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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7th March, 2018

CONTENT

STUDY PROTOCOL

STATISTICAL ANALYSIS PLAN

STUDY PROTOCOL

1. PARTICIPANTS

The sample size will be 24 participants per group (18 – 65 years old) males and females diagnosed with disordered gambling based on the Problem Gambling Severity Index (PGSI).

2. PROCEDURE

Participants will be split into 2 groups: participants seeking treatment for problem gambling and participants that are currently receiving treatment for problem gambling, which consists on cognitive behavioural therapy sessions. In each of these groups, participants will be allocated either to an experimental condition ("stimulation") or to a control condition ("sham"). Each participant will attend to a 20 minutes transcranial direct current stimulation (tDCS) weekly session for 5 consecutive weeks (5 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 or risk-taking behaviour). The session's structure will be:

a) Participant completes the questionnaires
b) Researcher sets up the neoprene cap and stimulation parameters
c) Participant completes the cognitive tasks
d) Researcher stops the stimulation and removes the neoprene cap

3. MATERIALS

a) Questionnaires (completed in session 1 and session 5)

- Gambling Related Cognitions Scale (GRCS): it is a questionnaire representing factors including illusion of control, predictive control, interpretative bias, gambling-related expectancies and perceived inability to stop gambling.

- UPPS Impulsivity Scale: it is a questionnaire to assess five impulsivity subscales: negative urgency, positive urgency, planning, perseverance and sensation seeking.

- Actively Open Minded Thinking Scale (AOT): it is a measure of an individual's thinking style. Assesses tendency to engage in flexible thinking and avoid dogmatic thinking and individuals' belief identification.

Substance abuse screening questionnaires:

- Severity of Alcohol Dependency Questionnaire (SADQ): alcohol dependency screening (Session 2)

- Nicotine Dependence Questionnaire (NDQ): Nicotine dependency screening (Session 3)

- Severity of Dependence Scale (SDS): Other drugs dependency screening (Session 4)

b) Transfer Tasks (completed in session 1 and session 5)

1. 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/

2. Multitasking test (MTT) based on the Attention Switching Task (AST): it measures control inhibition and cognitive flexibility. Participants must respond to an arrow stimulus by touching either of two choices depending on the direction in which the arrow points and change their criteria to respond following the correspondent instructions (8 minutes). http://www.cambridgecognition.com/cantab/cognitive-tests/executive-function/multitasking-test-mtt/

c) Training tasks (completed in sessions 2, 3 and 4)

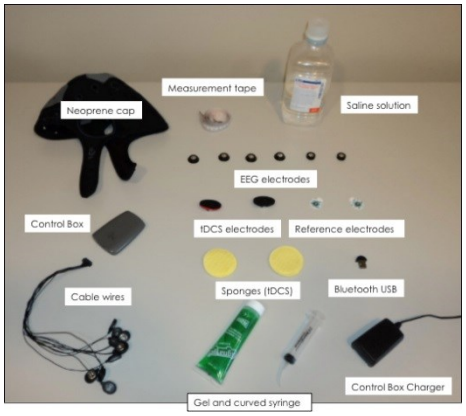
1. The Stop Signal Task (SST): it measures response inhibition or impulse control (up to 20 minutes). http://www.cambridgecognition.com/cantab/cognitive-tests/executive-function/stop-signal-task-sst/

2. 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/

3. One Touch Stockings of Cambridge (OTS): is a test of executive function, based upon the Tower of Hanoi test. It assesses both the spatial planning and the working memory subdomains (10 minutes). http://www.cambridgecognition.com/cantab/cognitive-tests/executive-function/one-touch-stockings-of-cambridge-ots/

d) 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.



4. EXPERIMENTAL DESIGN:

The intensity for neuromodulation will remain constant across all groups at 1.5mA, 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. Both active and return electrodes are circular, with a surface area of 2.5 cm^2. Electrodes will be soaked in a sodium chloride (NaCl) saline solution.

- Experiment 1:

Effect of 5 weekly tDCS stimulation sessions in tasks and questionnaires performance. Performance will be compared between session 1 and session 5 for transfer tasks and between session 2, 3 and 4 for training tasks. Participants will be allocated to either one of the two conditions (stimulation or sham).

- Experiment 2:

Effect of 5 weekly tDCS stimulation sessions combined with Cognitive Behavioural Therapy (CBT) treatment in tasks and questionnaires performance. Performance will be compared between session 1 and session 5 for transfer tasks and between session 2, 3 and 4 for training tasks. Participants will be allocated to either one of the two conditions (stimulation or sham).

5. 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.

6. 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 cognitive flexibility. Each participant will produce data at two time points for each transfer task and questionnaires and at three time points for each training task.

2. Analysis objectives

The overall objective is to study whether an intervention is effective to treat disordered gambling. The intervention (transcranial direct current stimulation – tDCS) will be applied with the aim to influence individual behavioural scores obtained from task's performance across sessions in two different treatment groups (tDCS alone and tDCS in combination with therapy CBT).

We will study whether the behavioural and cognitive data obtained from participants in different time points are significantly different between the two treatment groups. To explore this, two different experimental conditions will be employed: an experimental condition (stimulation) and a control condition (sham) to allow us to recognise whether or not the changes in tasks and questionnaires performance are produced as a result of tDCS stimulation. The overall 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.

3. Analysis sets/Subgroups

The following data sets subgroups will be analysed:

1. Experimental - Stimulation without CBT: Participants that attend to 5 weekly tDCS stimulation sessions.

2. Sham Comparator - Sham without CBT: Participants that attend to 5 weekly sessions of sham tDCS.

3. Experimental - Stimulation with CBT: Participants that attend to 5 weekly sessions of tDCS stimulation and that following the tDCS session, they attend also to a cognitive behavioural therapy (CBT) session.

4. Sham Comparator - Sham with CBT: Participants that attend to 5 weekly sessions of sham tDCS and that following the tDCS session, they attend also to a CBT session.

4. Variables and covariates

- Behavioural Dependent Variables (transfer tasks):

a) Cambridge Gambling Task's scores (changes between session 1 to session 5) for:
   1. Quality of decision-making
   2. Risk-taking behaviour
   3. Delay aversion

b) Multitasking Task's scores - based on Attention Switching Task (changes between session 1 to session 5) for:
   1. Inhibition
   2. Cognitive flexibility

- Behavioural Dependent Variables (training tasks):

a) Stop signal task's scores (changes from sessions 2, 3 and 4) for:

1. Inhibition

b) Information Sampling Task's scores (changes from sessions 2, 3 and 4) for:

1. Risk taking behaviour

c) One Touch Stockings of Cambridge Task's scores (changes from sessions 2, 3 and 4) for:

1. Planning
2. Working memory

- Independent Variables:

1. tDCS condition (Stimulation or Sham) – Experiment 1
2. Treatment (Sham tDCS + CBT or stimulation tDCS + CBT) – Experiment 2

- Cognitive Dependent Variables / Covariates:

1. Gambling Related Cognitions Scale. The level of cognitive distortions (biases) measured with this questionnaire could be influencing risk-taking behaviour.

2. UPPS Impulsivity Scale. The specific type of impulsivity (e.g. lack of premeditation/sensation seeking) measured with this questionnaire could influence the type of decisions and delay aversion measures.

3. Actively Open Minded Thinking Scale. The scores of cognitive flexibility measured with this questionnaire could influence the ability to perform in decision-making tasks.

4. Age (covariate)

5. Gender (covariate)

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

We will analyse the questionnaires for dependency with the behavioural dependent variables. Subject to these results, we will either use the questionnaires as covariates (if they show a relationship with the behavioural dependent variables) or just as a separate (cognitive) dependent variables if they don't.

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 condition on task performance across sessions, for each task, we will use a 2 x 2 mixed between– within ANCOVA covarying for the questionnaires with the between-groups factor being condition (active vs sham tDCS) and the within-participants factor being time (session 1 and session 5 in transfer tasks; session 2,3 and 4 in training tasks). Analyses will be tested for main effects of condition and time as well as the condition x time interaction. Questionnaire scores will be correlated using Pearson's correlation with the percentage change in tasks scores over the 5 active treatment sessions to examine whether questionnaire scores predicted tasks responses.

Scores from neuropsychological tests examining changes over the sessions (active or sham), and scores from tests administered immediately before and after sessions 1 and 5 (active or sham) will be also analysed with a mixed between–within ANOVA testing for main effects of condition and time as well as condition x time interactions. In addition, neuropsychological tests scores were separately analysed for participants who received 5 active treatments (i.e. active group), examining for a main effect of time across the 5 sessions using a repeated measures ANCOVA controlling for the percentage change in questionnaire scores over the same period.