TRANSCRANIAL MAGNETIC STIMULATION (TMS) INVESTIGATIONS IN ADULT PARTICIPANTS

1. SCOPE

Transcranial magnetic stimulation (TMS) is a valuable research technique that provides insights into the functional organisation 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 research groups using the TMS stimulators based at the Department of Experimental Psychology, the Oxford Institute of Biomedical Engineering (IBME) site on the Old Road Campus, 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.

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 (a CUREC 3 application will be required in that case)
- The TMS paradigm is one of the four described below (all TMS paradigms / stimulation protocols require departmental expert review prior to submission to the MS IDREC and those that differ from these four paradigms or that fall outside the safety limits outlined in Rossi et al. (2009), require CUREC 2 submission)
- The stimulation parameters of the TMS paradigm are in accord with published safety guidelines appended here from Rossi et al. (2009)
- All TMS equipment used was manufactured for research and clinical purposes (i.e. is CE marked) and distributed by a known established supplier (a CUREC 2 (device) application is required if this is not the case).

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. 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 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).

1. 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’).

2 & 3. 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.

4. 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 forms of patterned rTMS used to date (2021) and covered by this Approved Procedure are theta-burst stimulation (TBS) and quadripulse stimulation (QPS). In TBS, short bursts of 3 TMS pulses delivered at 50-Hz are repeated at a rate in the theta range (5 Hz) as a continuous (cTBS), or intermittent (iTBS) train. 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. QPS is very similar to TBS but uses 4 TMS pulses in each burst.

For TBS protocols, the parameters of Huang et al., (2005) will be followed and a maximum number of 600 pulses (over 40 seconds) is allowed. For QPS protocols, the parameters outlined in Rossi et al., (2021) supplementary table S3 will be followed.

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 and Table S3 of the Rossi et al., (2021) 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.

This Approved Procedure will cover stimulation parameters that fall within these published guidelines. In the 2021 update of the safety guidelines, the IFCN TMS safety consensus group suggested that, given the small number of seizures and other AEs seen with TMS, the technique can
“be considered basically safe” (Rossi et al., 2021). They suggest that all TMS protocols should remain well below the combination of the following parameters: intensity less than 100% of Maximum Stimulator Output (MSO), frequency lower than 25Hz for a stimulation train shorter than 10 seconds. For researchers wishing to use stimulation parameters outside the safety limits outlined by Rossi et al., (2009) but within the guidelines outlined by Rossi et al., (2021) a CUREC 2 application will be required.

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. 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 participants may be asked to perform and the measurement techniques that are used.

1.3 Combining TMS with EMG

Surface electromyography (EMG) non-invasively evaluates and records the electrical activity produced by skeletal muscles. Many TMS studies incorporate simultaneous EMG to measure muscle activity (usually from the hands/arms or lips), as this is a useful gauge of cortical excitability. Simultaneous surface EMG and TMS are permitted under this Approved Procedure.

EMG measures the activity of muscles at the surface of the skin by taping several electrodes (small silver discs) over these muscles. Before proceeding with the full research session, the intensity of TMS stimulation is varied until the EMG recording consistently shows activity in the muscle in response to the stimulation (usually 50-60% of the maximum intensity that the TMS setup can produce). The intensity of TMS stimulation used for the remainder of the study will typically be based on this.

1.4 Combining TMS with other methods or measurement

TMS studies may also employ electroencephalography (EEG), magnetoencephalography (MEG), magnetic resonance imaging (MRI), near-infrared spectroscopy (NIRS) to provide valuable insight into the nature of the cortical changes 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 (03, 08, 17 and 18 respectively).

Combining EEG, MEG, MRI and NIRS with TMS 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.

TMS may be performed simultaneously with recordings made by NIRS with no increased risk to safety, so can be submitted as a CUREC 1 application. However, the combination of TMS on-line with simultaneous recordings made by EEG and MRI requires further consideration, as detailed in the separate Approved Procedures for EEG (AP03) and MRI (AP17). Studies that simultaneously combine TMS with Approved Procedures 03 and 17 require a CUREC 2 submission. It is not currently possible to record brain activity using MEG while stimulating the brain magnetically. The combination of TMS with any brain imaging approach that is not within a CUREC Approved Procedure will require a CUREC 2 application.

The combination of TMS with Transcranial Current Stimulation (TCS), either off-line or on-line requires a CUREC 2 submission.
1.5 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 research 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 button presses; (ii) vocalisations, (iii) eye movements measured by an eye-tracking system. Some participants 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 participants.

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 may involve sessions lasting an entire morning/afternoon, depending on the study and repeated sessions. Participants must 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 the CUREC application.

1.6 References

- Brain Stimulation website: [http://www.brainstimjrnl.com](http://www.brainstimjrnl.com)

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 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 WIN 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 one of the methods outlined on the CUREC 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 (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 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 study 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 TMS 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 and will in no circumstances consist of course credits for student participants.

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.
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 participants using pro-epileptogenic medication. Considering the very large number of participants 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 (Rossi et al., 2009, and Rossi et al., 2021. The parameters within which a CUREC 1 application can be made are summarized here in the Appendix to this Approved Procedure). To further ensure that risks are minimised, participants 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 participant’s ongoing reactions to TMS and will avoid stimulating if the participant 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.

Brain stimulation can cause headache in susceptible individuals, therefore migraine sufferers should be excluded from participation.

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, participants are offered 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. Participants 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 participants tolerate them comfortably, some of these reactions have potential to cause discomfort. Again, participants 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. 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 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 participants 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 UNFORESEEN 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 if needed.

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. 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 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 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 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 (BPG08) 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 University’s Policy on the Management of Data Supporting Research Outputs; 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

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 TMS
AP21 Consent form
AP21 Participant information sheet
AP21 Advert
AP21 Approved Procedure Appendix

13. **CHANGE HISTORY**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>Incorporates reference to the University Safeguarding Code of Practice and related requirements. Retitled ‘Approved Procedure’ (previously ’Protocol’). Approved by CUREC, 19 November 2015</td>
<td>N/A</td>
</tr>
<tr>
<td>3.0</td>
<td>Removed requirement of study documents to be reviewed by CTRG prior to submission to the relevant IDREC. Updated document references for CUREC guidance.</td>
<td>2.0</td>
</tr>
<tr>
<td>3.1</td>
<td>Updated hyperlinks for new CUREC website</td>
<td>3.0</td>
</tr>
<tr>
<td>3.2</td>
<td>Changed references of Functional Magnetic Resonance Imaging of the Brain (FMRIB) to Wellcome Centre for Integrative Neuroimaging (WIN)</td>
<td>3.1</td>
</tr>
<tr>
<td>4.0</td>
<td>Complete revision – Quinquennial review</td>
<td>3.2</td>
</tr>
</tbody>
</table>