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ETHICS COMMITTEE FORM

These documents provide some guidelines as to the information that should be given to the *FIMS Research Ethics Committee* (Ethics Form) when preparing an application and to your participants (Informed Consent Form), when conducting an experiment using "standard TMS protocols". The forms outline the basic purpose of TMS (point 2), parameters of "standard protocols" (single pulse/paired pulse, repetitive; point 4) as well as their ethical and safety issues (points 5-6). All other points (1, 3/7-15) cover information specific to your project.

Please also read the document 'USING TMS FACILITIES AT THE CCNi' before designing your TMS experiment.

TITLE AND INVESTIGATORS

1. DESCRIBE THE BASIC PURPOSES OF THE PROPOSED RESEARCH

1.1. This proposal describes "standard TMS studies" as we propose to conduct them in CCNi.
The term "standard TMS studies" used throughout this document refers to studies conducted in normal adult volunteers, in which task performance is assessed, and/or for which brain activity is recorded, while the volunteer performs cognitive/motor tasks.
Each new study falling into the "standard TMS studies" category will require its own ethics approval, but the proposal will refer to the present document to ease the submission and review process. Each proposal will have to clearly indicate the type of protocol the experimenter proposes to use: namely, single-pulse, double-pulse, or repetitive TMS.
As outlined in the guidelines for using TMS at the CCNi, only investigators who have received formal training can carry out TMS. Studies not falling into the "standard TMS studies" category, for example, because they involve children, clinical patients, or stimulation of a deceitful or painful nature, will require submission to the Ethics Board with full details.

1.2. **Basic purpose of TMS:**
Transcranial magnetic stimulation (TMS) has become a standard tool to study the relationship between brain activity and behaviour- having good spatial and temporal resolution. The basic principle of TMS is to interfere, for a brief period of time (in the order of milliseconds), with the activity of a restricted part of the brain. If, as a consequence of this intervention, we observe a change in behaviour, then we can infer that the stimulated region was critically involved in a given cognitive process at the time of the stimulation. Stimulating different regions at different times allows us to build a chronometry of brain function- that is to establish which brain regions are involved in a given process and in which sequence. Alternatively, one can administer repetitive pulses in trains of stimuli. In this case, the pulse effects accumulate over time leading to a behavioural effect which outlasts the pulse train (in the order of 5-10 minutes). This allows us to use more flexible designs in which we apply TMS before and after, but not during, a task.
TMS complements advantageously other brain imaging techniques, such as MEG or fMRI, by allowing us to establish not only a correlation between a brain region and a behavioural task or cognitive process, but to causally implicate a brain region in these tasks or processes.

2. INDICATE WHO IS FUNDING THE RESEARCH (IF COMMERCIALLY FUNDED, ENSURE THAT PARTICIPANTS ARE INFORMED).

The TMS studies taking place at the CCNi will be funded by various funding bodies.

3. DESCRIBE THE DESIGN OF YOUR EXPERIMENT (E.G. CONDITIONS, NUMBER OF PARTICIPANTS, PROCEDURE AND EQUIPMENT WHERE APPROPRIATE) see BPS 2 & 8

3.1. **General information on TMS:**

Participants are first given general information about TMS. They are fully informed of the contra-indications through the information form and are encouraged to ask questions if unsure about any part of the procedure.

They are also informed that they may withdraw from the study at any time without prejudice.

3.2. **Equipment**

At the CCNi we are equipped with several TMS stimulators from the Magstim company. The intensity and frequency of stimulation can be controlled manually or automatically with computer programs.

3.3. **Screening for inclusion/exclusion criterion**

Before each study, participants are screened to ensure that they do not present with any contraindication for TMS.

They are required to complete and sign a safety questionnaire in the presence of the experimenter.

Even for participants without contra-indication, TMS might be uncomfortable, especially for individuals with high threshold (see below). Those participants will be excluded from the study.

3.4 **Procedure for a standard TMS experiment.**

We first explain the technique, procedure and the task to the participant, who will also read the information and the consent form. Participants will be encouraged to ask any questions they might have before signing the consent form and anytime thereafter. Typically, this is done one day before the experiment and also involves familiarisation of the participant with the technique, experimental setting and task (short training). Tasks typically involve pressing keys in response to stimuli or instructions given on a computer monitor.

During the experiments, participants are seated comfortably in a chair. A forehead and chin rest is used to restrain head movements. The TMS coil, which is embedded into a plastic cover, is placed against the participant's head. It is held in place by articulated mechanic arms attached to a solid frame, so that no pressure is applied directly to the participant's head. The coil can be removed at any moment by the participant or experimenter.

3.4.1 **Individual determination of motor or phosphene threshold prior to the experiment**

When applied over the motor cortex (the part of the brain that controls movement), a TMS pulse induces an overt motor response. When applied over the visual cortex (the part of the brain that allows us to see) a TMS pulse induces a visual sensation called a phosphene. The incidence and intensity of these responses depends on the intensity of the pulse, as well as on the participant's individual neuronal excitability. Threshold measurements are used for measuring individual neuronal excitability prior to the experiment to adjust the TMS intensity:

In a standard experiment the intensity of stimulation to any part of the brain is adjusted for each participant as a function of his/her motor or phosphene threshold. Thresholds are defined as the minimal intensity necessary to induce a response while stimulating the motor or visual cortex. The procedure to establish thresholds involves applying single pulses every 7-8 seconds while varying the location and the intensity, until the minimal intensity to elicit a response in 5 out of 10 trials is found.

In some individuals with high threshold, TMS can be source of discomfort, possibly due to peripheral muscle and facial nerves stimulation. To avoid discomfort during the study, a pre-screening will be carried out in each potential participant to assess comfort at stimulation intensity.

In some studies, the same intensity may be used for every participant (typically 60% of the maximum output of the machine- that is ~1.2 Tesla).

3.4.2 **Frameless stereotaxy**

Usually, the anatomical magnetic resonance image (MRI) of the participant's brain is used to guide the placement of the TMS coil. This is achieved by a system called frameless stereotaxy. The participant is asked to wear a headband on which a reflecting device is attached, which is tracked by an infrared camera. Another reflecting device is used to point at different landmarks on the head of the participant (ears, nose) while at the same time the same points are identified on the MRI scan. A software program is then used to register the MRI with the head of the participant. Tracking of the coil placement relative to the head (and MRI) by a camera and software allows the experimenter to correct, online, for deviations from optimal site of stimulation (e.g. because of movement of the participant) and to document exactly, over time, where in the brain the TMS pulses were delivered.

3.4.3 **Single and short-train TMS procedures**

The participant performs the task while single, double or short-trains of pulses are applied. A minimum of 5 seconds separate two single pulses. Double pulses consist of two pulses of the same, or different, intensities applied at very short interval (1-20ms). Double pulse TMS is often used to compare with the effect of single pulse TMS in studying intra-cortical facilitation or inhibition. A minimum of 5 seconds separate two double-pulses. Trains of pulses last for a few hundreds of milliseconds with a frequency of 5-20 Hz. A minimal interval between two trains of pulses will be maintained, depending on the pulse frequency and intensity in strict accordance with published safety guidelines.

When accurate temporal resolution is less crucial, short-train TMS is more efficient than single pulse in eliciting inhibitory effects.

In all cases, the experiments are divided into blocks of 5-10 minutes allowing for the participant to have sufficient breaks during which they can move and relax.

3.4.4 **Offline low-frequency repetitive TMS**
In this procedure, several minutes (typically 10-15) of repetitive TMS, at low-frequency (<= 1Hz), is applied while the participant sits comfortably, doing nothing. This induces transient changes in cortical excitability and connectivity lasting for a short period after stimulation (in the order of minutes). Here volunteers participate in behavioural, cognitive or brain imaging tests before and after the administration of TMS.

3.5 **Repeating sessions**
A standard TMS study will involve stimulating several brain regions separately- some sites of stimulation being used as control. In the case of low-frequency repetitive TMS, different sites are tested on different days. We therefore ask the participants to visit the lab several times. We may also ask the participants to come several times to the lab for the other procedures, when all the stimulation sites cannot be tested in a reasonable period of time (e.g., within 2 hours).

3.6. **Number of participants**
A standard TMS study will involve about 20 participants.

3.7 **Safety guidelines:**
Each study will comply with the safety guidelines, which have been established based on the wealth of TMS-studies worldwide by the International Society for Transcranial Stimulation (ISTS) (published in Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr Clin Neurophysiol 1998; 108:1-16) and the International Federation for Clinical Neurophysiology (IFCN) (published in Hallett M, Wassermann EM, Pascual-Leone A, Valls-Sole J. Repetitive transcranial magnetic stimulation. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl 1999; 52:105-13.)

4. DESCRIBE HOW THE PROCEDURES AFFECT THE PARTICIPANTS

There are a few potential adverse effects of TMS as well as contra-indications. All precautionary measures will be taken to avoid them and safety guidelines will be strictly applied,

Hearing disturbance: TMS produces a loud clicking sound when a current is passed through the stimulation coil. The peak sound pressure associated with the TMS pulse has been measured in a safety study[1]. At a distance of 10cm, and with maximum TMS intensity (100% stimulator output), the TMS pulse creates very brief (< 300 micro-sec) peak sound pressure levels of 110 dB (duration of bi-phasic TMS pulse: 300 micro-sec). Given that the threshold limits of impact noise would be reached only after 1'000-10'000 pulses per day (based on American Conference of Governmental Industrial Hygienists), the risk of TMS noise is considered small even without hearing protection[1]. The potential risk can be further diminished by the participant wearing very light weighted hearing protectors.

Headache: In susceptible individuals, TMS may cause transient tension-type headache. The headaches usually respond well to mild analgesics (e.g. paracetamol). The incidence of headache is estimated lower than 10%. If a headache develops, TMS will be discontinued immediately.

[1] Starck J, Rimpilainen I, Pyykko I, Esko T (1996) The noise level in magnetic stimulation. *Scand Audiol*. 25:223-226

Risk of seizure: There is no reported risk of seizure associated with single pulse, paired-pulse, or low frequency repetitive TMS. In the past, seizures have occurred during high frequency repetitive TMS. Under specific high-frequency conditions (high frequencies, high intensities, high number of pulses within trains, no breaks between trains), pulse effects can become cumulative so that seizures have been induced accidentally in healthy volunteers without risk factors for epilepsy (n=7 worldwide of the thousands of healthy volunteers tested in the literature). None of these 7 volunteers had a second seizure or any health problems resulting from the TMS-induced seizure. All the seizures have occurred in the early days of TMS or when TMS was applied outside the recommended safety margins. Within the safety margins (established by the ISTS[1] and the IFCN[2]), as it will be the case for the standard protocols proposed here, no adverse effect has been reported neither in healthy volunteers (nor patients) properly screened for contraindications.

5. STATE WHAT IN YOUR OPINION ARE THE ETHICAL ISSUES INVOLVED IN THE PROPOSAL (see BPS All Sections)

The main ethical issue is that no participant will be put at risk. TMS has been used in thousands of healthy volunteers worldwide without any side effect, but TMS is not recommended for certain populations. Each participant will be informed of the contraindications and will have to complete and sign a screening questionnaire.
Contraindications include:

- People with metal fragments or implants in the head, since these objects could be displaced or heated by the magnetic filed produced by the TMS.
- People with cardiac peacemaker since TMS could interfere with the device
- People with personal or family history of epilepsy since they might be susceptible to seizures.
- People under medication or drugs which might increase the seizure probability.
- Women who are pregnant or who think they might be pregnant. Also, although there is no data to support the fact that TMS might be harmful to foetus, as a matter of natural precaution our policy is not to include pregnant women in our studies.

The information and screening questionnaires will be given by a qualified person aware of potential risks (see document 'USING TMS FACILITIES AT THE CCNi"). Also, participants will be informed that TMS used for research cannot have any disagnostic value. It is also different from the TMS used in clinic for treatment and does not interfere with any sort of medical treatment.

6. SPECIFY THE NATURE OF THE PARTICIPANTS. INDICATE IF THE RESEARCH INVOLVES CHILDREN OR THOSE WITH MENTAL DISABILITIES OR HANDICAP (see BPS 3) IF SO, EXPLAIN THE STEPS TAKEN TO OBTAIN PERMISSION FROM L.E.A.s, HEADTEACHERS, PARENTS, ETC...

Participants will be normal adult volunteers.

7. STATE IF PAYMENT WILL BE MADE TO SUBJECTS

It is standard policy to give compensation of £6 an hour to participants.

8. DESCRIBE THE PROCEDURES FOR ADVERTISING, FOR RECRUITING PARTICIPANTS, AND FOR OBTAINING CONSENT FROM PARTICIPANTS (see BPS 3)

Participants will be recruited by adverts detailing the purpose and duration of the experiment. Screening questionnaire will be completed and written informed consent obtained from participants, prior to the study.

9. STATE WHETHER THE PROPOSAL IS IN ACCORD WITH THE BPS CODE OF CONDUCT (see BPS All Sections)

"Standard TMS studies" are in accord with the BPS code of conduct.

10. DESCRIBE HOW THE PARTICIPANTS' ANONYMITY AND CONFIDENTIALITY WILL BE MAINTAINED (see BPS 7)

Participants' anonymity will be assured by only referring to a participant number during data storage and analysis. Records of personal details will only be kept if participants agree (for example to contact them for other studies).

11. DATE ON WHICH PROJECT WILL BEGIN

TMS experiments will start at CCNi February 1st, 2008.

12. LOCATION AT WHICH THE PROJECT WILL BE CARRIED OUT

The projects will be carried out in one of the TMS laboratories in the Department of Psychology, University of Glasgow.

13. DESCRIBE HOW PARTICIPANTS WILL BE DEBRIEFED AT THE END OF THE EXPERIMENT (THIS MUST INCLUDE THE OPPORTUNITY TO CONTACT THE EXPERIMENTER - OR SUPERVISOR - FOR FEEDBACK ON THE GENERAL OUTCOME OF THE EXPERIMENT) (see BPS 5 & 10)

Participants will be given contact details of the senior-investigators of the CCNi (TMS facility) and the experimenters. They will be encouraged to ask questions about the experiment as well as more general questions about TMS - before, during and after the experiment.

14. ATTACH PARTICIPANT INFORMATION FORM AND CONSENT FORM (see BPS 3 & 6)