TRANSCRANIAL CURRENT STIMULATION (TCS) INVESTIGATIONS IN HEALTHY ADULT VOLUNTEERS

1. SCOPE

Many research groups within the Medical Sciences Division perform research investigating brain function using Transcranial Current Stimulation (TCS). TCS is a broad term covering Transcranial Direct Current Stimulation (TDCS), Transcranial Alternating Current (TACS) and Transcranial Random Noise Stimulation (TRNS). These are methods of delivering brain stimulation by applying weak electrical currents to the scalp.

Researchers working with TCS in the University believe that the potential risks are negligible and that effective guidelines have been long established and are clearly specified (see Nitsche et al., 2008), making TCS essentially safe. This fact is reflected in the lack of serious adverse effects reported in the literature (Poreisz et al., 2007; Adeyemo et al., 2012). This approved procedure is intended for use by research groups in the Medical Sciences Division of the University for studies that use TCS. It must be used in conjunction with the Standard Operating Procedures (SOP) for TCS studies.

This approved procedure is intended for use when:

- The study involves only healthy adult volunteers (aged 16 years or older) who are able to provide informed consent.
- The study does not involve any pharmacological agents.
- All answers in section D of the IDREC Checklist are “no” with the exception of D10 (invasive procedures).
- The type of TCS applied is one of TDCS, TACS and TRNS and the stimulator used was manufactured for research and clinical purposes (i.e. is CE marked) and distributed by a known established supplier (e.g. HDCStim via MagStim and NeuroConn via Rogue Resolutions).
- The stimulation parameters do not exceed the published guidelines and the manufacturers’ recommendations.

1.1 Transcranial Current Stimulation of the Brain

The techniques under the title of TCS: TDCS, TACS and TRNS, directly and non-invasively stimulate the brain by applying electrical currents to a small region of the scalp (Paulus 2011). The current is generated by a battery-powered stimulator and passed through rubber electrodes and conductive material (gel or saline-soaked sponges). At least one electrode is attached to the scalp with a band. The other electrode may be positioned on the scalp also or on the body (e.g. shoulder). The electrode size of the stimulators in use by research groups at present is large (~25-35 cm²) and the current strengths used are low (~1-3 mA) resulting in very low current densities (0.029 - 0.12 mA/cm²). The minor side-effects of tingling, itching or a mild burning sensation under the electrode...
are more likely with the higher current densities so are less desirable. Typical protocols apply no more than 20 minutes of stimulation in a single session.

Unlike TMS, TCS does not induce action potentials but instead may be considered neuromodulatory. TDCS modifies spontaneous neuronal excitability and activity by tonic de- or hyperpolarisation of resting membrane potential (Nitsche et al 2008). The effects of TDCS depend upon the polarity, duration and intensity of the stimulation. TACS and TRNS are normally used to interfere with, induce or entrain the on-going oscillatory activity of neuronal populations, but can induce neuroplastic effects similar to TDCS if applied in an appropriate manner.

1.2 Types of transcranial current stimulation

(i) TDCS
TDCS alters spontaneous cortical activity, and involves passing a weak electric current in the order of 1-2 mA through the skull and the underlying cortex via electrodes attached to the scalp. The active electrode is placed over the target region (e.g., left motor cortex) and the reference electrode is placed in task neutral position (e.g., over the contralateral supraorbital ridge). The polarity of the current flow induces a focal, prolonged but reversible change in the excitability of the stimulated brain area. Anodal TDCS (where the positive electrode is placed over the target region) increases excitability; cathodal TDCS (where the negative electrode is placed over the target) decreases excitability. ‘Sham’ stimulation is often used as a control condition, where the current is applied for a sufficiently brief duration to avoid any change in cortical excitability (up to 30 seconds), but long enough to produce the transitory sensation on the skin associated with TDCS. Sham stimulation allows the participants to perform tasks ‘blind’ to (i.e. unaware of) whether they are being stimulated. TDCS studies carried out under this approved procedure will use current strengths not exceeding 2mA, electrode sizes not smaller than 3cm^2 and the duration of stimulation in a single session will not exceed 30 minutes.

(ii) TACS and TRNS
The mechanism by which TACS influences brain activity differs from TDCS: TACS works by interfering with, inducing or entraining the oscillations of cortical networks (Kuo & Nitsche 2012). The delivery of both TACS and TRNS uses the same experimental set up as described above for TDCS, with stimulating and reference electrodes; though the reference electrode is often placed away from the brain, for example on the trapezius muscle (shoulder). In TACS and TRNS, however, both electrodes can be used to stimulate either in homologous locations bilaterally or at different regions simultaneously. TACS and TRNS studies carried out under this approved procedure will use peak-to-peak amplitudes of the current that do not exceed 4mA, electrode sizes not smaller than 3cm^2 and the duration of stimulation in a single session will not exceed 30 minutes.

Depending on the frequency of stimulation, TACS can modulate the activity of the brain area targeted by inducing, entraining or interfering with its intrinsic oscillatory activity (Ruffini et al., 2011). This important feature of TACS has enabled experimenters to modify both motor and sensory responses with frequency-specific results (Joudi et al., 2012; Feurra 2011a, b).

TRNS can be used to stimulate a region with a current that varies randomly in time. Such stimulation can induce excitability that lasts up to 60 minutes per 10 minutes of stimulation. TRNS can also be use to disrupt neural rhythms (Paulus 2011). Because of this it is sometimes required to match the frequency content of TRNS to TACS. For example, high-frequency filtered noise can be
generated by high-pass filtering random noise below 100 Hz to produce a noise stimulation without frequencies below 100 Hz.

Based on the parameters specified above, which have been used in previous studies without the report of adverse effects (e.g. for reviews see Filmer et al., 2015; Horvath et al., 2015) the current density for TDCS/TACS/TRNS should not be higher than 0.67mA/cm$^2$ and charge density should not exceed 800C/cm$^2$.

1.3 TCS Experiments

What varies between experiments, other than the type, intensity and duration of stimulation, is the specific brain region stimulated, the nature of the cognitive tasks that subjects may be asked to perform and the measurement techniques that are used. With respect to the latter, most studies will incorporate some form of behavioural measure. This approved procedure is intended to cover the three types of TCS described above used in association with behavioural tests. Please note that behavioural tests that include stimuli selected for their influence on affective state require CUREC-2 submission.

TCS stimulation studies can be combined with TMS, EEG, NIRS, MEG or fMRI since these can give a valuable insight into the nature of the cortical effects of the stimulation. EEG, NIRS, MEG and fMRI are all covered by existing approved procedures (03, 18, 08 and 17 respectively), but studies combining TCS with these procedures will require CUREC 2 submission. SOPs exist for the combination of TCS during MRI scanning to ensure safety.

Most TCS paradigms aim to induce effects in cognitive functioning lasting beyond the period of stimulation. Therefore, participants’ involvement in studies may last an entire morning/afternoon and measurements of effects may take place in sessions separated by hours, days, weeks or even months. For durations of stimulation that result in long-lasting aftereffects (1 hour or more), an intersession interval of 48 hours to 1 week is recommended (see Nitsche et al., 2008). This approved procedure does not cover studies aimed to induce stable changes in cortical function through repeated daily stimulation sessions for 5-10 sessions, such studies require CUREC 2 submission.

Questionnaires other than the attached TCS safety form will be detailed in study-specific applications.

1.4 References


Title: Transcranial Current Stimulation (TCS) Investigations in Healthy Adult Volunteers


2. TRAINING OF RESEARCH STAFF
All researchers involved in TCS studies are required to undergo regular (at least every three years) TCS safety training including resuscitation first aid training. We have developed a set of Standard Operating Procedures (see above) that are adhered to by researchers. TCS is administered according to our Standard Operating Procedures in the presence of experienced researchers. These individuals are trained in Oxford by laboratory Principal Investigators or, if post-doctoral, they may have received training in brain stimulation elsewhere. In addition, we organise basic training and safety talks on TCS on demand. Researchers are required to attend this training before administering TCS under the supervision of an experienced researcher.

3. METHODS FOR RECRUITING PARTICIPANTS
Potential participants will be identified by poster adverts, word-of-mouth and e-mail postings to specialist groups, departmental and college mailing lists, as well as website and newspaper advertisements. Advertisements will contain the contact details of the researcher or research group who will send further study information sheets (following this model “AP22 Participant Information”) to interested participants. Contact details of study researchers will be detailed in individual study Advertisements and Information Sheets. There should be no exceptions to these methods of recruitment.

4. INFORMATION PROVIDED TO PARTICIPANTS
The specific details provided to parents will vary depending on the study, but will always include:

- the name of the study
- the name(s) and status(es) (e.g. doctoral student) of the researchers carrying out the study and how to contact them
Central University Research Ethics Committee (CUREC)

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- a brief rationale of the study, including its purpose and value
- why potential participants are being invited to take part in the research
- an explanation of what the potential participant would do, including estimated duration of the test session and where it would take place
- that potential participants can ask questions about the study before they decide whether to participate
- that potential participants can choose whether they participate and, if they agree, they may withdraw from the study without penalty at any time by advising the researchers of this decision
- information about any additional personal information that would be obtained
- information about who would have access to the data, how it will be stored and what will happen to the data at the end of the study
- statement that the data would be anonymised
- what benefits (direct or indirect) may accrue to the participants in the study
- what risks are involved in the study
- that the project has received ethics clearance through the University of Oxford’s ethical approval process for research involving human participants.
- where applicable, a note to explain that the research will be written up as a student’s thesis and how the personal data included in that thesis will be published and stored
- the procedure for raising a concern or making a complaint

The Information Sheet is written in simple but non-patronising language. Most word-processing packages provide readability statistics for a document, and one should aim for a 12-year-old (Year 7) reading level for adults.

Please refer to the Information Sheet associated with this Approved Procedure

5. CONSENT OF PARTICIPANTS

Written consent will be obtained from all participants on the day of the first session of the study following a suitable (at least 24 hour) period during which they will have had an opportunity to read the Information Sheet and discuss their participation with others and with the researchers. An experienced researcher will answer any and all questions about the study before consent is obtained. Written consent will be obtained from all participants using the Consent Form associated with this Approved Procedure. Participants will be reminded that they are able to change their mind and withdraw from the study at any point without penalty. Vulnerable populations or volunteers who are unable to provide informed consent in English are not covered by this approved procedure. Copies of the signed consent forms will be provided to the volunteers along with the information sheet. The originals, along with the TCS safety questionnaires administered before every session, will be kept in the files of the researchers.

Guidance on the informed consent process can be found at: http://www.admin.ox.ac.uk/curec/resources/informed-consent/
6. **FINANCIAL AND OTHER REWARDS TO PARTICIPANTS**

Compensation (either financial or in kind) may be offered to subjects for their time and travel expenses. Some studies (for example, those investigating reward processing) may offer a performance-related reward. Individual study proposals will detail the value (if any) of compensation to be offered. Compensation is limited to the time and inconvenience incurred as well as reasonable travel expenses.

7. **POTENTIAL RISKS TO PARTICIPANTS/RESEARCHERS/OTHERS AND WHAT WILL BE DONE TO MINIMISE**

*Risks to participants*

i) Potential adverse reactions to TCS

Large meta-analyses of the adverse effects of TCS have shown there to no serious adverse effects reported for TCS (Poreisz et al., 2007; Adeyemo et al., 2012). Additionally, safety studies have been undertaken for frequently used TCS protocols. When the stimulation parameters used in these protocols were tested they did not: (a) cause heating effects under the electrode; (b) elevate serum levels of neuron-specific enolase (NSE), which is a sensitive marker of neuronal damage; or (c) result in changes of diffusion-weighted or contrast-enhanced MRI brain scans, or cognitive distortion. Moreover, the protocols examining TCS were tested in more than 2000-3000 subjects in laboratories worldwide with no serious side effects, except for a slight itching or tingling under the electrode, and seldom-occurring headache, fatigue, and nausea. It is also possible that longer-lasting protocols are safe, because stimulation of up to 50 minutes did not cause either cognitive or emotional disturbances in healthy subjects. Therefore, there are no significant safety issues with TCS when it is carried out within the standard parameters.

With respect to the skin contact, there is the risk of electrochemically-produced toxins and electrode dissolution products at the electrode tissue interface. The use of water-soaked sponge electrodes should minimize any chemical reactions at the interface; however, daily TCS was reported to cause clinically significant skin irritation under the electrodes in some individuals. Participants should therefore be interviewed for the existence of skin diseases and the condition of the skin under the electrodes should be inspected before and after stimulation. Researchers will inform participants of the likely irritation caused in sensitive individuals and assess on a case-by-case basis whether to proceed with the experiment. Proneness to skin reactions is not a contra-indication.

Because TCS neither causes epileptic seizures nor reduces the threshold for induced seizures in animals, seizures do not appear to be a risk for healthy subjects. However, this may not be true for patients with epilepsy. As a result, for TCS studies with healthy subjects, general exclusion criteria available for electrical and magnetic stimulation apply: subjects should be free of unstable medical conditions, or any illness that may increase the risk of stimulation, for example, neurological diseases such as epilepsy or acute eczema under the electrodes. Please refer to the enclosed, Appendix-4 TCS Safety Screening Questionnaire for a complete list of contraindications. Furthermore, subjects should have no metallic implants near the electrodes. They should be informed about the possible side effects of TCS, such as headache, dizziness, nausea, and an itching sensation as well as skin irritation under the electrodes.
ii) Discomfort:
At the beginning of stimulation, subjects are likely to perceive a slight itching sensation under the sponge electrode. Also, instantaneous making or breaking of the simulating circuit results in alternating current transients that can cause neuronal firing. For electrodes near the eyes, this can result in brief retinal phosphenes, or a startle-like response if the reference electrode is located off the head. Ramping the current up and down at the beginning and end of stimulation respectively can eliminate these effects. This can also help to prevent dizziness or vertigo, which is occasionally reported after stimulation. Electrodes above the mastoids, sometimes used for galvanic stimulation of the vestibular system may result in sensations of nausea.

iii) Cumulative effects of brain stimulation
The risk associated with stimulation over repeated sessions does not exceed the minimal risks associated with a single session, excluding the possibility of skin irritation described above. Nevertheless, the risks associated with interactions between brain stimulation studies (TMS and TCS) need to be considered. We wish also to have consistent information regarding participation in both kinds of brain stimulation. For this reason, we recommend that a subject should participate in different brain stimulation experiments on no more than two consecutive days and no more than four sessions in a month. While no guideline has been provided for a “cooling-off” period between stimulation sessions, some have suggested it to be between 48 hours to one week after stimulation. We recommend that the period of abstinence between different brain stimulation experiments would be at least one week. Exceptions to these recommendations are anticipated for TCS studies aimed to induce stable changes in cortical function through repeated daily stimulation sessions for 5-10 sessions. Such “training” or “treatment” studies are not covered by this approved procedure and will require separate CUREC 2 submission.

TCS risks to researchers
There are no known risks to researchers associated with administering TCS.

8. MONITORING AND REPORTING OF ADVERSE OR UNFORSEEN EVENTS
In the event of an unexpected emergency incident, such as a loss of consciousness, researchers will first protect the volunteer from injury, call an ambulance or the crash team on the hospital sites, cushion the volunteer’s head and aid breathing by gently placing the volunteer in the recovery position. For studies carried out in the Department of Experimental Psychology (i.e. not on a hospital site), brain stimulation experiments are allowed only during office hours (Monday-Friday 9am-5pm) and there will always be two researchers present when TCS is delivered (see SOPs). The department also has named First Aid Officers who are present during office hours. The experienced researchers or other members of the team or both will deal with participants who experience milder sensations of feeling unwell or distressed. The assistance of the departmental First Aid Officers may also be sought if necessary. TCS is administered in rooms where telephones can be used to contact First Aid Officers and the Emergency Services.

Adverse or unforeseen events are reported to the departmental safety officer in the first instance and may be followed up by the University Safety officer if deemed necessary.

9. COMMUNICATION OF RESULTS
Study results may be written up for publication in peer-reviewed scientific journals, presented at scientific conferences (in abstract or presentation formats), submitted as part of course degrees and
may form part of grant applications. In all cases, results will be fully anonymised and not contain any data that could be linked to the volunteers.

10. DUTY OF CARE ISSUES / CONFIDENTIALITY

Personal data (such as date of birth, and personal questions relating to TCS safety) as well as questionnaire responses may be necessary for individual studies. Study Information Sheets will detail this and explain that any personal information will be anonymised wherever possible, and information about volunteers maintained in strict confidentiality.

We do not foresee that participation in TCS studies is likely to reveal information about health problems or risks. In the unlikely event that this occurs we will follow the guidelines below. Some studies may use validated questionnaires asking volunteers about state and trait anxiety and/or depression to interpret how these factors influence processing and perception of study stimuli. These questionnaires are not used for recruitment or screening purposes, however, if a researcher, as a result of these questionnaires, has concerns that a volunteer may have an undiagnosed psychiatric condition that is causing distress, CUREC guidelines (MSD/GUIDE/1.1) will be followed. The researcher will seek advice from the Principal Investigator who may discuss the symptoms in greater detail with the volunteer and/or offer the opportunity to speak with a senior clinical researcher if they are not clinically trained themselves.

11. DATA PROTECTION ISSUES

Any electronic data (e.g. behavioural data files, questionnaires) will be labelled with a code number rather than a name or initials. Data will be stored within password-protected folders. With the written informed consent of the volunteer, fully anonymised data may be shared with other research institutions, including researchers outside of the EU, for other and future research studies.

If it is necessary to retain any personal information (such as contact details), the keys linking codes to personal details will be kept in lockable filing cabinets with access only by the researchers. Personal data may be retained after the end of the study where the participant agrees to be contacted for future studies. For volunteers who do not wish to be contacted in the future, personally identifiable data will be shredded as soon as possible after completion of the study and within one year of completing study analyses. Personal data may be viewed by regulatory bodies and designated individuals within the University of Oxford for the purposes of monitoring and auditing the research with the written consent of the volunteer.

12. FURTHER INFORMATION

Safety questionnaire, standard operating procedures for TCS, sample consent form, participant information sheet and poster advertisement.

13. CHANGE HISTORY

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