UNIVERSITY OF EAST LONDON

The role of neuromodulation for cognitive processing and behavioural inhibition in disordered gambling

PROTOCOL AND STATISTICAL ANALYSIS PLAN

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STUDY PROTOCOL

1. PROCEDURE

The research consists on studying the effects of tDCS in combination with cognitive behavioural therapy (CBT) in adults diagnosed with gambling disorder that attend the UK National Problem Gambling Clinic. The design of the study consists on a double blind randomized control interventional trial with parallel assignment (two interventions – tDCS in combination with CBT that will be evaluated against CBT alone).

Participants will be split in two groups depending on the treatment they receive. The treatment groups will be: tDCS real stimulation with CBT or tDCS sham with CBT. Real stimulation condition involves the application of tDCS stimulation for 20 minutes whereas sham condition is used as a control (similar to a placebo).

The investigators aim to have a total of 32 participants diagnosed with gambling disorder based on the Problem Gambling Severity Index (PGSI). There will be 16 participants per condition, having two conditions (real stimulation and sham).

Treatment 1. Participants will attend 8 weekly sessions where they receive tDCS real stimulation while complete CANTAB cognitive tasks to measure cognitive functions and following this, they will attend a CBT session.

Treatment 2. Participants will attend 8 weekly sessions where they receive sham tDCS, while complete CANTAB cognitive tasks to measure cognitive functions and following this, they will attend a CBT session.

Primary endpoint/outcomes

1. Change in scores on the Yale-Brown Obsessive Compulsive Scale adapted for Pathological Gambling (PG-YBOCS). [Time Frame: Change from baseline PG-YBOCS scores at week 2, 3, 4, 5, 6, 7 and 8].

2. Change in scores on the Visual Analogue Scale (VAS). [Time Frame: Change from baseline VAS scores at week 2, 3, 4, 5, 6, 7 and 8].

3. Change in scores on the Gambling Symptom Assessment Scale (G-SAS). [Time Frame: Change from baseline G-SAS scores at week 8].

4. Change in scores on the Cambridge Gambling Task (CGT). [Time Frame: Change from baseline CGT scores at week 8].

Secondary endpoints/outcomes

1. Change in scores on the Information Sampling Task (IST). [Time Frame: Change from baseline IST scores at week 2, 3, 4, 5, 6, 7 and 8].

2. Change in scores on the Stop Signal Task (SST). [Time Frame: Change from baseline IST scores at week 2, 3, 4, 5, 6, 7 and 8].

3. Changes in encephalography (EEG) neural oscillatory activity. [Time Frame: Correlation of tDCS and EEG activity in weeks 1, 2, 3, 4, 5, 6, 7 and 8].

Primary objective

The main objective is to study whether 8 weekly sessions during 8 consecutive weeks of tDCS simulation will help to decrease cravings and addiction symptoms such as risk-taking behaviour and impulsivity in patients diagnosed with gambling disorder attending the UK National Problem Gambling Clinic, exploring whether tDCS combined with CBT will improve the treatment outcomes – reducing significantly more the symptomatology, compared to CBT treatment alone.

Hypothesis 1:

Null hypothesis (H_0): The primary outcome measures results will be the same in the group of participants that receive tDCS real stimulation combined with CBT and the control group (sham tDCS + CBT).

Alternative hypothesis (H_A): The primary outcome measures results will not be the same in the group of participants that receive tDCS real stimulation combined with CBT and the control group (sham stimulation + CBT).

Hypothesis 2:

H_0: The primary outcome measures results obtained in the baseline will be the same to the outcome measures results at the end of the treatment.

H_A: The primary outcome measures results obtained in the baseline will not be the same to the outcome measures results at the end of the treatment.

Secondary objectives

To investigate if electrophysiological measures (EEG resting state) predict behavioural outcomes obtained from the cognitive task performance during tDCS experiments, as well as studying the task performance progression comparing every week´s results to the baseline.

Hypothesis 1:

H_0: The secondary outcome measures results obtained from the EEG resting state will be the same in the group of participants that receive tDCS real stimulation combined with CBT and the control group (sham tDCS + CBT).

H_A: The secondary outcome measures results obtained from the EEG resting state will not be the same in the group of participants that receive tDCS real stimulation combined with CBT and the control group (sham tDCS + CBT).

Hypothesis 2:

H_0: The secondary outcome measures results obtained in the baseline will be the same to the outcome measures results at the end of the treatment.

H_A: The secondary outcome measures results obtained in the baseline will not be the same to the outcome measures results at the end of the treatment.

2. MATERIALS

Participants

The sample size will be 16 participants per group (2 groups) that attend 8 treatment sessions.

Inclusion criteria

Male or females between 18 and 65 years of age diagnosed with disordered gambling based on the Problem Gambling Severity Index (PGSI) who can speak and read English, capable of giving informed consent**,** and don't have any of the exclusion criteria.

Minimum Age: 18 Years
Sex: All
Gender Based: No
Accepts Healthy Volunteers: No

Exclusion criteria

a. History or evidence of chronic or residual neurological disease.
b. A pacemaker or deep brain stimulation.
c. Metal implants in head or neck area (e.g. postoperative clips after intracerebral aneurysm; arterial aneurysm in the vascular system, implantation of an artificial hearing aid).
d. Intracerebral ischemia/history of bleeding.
e. Prior evidence of epileptic seizures, history of epilepsy.
f. History of head injury with loss of consciousness.
g. Any serious medical conditions (disease of the internal organs).
h. Pregnancy or breast-feeding.
i. Negative screening from the clinic psychiatrist

Software

This research uses a CE marked medical device, transcranial direct current stimulation (tDCS) built in the international company Neuroelectrics (https://www.neuroelectrics.com/products/). Specifically, Starstim® is a wireless hybrid EEG/tCS neurostimulator system. It includes the comfortable neoprene head cap where the electrodes can be easily inserted. Starstim® complies with the European legislation for clinical research.

Cognitive and physiological measurement tools

Primary outcomes:

1. Yale-Brown Obsessive Compulsive Scale adapted for Pathological Gambling (PG-YBOCS): it is a 10-item questionnaire that measures the gambling severity. The scores range from 0 to 4. The questions 1 to 5 assess urges and thoughts associated with gambling disorder, and the rest of the questions assess the behavioural component of the disorder in the past week. The total score will be calculated as well as the separate scores. Gambling severity will be higher with higher scores (we will obtain measures of PG-YBOCS in all sessions 1,2,3,4,5,6,7 and 8).

2. Visual Analogue Scale (VAS) for gambling cravings: it is a horizontal line which length is 100 mm where the left side corresponds to the lower score and the right side to the highest score (it ranges from 0 to 10). The participant will draw a line starting from the lowest level to the level that better represents their gambling cravings at the current time. The score will be calculated by measuring this line (in millimetres). The gambling cravings will be higher with higher VAS scores (we will obtain measures of VAS in all sessions 1,2,3,4,5,6,7 and 8).

3. Gambling Symptom Assessment Scale (G-SAS): it is a 12-item scale to measure gambling symptoms. Each of the 12 questions has a score ranging from 0 to 4 based on the last week, which makes it useful to measure changes during treatment. The total score ranges from 0 to 48. The symptoms severity will be higher with higher G-SAS scores.

4. Cambridge Gambling Task (CGT): it is a cognitive task that dissociates risk taking from impulsivity, because in the ascending bet condition the participant who wants to make a risky bet has to wait patiently for it to appear (10 minutes). http://www.cambridgecognition.com/cantab/cognitive-tests/executive-function/cambridge-gambling-task-cgt/

Secondary outcomes:

1. Information Sampling Task (IST): it tests impulsivity and decision making. The participant is instructed that they are playing a game for points, which they can win by making a correct decision (up to 15 minutes). http://www.cambridgecognition.com/cantab/cognitive-tests/information-sampling-task-ist/

2. The Stop Signal Task (SST): it measures response inhibition or impulse control (up to 20 minutes). http://www.cambridgecognition.com/cantab/cognitive-tests/executive-function/stop-signal-task-sst/

3. Encephalography (EEG) activity: EEG resting state oscillatory neural activity will be obtained before and after tDCS stimulation to study the correlation of tDCS effects and neurophysiological changes in the brain.

Trial design

- Study Type: Interventional
- Primary Purpose: Treatment
- Framework: Superiority (Treatment will be superior to placebo (sham condition)).
- Interventional Study Model: Parallel Assignment. Investigation of the effects of transcranial direct current stimulation (tDCS) in combination with cognitive behavioural therapy (CBT) against the effects of CBT alone.
- Number of Arms: 2
- Masking: Double (Participant and Operator) Participants will be allocated either to a tDCS Stimulation condition or to a tDCS Sham condition.
- Allocation: Randomized

Trial setting

The trial will run at The UK National Problem Gambling Clinic (NPGC), in London. This is a single centre and it consists on an educational project and therefore a non-commercial trial.

There are not specific requirements to run the trial or different types of site. All participants will be recruited at the NPGC through members of the staff when potential participants contact the clinic to receive treatment for gambling disorder.

Patients that contact with the health care team at the NPGC will be offered the opportunity to participate voluntarily in the research. If they are interested they will need to confirm that they meet the inclusion criteria of the study which appears in the invitation letter and will be given the researcher contact details to obtain more information about the trial.

Trial procedures

The intensity for neuromodulation will remain constant across all groups at 1.8 milliamps (mA), which is a standard intensity for induced cognitive change in the tDCS literature. In the sham condition, participants will experience only 60 seconds of tDCS stimulation with 1.8 mA intensity (30 seconds ramp up and 30 seconds ramp down), which is enough to induce a tingling sensation that is associated with tDCS neuromodulation but at the same time this is not enough to alter neural activity and the left 19 minutes of the tDCS intervention they will receive 0 mA intensity. Electroencephalography (EEG) resting state oscillatory activity will be recorded during 5 minutes before and 5 minutes after tDCS.

Participants will be randomly allocated either to a real stimulation condition or to a control condition (sham). Each participant will attend to a 20 minutes transcranial direct current stimulation (tDCS) weekly session for 8 consecutive weeks (8 sessions). During the sessions they will complete cognitive tasks and questionnaires for a total time of 1 hour to assess individual characteristics (e.g. impulsivity, risk-taking behaviour) and where EEG resting state will be recorded to inform about the neurophysiology of tDCS effects in task performance.

The participant will complete:

- The consent form
- A series of questionnaires to assess cravings, addiction severity and gambling symptoms.

Consecutively, the researcher will set up of equipment and parameters (place the cap on the participant´s head); apply tDCS stimulation (20 minutes) while participant complete cognitive computer based tasks; remove the cap to conclude the session.

- In session 1 and session 8 participant will complete the next questionnaires and cognitive task before the tDCS/EEG protocol:

    1. Gambling Severity Symptom Assessment Scale (G-SAS).
    2. Cambridge Gambling Task (CGT).

- In sessions 1, 2, 3, 4, 5, 6, 7 and 8 participants will complete the next questionnaires and cognitive tasks (tests 1-3 before tDCS/EEG protocol and task 4 during tDCS stimulation). EEG resting state will be recorded before and after tDCS:

    1. Yale-Brown Obsessive Compulsive Scale adapted for Pathological Gambling (PG-YBOCS)
    2. Visual Analogue Scale (VAS) for gambling cravings.
    3. Information Sampling Task (IST)
    4. Stop Signal Task (SST)
    5. EEG resting state recording

Randomization method

Simple randomization will be employed. This method is based on a single sequence of random assignments. Computer-generated random numbers will be used for simple randomization of subjects prior to the experiment start – assigning randomised numbers to the order in which participants sign up - to ensure equivalent numbers of participants per arm. This technique guarantees randomness of the assignment of a subject to a particular group.

Masking

Neuroelectrics tDCS software will be set up in double blind mode, which ensures that neither the investigator (who conducts the experimental session) nor the participant, will know the condition (real stimulation or sham) the participant has been allocated to. Participant allocation to each stimulation group will be randomized prior the study commences as stated above, and tDCS templates will be created for each participant, to ensure that they will remain during the 8 stimulation sessions in the same group.

3. ETHICAL CONSIDERATIONS

Ethical approval to conduct the study was obtained from the University Research Ethics Committee (UREC) at the University of East London and from the Health Research Authority (HRA) and will be conducted with Central and North West London (CNWL) NHS trust. Potential risks associated with tDCS are minor discomfort from wearing the tDCS electrode net and minor itchiness that immediately cease after stimulation, this is explained to the participants prior to starting. Participants will be reminded that they could stop the experiment at any time they wish, if they felt too much discomfort or distress.

4. DATA PROTECTION

All data will be anonymised, treated confidentially and retained in accordance with the Data Protection Act, stored for a limited period of time on password protected hard drives. Each participant will be given a participant number that can be de-coded by the researcher. Hard copies of questionnaires and consent forms will be stored in a locked filing cabinet in a lockable room then destroyed in accordance with the university's data protection policies.

5. STATISTICAL ANALYSIS PLAN

Data source

Behavioural data sets will be obtained from computer-based cognitive tasks and questionnaires that participants complete during the stimulation sessions. The results obtained from completing these tasks and questionnaires generate measures for addiction-related symptoms such as cravings, impulsivity, risk-taking behaviour, delay aversion and control inhibition. Each participant will produce data at two time points for G-SAS and CGT measures and at eight time points for VAS, PG-BOCS and secondary measures. Electroencephalography (EEG) resting state neural oscillatory activity will be recorded for 5 minutes prior and 5 minutes after the tDCS intervention.

Analysis objectives

The investigators will study whether the behavioural and cognitive data obtained from participants in different time points are significantly different between the two treatment groups. In addition, the investigators will investigate if electrophysiological measures (EEG resting state) predict behavioural outcomes obtained from the cognitive task performance during tDCS experiments, as well as studying the task performance progression comparing every week´s results to the baseline.

Analysis sets/Subgroups

The following data sets subgroups will be analysed:

1. Experimental - Stimulation with CBT: Participants that attend to 8 weekly sessions of tDCS stimulation and that following the tDCS session, they attend to a cognitive behavioural therapy (CBT) session.

2. Sham Comparator - Sham with CBT: Participants that attend to 8 weekly sessions of sham tDCS and that following the tDCS session, they attend to a CBT session.

The aim is to study whether the combination of stimulation and therapy help to improve the treatment outcomes in comparison with CBT alone.

Variables and covariates

Primary Dependent Variables:

1. Pathological Gambling adapted Yale-Brown Obsessive Compulsive Scale (PG-YBOCS) scores for gambling severity.
2. Visual Analog Scale (VAS) scores for gambling cravings.
3. Gambling Severity Symptoms Assessment (G-SAS) for gambling symptoms.
4. Cambridge Gambling Task's (CGT) scores for gambling behaviour.

Secondary Dependent Variables:

1. Stop signal task's (SST) scores for inhibition control.
2. Information Sampling Task's (IST) scores for impulsivity.
3. EEG resting state oscillatory neural activity.

Independent Variables:

1. tDCS condition (Stimulation or Sham)
2. Time (sessions 1 to 8)

Covariates:

1. Age
2. Gender

Handling of missing values

We expect to have very few cases of missing values due to the methodology used in the study. The variables will be measured with a computer software that doesn't allow to continue with the test unless one of the options is selected. The only possible missing values would come by an error on the whole task, which will result in no data at all. In this case, we would withdraw this participant from the analysis of that specific task.

The possible missing values that we would expect to deal with, will come from the covariates measures that are obtained from paper-based questionnaires. The researcher checks before the participant leaves the session that they have completed all the questions. However, if we have to deal with missing values, we will use common-point imputation that is commonly used for rating scales, which is the case in our questionnaires. With this technique we would use the most commonly chosen value for the rest of the questions and substitute it for the missing value

Statistical Procedures

The analysis performed will be as in Loo et al (2012): the two treatment groups will be analysed for differences in demographic and clinical variables at baseline using X2 -tests for categorical variables

and t-tests for continuous variables. To test the effect of tDCS on test performance, a 2 x 2 mixed between–within ANOVA will be conducted. The between-groups factor will be stimulation condition (real stimulation vs sham) and the within-participants factor will be time (change from baseline). Analyses will test for main effects of stimulation condition and session as well as the stimulation-session interaction.

Secondary measures involve cognitive tasks and EEG resting state neural oscillations recording. Differences between sessions scores will be analysed with mixed between-within repeated measures ANOVA. The between-groups factor will be tDCS condition (real tDCS vs sham tDCS) and the within-participants factor will be time (change from baseline). Analysis will test for main effects of group (tDCS condition) as well as for tDCS-time interaction to investigate the presumable accumulative effects of tDCS. This analysis will serve to study if specific EEG resting state oscillatory activity correlates with the modulatory effect of tDCS on task performance and to explore the presumable accumulative effect of tDCS across time.