Stimulating the Cortex in Humans using Transcranial Magnetic Stimulation

ETHICS-SOP\_METHODS\_TMS-018

# Document Sign-offs

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# Current Status

Approved

# Revision information

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# Glossary of Terms

TMS: Transcranial Magnetic Stimulation: an experimental technique used to stimulate structures in the human brain

MEP: motor evoked potential: a twitch evoked in the targeted muscle

EMG: surface electromyography: used to record and quantify MEP

MRI: Magnetic Resonance Imaging

# Purpose

Transcranial Magnetic Stimulation (TMS) is an experimental technique used to stimulate structures in the human brain including the cerebral cortex, the cerebellum and the brainstem. Stimulation is non-invasive and performed in awake participants.

TMS is performed using a machine that passes an electrical current through a metallic coil, which induces a magnetic field perpendicular to the coil. When placed against the skull, this brief magnetic field stimulates the cortex by causing a flux of ions within the neuronal axon evoking an action potential. If TMS is used to activate the motor pathways via the primary motor cortex, a twitch is evoked in the targeted muscle termed a motor evoked potential (MEP). The MEP can be recorded and quantified using surface electromyography (EMG).

TMS can be delivered in various patterns and depending on the frequency, intensity and number of stimuli, a variety of effects can be produced.

* **Single pulse TMS** can be used to cause a single depolarization of a population of neurons and is commonly used to activate the motor pathways.
* **Paired pulse TMS** is also commonly used over the motor cortex to measure the effects of cortical interneurons and is also used to investigate the interaction between different cortical areas. It involves the application of two separate stimuli spaced anywhere from 1-200 ms apart at both sub- and suprathreshold intensity levels.
* **Repetitive TMS** that is used to modulate the excitability of a population of neurons and has been used throughout the brain. It can involve the application of anywhere from 10 to 1500 stimuli at varying frequencies or patterns to evoke increases or decreases in synaptic activity.

**Comparing TMS to Magnetic Resonance Imaging (MRI),** the TMS machine can generate a magnetic pulse of up to a maximum of 2 Tesla while MRI machines require much higher magnetic fields ranging anywhere from 3 to 7 Tesla

# Scope

This SOP should be used by anyone accessing the TMS equipment.

At the University of Guelph, the neurophysiology laboratory of Dr. Leah Bent is in possession of a Magstim BiStim2 TMS stimulator, which is capable of single and paired pulse stimulation.

# Responsibility

L. Bent: Maintenance of equipment

PI: Must be present during process until student is sufficiently trained.

Student: Must be sufficiently trained by the PI. Graduate students are capable of performing this technique (MSc and PhD) after sufficient training. Undergraduates can perform this technique after sufficient training, but only under the supervision of a trained graduate student, or the PI. There must always be two people present during testing (other than the participant). An individual is considered trained, when the PI feels they are able to safely and effectively administer the stimulation, can make educated decisions about the stimulation and have demonstrated these skills to the PI.

Medical Questionnaire screening: Graduate students (or undergraduate students under the supervision of graduate students) are able to administer the screening questionnaire. Dr. Bent must review the screening prior to testing if there are any risks identified.

# Distribution of Copies

To be posted on website.

# Procedure

The following procedure will be followed in order to reduce the risk of injury:

1. Before testing, participants will be required to complete a **medical history questionnaire** that identifies if they are at risk of injury by being exposed to TMS (see questionnaire attached). They will have to indicate whether they have a history of epilepsy, seizures or fainting, if they take medications or recreational drugs that decrease seizure threshold or suffer from other diseases that affect cortical excitability. Also, although there is no evidence of adverse effects on fetal development, as a safety measure, it is advised that TMS should not be performed on, or by pregnant women. If the subject falls within the criteria, they will be excluded from the study. This questionnaire should be administered actively allowing interaction between the participant and the research team so that participants can ask questions and the research team member can probe to ensure that the correct information is being provided, and that participants are fully aware of the risks of providing inaccurate information.
2. Subjects will be asked to remove glasses, watches, bankcards and all jewelry as TMS exerts attractive forces on ferromagnetic objects. TMS does not affect dental fillings. Participants will also be required to wear ear protection because TMS stimuli produce loud clicking noises that can cause temporary loss in hearing or ringing in the ears[1]. New earplugs will be supplied for each individual.
3. Depending on the study, subjects will be seated in an adjustable treatment chair for the entirety of the TMS procedure. Surface EMG will be placed on the muscle of interest (most commonly first dorsal interosseous of the right hand) and will record the resultant MEP from the stimulation. See SOP for surface EMG for description of electrode type and application procedure.
4. The TMS procedure begins with the determination of stimulation intensity and threshold level. The stimulation is generated by a Magstim BiStim2 unit (Magstim® Company Ltd, U.K.) (see figure 1) and output through a Double 110mm Cone coil (P/N 9902-00) or a 70mm Figure-8 coil (P/N 3190-00) (see figure 2 A and B). The output of the machine is denoted as a percentage of the maximal output. The coil is rested tangentially on the scalp of the subject at the site of stimulation over the motor cortex, with the handle pointing posteriorly (see figure 3). The intensity is set at a level thought to be slightly above resting threshold (30% of maximal output). To stimulate, the experimenter will depress 2 buttons located on the handle of the stimulating coil. The two buttons provide a safety catch to avoid inadvertent stimulation. Throughout stimulation, subjects are asked to either maintain a completely relaxed posture, or maintain a slight isometric contraction of the target muscle (upper or lower limb) to enhance cortical excitability(active condition). After stimulation, the experimenter will assess the size of the MEP, and will either increase or decrease the stimulation intensity accordingly. Threshold is defined as the level of stimulation to evoke a MEP with an amplitude of 1 millivolt, peak to peak in 5 out of 10 trials.
5. If the participant finds the stimulation level uncomfortable at any time, the level can be decreased. If the stimulation intensity falls to a level that is no longer able to generate a MEP, the participant will be thanked for their time and will no longer be used for testing. This is important as their response (or lack of) may compromise the interpretation of results.
6. As indicated above in the description of risks, some subjects might experience neck stiffness and pain due to the straight posture of the head and neck during the application of TMS. Participants are asked to advise the researcher at the first opportunity if they experience any neck stiffness or soreness. In this situation, the participant may opt to withdraw from the study or to rest and change posture for several minutes before the procedures are resumed.



Figure 1 – Magstim BiStim2 unit (Magstim® Company Ltd, U.K.)

A

B

Figure 2 A – Double 110mm Cone coil (P/N 9902-00) B – 70mm Figure-8 coil (P/N 3190-00).



Figure 3 – Coil placement over motor cortex with handle facing backwards. Bottom left corner illustrates the shape of a MEP.

## Risks/Adverse Events

A series of adverse effects that can be induced by TMS have been identified. There is no evidence that the procedure is harmful if appropriate guidelines are followed[1,2,3].

**Stiffness**

The procedure is painless, although it can cause muscles to contract immediately after stimulation, which may lead to residual soreness caused by muscle fatigue over the duration of the experiment. Approximately 1 in every 100 research participants undergoing TMS experiences neck stiffness and pain. This is believed to be due to the straight posture of the head and neck during the application of TMS.

1. Breaks will be scheduled, and experimenters will be trained to alleviate pressure due to the coil as much as possible. This will be accomplished by removing the coil from the head during periods where there is no stimulation (rest periods) and by securing the coil cable to reduce weight on the participants head.
2. If neck stiffness and pain persist you will be directed to on-campus Health Services, to a walk-in clinic or family doctor. Please notify the study team if you experience any of these symptoms.”
3. **Ringing in Ears**

At higher levels of TMS, The stimulation can produce a loud clicking noise when the current passes through the coil. This loud click can result in tinnitus (i.e., “ringing” in the ears) and temporary decreased hearing if no ear protection is used. Researchers will provide ear plugs – a new set will be provided to each participant.

**Seizure**:

In the event that this technique induces a seizure in the subject, the following detailed protocol of the medical management will be followed:

* 1. There will always be two or more experimenters present during the application of TMS and all persons in the laboratory will be familiar with the following emergency protocol. There is both a telephone and First Aid kit in the laboratory.
  2. First responder provides the following care:
     1. aids in laying the participant down on a physio bed
     2. removes harmful objects from surrounding area
     3. loosens restrictive clothing around the neck
     4. does not restrict movements unless it is necessary to keep the person safe
     5. does not place anything in the mouth of the subject
  3. Second responder calls extension 52000 for medical emergency.
     1. states medical emergency
     2. states location:

University of Guelph, (50 Stone Road East)

Animal and Nutrition Building, (Building 70)

Room 373

Telephone Extension 52116

* + 1. clears the room and hallway for access and transport and goes to the main entrance to direct EMS to the emergency site

Cumulative exposure to TMS has been shown not to cause any adverse side effects. As stated in an article by Rossi et al. (2009), there have been patients who received over 400,000 stimuli in a year, receiving 6000 stimuli every session.

# Wording for Consent Forms

* See TMS Info Sheet (Appendix)

Comparing TMS to Magnetic Resonance Imaging (MRI), the TMS machine can generate a magnetic pulse of up to a maximum of 2 Tesla while MRI machines generate much higher magnetic fields ranging anywhere from 3 to 7 Tesla. There is no known risk to hearing at these levels. Additionally, the TMS stimulation is 100 micro seconds long and total exposure over an entire stimulation protocol is less than 5 minutes. According to Pascual-Leone in 1992 there is no evidence for hearing loss in humans with TMS: <http://www.ncbi.nlm.nih.gov/pubmed/154923>.

* Description of Risks Associated with Use of rTMS for Research Participants (the following information is provided to research participants in the Information Consent Letter):

1. The procedure is painless, although it can cause muscles to contract immediately after stimulation, which may lead to residual soreness caused by muscle fatigue over the duration of the experiment.
2. Approximately 1 in every 100 research participants undergoing TMS experiences neck stiffness and pain. This is believed to be due to the straight posture of the head and neck during the application of TMS.
3. TMS produces a loud clicking noise when the current passes through the coil. This loud click can result in tinnitus (i.e., “ringing” in the ears) and temporary decreased hearing if no ear protection is used. Ear plugs will be provided.
4. TMS can induce a convulsion even in the absence of brain lesions, epilepsy or other risk factors for seizures. Only 7 cases of convulsions have been reported using single pulse TMS in patients with pre-existing brain damage despite extensive use in both the healthy and patient population. The use of single, paired pulse or very low frequency (repetitive) TMS has never induced a seizure in a healthy participant. The overall risk for seizures during TMS is thought to be in the order of 1 in 1000 studies. However, the forms of magnetic stimulation are well within the limits recommended by the guidelines outlined in the review by Rossi et al. (2009) and are deemed safe.

# Wording for Website

SOP will be posted

# Documentation/Record Keeping

PI to document all adverse event observations and report to the REB as soon as possible.

# External Regulatory Requirements

N/A

# Internal Related, or Referenced Policies, Procedures

SOP 010 for EMG found on the [Human Research Ethics website](http://www.uoguelph.ca/research/services-divisions/ethics)

# References

[1] Rossi S., Hallett M., Rossini P.M., Pascual-Leone A., (2009). Safety, ethical considerations and application guidelines for the use of transcranial magnetic stimulation in clinical practive and research. Clinical Neurophysiology: (120), 2008-39.

[2] Wasserman, E.M. (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop of Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr. Clin. Neurophysiol. 108: 1-16.

[3] Pascual-Leone, A., Bartres-Faz, D., and Keenan, J.P. (1999) Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of ‘virtual lesions’. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 354: 1229-1238.

# Revision History

| Revision # | Reviewer | Reason | Date Last Reviewed | Next Review Date |
| --- | --- | --- | --- | --- |
| 1.0 |  |  | December 18, 2013 |  |
| 2.0 | L. Bent | To update | 20141015 | 20151015 |

# Review Cycle

Annual

# Appendix

Participant Questionnaire

TMS Info Sheet