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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CONTENT

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 non-randomized interventional trial with parallel assignment (two interventions – tDCS in combination with CBT that will be evaluated against a 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 CBT alone (sham condition). Real stimulation condition involves the application of tDCS whereas sham condition is used as a control (similar to a placebo). In this way, the design comprises 2 arms.

The investigators aim to have a total of 48 participants diagnosed with gambling disorder based on the Problem Gambling Severity Index (PGSI). There will be 24 participants per condition, having two conditions (real stimulation and sham).

Treatment 1. Participants will attend 8 weekly sessions where they receive tDCS real stimulation for 20 minutes, while complete CANTAB cognitive tasks to measure cognitive functions and following this, they will also attend to a weekly CBT session.

Treatment 2. Participants will attend 8 weekly sessions where they receive sham tDCS for 20 minutes, while complete CANTAB cognitive tasks to measure cognitive functions and following this, they will also attend to a weekly CBT session.

2. MATERIALS

a) Participants

The sample size will be 24 participants per group (2 groups), males and females between 18 and 65 years old, diagnosed with gambling disorder based on the Problem Gambling Severity Index (PGSI). The total sample anticipated will be 48 participants that attend 8 treatment sessions.

b) Software

- EEG-tDCS kit: in the next picture is shown the EEG-tDCS kit (Starsttim, Neuroelectrics) that will be employed: neoprene cap, Control Box, cables, electrodes, measurement tape, saline solution and Bluetooth USB.

c) Cognitive and physiological measurement tools

Primary outcomes:

Measures obtained in sessions 1 and 8:

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.

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.

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:

Measures obtained in sessions 1, 2, 3, 4, 5, 6, 7 and 8:

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.

Other measures

Substance abuse screening questionnaires obtained in the baseline:

- Severity of Alcohol Dependency Questionnaire (SADQ): alcohol dependency screening

- Nicotine Dependence Questionnaire (NDQ): Nicotine dependency screening

- Severity of Dependence Scale (SDS): Other drugs dependency screening

3. EXPERIMENTAL 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: Single (Participant) Participants will be allocated either to a tDCS Stimulation condition or to a tDCS Sham condition.
- Allocation: Non-Randomized

The intensity for neuromodulation will remain constant across all groups at 2mA, which is the standard intensity for induced cognitive change in the tDCS literature. In the sham condition, participants will experience only 40 seconds of tDCS stimulation which is enough to induce a tingling sensation that is associated with tDCS neuromodulation (Brunoni et al, 2012), but at the same time this is not enough to alter neural activity. A fade-in and fade-out duration of 20 seconds each will be used in both conditions for the comfort of participants, this gradual increases and decreases the stimulation, respectively.

- Experiment:

Effect of 8 weekly tDCS stimulation sessions combined with Cognitive Behavioural Therapy (CBT) treatment in tasks and questionnaires performance as well as EEG resting state recording. Performance will be compared between baseline and session 8 for primary outcomes and between baseline and the rest of the weeks for secondary outcomes. Participants will be allocated to either one of the two conditions (stimulation or sham).

4. ETHICAL CONSIDERATIONS

Ethical approval to conduct the study was obtained from the University Research Ethics Committee (UREC) at the University of East London. 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.

5. 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.

STATISTICAL ANALYSIS PLAN

1. 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 individual characteristics such as impulsivity, risk-taking behaviour, delay aversion and control inhibition. Each participant will produce data at two time points for primary outcomes measures and at eight time points for each secondary outcomes measures. Electroencephalography (EEG) resting state neural oscillatory activity will be recorded for 5 minutes prior and 5 minutes after the tDCS intervention.

2. Analysis objectives

The primary research question of the project is to investigate whether transcranial direct current stimulation (tDCS) can help to decrease impulsivity and risk taking behaviour, and therefore offer improved opportunities for the treatment of gambling disorder. In the trial the investigators will compare different treatments for gambling disorder: tDCS real stimulation combined with cognitive behavioural therapy (CBT) or CBT alone.

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.

3. 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 the tDCS stimulation or CBT alone.

4. Variables and covariates

a) Primary Dependent Variables (obtained in sessions 1 and 8):

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

b) Secondary Dependent Variables (obtained in the sessions 1,2,3,4,5,6,7 and 8):

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

c) Independent Variables:

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

d) Covariates:

1. Age

2. Gender

5. 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

6. 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.