes related to decision making in individuals with OUD. The present results are in line with the studies that found no improvement in response inhibition after tDCS over the DLPFC[78,79] and repetitive Transcranial Magnetic Stimulation over the DLPFC in alcohol use disorder[80] although a small but significant effect has also been reported in a recent meta-analysis.[81] Overall, multiple tDCS sessions might be needed to improve response inhibition in individuals with OUD.

Some strengths of the present study should be designated. First, all participants were regular attendees of the BNMT program which might contribute to the clinical implications of the study as an adjuvant relapse prevention strategy in the BNMT program. Second, the present study reported the first results of the effect of tDCS combined with CT in OUD. Third, the study had a triple-blind design. Nonetheless, limitations of the study encompassing the single-session pilot design and thereby lack of clinical outcomes and follow-up assessments should be marked. Due to exploratory nature of the study and a relatively low sample size, corrections for multiple comparisons were not performed. Further, integrity of the participant blinding was not assessed. Moreover, only a few female individuals participated in the study.

Further studies with multiple sessions evaluating the effect of tDCS combined with CT on both clinical and cognitive outcomes in the short and long-term periods are entailed.

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Abbreviations:

BART   Balloon Analogue Risk Task
BAS   Beck Anxiety Scale
BDI   Beck Depression Inventory
BNMT   Buprenorphine Naloxone Maintenance Therapy
CT   cognitive training
DLPFC   dorsolateral prefrontal cortex
GDT   Game of Dice Task
IGT   Iowa Gambling Task
LNS   Letter Number Sequencing
OUD   Opioid Use Disorder
tDCS   transcranial Direct Current Stimulation
TMT   Trail Making Test

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