TRANSCRANIAL CURRENT STIMULATION (TCS) INVESTIGATIONS IN ADULT PARTICIPANTS

1. SCOPE

Many research groups within the Medical Sciences Division perform research investigating brain function using Transcranial Current Stimulation (TCS), also known as Transcranial Electrical Stimulation (TES). TCS and TES are broad terms covering Transcranial Direct Current Stimulation (TDCS), Transcranial Alternating Current Stimulation (TACS) and Transcranial Random Noise Stimulation (TRNS). These are all 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 for studies that employ TCS. It must be used in conjunction with the Standard Operating Procedure (SOP) for TCS studies.

This Approved Procedure is intended for use when:

- The research involves only adult participants (aged 18 years or older) who are able to provide informed consent.
- no licensed drug or other (non-drug) substance will be administered.
- The type of TCS applied is one of TDCS, TACS or TRNS and the stimulator used was manufactured for research and/or clinical purposes (i.e. is CE marked) by an established TCS equipment provider (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, e.g. 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 typically large (~25-35 cm^2) and the current strengths used are low (~1-3 mA) resulting in very low current densities (typically 0.029 - 0.12 mA/cm^2). 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 up to 20 minutes of stimulation in a single session.

Unlike Transcranial magnetic stimulation (TMS), TCS does not induce action potentials but instead may be considered neuromodulatory. TDCS modifies spontaneous neuronal excitability and activity by tonic de- or hyper-polarisation 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., 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 (Joundi 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 used 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 the charge density should not exceed $800C/cm^2$.

1.3 TCS Experiments

What varies between studies, other than the type, intensity and duration of stimulation, is the specific brain region stimulated, the nature of the cognitive tasks that participants may be asked to perform and the measurement techniques that are used. 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 full committee review.

1.4 Combining TCS with EMG

Surface electromyography (EMG) non-invasively evaluates and records the electrical activity produced by skeletal muscles. Some TCS studies may incorporate simultaneous EMG to measure muscle activity (usually from the hands/arms or lips), as this may be a useful gauge of cortical excitability. Simultaneous surface EMG and TCS are permitted under this Approved Procedure. EMG measures activity of muscles at the surface of the skin by taping several electrodes (small silver discs) over these muscles.

1.5 Combining TCS with other methods or measurement

TCS studies may also employ electroencephalography (EEG), magnetoencephalography (MEG), magnetic resonance imaging (MRI), and/or near-infrared spectroscopy (NIRS) to provide valuable insight into the nature of the cortical changes induced by TCS. Measurements using these methods may be made either on-line (i.e. during stimulation) or off-line (i.e. before and/or after stimulation) to determine the effects on brain areas stimulated and distal to the stimulation. EEG, MEG, MRI and NIRS are all covered by existing CUREC Approved Procedures (03, 08, 17 and 18 respectively).

Combining EEG, MEG, MRI, TMS (single pulse or very short trains of 2-3 pulses in quick succession) and NIRS with TCS delivered **off-line (i.e. before and/or after)** poses no additional risk than any of these procedures performed in isolation. This Approved Procedure can be used, therefore, for such studies in conjunction with another Approved Procedure.

TCS may be performed **simultaneously** with recordings made by NIRS with no increased risk to safety. However, the combination of TCS **on-line** with simultaneous recordings made by EEG, MEG and MRI requires further consideration, as detailed in the separate Approved Procedures for EEG (03), MEG (08) and MRI (17). Studies that combine TCS simultaneously with Approved Procedures 03, 08 and 17 will require review by full committee.

Studies using repetitive TMS and TCS in the same session, either off-line or on-line, cannot cite this procedure as full committee review is required.

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 after-effects (1 hour or more), an inter-session 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 (e.g. for 5-10 sessions), such studies require review by full committee.

Questionnaires other than the TCS safety form will be described in more detail in the application.

1.6 References

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2. TRAINING OF RESEARCH STAFF

The Oxford Non-invasive Brain Stimulation research community have developed a set of Standard Operating Procedures (SOPs) that must be adhered to by researchers using this Approved Procedure. All TCS operators are trained in TCS. TCS is administered in the presence of at least one experienced researcher. An experienced researcher is defined as the Principal Investigator (PI) or person delegated this responsibility by the PI. It is expected that an experienced researcher would be someone who has had supervised experience of TCS research to a standard deemed appropriate by the PI and who has attended first aid/basic life support training in the past three years.

3. METHODS FOR RECRUITING PARTICIPANTS

Potential participants will be identified by one of the methods outlined on the application. When a potential participant registers interest, further information (prepared using the associated template information sheet) will be sent, together with details as to how to confirm they would like to take part.

4. INFORMATION PROVIDED TO PARTICIPANTS

The information provided should be appropriate to your specific research and presented in an accessible way. If there is not enough information, potential participants might not be able to make an informed decision. On the other hand, if the information sheet is too long or unclear (e.g. through using overly-technical language) they might not read it properly or it could deter them from taking part. 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, and use, the template **Information Sheet associated with this Approved Procedure**

5. CONSENT OF PARTICIPANTS

Written consent will be obtained from all participants using the **Consent Form associated with this Approved Procedure.**

Written consent will be obtained from all participants on the day of the first session, following a suitable (typically 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 before consent is obtained. Consent will be taken by a member of the research team who has appropriate training, as confirmed by the Principal Investigator. Participants will be reminded that they are able to change their mind and withdraw from the research at any point without penalty. Vulnerable populations or participants 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 participants 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.

Please also see CUREC's guidance on the informed consent process.

6. COMPENSATION

Compensation (either financial or in kind) may be offered to participants for their time and travel expenses. Some studies (for example, those investigating reward processing) may offer a performance-related reward. Individual 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.

Consideration should be given to how and when participants are told about any recompense. Participant information sheets and recruitment materials should state that recompense will be made so that potential participants are not discouraged from participating by the associated costs. As a general rule, recruitment material should not state the value. However, if this is necessary (e.g. it is a requirement of a third-party recruiter), advertisements must not emphasise the value of the payment (for example, through the use of formatting). Further guidance is available within CUREC's Best Practice Guidance 05 on Payments and incentives in research.

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 participants 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 participants. 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 participants. However, this may not be true for patients with epilepsy. As a result, for TCS studies, general exclusion criteria available for electrical and magnetic stimulation apply: participants 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, participants 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, participants 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 reduce or 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. 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 participant 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 studies aimed to induce stable changes in cortical function through repeated sessions (e.g. for 5-10 sessions). Such "training" or "treatment" studies are not covered by this Approved Procedure.

TCS risks to researchers

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

8. MONITORING AND REPORTING OF ADVERSE OR UNFORESEEN EVENTS

In case of an adverse or unforeseen event, TCS is administered in rooms where telephones can be used to contact departmental First Aid Officers or the Emergency Services if required.

In the event of an unexpected emergency incident, such as a loss of consciousness, researchers will follow the pathways specified in their basic life support training and departmental risk assessments / SOPs. Basic life support training includes thresholds for lengths of seizures and loss of consciousness before involving emergency services. In the case of a participant who is unresponsive, BLS training includes CPR, so researchers should begin resuscitation before calling emergency services. In all instances, participants should be protected from further injury.

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. Any serious adverse event related (resulted from administration of any of the research procedures) and unexpected (the type of event is not listed as an expected occurrence) should be reported to the Research Ethics Committee as soon as possible once the Principal Investigator becomes aware of the event. In line with the published guidelines (Rossi et al., 2009) for TMS, in the case of a seizure that is possibly related to a TCS session, details should be forwarded to the editor of the journal *Brain Stimulation.*

9. COMMUNICATION OF RESULTS

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, published results should be anonymised and not contain any data that could be linked to the participants.

10. MANAGEMENT OF INCIDENTAL FINDINGS

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 participants 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 participant may have an undiagnosed psychiatric condition that is causing distress, CUREC guidance (BPG 08) will be followed. If the researcher has any concerns from the answers to questionnaires, or the EMG traces, they will seek advice from the

Principal Investigator who may discuss in greater detail with the participant and/or offer the opportunity to speak with a senior clinical researcher if they are not clinically trained themselves.

11. DATA MANAGEMENT AND PROTECTION

The research must be conducted in accordance with the Research Data Policy; CUREC's Best Practice Guidance 09 on Data collection, protection and management; and Research Data Oxford's guidance on data backup, storage and security.

Participants' informed consent must be obtained for participation in the study, which includes the collection, storage and retention of all data related to the study. Directly identifiable personal information held by the research team (such as contact details, consent forms and screening forms, which include name or other identifiers) must be held securely - either in paper format in lockable filing cabinets with access only by the University researchers, or in a password-protected database, on an encrypted machine or on a protected server. These should be servers provided by the University where the risks and access have been professionally managed. Other servers will require security assessment by University Information Security. Other research data (e.g., EEG files, behavioural reaction time files, questionnaires) must be labelled with a code number rather than a name or initials, and accessed via a password- and firewall-protected server.

The keys linking personal details to the codes used to label other research data may be kept in paper format in lockable filing cabinets with access only by the researchers, or in a password protected spreadsheet on University approved servers. The keys should be kept separately from other study data. Such keys should be destroyed as soon as no longer needed, as should other personal data (with due regard to University and other guidelines on data retention, e.g. of consent forms).

Contact details may be retained after the end of the research where the participant agrees to be contacted for future studies. These should be held separately from the study data, and a copy of the consent form retained as evidence of agreement to be contacted. For participants who do not wish to be contacted in the future, contact details will be destroyed as soon as possible after completion of their research participation. Personal and research 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 participant.

Anonymised data may be shared with other research institutions, including researchers outside of the UK and the EU, for use in other and future research studies. For detail on anonymisation, please refer to the Information Commissioner's Office (ICO) Code of Practice –'Anonymisation: managing data protection risk', especially Appendix 2 and Annex 1.

Where data has been anonymised (all identifying information removed, including any linkage document), there is no limit as to how long this may be retained by the researchers. However, the period of retention should be stated on participant information.

Sharing of Data

Research teams will be encouraged to make their data available for reuse and validation. In all cases, the data will be shared as openly as possible and as closed as necessary in order to protect the privacy of participants. Online repositories will be assessed by research teams for their appropriateness with regard to:

- the required treatment and de-identification of unique brain and biometric data in line with UK GDPR;

- control of how the data are accessed and re-used, including terms to protect the ongoing privacy of participants;
- required attribution of the data to the originating research team, the University and funding bodies;
- management of data withdrawal requests made by participants.

12. FURTHER INFORMATION

Safety screening form
Standard operating procedures for TCS
AP22 Consent form
AP22 Participant information sheet
AP22 Advert

13. CHANGE HISTORY

Version No.	Significant Changes	Previous Version No.
2.0	Incorporates reference to the University Safeguarding Code of Practice and related requirements. Retitled 'Approved Procedure' (previously 'Protocol'). Approved by CUREC, 19 November 2015	N/A
3.0	Removed requirement of study documents to be reviewed by CTRG prior to submission to the relevant IDREC. Updated document references for CUREC guidance.	2.0
3.1	Updated hyperlinks for new CUREC website	3.0
3.2	Updated to improve accessibility	3.1
4.0	Complete revision – Quinquennial review	3.2
4.1	Added reference to Worktribe Ethics online application system	4.0
5.0	Revised wording about reporting adverse events (section 8) Whole document revised to reflect implementation of online ethics application system	4.1