Martinos Center TMS Standard Operating Procedure

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

The purpose of this document is to instruct how to use TMS for research at the Martinos Center. The instructions for TMS are quite similar to other imaging modalities at the Center, and their purpose is to maximize safety for subjects and experimenters. Projects and users new to the Martinos Center should follow the general instructions for starting a new project. This manual is created and updated by the Martinos Center TMS Laboratory Committee.

A. Accreditation and training. Each new prospective TMS user must participate in the Martinos Center 1-day Basic TMS Course. Successful completion of this course is a prerequisite for gaining access to our TMS laboratory, and will lead to accreditation at the Basic Level (yellow badge). Since this course includes Martinos Center specific information, all users regardless of previous TMS expertise need to participate. Those wishing to take their accreditation to the Advanced Level (blue badge) must show written proof of extensive TMS training and experience, and additionally observe 10 TMS sessions and then conduct 10 supervised sessions. All levels additionally require proof of Basic Life Support (BSL) or corresponding medical training. For more information see TMS Training Information.

B. Background information. Each investigator wishing to use TMS needs to read the following documents (discussed at the 1-day course):

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 research. Clin Neurophysiol 120(12):2008-39.

Ilmoniemi RJ, Ruohonen J, Karhu J. Transcranial magnetic stimulation--a new tool for functional imaging of the brain. Crit Rev Biomed Eng. 1999;27(3-5):241-84. PMID: 10864281.

Martinos Center TMS Safety Guidelines (IRB-approved)

Martinos Center TMS Screening Form (IRB-approved)

C. Safety Review by the Martinos Center TMS Laboratory Committee. Based on Rossi et al. (2009) 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. The PI will submit this Safety Review to the Committee that will require modifications if needed.

D. MGH IRB, FDA IDE, and HCCRC Review(s). After receiving approval of the Safety Review, the PI will submit MGH IRB application. Studies that involve non-significant risk require only IRB approval. Studies that involve significant risk additionally require FDA

IDE (applying for this may be a lengthy and intensive process). More information of the MGH IRB requirements is given at the 1-day course.

E. Requesting a TMS account. After receiving Safety Review and IRB (and potentially FDA IDE) approvals the PI submits a copy of the approval letters to Karen Dervin and requests a TMS account. Once the request is approved, the PI will receive a 3-letter code that is used for reserving and charging for TMS time. Unfunded studies that need to collect small amounts of pilot data for grant applications may apply for a Pilot Account.

F. Reserving TMS time slots. Users approved by Karen Dervin must reserve the TMS equipment and room for each TMS session using the Martinos Center Scanner Schedules page.

G. Safety Screening Forms. Before a TMS session is conducted a TMS Safety Screening for must be filled out by the subject. This needs to be done prior to any TMS session whether it is for IRB-approved human subject research, teaching or technical QA testing of the equipment. To avoid unnecessary cancellation of TMS slots, it is also recommended to employ a pre-screening form to exclude participants prior to study enrollment & scheduling the first visit(s).

H. Pregnancy. Healthy subjects may not receive TMS for research purposes while pregnant. This also applies to pregnant patients, unless they are in the study population, the additional risks and benefits are ethically justified through potential for direct benefit to the patient, the study is IRB approved, and potential risks are disclosed to the patient. Pregnancy in women of child bearing potential is excluded similarly as for MRI/fMRI research. For MGH IRB recommendations, see

https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Pregnancy-Testing-in-Research-Involving-Radiation.pdf

Specifically, document the subject's responses to the following questions in the Safety Screening Form:

Do you believe that you could be pregnant? Yes/No

Are you currently trying to become pregnant? Yes/No

Are you using reliable contraception? Yes/No

When did your last period start? Date:_____

Pregnancy may be excluded if answers to the above questions indicate that the subject is not pregnant. If the subject thinks she could be pregnant, or answers to these questions suggest pregnancy is possible, a urine pregnancy test prior to the TMS session is needed to rule out pregnancy.

I. Personnel during TMS sessions. During TMS delivery at least two researchers must be present at all times. The person operating the TMS instruments ("Operator") must have Advanced Level training. The second researcher ("Investigator") can have either Basic or Advanced Level training. Personnel without TMS badges are not allowed to be present during TMS. The IRB/FDA-IDE protocol may additionally require medical equipment (e.g., code cart) and/or a Covering MD to be present.

J. Use correct TMS parameters and correct subjects. Using too high frequencies for too long and/or at too high intensities strongly increases the risk for serious side effects. The Operator is responsible for knowing the published safety limits (Rossi et al. 2009), for using only TMS sequences and intensities listed in the protocol, and setting these parameters correctly into the TMS stimulator. The Investigator is responsible for ensuring that the subject matches the protocol requirements and does not have contraindications for TMS or conditions that increase risk for serious side effects (unless these are justified by the risk/benefit analysis, allowed by the protocol, and disclosed to the subject).

K. Observe the subject during TMS. If the subject is uncomfortable, make adjustments until the problem is solved. If this cannot be done, terminate the experiment. Keep a constant eye on the subject and if any sign of spread of activation is observed or you suspect a focal or generalized seizure, stop TMS immediately and follow the TMS Seizure Plan (paragraph 13 in the Martinos Center TMS Safety Guidelines; see also below).

L. Observe the subject after TMS. After stopping TMS keep the subject in Martinos Center until all behavioral effects of TMS have disappeared. For single and dual pulse studies this happens immediately. For rTMS this may take up to 10 minutes. For unconventional sequences (theta burst, quadripulse) this may take up to 70 minutes.

M. Clean up. Shut down the equipment and remove trash. Return coils in their boxes to the closet. Return stimulators, navigators, and other carts to their places. Move the chair out of the way.

N. Malfunctions and broken equipment. You must report these immediately to the TMS Core Laboratory Personnel (A. Nummenmaa). Broken equipment is useless and can be dangerous.

O. START and END inspections of the coils. For every TMS session, the Operator is responsible for visually inspecting the coils. The TMS coils and especially the navigation reflectors attached to them are the most sensitive part of the entire TMS system. Handle them with extreme care and do not touch the reflectors with bare hands or let them touch anything else. Dropping a coil may render it unsafe to use. Even slightly knocking the reflector holder may severely degrade navigation accuracy.

P. Treating adverse events and side effects. All serious adverse events and side effects must follow the TMS Seizure Plan (see below). For mild adverse events the PI must

decide if they require treatment and/or follow-up (if needed, consult Covering MD, or if the protocol does not have one, contact Dr. A. Nummenmaa).

Q. Reporting adverse events and side effects. All serious adverse events are immediately reported by the PI to the Martinos Center TMS Laboratory Committee and to MGH IRB. All adverse events and expected side effects that are not serious 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. Additional reporting requirements to FDA IDE may apply as indicated in the protocols.

EMERGENCIES. In all emergencies follow the 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.