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Measuring cortical dynamics of inhibitory control before, during, and after transcranial Direct Current Stimulation (tDCS).

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Short title:	tDCS and Inhibitory Control
Acronym:	N/A
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Study Sponsor:	University of Nottingham
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STUDY PERSONNEL AND CONTACT DETAILS

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Study Statistician: N/A

Study Coordinating Centre: Division of Psychiatry and Applied Psychology and School of Physics and Astronomy.

SYNOPSIS

Title	Measuring cortical dynamics of inhibitory control before, during, and after transcranial direct-current stimulation (tDCS).
Acronym	N/A
Short title	tDCS and Inhibitory Control
Chief Investigator	Dr Najat Khalifa
Objectives	To further our understanding of the neurobiological mechanisms underpinning Rapid Response Impulsivity and how these can be influenced by tDCS, we aim to examine the influence of anodal tDCS on beta-band and alpha-band oscillatory activities, using an anti-saccade task administered before, during and after tDCS stimulation. We hypothesise that: (i) a generalised mechanism for top-down inhibitory control will play a vital role, whereby prefrontal beta-band activity initiates alpha-band activity for functional inhibition over the frontal eye fields and other areas in the neuro-circuitry involved in RRI (ii) anodal tDCS (as opposed to sham) delivered over the right DLPFC will enhance this mechanism; and (iii) there will be no significant correlations between measures of self-report impulsivity and performance on the anti-saccade task and measures of oscillatory activity.
Study Configuration	Single session, healthy controls, proof of concept, MEG, tDCS, Impulsivity.
Setting	Sir Peter Mansfield Imaging Centre, University Park, University of Nottingham.
Sample size estimate	Up to 60 participants will be sought. This is based on a power calculation using an independent-sample t-test (G*Power; Faul et al., 2007). This yielded a total sample size of 60 participants, with an effect size of d = 0.65, 80% power and alpha error probability of α = 0.05 (one tailed testing).
Number of participants	Up to 60 healthy controls
Eligibility criteria	Aged 18-40, studying or working at UoN, no history of epilepsy or other neurological conditions, significant head injury, substance misuse, major mental disorder, or those currently receiving psychotropic medication.
Description of interventions	tDCS. Study will also involve brain imaging (MEG and MRI).

Duration of study	12 months
Methods of analysis	Analysis of beta and alpha band MEG data will follow Hwang et al (2014). Between subjects' differences in the effects of tDCS on task performance will be examined using the Reaction Time and failure to saccade before and after stimulation. Independent samples t-test will be used for normally distributed data. Otherwise, the Mann-Whitney tests will be used. Correlational analysis will be used to examine the relationship between scores on UPPS-P, anti-saccade task performance and oscillatory activity over regions of interest.

ABBREVIATIONS

ACC	Anterior Cingulate Cortex
CI	Chief Investigator overall
CRF	Case Report Form
DLPFC	Dorsolateral pre-frontal cortex
GCP	Good Clinical Practice
MEG	Magnetoencephalography
MRI	Magnetic Resonance Imaging
NHS	National Health Service
PI	Principal Investigator at a local centre
Pre-SMA	Pre-Supplementary Motor Area
PIS	Participant Information Sheet
RRI	Rapid Response Impulsivity
REC	Research Ethics Committee
R&D	Research and Development department
tDCS	Transcranial Direct-Current Stimulation
UPPS-P	Urgency, Pre-meditation, Perseverance, Sensation-Seeking Questionnaire (Positive Urgency)
UoN	University of Nottingham

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STUDY BACKGROUND INFORMATION AND RATIONALE

Rapid Response impulsivity (RRI) is a form of impulsivity characterised by failure to refrain from action initiation or stop an ongoing or pre-potent action. It is a common feature of many psychiatric disorders (e.g., conduct, antisocial personality, or substance use disorders, and Attention Deficit Hyperactivity Disorder, ADHD), and has been associated with serious consequences for individuals and others (e.g., self-harm, violence).

Brain regions implicated in RRI include the prefrontal structures (particularly dorsolateral prefrontal cortex, DLPFC), Anterior Cingulate Cortex (ACC), pre-supplementary motor area (Pre-SMA) and limbic structures (Castellanos-Ryan & Séguin, 2015; Brevet-Aeby et al., 2016). However, little is known about what specific executive function the DLPFC fulfills. A generalised mechanism for top-down inhibitory control has been suggested (Hwang et al, 2014), whereby a prefrontal beta-band activity initiates alpha-band activity for functional inhibition of the effector system.

tDCS is a non-invasive brain stimulation technique that modulates 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 modulate impulsivity, but firm conclusions regarding its efficacy and mechanism of action in relation to RRI cannot be drawn from the available literature owing to limited knowledge of the neurobiological underpinnings of RRI.

Of importance is the integration of tDCS with multiple forms of imaging that offer complementary information with clinically relevant measures. If we find RRI can be modulated by tDCS, this has implications for working with clinical populations to reduce harm in the future.

STUDY OBJECTIVES AND PURPOSE

PURPOSE

To further our understanding of the neurobiological mechanisms underpinning RRI and how these can be influenced by tDCS, we aim to examine the influence of anodal tDCS on beta-band and alpha-band oscillatory activities, using an anti-saccade task administered before, during and after tDCS stimulation.

PRIMARY OBJECTIVE

We hypothesise that:

i. a generalised mechanism for top-down inhibitory control will play a vital role, whereby prefrontal beta-band activity initiates alpha-band activity for functional inhibition over the frontal eye fields and other areas in the neuro-circuitry involved in RRI;
ii. anodal tDCS (as opposed to sham) delivered over the right DLPFC will enhance this mechanism; and
iii. there will be no significant correlations between measures of self-report impulsivity and performance on the anti-saccade task and measures of oscillatory activity.

SECONDARY OBJECTIVES

To examine study feasibility including recruitment rate, and acceptability of the study protocol.

STUDY DESIGN

STUDY CONFIGURATION

This will be a single-centre, one-off study using randomisation to anodal tDCS or sham using a computer generated code. Participants will be blind to tDCS condition. Pre and post task performance will be measured to examine changed in RRI before and after tDCS.

RANDOMIZATION AND BLINDING

Consenting participants will be randomly allocated, using a computer generated code, to receive either anodal tDCS or sham. Randomization will be conducted by Dr. Elizabeth Liddle (Assistant Professor, Division of Psychiatry and Applied Psychology) as she is external to the project, but is familiar with such randomization techniques in other related MEG work.

Maintenance of randomisation codes and procedures for breaking code

The study is single blind, thus there will be no procedure for breaking code.

STUDY MANAGEMENT

The study will be conducted in line with the standards set out in the University of Nottingham Code of Research Conduct and Research Ethics (2016). The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator (Dr Najat Khalifa). Members of the research team will meet monthly to discuss the project implementation plan and the overall progress.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

Study Duration: 12 months (February 18- 19)

Participant Duration: One off session (approximately 4 hours) between February 18 and end of the study.

End of the Study

The end of the study will be defined as the last visit of the last recruited participant. There is no follow-up period. Final data analysis and write up will take place after this.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

The study setting will be UoN (UK campus). This setting has been chosen for convenience, and because healthy controls (rather than a clinical population) will be sought.

All participants will be staff and students aged 18-40 at UoN. As well as general online and poster advertising across the university, targeted advertising will be conducted at UoN

societies where recreational activities are associated with a high degree of risk (e.g. speed, height, or high level of physical exertion). This is because, it is thought people who take part in such activities are more likely to have a 'thrill-seeking' personality (Self et al., 2007). For example, the following societies have been identified: UoN Gliding Club, UoN Equestrian Club, UoN Climbing Club, UoN Sky Diving Club, UoN Motorsport. Societies will be approached through e-mail, or the society social media page. As well as targeted recruitment, posters will be placed across the university (e.g., Student's Union, Library).

Participants will be recruited from adverts (posters and information) placed online and in buildings around UoN (UK campuses e.g. University Park, Jubilee). Interested participants can choose to take part in the study by contacting one of the researchers by e-mail or telephone (contact details are provided on all advertising material).

After the participant has contacted the researcher, further information will be provided (brief explanation of the study, Participant Information Sheet and information about tDCS will be sent by e-mail, and researcher will review a brief safety screening questionnaire to ensure the participant is eligible to have tDCS and to go in the scanner). If eligible, participants will be booked in to attend the Sir Peter Mansfield Centre for the 4-hour appointment.

On the day of the study, participants will be given a chance to ask any questions about the study, and their safety questionnaire will be reviewed again by the researcher before signing the consent form to begin the study

It will be explained to the potential participant that entry into the study is entirely voluntary and that their withdrawal will not affected their studies or employment at UoN. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

N.B. Data should not be erased as it should be possible to recreate a participant's participation up to their point of withdrawal. Also once data has been entered onto the UoN secure network, data cannot be erased as UoN backups cannot be tampered with. This is covered on clause 2 of the consent form and the withdrawal section of the participant information sheet template.

Eligibility criteria

Main points of consideration are:

- Over 18
- Able to give informed consent (participants will be studying or working at UoN and therefore will be able to read and understand English)
- Participant safety for tDCS or scanning (e.g., See below for exclusion criteria)

Inclusion criteria

- Aged 18-40
- Studying or working at UoN
- Able to give informed consent

Exclusion criteria

A tDCS safety questionnaire will be used to assess suitability for the procedure. Typical reasons a participant may be excluded from the study will be due to:

- History of epilepsy or other neurological conditions
- Significant head injury
- Current substance misuse
- Major mental disorder
- Currently receiving psychotropic medication.

Expected duration of participant participation

Study participants will be participating in the study for up to 4 hours.

Participant Withdrawal

Participants may withdraw from the study due to:

- Safety reasons (including pregnancy)
- Failure of participant to adhere to protocol requirements
- Withdrawal of consent

Note that participants must be withdrawn from study if consent is withdrawn.

Participants may be withdrawn from the study either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the Participant Information Sheet and Consent Form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Informed consent

All participants will provide written informed consent. The Consent Form will be signed and dated by the participant before they enter the study. The Investigator will explain the details of the study and review the Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

One copy of the Consent Form will be kept by the participant and one will be kept by the investigator.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the study, continuing consent will be obtained using an amended Consent Form which will be signed by the participant.

Completion and subsequent return of questionnaires will be taken as informed consent and separate written informed consent will not be sought

STUDY REGIMEN

Pilot study

Prior to the main study, a brief pilot study (up to 5 participants) will be conducted to test the protocol. Participants will spend up to 1 hour in MEG for the purpose of optimising performance of the MEG system during concurrent tDCS and MEG.

Before the appointment

- Participant sees study advert and contacts researcher by e-mail or telephone to find out more detail about the study (see study advert for details).
- Researcher supplies information to participant by telephone or e-mail (Participant Information Sheet and tDCS Information Sheet will be sent by e-mail at least 24 hours before the study). Researcher conducts tDCS and imaging screening questionnaire over the telephone.
- If eligible, researcher books participant in for the study.

At the appointment

- Step 1. Researcher reviews participant information sheet with participant and answers any questions the participant may have about the study. Researcher confirms safety to proceed.
- Step 2. Informed consent is given.
- Step 3. Computer generated code supplied and participant allocated to either sham or anodal tDCS.
- Step 4. UPPS-P Questionnaire completed by participant (5-10 minutes).
- Step 5. tDCS equipment shown to participant and attached. Example stimulation given to the participant (10- 20 seconds)
- Step 6. MEG scanner briefing
- Step 7. 3 x Anti-saccade tasks completed in the MEG (20 minutes each) while participant is delivered either anodal or sham tDCS.
- Step 8. Anatomical MRI acquisition.15 minute scanning session on either the 3 or 7 tesla MRI systems.
- Step 9. Participant asked to guess the randomisation procedure, and response noted. Participant thanked, post-tDCS questionnaire completed, participant debriefed and paid £40.

Compliance

N/A as this is a one-off study.

Criteria for terminating the study

It is unlikely the study will be terminated. However, should this occur, it is likely to do with pragmatic reasons due to tight 12-month funding (study finishing end of February 2019).

Stopping whole study:

- Funders decide to terminate the study early.
- Long-term difficulties with the facility (unforeseen circumstances). For example, if the MEG scanner is not working.

tDCS and imaging safety:

The tDCS safe procedure is considered to be low risk. Current evidence from extensive work shows there are no major side effects apart from skin irritation at the site of stimulation and headache. In principle, tDCS might induce seizures but this has never been reported in the literature (Poreisz et al., 2007). If during the course of the study any evidence emerges of significant risk then we will stop the study.

Similarly, at present there is low risk for taking part in MRI or MEG studies, but should significant safety concerns arise during the course of the study, the study will be terminated.

Stopping single participant:

A single participant testing session may be terminated if:

- The participant requests to leave the study
- The participant is experiencing significant adverse effects from the study (e.g., a headache).

ANALYSES

Methods

All members of the study team will be involved in the evaluation, analysis and write up of findings.

Analysis of beta and alpha band MEG data will follow analysis cited by Hwang et al (2014). Between subjects' differences in the effects of tDCS on task performance will be examined using the Reaction Time and failure to saccade before and after stimulation. Independent samples t-test will be used for normally distributed data. Otherwise, the Mann-Whitney tests will be used. Correlational analysis will be used to examine the relationship between scores on UPPS-P, anti-saccade task performance and oscillatory activity over ROI.

SPSS (version 24) will be used for analysis as well as in-house Matlab protocols. Analysis will take place on UoN computers and backed up to the UoN servers.

Sample size and justification

A sample size of 60 was estimated. This is based on a power calculation using an independent-sample t-test (G*Power; Faul et al., 2007). This yielded a total sample size of 60 participants, with an effect size of d = 0.65, 80% power and alpha error probability of α = 0.05 (one tailed testing).

ADVERSE EVENTS

It is unlikely that adverse events will occur as a result of participation in the study. However, as the study involves stimulation of the brain, a management plan for adverse events will be briefly described here.

Participants will be provided with written information on the debriefing sheet with contact details (mobile phone number) for Dr Najat Khalifa (CI and Consultant Forensic Psychiatrist) should they experience any adverse events (e.g., headache). Dr Khalifa will speak to the participant to understand the nature of the concern or complaint, and either provide reassurance or, if appropriate, recommend the person goes to see their GP.

Any adverse events data will be collected and stored during the course of the study.

ETHICAL AND REGULATORY ASPECTS

It is not anticipated any sensitive or personal information will be disclosed as a result of a person's participation in the study. The only anticipated ethical issue is outlined here.

Patient safety

Participants will be selected carefully using the tDCS safety questionnaire such that those with a history of epilepsy, brain injury or other neurological conditions or those who have metal implants (contraindications to the use of tDCS) will be excluded (this is also clearly stated in study advertising).

A dual safety check will be conducted with an initial safety screening for tDCS and imaging conducted over the telephone prior to booking, and an additional check on the day of the appointment. All researchers conducting such screening are familiar with, and trained in, the safety of participants using tDCS and brain imaging.

In addition to this, a separate tDCS Information Sheet (attached) will be given to participants with the standard Participant Information Sheet so they are aware of potential side effects. Additionally, a tDCS side effect questionnaire will be completed for each participant at the end of the tDCS session, and each participant will be debriefed. As described above, should adverse effects occur after the study has been completed, participants can contact Dr Najat Khalifa directly to discuss the issue with him directly. It is likely to be suggested the participant make an appointment to see their GP.

The duration of the study is 4-hours and participants may become fatigued. They will be informed they can take a break when they want to.

ETHICS COMMITTEE AND REGULATORY APPROVALS

The study will not be initiated before the protocol, consent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator and the participant shall both sign and date the Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Study records.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No study-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Consent Form by the REC and use of the amended form (including for ongoing participants).

For Questionnaires:

Completion and subsequent return of questionnaires will occur during the study session and therefore separate written informed consent will not be sought.

RECORDS

Case Report Forms

Each participant will be assigned a study identity code number, for use on CRFs, other study documents and the electronic database.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, Participant Study Number, to permit identification of all participants enrolled in the study, in case additional follow-up is required.

CRFs shall be restricted to those personnel approved by the Chief or local Investigator and recorded as such in the study records.

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, study records, field notes, interview transcriptions and audio records. A CRF may also completely serve as its own source data. Only study staff shall have access to study documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities.

DATA PROTECTION

All study staff and investigators will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the study. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the study staff and investigators and any relevant regulatory authorities (see above). Computer held data including the study database will be held securely and password

protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Information about the study in the participant's record will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for clinical study participants and study staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but study participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

STUDY CONDUCT

Study conduct may be subject to systems audit for inclusion of essential documents; permissions to conduct the study; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs.

STUDY DATA

Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the study database will be checked. Where corrections are required these will carry a full audit trail and justification.

Study data and evidence of monitoring and systems audits will be made available for inspection by the REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible

investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The study documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all anonymised audio recordings, study databases and associated meta-data encryption codes.

DISCONTINUATION OF THE STUDY BY THE SPONSOR

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical or personal information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this study will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

We intend to publish findings in peer-reviewed journals, and present findings at academic conferences. Participants will not be identified in any publications.

USER AND PUBLIC INVOLVEMENT

Prior to the main study, a brief pilot study (up to 5 participants) will be conducted to test the protocol. Participants will spend up to 1 hour in MEG for the purpose of optimising performance of the MEG system during concurrent tDCS and MEG.

Participants will not be involved in the dissemination of the study.

STUDY FINANCES

Funding source

This study is funded by Medical Research Council (Nottingham Confidence in Concept Award, School of Medicine).

Participant stipends and payments

Participants will be paid £40 for their participation in the study (Approximately £10 p/hour). Travel expenses will not be offered.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name) Dr Najat Khalifa

Signature:_____

Date: 08.01.2018

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