Martinos Center TMS Safety Guidelines

Version 5/5/2023 (T. Raij & A. Nummenmaa)

1. These safety guidelines apply to Transcranial Magnetic stimulation (TMS) research conducted at the Martinos Center. MGH IRB and FDA may require additional safety measures depending on study type.

2. Necessary approvals differ for research, education, technical QA testing, and therapy, as follows:

a. For research, IRB is required, and FDA Investigational Device Exemption (IDE) may be required in addition (depending on type of study, devices, stimulation parameters).

b. For TMS education, no IRB or FDA approvals are required but the TMS Educational Consent guidelines must be followed. TMS education is only provided by authorized staff of Martinos TMS Core Laboratory. Contact Dr. A. Nummenmaa about TMS Education events. For TMS education, the TMS Screening Form must be filled in by the participant signed by authorized TMS Safety Training Faculty prior to administering any stimuli.

c. For technical QA testing of TMS systems in humans, no IRB or FDA approvals are required but the TMS Technical QA Testing Consent guidelines must be followed. TMS Technical QA testing is only performed by authorized staff of Martinos TMS Core Laboratory. Contact Dr. A. Nummenmaa about TMS technical QA testing. For TMS technical QA testing, the TMS Screening Form must be filled in by the Participant and signed by the Participant and Operator (see, below) prior to administering any stimuli. Note also that the data collected during technical testing can be used for QA purposes only but CANNOT be published in any shape or form.

d. At this time we will not engage in treatment of patients with TMS at the Martinos Center.

3. Subjects at increased risk for TMS-induced seizure and other adverse events will be identified with a screening form and disqualified from participation, unless they are in the specific study population and the additional risks and benefits are ethically justified, IRB approved, and disclosed to the subject. The TMS Screening Form must be filled in by all Participants and signed by the Participant and Operator (see, below) before each session and prior to administering any stimuli.

4. For research, TMS parameters (for example pulse intensity and frequency) should normally follow the published safety limits (Rossi et al., 2009). If parameters outside these are used, the study has to be considered non-significant risk by MGH IRB, or, more likely, be considered significant risk and therefore receive FDA IDE in addition to MGH IRB.

5. During TMS administration at least two researchers need to be continuously present: (i) Operator and (ii) Investigator.

6. There are two levels of TMS certification: Basic and Advanced. All researchers (PIs, Operators, Investigators) conducting TMS studies must pass the Martinos Center Basic TMS course (1 day) focused on safe and technically correct TMS administration in our environment, leading to certification at the Basic level. Operators must additionally be certified at the Advanced level, which can be achieved by passing the Martinos Center Advanced TMS course or showing proof of corresponding training (e.g., BIDMC TMS Intensive Training). In addition, Operator candidates are required to observe 10 sessions and then deliver TMS in 10 supervised sessions before being considered for Advanced certification. All TMS users must also have undergone Basic Life Support (BLS) training. All TMS users must display a badge indicating their certification level when inside the TMS laboratory.

7. Before submission to IRB and/or to FDA, based on Rossi et al. (2009), Appendix A, and paragraphs 8 – 11 below, the PI will (a) classify the study as Risk Class 1, Class 2, or Class 3; (b) determine if a covering MD is needed; and (c) perform a risk/benefit analysis showing that any possible risk is justified by expected benefits. The PI will submit this Safety Review to the Martinos Center TMS Laboratory Committee that will require modifications if needed. The TMS Laboratory Committee includes at least one MD member.

8. Each TMS research protocol that carries significant risk must have a covering MD who is available (in-house in Building 149) during the TMS session. The covering MD must be licensed to practice medicine in MA, be familiar with TMS and management of its possible side effects, and know these Safety Guidelines. During TMS administration, the Investigator and Operator need to be able to immediately reach the covering MD. To determine when a covering MD is required or not required for different Risk Classes, see paragraphs 9 – 11 below.

9. Healthy subjects in Class 3 and Class 2 studies. Single pulse, paired pulse, conventional rTMS, or patterned TMS protocols where TMS parameters fall within safety consensus (Rossi et al. 2009) do not require a covering MD. If conventional rTMS or patterned TMS exceeding the safety parameters (Rossi et al. 2009) are used, a covering MD is required as described above.

10. Patients in Class 3 and Class 2 studies. Single pulse, paired pulse, or conventional rTMS protocols where TMS parameters fall within safety consensus (Rossi et al. 2009) require a covering MD during TMS only if risk for seizure or other serious adverse event is increased due to the patient's condition. Conversely, if risk for seizure or other serious adverse event is not increased, the study does not require a covering MD. If conventional rTMS exceeding the safety parameters (Rossi et al. 2009) or patterned rTMS are used, a covering MD is required.

11. Patients in Class 1 studies. A covering MD is always required.

12. For education or technical Q/A testing, no covering MD is required and there are no requirements for the presence of medically trained personnel during TMS.

13. TMS Seizure Plan. In the event of a suspected partial or generalized seizure, the TMS Operator immediately stops TMS and keeps the subject from hurting him/herself during convulsions (that typically last less than 60 seconds). There is no useful anticonvulsive medication that would need to be administered. For significant risk studies, the Investigator will next alert the covering MD to arrive to the TMS laboratory immediately; for non-significant risk studies, the Investigator will alert MGH security to arrange for transfer with an ambulance to MGH ER. The Operator will continuously monitor the subject until the covering MD or ambulance personnel arrives. These steps must be taken in all suspected seizure events immediately and regardless of rate of recovery of the subject. In significant risk studies the covering MD then evaluates if transfer to the MGH ER is required or not. In non-significant risk studies all subjects with a suspected seizure are transferred to the MGH ER for medical evaluation.

14. All adverse events and expected side effects are recorded by the PI and reported to the Martinos Center TMS Laboratory Committee every 3 months, in addition to other reporting requirements to MGH IRB, and possible other instances indicated in the IRB protocols.

15. All serious adverse events are immediately reported by the PI to the Martinos Center TMS Laboratory Committee, MGH IRB, and possible other instances indicated in the IRB protocols.

Reference: Rossi S, Hallet M, Rossini PM, Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and reseach. Clin Neurophysiol 120(12)2008-39.

APPENDIX A: Excerpts from Rossi et al. (2009):

7.1.1. Types of rTMS studies

Permissible rTMS studies may be divided into three classes in the order of their demand for protection of the subjects and expected benefits. Full consensus has been reached on the types of rTMS studies defined herein. In any case, the decision on the risk/benefit ratio of a given rTMS study needs to be made by each principal investigator and her or his IRB or Ethic Committee:

– Class 1 (direct benefit, potential high risk): studies in patients with diagnostic or therapeutic primary objective, including the development of new therapeutic indication or protocols, with potential direct individual clinical benefit. Normal subjects should not ordinarily participate in such studies, and the risk level for patients can be theoretically high for stimulation protocols that have been not yet tested for safety.

– Class 2 (indirect benefit, moderate risk): studies in patients where the potential clinical benefit is more speculative or where no clinical benefit is expected, but the study is anticipated to yield valuable data for the development of treatments, safety assessment

of a cortical stimulation protocol, or improved understanding of pathophysiological mechanisms of neurological or psychiatric diseases. Normal subjects may participate as control subjects. In these studies, regimens that will place subjects at significant risk of seizures or other serious adverse effects should employ only patients and not normal subjects, because exposure to adverse effects is unacceptable for normal subjects when clinical benefit is questionable.

– Class 3 (indirect benefit, low risk): studies in normal subjects and patients that are expected to yield important data on brain physiology or on safety, but have no immediate relevance to clinical problems. Normal volunteers should be permitted to participate in rTMS research when it is likely to produce data that are of outstanding scientific or clinical value.

The increasing use of TMS makes it necessary to consider places where TMS can be carried out safely, taking into consideration both research and clinical needs. For diagnostic and therapeutic applications of TMS in patients (Class 1 and Class 2 studies) a medical setting is required. For Class 3 studies and Class 2 studies on normal subjects, carried out with TMS or rTMS parameters not exceeding those of Tables 4–6, conduct of the study in a medical setting may not be required. The referring IRB is the final arbiter for such considerations.

The Principal Investigator of a TMS or rTMS study does not need to be a licensed physician, but should be an expert in TMS with knowledge about principles, physiology and potential side effects of the technique. In addition, appropriate emergency medical attention for possible TMS complications should be planned for. A licensed physician that is intimately familiar with the study protocol, the risks of TMS, the treatment of any of its possible complications and side effects, and the condition of any patients undergoing TMS, should be involved in the design and conduct of study protocols. Therefore, TMS and rTMS protocols should identify a principal investigator and a medically responsible physician. Possible uses and settings of TMS, based on what is more extensively discussed in previous paragraphs, are summarized schematically in Table 7. It is clear that the risk of a given TMS study has to take into consideration all aspects of the study, not simply the TMS parameters. The responsibility to assess the risk of a TMS study, like that of any study, lies with the Principal Investigator who has to obtain the appropriate approval from his/her IRB.

7.2.7. Hospital, outpatient setting or research labs?

To date, research with single-, paired-pulse and conventional rTMS has been carried out safely in many laboratories outside of medical setting across the world (i.e., psychology, physiology, robotics). Despite it being very low, the risk of an adverse effect is, however, not completely absent. Therefore, the Principal Investigator of the study has to balance this possibility, plan for possible complications, and fully comply with the local IRB rules. A medical setting (hospital or appropriately equipped outpatient clinic) is needed for all clinical applications of TMS (i.e., diagnostic or interventional procedures of neuromodulation). Outpatient TMS treatments can be delivered outside of a hospital.

However, it is strongly advisable that in these settings and in other medical environments, appropriate life-support equipment and emergency medical facilities be available. All medical applications of TMS should be done under the supervision of a responsible physician, who is responsible for handling all adverse events and complications. Whether the responsible physician has to be present in the laboratory at the time of TMS/rTMS application or not, depends on the circumstances and is a decision to be made by the study's Principal Investigator, and the responsible physician in collaboration with their local IRB, Ethics Board, or Medical Board.

Table 7 from Rossi et al. (2009)

Table 7
Possible uses and settings of TMS

Use	Single-pulse	Paired-pulse, rTMS ⩽1 Hz	Conventional rTMS, >1 Hz	Patterned rTMS (TBS, QPS)	Conventional or patterned rTMS with parameters exceeding those of Tables 3–5
Research (Class 3 studies; Class 2 studies in normal subjects)	□	□	□	□ ○	■ ○
Diagnostic applications	■ ●	■ ●	■ ●	Currently not done	Currently not done
Therapy/neuromodulation (Class 1 studies and Class 2 studies in patients)	Currently not done	■ ●	■ ●	■ ●	■ ●

□ = Non medical setting allowable (i.e., psychology labs, robotics labs, research institutions, etc.). Presence of a Physician in the premises may not be required.
■ = Medical setting required
● = A medically responsible physician is required. Personnel skilled in the management of syncope and seizure is required in the lab.
○ = Emergency medical assistance is strongly recommended. Personnel skilled in the management of syncope and seizure should be present in the lab.