TRANSCRANIAL MAGNETIC STIMULATION (TMS) INVESTIGATIONS IN
HEALTHY ADULT VOLUNTEERS

1. SCOPE

Transcranial magnetic stimulation (TMS) is a valuable research technique that provides insights into the functional organization of the living brain. It is currently in use by many research groups within the Medical Sciences Division at the University of Oxford.

This approved procedure is intended for use by these research groups for studies that use TMS stimulators based at the Department of Experimental Psychology or the research laboratories at the Warneford Hospital and the John Radcliffe Hospital sites. It must be used in conjunction with the Standard Operating Procedures (SOP) for TMS studies (“P21.1 Standard operating procedure”).

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 TMS paradigm is one of the four described below (new TMS paradigms/stimulation protocols require an external review and CUREC 2 submission)
- The stimulation parameters of the TMS paradigm are in accord with published safety guidelines appended here from Rossi et al., (2009)

1.1 Magnetic brain stimulation

TMS operates on the principle of electromagnetic induction: an electrical current passed through one coil can induce a current in a nearby second coil. In TMS experiments, instead of a second coil, the aim is to induce a small current to flow in brain tissue such that the induced electric field elicits neuronal activity. The key features of the technique are that the TMS machine delivers a large current through the TMS coil in a short period of time — the current then produces a magnetic field (1.5-2.0 Tesla at the surface of the coil) which, if changing rapidly enough, will induce an electric field in the cortex up to about 150V/m, which is sufficient to stimulate neurons or change the resting membrane potentials in the underlying cortex. Depending on the stimulation intensity (output of the stimulator), cortical neurons at a depth of 1.5-3.0cm beneath the scalp can be activated using standard coils (figure 8, circular or double-cone coils). Experiments typically use intensities of 120% or less of motor threshold (the minimum output used to produce a muscle twitch). Such intensities cannot induce direct activation of neurons at a depth of more than 2cm beneath the scalp (Rossi et al., 2009).
1.2 Types of magnetic brain stimulation

The ability to stimulate the brain using TMS has many potential applications, which vary depending on the specific stimulation paradigm used. This approved procedure refers to four TMS paradigms that have previously been approved by NHS Research Ethics Committees (now NRES) for use in laboratories in the University of Oxford.

These are:
- single-, dual-/paired- or triple-pulse TMS (collectively referred to as ‘multi-pulse TMS’);
- low-frequency repetitive TMS (rTMS) where the stimulation rate is 1Hz or below;
- high-frequency rTMS where the stimulation rate is above 1Hz and the duration is short;
- patterned rTMS (trains of short very high frequency bursts of rTMS interleaved by short pauses of no stimulation e.g. theta burst).

Multi-pulse TMS studies are those in which single pulses (or very short trains of 2 or 3 pulses in quick succession) are given at low rates (<1Hz) and often random intervals. These paradigms can be used to elicit a measurable response, such as a muscle twitch (the size of which gives an indication of cortical excitability) or a visual effect. They can also be applied "on-line" to disrupt on-going brain processes during performance of a task simultaneous with the pulse delivery. This can give information about WHEN an area is optimally involved in a specific task (so-called ‘TMS chronometry’).

Repetitive TMS paradigms involve extended low-frequency or brief high-frequency stimulation of the target brain areas. This type of stimulation results in a temporary disruption to the neural processes occurring in the stimulated region (‘virtual lesion’). The period of disruption depends on the paradigm employed; 15 minutes of 1Hz (low frequency) rTMS results in approximately 15 minutes of disruption whereas the effects of high frequency stimulation are to disrupt on-going processes and last only seconds.

Patterned rTMS involves the repetitive application of short rTMS bursts at a high inner frequency interleaved by short pauses of no stimulation. The most common form of patterned rTMS used to date (2012) and covered by this approved procedure is theta-burst stimulation (TBS). In TBS, short bursts of 50-Hz rTMS are repeated at a rate in the theta range (5 Hz) as a continuous (cTBS), or inter-mittent (iTBS) train which has a total duration of less than a minute. The effects of cTBS in the motor system are inhibitory, whereas the effects of iTBS in the motor system are excitatory (Huang et al., 2005). The effects of TBS can last for up to an hour depending on the train duration.

Despite the variation in the length of the effect for different paradigms, the effects of TMS on brain function are temporary; there are no permanent effects on brain function.

The relevant parameters to consider for TMS studies using one of the four paradigms above are the duration of the rTMS-train, stimulation rate (frequency), the inter-train interval, the number of trials in the experiment and the stimulation intensity (expressed as % of motor threshold or stimulator output). The combination of these parameters is important, with short durations, low frequency, long intervals, small number of trials and low intensities carrying less risk. Tables 3, 4 and 5 of the Rossi et al., (2009) paper are appended here and describe the consensus reached for ranges of these parameters that would avoid possible side-effects of TMS and allow research to be performed within safe margins (see Appendix 2, “P21 Parameters”). This approved procedure will cover stimulation parameters that fall within these published guidelines. For TBS protocols, the
parameters of Huang et al., (2005) will be followed and a maximum number of 600 pulses is allowed.

What varies between experiments, other than the frequency and timing 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, however, many studies also use simultaneous electro-myography (EMG) since muscle activity elicited by TMS is a useful measure of cortical excitability. This approved procedure is intended to cover the four paradigms referred to above, which may be used in association with behavioural tests or EMG or both.

1.3 Combining TMS with other methods or measurement

Brain stimulation studies may also employ EEG, MEG, MRI or near-infrared spectroscopy (NIRS) to provide valuable insight into the nature of the cortical disruption induced by TMS. Measurements using these methods may be made either on-line (i.e. during stimulation) or off-line (i.e. before and 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 (CUREC_Approved_Procedure_IDREC_03, CUREC_Approved_Procedure_IDREC_08 and CUREC_Approved_Procedure_IDREC_17 respectively).

Combining TMS off-line with EEG, MEG, MRI and NIRS 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. However, studies that combine existing approved procedures will require a CUREC 2 submission.

Similarly the combination of TMS on-line with simultaneous recordings made by EEG and MRI requires further consideration in a separate approved procedure. It is not possible to record brain activity using MEG while stimulating the brain magnetically. TMS may be performed on-line with recordings made by NIRS with no increased risk to safety.

1.4 Studies using TMS

The targeted brain functions in studies intended to be covered by this approved procedure include, for example, the brain control of movement, sensation involving audition, vision, somatosensation, production or comprehension of language, problem solving and decision making. All experiments will use combinations of the following types of stimuli: (i) sensory stimuli delivered through headphones, on a screen or by touch; (ii) spoken or written language presented visually or aurally; (iii) pictures and drawings depicting emotional or non-emotional scenes and objects. Responses will involve (i) simple or repetitive movements of effectors e.g. to make a button presses; (ii) vocalizations, (iii) eye movements measured by an eye-tracking system. Some subjects may be asked to solve reasoning problems presented visually or verbally either with or without simple reinforcements (including small amounts of money). Importantly, these defined types of studies represent only standard experimental designs with little associated hazard or discomfort for the subjects.

Cognitive and performance measurements may be acquired before, during and after stimulation. The testing sessions may last in total between 30 minutes and three hours. Participation in the study may involve sessions lasting an entire morning/afternoon depending on the study and repeated sessions. Participants will be allowed to take breaks as needed during testing sessions.
Questionnaires other than the TMS safety form, if used, will be described in more detail in study-specific applications.

1.5 References
Brain Stimulation website: http://www.brainstimjrn.com

2. TRAINING OF RESEARCH STAFF
We have developed a set of SOPs (see Appendix 1, “AP21 Standard Operating Procedure”) that must be adhered to by researchers using this approved procedure. All TMS operators are trained in TMS and undergo regular (at least every two years) resuscitation first aid training. TMS is administered in the presence of experienced researchers. 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 a graduate who has had supervised experience of TMS research for a minimum of 10 sessions and who had attended safety training and basic life support training in the past two years. In addition, basic training and safety talks on TMS are available on demand from researchers in the Department of Experimental Psychology and FMRIB Centre. New researchers are advised to attend this training before administering TMS under the supervision of an experienced researcher.

3. METHODS FOR RECRUITING PARTICIPANTS
Potential participants will be identified by poster adverts (sample on website) word-of-mouth and e-mail postings to departmental and college mailing lists, which will contain the contact details of the researcher who will send further study information sheets (“AP21 Participant Information”) to interested participants. Contact details of study researchers will be detailed in individual study Adverts 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
- 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
central university research ethics committee (CUREC)

approved procedure: IDREC_21_Version 2.0

Title: Transcranial Magnetic Stimulation (TMS) Investigations in Healthy Adult Volunteers

- 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 all and any 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 TMS 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 and will in no circumstances consist of course credits for student volunteers.

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

Participants

*(i) Potential adverse reactions to TMS (e.g. seizures, syncope, migraines)*

TMS is widely considered to be a safe technique, but has induced brief seizures in a small number (<20) of individuals worldwide. As a result of these reported incidents, guidelines were published specifying safe operating parameters for stimulation with respect to intensity, frequency and duration (Wassermann, 1998). Since 1998, seizures due to TMS have occurred, but mostly in studies operating outside the safe limits previously defined. Incidents of seizures in studies operating within the safe parameters occurred in subjects using pro-epileptogenic medication. Considering the very large number of subjects who have participated in TMS studies since 1998 and the small number of seizures, the risk of TMS inducing seizures is considered to be very low (Rossi et al., 2009).

Because of these potential risks, all researchers carrying out TMS within Oxford do so according to the parameters for intensity, frequency and duration described in the international guidelines (Wasserman 1998; Rossi et al., 2009 and summarized here in Appendix 1). To further ensure that risks are minimised, subjects are also required to fill out a TMS safety screening form before participating to rule out other contraindications to participation. These may include, but are not restricted to: a personal or close family (first-degree relative e.g. parent, sibling, child) history of epilepsy, another significant neurological or psychiatric disorder likely to lower seizure threshold; or a transient lowering of seizure thresholds as a result of lack of sleep, high consumption of alcohol, caffeine, or through taking anti-malarial medication. Please refer to the **TMS Safety Screening Questionnaire** (“AP21 Safety Screening Form”) for a complete list of contraindications.

TMS can cause syncope, or fainting in some participants. This reaction is often caused by situations of anxiety and psycho-physical discomfort and is a more common adverse reaction to TMS than a seizure. Screening prior to stimulation will not reliably rule out any predisposition to fainting, so to avoid inducing syncope it is important to ensure that participants are fully informed and comfortable with the procedure before beginning. Researchers should monitor a subject’s ongoing reactions to TMS and will avoid stimulating if the subject appears to be uncomfortable. Researchers undergo basic life support training so they are able to ensure the participant’s safety and comfort in the event of syncope.

*(ii) Discomfort*

A loud clicking sound is produced each time the stimulator discharges. Since the coil is usually held in close proximity to the ears, subjects are given earplugs during stimulation.

TMS causes localised tapping sensations on the scalp at the point of stimulation. Stimulation of motor cortical regions may also cause localised motor discharges, which manifest as muscle twitches. Neither of these effects should be unpleasant but may become uncomfortable when stimulating at high intensities and for long periods. Subjects are encouraged to let the researcher know if TMS is causing undue discomfort. Sometimes, muscles on the head or peripheral facial
nerves are stimulated directly causing muscle contractions, jaw movements or eye blinks. Whilst these are not dangerous, and many subjects tolerate them comfortably, some of these reactions have potential to cause discomfort. Again, subjects are encouraged to make the researcher aware if they are at all uncomfortable. Researchers minimise these reactions through monitoring the state of the participant and adjusting coil position and output intensity accordingly.

Headaches have been reported as a side effect of participation in brain stimulation studies. This risk can be minimised by ensuring participants are physically comfortable and take regular breaks if necessary. Participants are made aware from the start that a headache is a potential minor risk of TMS and that these usually respond well to over-the-counter analgesics (e.g. paracetamol).

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.

TMS risks to researchers
There are no known risks to researchers associated with administering TMS. To be consistent with pregnancy as a contraindication for volunteers in TMS studies, researchers who are pregnant should not deliver TMS. There is no known potential for harm to the unborn child, however.

8. MONITORING AND REPORTING OF ADVERSE OR UNFORSEEN EVENTS
In case of an adverse or unforeseen event, TMS is administered in rooms where telephones can be used to contact departmental First Aid Officers or 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. The Research Ethics Committee will also be notified of such events. In agreement with the published guidelines (Rossi et al., 2009), in the case of a seizure that is possibly related to a TMS session, details will be forwarded to the editor of the journal Brain Stimulation.

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 MRI 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 TMS 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 TMS, sample consent form, participant information sheet and poster advert.

13. CHANGE HISTORY

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