ELECTRICAL AND/OR MAGNETIC BRAIN STIMULATION IN RESEARCH

This guidance document is intended for investigators planning to conduct brain stimulation in research. Should you need additional assistance, please contact the Office for Protection of Human Subjects (OPHS) at 510-642-7461 or ophs@berkeley.edu.

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A. Introduction

These guidelines outline standard procedures and language accepted by the Committee for Protection of Human Subjects (CPHS) for UC Berkeley research involving electrical and/or magnetic brain stimulation, including Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS). These guidelines relate to FDA-approved devices that are used as clinically indicated. Studies that fall outside of what is clinically indicated or involve use of unapproved devices will be reviewed on a case-by-case basis by CPHS.

B. Definitions

1. ***Transcranial Direct Current Stimulation (tDCS):*** tDCS is a non-invasive brain stimulation technique in which a weak electrical current is applied to the head. tDCS protocols generally involve the application of two surface electrodes, one serving as the anode and the other as the cathode. The current flows from the anode to the cathode, with some current passing along the scalp and some passing through the brain. The current passing through the brain produces small changes in the excitability of the brain regions falling within the current flow. The current may be applied in a continuous manner (tDCS) or in an alternating manner (tACS - transcranial Alternating Current Stimulation).

2. ***Transcranial Magnetic Stimulation (TMS):*** TMS is a non-invasive method for stimulating the brain. This device can store and rapidly discharge electricity into a coil of electrical wire that is encased in shielded plastic. The surface of the coil is placed on the scalp above the targeted brain area. A single TMS pulse produces a magnetic field that passes through the skin and skull, inducing a brief change in the electrical activity in the brain. The magnetic pulse alters neural activity in a transient manner in brain areas lying directly beneath the coil (roughly 1 cm volumetric area). *Repetitive TMS (rTMS)* involves multiple TMS pulses in rapid succession to increase the effectiveness and duration of changes in the cortical excitability.

C. Protocol and Consent Form Information

The protocol should reflect the following information (under "Screening," "Procedures," "Risks/Discomforts," etc., as applicable).

1. Screening

   When using electronic or magnetic brain stimulation in research, the following are exclusionary criteria due to elevated risk or unknown risk:
   a. History of seizures or family history of seizures.
   b. History of migraines or other types of severe or frequent headaches.
   c. Metallic implants in the head.
   d. Severe head injury and/or frequent loss of consciousness.

2. Exclusions

   Researchers should either consider the following populations/ conditions/ situations as exclusion criteria, or provide a rationale for their inclusion in the protocol.
   If subject is:
   a. A minor
   b. Pregnant
   c. Very fatigued
   d. Currently or very recently experienced jet lag, or significant sleep disruption
   e. Using a medication known to increase risk of seizures
   f. Using a medication known to increase risk of stroke
   g. Using psychiatric medications (antipsychotic, antidepressants) and has not yet consulted with personal physician to get approval to participate in the study

   If subject has ever had experience of:
   a. Anxiety disorder
   b. Stroke
   c. Neurodegenerative disorders such as Parkinson's Disease
   d. Loss of consciousness/syncope

3. Determination of Risk Level

   The CPHS accepts the current literature reports that use of tDCS or rTMS with an FDA-approved device as clinically indicated is a minimal risk procedure. However, inclusion of research subjects for whom participation may be greater than minimal risk will necessitate the full Committee's deliberations.

   Similarly, the CPHS has accepted that studies using TMS within the parameters as reported by Wasserman (1998) from the National Institutes of Health (NIH) 1996 workshop on rTMS safety can be reviewed at the expedited level. Researchers must attest in the protocol that the proposed use of TMS is within those parameters. Researchers who wish to conduct research outside of those approved parameters must provide an evidence-based rationale for such use of TMS for the Committee's consideration.

4. Risks/Discomforts

   - The protocol and the informed consent documents should describe the known risks of TMS. In particular, TMS has an estimated 1% chance of inducing neurological seizures in someone with an undetected brain tumor or abnormality. For neurologically healthy individuals, no reports of seizures have occurred while using TMS under the safety precautions and practice recommendations reported by Wasserman (1998).

   - Brain stimulation devices may cause onset of a mild headache of short duration. These have been reported to occur with a frequency of approximately 2%, and are mild and of short duration when they do occur. However, subjects should not participate if they have a history of migraines or other types of severe or frequent headaches. Subjects must be advised that if they experience a headache at any point during the experiment, they should tell the researcher immediately and the experimental session will be terminated.

   - The sound of the devices is loud enough to possibly cause hearing damage, and ear protection should be used to mitigate this risk. If the stimulation device pulses target the cerebellum, there is increased risk of nausea. A risk of neck stiffness or pain is present due to requirement to maintain the posture of the head and neck during the use of the device. The device could cause discomfort or pain to the head. The use of sandpaper and alcohol to prep the skin may cause skin irritation and dryness. Stimulation devices may cause muscle twitching in hands or face that can be uncomfortable.

5. Minimizing risks

   - Researchers must describe measures for minimizing the known risks of electric or magnetic brain stimulation devices in their protocols, including but not limited to

screening subjects for contraindications and other considerations for exclusion, informing subjects they may stop the experiment at any point, and requiring ear protection while in and around the device.

- Research personnel using a brain stimulation device must: be properly trained for its use, possess current cardiopulmonary resuscitation (CPR) certification; and be familiar with procedures to handle unanticipated problems and adverse events.

- The protocol should include a plan for dealing with unanticipated problems and adverse events. Researchers are directed to call campus police (510/642-3333) from a cell phone or 911 from a land line in the event of a seizure or other emergency. For non-emergency/minor side effects, subjects should be referred to their regular physician.

6. Incidental medical findings

   The protocol should include a plan for dealing with incidental findings, and participants should be fully informed as to what the policies and procedures for such incidental findings are. This plan should identify appropriate personnel or consultant(s) who will report such findings to the participants and/or their physicians. If a physician is involved in the study, he/she would be an appropriate person to report findings. In non-medical settings, the principal investigator or other responsible and qualified individual may be an appropriate person to serve in this role.

   In the informed consent documents, subjects must be told that the use of the instrument is for research, not clinical purposes (e.g., diagnosis or treatment). They must also be told, however, if an abnormality is discovered in the course of the research, how and to whom the researchers will report this abnormality.

D. Recommended Consent Form Language

- During the behavioral tasks, you will have transcranial magnetic stimulation (TMS) applied in the following way: [*describe procedures subjects will be asked to do in chronological order*].

- A magnetic pulse will be generated by the coil in order to locate the motor cortex. You will likely feel a gentle flick and hear an audible click. This pulse should not be painful, but it may cause a twitch of your hand or face muscles. At times during the experiment, the coil will not induce any electrical activity in the brain, though you will not be aware of this. During the main part of the experiment, the coil will be located over different parts of the brain. We are comparing the effects of stimulation over these different regions to examine how they affect different aspects of cognition and/or motor control.

- You are free to terminate the session at any time.

- While the [*name the device*] is deemed electronically safe, TMS has been reported to induce seizures. The risk of a seizure occurring is greater for someone with an undetected brain tumor or abnormality. Based on the rates at which seizures occur in people with known brain abnormalities, we would estimate the risk to be around 1% for someone with an undetected abnormality. The researchers in the TMS laboratory have been trained to recognize signs of seizure and how to respond if such an event should occur.

- Low frequency repetitive TMS makes a clicking sound and may cause a twitch of muscles in the hand or face. However, it is not usually painful, nor are there any known physical risks.

- Because the sound emitted by the stimulator is so brief, it is not perceived as being loud, but this sound is loud enough that it could potentially cause hearing damage. Thus, we will require that you wear ear protection during the experiment. The use of ear protection minimizes the risk of hearing impairment.

- In some brain stimulation studies, electromyography (EMG) is used in combination with TMS to measure changes in motor pathway excitability. Many people have been studied using EMG instruments without reported harm. There is a slight chance of skin irritation or dryness due to the sandpaper and alcohol pre-treatment. If you have allergy or skin sensitivity to metal, there may be a skin reaction. If any of these reactions occur, we will provide you with an ointment to reduce skin irritation.

- For studies in which the TMS pulses target the cerebellum, there is a possibility that you may become nauseated. Short-lasting sensations of nausea have been reported in a few similar studies. If you feel nauseated at any point during the experiment, please tell us immediately.

- It is also possible that you will experience some neck stiffness or neck pain. This is believed to be due to the fact that participants tend to maintain a particular posture of the head and neck during the experiment. If you experience neck stiffness or discomfort at any point during the experiment, please report this immediately.

- It is important to let the researcher know immediately if you are experiencing anxiety due to the procedure.

Reference

Wassermann, E. M. (1998). 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. Electroencephalography and Clinical Neurophysiology: Evoked Potentials, 108, 1-16.