

**Queen's University**  
**Centre for Neuroscience Studies and Department of Psychiatry**  
**Research Protocol**

**Version 2**  
**Date: January 20, 2019**

**Study Title**

The use of combined Anodal transcranial Direct Current Stimulation (tDCS) and cognitive training to modulate decision-making in healthy people

**Principal Investigator**

Dr. Najat Khalifa, *MBChB, MRCPsych, DM*  
Associate Professor in Forensic Psychiatry  
Division of Forensic Psychiatry  
Department of Psychiatry, Queen's University  
c/o Providence Care Hospital  
752 King Street West, Kingston, ON, K7L 4X3. Tel: 616-770-2434  
Email: [nrk2@queensu.ca](mailto:nrk2@queensu.ca)

**Co-Investigators**

Dr. Tariq M. Hassan, *MBBS, MRCPsych, FRCPC*  
Associate Professor  
Divisional Chair and Clinical Director  
Division of Forensic Psychiatry  
Department of Psychiatry  
Queen's University  
Email: [hassant@providencecare.ca](mailto:hassant@providencecare.ca)

Dr. Katy Jones, PhD  
Assistant Professor of Applied Psychology  
Division of Psychiatry and Applied Psychology  
School of Medicine  
University of Nottingham, UK  
Email: [katy.jones@nottingham.ac.uk](mailto:katy.jones@nottingham.ac.uk)

Professor Peter Liddle, PhD  
Professor of Psychiatry  
Division of Psychiatry and Applied Psychology  
School of Medicine  
University of Nottingham, UK

Email: [peter.liddle@nottingham.ac.uk](mailto:peter.liddle@nottingham.ac.uk)

Dr. Roumen Milev, *MD, PhD, FRCPsych, FRCPC*  
Professor of Psychiatry and Psychology  
Director of Centre for Neuroscience Studies  
Division of Community Psychiatry  
Department of Psychiatry, Queen's University  
Email: [milevr@providencecare.ca](mailto:milevr@providencecare.ca)

### **Funding and Duration**

Funding Body: Department of Psychiatry, Queen's University  
Duration: 18 months  
Start date: February 4, 2019

### **Background**

Decision-making is regarded as a form of goal-directed behaviour that entails forming preferences, selecting and performing actions, and evaluating outcomes on choices (Ernst & Paulus, 2005). It is underpinned by a complex interaction between affective processing and behavioural regulation (Hughes et al., 2016), and this interaction is influenced by the activation of a neuronal circuit encompassing several cortical (e.g. ventromedial frontal cortex (vmPFC), dorsolateral prefrontal cortex (DLPFC)) and subcortical areas (e.g. amygdala, hippocampus, anterior cingulate cortex) (Bechara et al., 1994; Beszterczey et al., 2013). Decision-making overlaps significantly with impulsivity, which in turn reflects a failure to plan ahead and inability to control or regulate emotions and behaviours, often with negative consequences for the individuals concerned and others (Farrington, 2010; Castellanos-Ryan & Séguin, 2015). Deficits in decision-making may result in an elevated risk of violent and antisocial behaviour (Howard, 2006;). Therefore, and in order to reduce the harm caused by impaired decision-making capacity, the importance of developing specific interventions to enhance decision making is paramount.

Transcranial Direct Current Stimulation (tDCS) is a non-invasive brain stimulation technique that has been used to modulate brain activity through a weak direct electric current which stimulates the brain area beneath the stimulation site and deeper structures through connected neuronal networks. tDCS has been used to treat various psychiatric disorders, such as depression (Palm, et al., 2016) and Obsessive Compulsive Disorder (Brunelin, et al., 2018). It has been also used to modulate decision-making with some promising results (e.g. Ouellet et al., 2015; Casula et al., 2017).

In recent years, research interest has grown in combining tDCS with cognitive training paradigms in the hope of maximizing training benefits, leading to task-specific cognitive enhancement (Filmer et al., 2017). Earlier meta-analyses of cognitive training research revealed mixed evidence for training effects and generalizability of effects to other tasks (Owen et al., 2010; Shipstead et al., 2012). However, more recent evidence suggests that combined tDCS and cognitive training can enhance performance on tasks designed to assess motor functioning (Stagg et al., 2011), language (Flöel et al. 2008), numeracy (Kadosh et al., 2010), decision making (Filmer et al., 2017) and inhibitory control (Berkman et al., 2014). Furthermore, Filmer and colleagues reported that

combined tDCS and cognitive training can enhance decision-making and these effects are generalizable to both trained and untrained tasks (Filmer et al., 2017).

### **The proposed study**

Deficits in decision-making under conditions of uncertainty and risk has been implicated in maladaptive personality development and violent behaviour (Howard, 2006; Hughes et al; 2016). To our knowledge, no studies have examined the effects of combined tDCS and cognitive training on decision-making under conditions of uncertainty and risk. It is also unclear if these effects are generalizable to tasks in other domains such as response inhibition (also known as motor impulsivity).

To examine these issues further, we propose to apply either active or sham tDCS over the anterior frontal cortex (including the vm-PFC) while participants undertake decision-making training using the Iowa Gambling Task (IGT; Bechara, 2007). Decision-making will be assessed using the IGT, which is a computerized gambling task used to assess decision-making under conditions of uncertainty and risk. IGT is sensitive to damage to the vmPFC (Bechara et al., 1994), which is considered to play a key role in decision-making. Motor impulsivity will be measured using the Stop Signal Task (SST). A self-report measure of impulsivity will be used to assess the effects of individual differences in trait impulsivity on test results. The UPPS+P Impulsive Behaviour Scale (Cyders et al., 2007) will be used to index trait impulsivity. The Profile of Mood States (POMS; Grove & Prapavessis, 1992) will be used to measure state emotion before and after tDCS.

### **Study Aims and Hypothesis**

We aim to (i) assess the effects of combined tDCS and cognitive training on decision-making on the trained task (in this case, IGT); and (ii) test generalization to a closely related cognitive domain, namely motor impulsivity). Based on the work of others (e.g., Casula et al., 2017; Filmer et al, 2017; Quellet et al., 2015), we hypothesize that combined anodal tDCS and cognitive training will result in more advantageous decisions and better impulse control than sham tDCS.

### **Methods**

#### **Study Design and Sample**

A single blind parallel arms randomized controlled trial will be conducted, involving a sample of healthy volunteers aged between 18 and 40. Eligible participants will be identified using a tDCS safety questionnaire (Appendix 1) such that individuals with epilepsy, other neurological conditions and history of significant head injury will be excluded. Individuals with a history of substance misuse, major mental disorder and those receiving psychotropic medication will be also excluded. Participants will be recruited through adverts displayed on notice boards at Queen's University including sports clubs and student societies.

#### **Psychometric tools**

##### **UPPS+P**

The UPPS+P Impulsive Behavior Scale (Cyders et al, 2007) will be used to index impulsivity. UPPS+P is a 59 item self-report measure of trait impulsivity with 5 subscales; Negative Urgency, (Lack of) Premeditation, (Lack of) Perseverance, Sensation seeking and Positive Urgency. Each

item is rated on a scale of 1-4 (1=totally disagree, 4=totally agree). Higher scores indicate stronger presence of these traits.

#### *Profile of Mood States (POMS)*

POMS (Grove & Prapavessi, 1992) is a 40-items self-report questionnaire that captures transient, distinct mood states. It measures 7 distinct mood states; tension, anger, fatigue, depression, esteem related effect, vigour, and confusion. Each item is rated on a scale of 0-4 (0=not at all; 4=extremely), yielding a Total Mood Disturbance score and scores for 7 mood states. POMS takes approximately 5 minutes to complete.

#### *IGT*

The IGT (Bechara, 2007) is a computerized gambling task. Individuals choose from four decks of cards (A, B, C, D) which differ in terms of their reward-punishment profiles. Repeated selection from decks C and D (advantageous decks) results in an overall net profit; whilst repeated selection from the decks A and B (disadvantageous decks) results in greater losses. The main measure of performance is the difference between the numbers of choices from the advantageous decks minus the number of choices from the disadvantageous decks, giving an overall 'net' score. The IGT takes approximately 20 minutes to complete.

#### *SST*

SST is a measure of inhibitory control. SST entails presenting a circle on the computer screen with an arrow inside pointing either to the right or left of the screen (the go signal). The participant is instructed to use a pad to register their responses by pressing the left hand button on the pad for arrows pointing to the left or the right hand button for arrows pointing to the right. The participant is instructed to withhold response upon hearing a beeping sound (the auditory stop signal) which is randomly generated shortly after the presentation of the arrows in 25% of the trials. The task consists of five blocks with 64 trials in each block. The difficulty of the task is manipulated by changing the stop signal delay (SSD), which refers to the time interval between the go signal and the onset of the stop signal, such that the sooner the stop signal occurs after the onset of the go signal, the easier it becomes for the participants to inhibit their responses. Four interleaved stepwise functions will be used (100, 200, 400, and 500ms) to make it difficult for the participant to predict the onset of the stop signal. The test is calibrated such that the difficulty of the next trial is increased following a successful withhold response by increasing the SSD by 50ms. Conversely, failure to inhibiting a response reduces the difficulty of the next trial by reducing the SSD by 50ms. Stop Signal Reaction Time (SSRT) is the primary outcome measure for SST. It is defined as the mean reaction time on go trials minus the mean SSD at which the participant successfully withholds a response on 50% of the trials. Lower SSRT values corresponds to poorer response inhibition. The task takes approximately 15 minutes to complete.

#### *tDCS*

Soterix tDCS kit will be used to deliver the stimulation using two sponge electrodes soaked in saline. The stimulation montage will comprise of anterior PFC anodal or sham stimulation. The anodal electrode will be placed over the area corresponding to the anterior PFC (FpZ of the EEG10-20 international system) and the reference (cathodal) electrode over the posterior occipital area (OZ of the EEG10-20 international system). This montage has been utilized in other

studies to stimulate the anterior OFC (Casula et al., 2016; Fumagalli et al., 2010). It is considered to enhance the anterior-posterior current flow via the vmPFC region of the anterior PFC and to reduce the lateral shunting along the skin (Casula et al., 2016; Fumagalli et al., 2010).

The active stimulation condition will use a constant current of 2mA, delivered via gradual increase and decrease over 10 seconds at the onset and offset of stimulation (current ramps), respectively. For sham stimulation, the current will be delivered only in the first 10 seconds, after which the stimulation will cease but with the electrodes still in place throughout the session. The duration of each tDCS session will be 20 minutes.

### *Procedure*

A brief overview of the experiment is provided in figure 1 below. The experiment is divided into three phases (baseline, cognitive training, endpoint). In the first phase, participants will be asked to complete the UPPS+P Impulsive Behaviour Scale, POMS, SST and IGT. In the second phase, participants will undertake cognitive training by repeating the IGT with either anodal or sham tDCS applied over the anterior PFC. In the third phase, the participant will repeat the POMS, IGT and SST. Additionally, a tDCS adverse effects questionnaire (Appendix 2) will be administered at the end of the experiment to detect adverse effects.

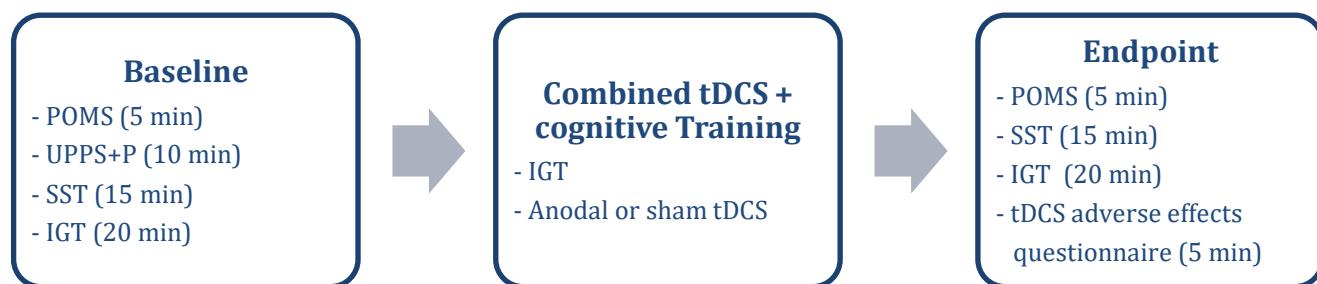


Figure 1: Experiment Overview

### *Statistical Analysis*

A power calculation conducted using an independent-samples *t*-test (G\*Power) yielded a total sample size of 60 participants (effect size=0.65, power=80%,  $\alpha = 0.05$ , one tailed testing). Data will be analyzed using the Statistical Package for Social Sciences (SPSS). A Repeated Measures ANOVA will be performed with group allocation (active tDCS vs. sham) and time (pre- vs. post-tDCS stimulation). Mean scores on UPPS+P will be entered into the model as co-variates. Within-subject factors will be used to compare changes in outcome variables between the groups over time. A *p* value of  $< 0.05$  will be considered as statistically significant.

### *Research ethics approval and informed consent*

Research ethics approval will be obtained from the Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB) at Queen's University. Written informed consent will be obtained from all participants. Eligible participants will be selected carefully using a tDCS safety questionnaire (Appendix 1). Each participant will be assigned a unique identity code, and no participant identifiable information will appear on paper or electronic data formats. A code breaker will be saved on a secure University computer that is only accessible to the research team and other authorized individuals within Queen's University.

### Research management

A Research Management Group comprising study investigators will be established to manage the overall governance of the project and day-to-day operations. The group will meet monthly to discuss progress and to ensure that the study is conducted in accordance with the requirements of the research ethics approval.

### **Expected Impact of Research Proposal**

There currently exist no specific interventions to target impaired decision making. The proposed study will assess whether combined tDCS (applied over the anterior PFC) and cognitive training can enhance decision making and impulse control. Further funding will be sought to develop the concept on a wider scale to examine the neurobiological underpinning of decision making, for instance, by combining tDCS and cognitive training with neuroimaging techniques such as fMRI or MEG.

### **Resources and the Research Team**

The study will be conducted under the auspices of the Centre for Neuroscience and Department of Psychiatry at Queen's University. The Neuroconn tDCS or Soterix kit will be purchased via the relevant supplier.

Dr. Khalifa, Dr. Jones and Professor Liddle have expertise in brain stimulation, impulsivity and decision-making research. Professor Liddle is a world-renowned expert in neuroimaging and psychiatry research. Together, they are currently conducting a concurrent tDCS - Magnetoencephalography (MEG) study, examining the cortical correlates of impulsivity. Dr. Tariq Hasan is an established senior clinical academic with a track record of academic achievements. Professor Milev is the Director of Centre for Neuroscience Studies, Queen's University. Between 2007 and 2017 he was the Head of Department of Psychiatry at Queen's University between. He is actively involved in research with patients with Depression, Bipolar Disorder, Anxiety Disorders, and other Affective Disorders. Main areas of his research include issues of Stigma and ways of dealing with it, Sleep architecture, psychopharmacological and rTMS treatments.

## References

1. Bechara, A., Damasio, A.R., Damasio, H. & Anderson, S.W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, 50, 7-15.
2. Bechara, A. (2007). *Iowa Gambling Task*. Psychological Assessment Resources, Inc. USA.
3. Berkman, E.T., Kahn, L.E., & Merchant, J.S. (2014). Training-Induced Changes in Inhibitory Control Network Activity. *The Journal of Neuroscience*, 34(1):149 -157.
4. Beszterczez, S., Nestor, P. G., Shirai, A., & Harding, S. (2013). Neuropsychology of decision making and psychopathy in high-risk ex-offenders. *Neuropsychology*, 27(4), 491.
5. Brunelin, J., Mondino, M., Bation, R., Palm, U., Saoud, M., & Poulet, E. (2018). Transcranial Direct Current Stimulation for Obsessive-Compulsive Disorder: A Systematic Review. *Brain Science*, 8(2): 37. doi: 10.3390/brainsci8020037
6. Cambridge Cognition. (2016). CANTAB® [Cognitive assessment software]: CANTAB Technology.
7. Castellanos-Ryan, N., & Séguin, J. R. (2015). Prefrontal and Anterior Cingulate Cortex Mechanisms of Impulsivity. Beauchaine, T. P. & Stephen P. Hinshaw, S. P. (editors). *The Oxford Handbook of Externalizing Spectrum Disorders*. Oxford University Press – New York. DOI: 10.1093/oxfordhb/9780199324675.013.13
8. Casula, E.P., Testa, G., Bisiacchi, P.S. et al. (2017). *Journal Cognitive Enhancement*, 1:318. doi.org/10.1007/s41465-017-0030-7.
9. Cyders, M. A., Smith, G. T., Spillane, N. S., Fischer, S., Annus, A. M., & Peterson, C. (2007). Integration of impulsivity and positive mood to predict risky behavior: Development and validation of a measure of positive urgency. *Psychological Assessment*, 19(1), 107-118. doi:10.1037/1040-3590.19.1.107
10. Ernst, M., & Paulus, M. P. (2005). Neurobiology of decision making: a selective review from a neurocognitive and clinical perspective. *Biological Psychiatry*, 58(8), 597-604.
11. Farrington, D. P. (2010). The developmental evidence base: psychosocial research. In Towl, G. J. & Crighton, D. A. (eds). *Forensic Psychology*. BPS Blackwell. Blackwell Publishing Ltd.
12. Filmer, H.L., Varghese, E., Hawkins, G.E., Mattingley, J.B. & Dux, P. E. (2017). Improvements in Attention and Decision-Making Following Combined Behavioral Training and Brain Stimulation. *Cerebral Cortex*, 27: 3675-3682.
13. Fumagalli, M., Vergari, M., Pasqualetti, P., Marceglia, S., Mameli, F., Ferrucci, R., Mrakic-Sposta, S., Zago, S., Sartori, G., Pravettoni, G., Barbieri, S., Cappa, S., & Priori, A. (2010). Brain switches utilitarian behavior: does gender make the difference? *PloS One*, 5(1), e8865.
14. Flöel, A., Rösner, N., Michka, O., Knecht, S., & Breitenstein, C. (2008). Noninvasive brain stimulation improves language learning. *Journal of Cognitive Neuroscience*, 20(8):1415-1422.
15. Grove, J.R., & Prapavessis, H. (1992). Preliminary evidence for the reliability and validity of an abbreviated Profile of Mood States. *International Journal of Sport Psychology*, 23, 93-109.
16. Howard, R. (2006). How is personality disorder linked to dangerousness? A putative role for early-onset alcohol abuse. *Medical Hypotheses*, 67, 702-708.
17. Hughes, M. A., Dolan, M. C., & Stout, J. C. (2016). Decision-making in Psychopathy. *Psychiatry, Psychology and Law*, 23(4), 521-537.

18. Kadosh, R.C., Soskic, S., Iuculano, T., Kanai, R., & Walsh, V. (2010). Modulating neuronal activity produces specific and long-lasting changes in numerical competence. *Current Biology*, 20 (22):2016-2020.
19. Palm, U., Hasan, A., Strube, W., Padberg, F. (2016). tDCS for the treatment of depression: a comprehensive review. *European Archives of Psychiatry and Clinical Neuroscience*, 266(8):681-694.
20. Ouellet, J., McGirr, A., Van den Eynde, F., Jollant, F., Lepage, M., & Berlim, M.T. (2015). Enhancing decision-making and cognitive impulse control with transcranial direct current stimulation (tDCS) applied over the orbitofrontal cortex (OFC): A randomized and sham-controlled exploratory study. *Journal of Psychiatric Research*, 69, 27-34.
21. Owen, A.M., Hampshire, A., Grahn, J.A., Stenton, R., Dajani, S., Burns, A.S., Howard, R.J., & Ballard, C.G. (2010) Putting brain training to the test. *Nature*, 465: 775–778.
22. Shipstead, Z, Hicks, K.L., & Engle, R.W. (2012) Cogmed working memory training: does the evidence support the claims? *Journal of Applied Research in Memory and Cognition* 1:185–193.