UCLA TMS Laboratory Safety Manual

Manual updated: July 9, 2008

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1 General Information

1.1 Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive brain mapping method which can stimulate the brain with an external electromagnetic coil placed on the head. A large current (~8000 amps) is passed through an insulated wire coil held flat on the surface of a subject's scalp in a fraction of a millisecond. This current pulse induces a weak electrical current within surface brain cortex.

Single- or paired-pulse TMS are used to test the excitability over the motor cortex or as a transient perturbation during a given task. Repetitive trains of TMS pulses (repetitive TMS or rTMS) can transiently modulate corticospinal excitability either up or down following the rTMS train. This permits the opportunity to perform "virtual lesion" experiments before and after rTMS trains when the application of TMS itself may interfere with a behavioral task of interest.

1.2 Risks associated with the TMS Lab

In spite of the ability for TMS to interact directly with the brain in awake human subjects, it is a non-invasive technique and, when operated under appropriate guidelines, free of serious side-effects. Risks include:

- High-voltage fields. All TMS equipment operates at high-voltage and requires extreme precaution when connecting TMS coils, turning on or off TMS machines or booster modules, or triggering TM.

- Electromagnetic field generated by the coil. When discharged, the magnetic field generated by the coil will interfere with neighboring electrically conductive or magnetic objects (including scalp muscle, brain, credit cards, and electrical equipment).

- For subjects, electromagnetic stimulation over the head affects scalp muscles, nearby scalp/facial nerves, and brain) which can produce scalp or facial muscle twitches or eye blinking, headaches, and hearing threshold shifts. TMS induced seizures have been reported with repetitive magnetic stimulation (rTMS).

1.3 Reduction of risks

For electromagnetic risks, be sure all connections to and from the TMS coil and equipment are securely fastened before operating equipment. Avoid touching exposed wiring or exposed terminals on equipment or cabinets. Be aware of the status of the TMS machine and coil at all times and guard against the accidental discharge of the coil when near electromagnetic devices (including the TMS machine itself).

Safety certification by Dr Wu and Dr Iacoboni is required before operating TMS Lab equipment. This certification procedure requires review of this manual, didactic practice with TMS equipment, and review of safety procedures for handling risks described above. In particular, review of human subject risks including being capable of being a first-responder in the event of a seizure is mandatory.

All adverse events must be reported to Dr Allan Wu and Dr Marco Iacoboni as soon as possible and no more than 24 hours after the incident. Contact information follows in section 1.4. When appropriate, such events must also be reported to the UCLA IRB.

A copy of this manual is always available in the TMS Laboratory. Please notify Allan Wu for any changes or material that is out of date.

1.4 Contact information

- *Medical emergency on call*: 911 (Not 8-911). See section 3.2.1 (emergency procedures) for details
  State emergency and location
  - Ahmanson-Lovelace Brain Mapping Center,
    660 Charles E Young Drive South, Room 159
    310-206-3576
  - Have the front door opened to allow access.

- *Pager* . Call 231, enter the pager ID for one of the neurologists (Dr. Wu) listed below, enter the call back number (63576) and hang up.
  Alternatively, you can go to *www.mednet.ucla.edu*, click the 'Paging' button, enter the pager ID, enter a brief text message indicating the problem, and enter the call back number, then click 'Page' button. The pager message will be sent.

- *Brain Mapping contacts:*
  - Allan Wu, MD pager #24225, (email: allanwu@mednet.ucla.edu)
    310-206-6496 (office);
    310-825-2188 (Reed lab);
    310-206-9799 (Movement Disorders Division)
  - Marco Iacoboni (310) 206-3992 (office)

  - TMS Lab phone number: 310-206-3576
  - Leona Mattoni (Brain Mapping Ctr) 310-825-2699
  - Roger Woods, MD 310-794-4057
  - John Mazziotta, MD, PhD 310-825-2699
  - Choi Deblieck: 310-794-4964
  - Janice (Chien-ho) Lin: 310-825-2188

2 Regulatory, Ethical, Safety issues with TMS

2.1 TMS parameters: location, intensity, frequency, duration

Four important parameters in applying TMS are the location of stimulation, intensity of stimulation, the frequency of stimulation, and the duration of a train of stimulus pulses.

Location: In most studies with TMS, the location of the coil is described relative to either landmarks on the surface of the head or the site at which motor evoked potentials were produced (i.e., the motor cortex). Unfortunately, differences in the overall size and gross cortical anatomy of the brain renders the absolute distances between cortical sites and/or scalp landmarks two sites variable across individuals. We use Brainsight, a frameless stereotaxy system, in the TMS Lab to co-register the location of the TMS coil relative to a structural MRI of an individual subject in real-time to assist with determination of TMS location.

Different TMS coils will affect the location/size/distribution of brain stimulation. Round coils provide more powerful stimulation across a wide circular region of brain (14 cm in diameter) and can be useful when stimulating bilateral motor cortex or lower extremity motor cortex (located within the interhemispheric fissure). Figure-8-shaped coils provide current that flows in the opposite directions through two adjacent coils. The effects of the currents are additive, so that stimulation intensity is doubled in the center of the coil. Figure-8 coils are preferred for relatively focal stimulation.

Intensity: The intensity of stimulation can be expressed as either a percentage of maximum stimulator output (MSO) or is usually individualized in terms of the individual's "motor threshold". Motor threshold (MT) is commonly defined as the minimum intensity of stimulation needed to evoke a motor evoked potential (MEP) in a target hand muscle after single pulse TMS over the motor cortex. TMS intensity is then expressed as a percentage of the subject's motor threshold (e.g. 90%, 100%, 110% MT).

Frequency: The frequency (or speed) of stimulation is expressed as the number of pulses delivered per second (Hz). This is the key parameter which determines the form of TMS (see 2.2) and is important in assessing safety of TMS.

Duration: In repetitive TMS (rTMS), stimulation is delivered in a train of pulses for a given duration. High frequency stimulation over a long durations (and higher intensities) may occasionally trigger a seizure in individuals from susceptible populations or, rarely, in an healthy control subjects. For this reason, safety guidelines were established specifying the safe duration of stimulus trains at different intensities and frequencies of stimulation (Wassermann 1998); see Appendix 5.2).

For repetitive trains of stimuli, an intertrain interval is applied to allow the brain to recover before resuming another train of rTMS for longer stimulation durations (5 sec in our lab, see Appendix 5.2).

2.2 Forms of TMS

The 3 basic forms of TMS (there are others) are based upon frequency of stimulation (International Consensus Conference of Safety of TMS, June 1996, Bethesda, MD; adopted & published by the International Federation of Clinical Neurophysiology (Wassermann 1998).

- Single Pulse TMS: a single stimulus applied at random intervals every 5 to 10 s
- Paired Pulse TMS: a subthreshold stimulus (conditioning stimulus) followed by a suprathreshold stimulus (test stimulus) after an interstimulus interval of 1-20 ms delivered through a single stimulation coil to a single brain area.
- Repetitive TMS (rTMS): trains of repeated TMS stimuli delivered through a single stimulation coil to a single brain area
  - Slow (low frequency) rTMS ≤ 1 Hz
  - Fast (high frequency) rTMS > 1 Hz

2.3 FDA device regulations and terminology

Magnetic stimulator devices are approved by the Food and Drug Administration (FDA) for peripheral nerve stimulation. They may be classified as Investigational Devices with greater than minimal risk when used for cortical (brain) stimulation. FDA delegates local IRBs the authority to decide whether specific TMS protocols require Investigational Device Exemption (IDE) from FDA.

In June 1996, at the International Safety Conference on Transcranial Magnetic Stimulation held at the National Institutes of Health, there was consensus that the cumulative experience over the previous 15+ years supported the safety of single-pulse TMS and low-frequency rTMS (i.e. ≤ 1 Hz) (Wassermann 1998). Following that conference, the FDA expressed the opinion that single-pulse TMS and slow rTMS are non-significant risk procedures, even when applied to subjects at risk for seizure, or to those with underlying brain pathology as stroke.

Single-pulse, paired-pulse, and low-frequency (≤ 1 Hz) rTMS are generally considered low risk applications and no IDE (Investigational Device Exemption) is usually required. In general, use of repetitive TMS devices at low-frequency rates (≤ 1 Hz) in cortical stimulation do not require an IDE. An Investigational Device Exemption (IDE) number may be required for studies involving cortical stimulation at rates greater than 1 Hz.

2.4 Safety overview of TMS

Since 1985, thousands of patients and normal subjects have received single-pulse and low-frequency rTMS without adverse effects (Weber and Eisen 2002).

There is consensus that single- and paired-pulse TMS are considered safe in most subjects.

An additional risk consideration in repetitive TMS (rTMS) is the potential for inducing a seizure. Seizures from rTMS are rare (less than 10 in the literature) and occur with high-frequency, mostly suprathreshold intensity, rTMS (Wassermann 1998). A consensus statement exists for repetitive TMS (Appendix 5.1).

2.5 Ethical Considerations

2.5.1 The Belmont ethical principles

Three ethical principles apply to all research on human subjects (Belmont Report, 1979).

- *The principle of respect for persons*. This principle implies that the choice of a given volunteer to participate in TMS research must be a free and voluntary one. This choice must be based on the provision of all relevant information including disclosures of all significant risks, possible benefits, and alternatives to participation.

- *The principle of beneficience*: This principle embodies maximizing benefit and minimizing harm. There must be a favorable balance of benefit to risk ratio in all research activities. These are can be classified as follows.

  - *Class I*. Direct clinical benefit is expected (i.e. rTMS treatment of depression). Level of acceptable risks (i.e. seizure) are moderate
  - *Class II*. Potential, but unproven benefit (i.e. rTMS treatment of Parkinson's disease). Level of acceptable risk is low.
  - *Class III*. No expected benefit. Will advance general understanding. Requires stringent safety guidelines.

  Note that this principle means that all TMS studies on normal subjects are done with a higher ethical guideline than studies on patients with neurological disorders. Given that there may be a potential for benefit to those with a neurological disorders provides a measure of benefit in the risk-benefit ratio that does not exist in neurologically normal subjects.

- *The principle of justice*. This principle states that the risks of TMS research should be equally distributed through society and should avoid subject populations rendered vulnerable by economic, social or physical conditions and who are likely to bear only the burdens of research and not its benefits (e.g., children, prisoners, pregnant women, mentally disabled people or economically and educationally disadvantaged individuals).

2.5.2 Recommended ethical guidelines for TMS studies

- Use the lowest risk form of TMS suitable for the research,
- Adhere to well-developed exclusion criteria,
- Ensure full and informed consent on the part of research subjects,
- Pay careful attention to immediate risks of research (e.g., researchers must be well-trained and experienced and research should only take place in clinical settings equipped for seizure and other side-effect management),

- Ensure continuous monitoring of subjects,
- Develop evidence-based safety limits for the conduct of TMS research,
- Ensure objective assessment of patient condition following TMS by competent clinicians.

2.6 Contraindications for TMS (consider for exclusion criteria in TMS protocols)

In general, although it has been stated that there are no absolute contraindications to TMS, in practice, strong relative contraindications are usually incorporated in all TMS protocols unless specific reasons exist to permit them to be included.

- Conditions that are or may be affected by the magnetic field
  - Metal anywhere in the head, excluding the mouth
  - Any metallic hardware near coil
  - Pacemakers
  - Implantable medical pumps
  - Ventriculo-peritoneal shunts
  - Electrodes inside the heart (intracardiac lines)

- Conditions that will or may increase the risk of seizure
  - History of seizures or history of epilepsy in a first degree relative
  - Medicines which reduce seizure threshold (specifically, tricyclic antidepressants and typical antipsychotics/neuroleptics)[1]
  - History of serious head trauma
  - History of substance abuse
  - Stroke or brain tumor

- Conditions that will increase the risk to patient's health in the event of a seizure
  - Serious heart disease
  - Subjects who are pregnant (but note that case studies have not shown complications)
  - After recent brain surgery
    Increased intracranial pressure

2.7 TMS adverse events and reductions of risk

The routine adverse events that are discussed include headache/neck aches, hearing threshold shifts, fainting, burns from electrodes/metal on scalp, inadvertent seizure (for rTMS protocols), and the potential for unanticipated side-effects.

All adverse events must be reported immediately to a TMS staff member immediately. The designated TMS physician for each TMS session will be available to assist with evaluating any adverse events.

2.7.1 Headaches, neck aches

About 5% of subjects undergoing TMS experience headaches, neck stiffness or neck pain. This is attributed to local stimulation of muscles and nerves near the stimulating coil, a tapping of the scalp by the coil during discharge, and wearing a tight-fitting swim cap. Other stimulation-related effects include teeth aches, facial twitches, odd taste in mouth, and discomfort from blinking and twitches of scalp muscles.

[1] Typical antipsychotics: haloperidol (Haldol), fluphenazine (Prolixin), chlorpromazine (Thorazine), pimozide (Orap), clozapine, etc; Tricyclic antidepressants: amitriptyline (Elavil), nortriptyline (Pamelor), desipramine, imipramine, doxepin, etc.

Efforts to minimize TMS intensity and to avoid sensitive areas of scalp muscles or nerves can be done. However, these symptoms may be cause to discontinue the protocol. All symptoms resolve after cessation of the TMS protocol. The headaches are no different than usual headaches and respond to ibuprofen or acetaminophen which is available in the laboratory.

2.7.2 Fainting.

In subjects with history of fainting, TMS may induce fainting or feelings of lightheadedness or dizziness.

If symptoms of dizziness, lightheadedness, or feeling faint occur, the TMS protocol should be stopped. The subject will be allowed to lay down or put their head down to prevent fainting. If subjects faint, they must not be allowed to leave the laboratory until fully recovered.

2.7.3 Hearing threshold shifts

TMS produces a loud clicking sound when a current is passed through the stimulation coil. This loud click can result in temporary ringing in the ear and subclinical auditory threshold shifts.

In order to prevent transient hearing threshold shifts due to TMS, subjects and investigators will be offered earplugs during TMS. Repetitive TMS or TMS applied near the ear may be at higher risk and may mandate use of earplugs. Investigators may elect to use earplugs as well.

2.7.4 Burns from scalp electrodes.

The mechanism is through the direct induction of eddy currents within circular EEG electrodes or wires with loops with increases in temperature.

Use special scalp electrodes specifically approved for use with TMS and an appropriate safety-monitoring plan. Avoid direct stimulation of electrodes and do not place electrodes directly underneath the TMS coil.

2.7.5 Inadvertent seizure.

Repetitive TMS can induce a seizure even in the absence of a pre-existing brain lesion or epilepsy. This complication is rare with less than 10 cases of rTMS-induced seizures in subjects without risk factors for epilepsy reported despite thousands of subjects having been studied worldwide for more than 15 years. Our overall estimate is that seizure risk is < 1:1000 (0.1%) (see section 2.7.5.2, Review of seizures reported with rTMS).

None of the subjects who had TMS-induced seizures have suffered lasting physical sequelae. Electroencephalographic and neuropsychological measures return to normal within 1-2 days. Furthermore, there is no evidence to suggest that a TMS induced seizure makes another seizure more likely in an otherwise healthy individual.

This risk is considered applicable to repetitive TMS, and in particular, high-frequency (> 5 Hz) rTMS. Longer durations, higher-intensity stimulation increase this risk. Seizures are generally not considered a significant risk in single-, paired-pulse TMS or low-frequency (<= 1 Hz) rTMS.

The mechanism of seizure induction is likely repeated brain stimulation at high-frequency which gradually overcomes natural surround inhibition allowing a spread of excitation. These can be observed with surface EMG recordings of muscles while the motor cortex is being stimulated with TMS. With high-frequency stimulation, afterdischarges ("mini-seizures") can be seen (these are transient motor evoked potentials seen in a target muscle that persist after rTMS is stopped. Also, muscles adjacent to the target muscle may begin to twitch. Both of these events are considered precursors to this loss of surround inhibition and indicate that the TMS protocol must be stopped and the safety of the subject checked.

2.7.5.1 Protections against seizure induction

- Investigators using any form of repetitive TMS must be aware of the International Society for Transcranial Magnetic Stimulation (ISTS) statement on managing risks with repetitive TMS (Appendix 5.1).

- Screening and enrollment procedures will exclude subjects for whom rTMS is contraindicated or who are at increased risk of seizure or for whom the potential consequences of a seizure are increased. See section 2.6 for the general list of such contraindications.

- The informed consent process will include disclosure of the potential risk of seizures with rTMS and should mention possible medical and social consequences. There is no evidence that an rTMS induced seizure increases the risk of having a second seizure in an otherwise healthy individual.

- Use the lowest risk TMS method in each study. Plan the lowest intensity, frequency and total number of TMS pulses necessary for each study. Follow current safety guidelines regarding rTMS parameters. Table 1 presents the published maximum safe duration (sec) for single trains of rTMS (Wassermann 1998). However, existing UCLA IRB-approved parameters must be followed are more conservative by 25% than published in Table 1 (see Table 2, also Appendix A.2, section 5.2).

  For repetitive trains of stimuli, the minimum intertrain interval will be 5 sec, a duration identified as safe in studies involving up to 10 trains of stimulation (Chen, 1997). There will be at least a five-minute break between stimulation at each location.

Table 1: Maximum safe duration (sec) of single trains of rTMS (Wassermann 1998)

frequency	Intensity (% of MEP threshold)					
(Hz)	100	110	120	130	140	150
1	>1800	>1800	360	>50	>50	>50
5	>10	>10	>10	>10	7.6	5.2
10	>5	>5	4.2	2.9	1.3	0.8
20	2.05	1.6	1.0	0.55	0.35	0.25
25	1.28	0.84	0.4	0.24	0.2	0.24

Table 2: Maximum duration (sec) of single trains of rTMS in UCLA TMS Lab

frequency	Intensity (% of MEP threshold)					
(Hz)	100	110	120	130	140	150
1	270	270	180	37.5	37.5	37.5
5	7.5	7.5	7.5	7.5	5.7	3.9
10	3.8	3.8	3.2	2.2	1.0	0.6
20	1.5	1.2	0.8	0.4	0.3	0.2

Minimum intertrain duration 5 seconds

- Continuous EMG and visual monitoring will be conducted during application of rTMS to detect any spread of motor evoked potentials (MEP's), EMG after-discharges, or unintended muscle twitches that may represent early reduced inhibition that could herald the onset of a seizure (Pascual-Leone, Houser et al. 1993). The investigator will terminate the study at the first sign of spread of excitation outside the area of stimulation.

- All investigators certified to operate the TMS Lab equipment independently must be trained as a "first responder" to possible complications such as a seizure. The Brain Mapping Center is a 911 building for medical emergencies. The TMS Lab also has access to immediate life-support equipment (airway protection, bag & mask, IV kit and antiepileptic drugs).

- Both medical and psychological support will be provided to patients and normal subjects who have TMS-induced seizures. Subjects who experience a TMS-induced seizure will be informed of the fact that an induced seizure does not place them at greater risk for further seizures than before. The seizure event does become documented in the subject's medical record. Documentary support of a healthy subject's claim that a provoked seizure carries no adverse prognosis will be provided in cases where the report of the seizure in the subject's medical record could be misinterpreted or deliberately used as a pretext for the denial of employment or medical insurance. Prospective subjects will be informed of this potential consequence.

- Following rTMS sessions, as dictated by the type and location of rTMS, subjects should be asked about and examined for any potential adverse events. All adverse events must be reported to Dr Allan Wu and Dr Marco Iacoboni as soon as possible and no more than 24 hours after the incident. Contact information is listed in section 1.4. When appropriate, such events must also be reported to the UCLA IRB.

2.7.5.2 Review of seizures reported with rTMS

As of 1998, seven seizures had been produced by high-frequency rTMS (Wassermann 1998). One was in a patient with temporal lobe epilepsy, one in a patient with depression, and five in normal control subjects. For the purposes of estimating the probability of a TMS induced seizure, we refer to the numbers given by Wassermann (Wassermann 1998) of seizures that occurred at the NINDS: 5 seizures in 250 patients or control subjects, many of whom were stimulated on multiple occasions. This suggests a seizure probability of 1.6%. However, one subject was a patient with epilepsy. Of the four seizures in control subjects, one occurred before safety guidelines were developed, during rTMS at a long duration. Two more occurred during stimulation at frequencies and intensities near the edges of the parameters described as safe. The fourth seizure occurred when a short intertrain interval was used. These events prompted revision of the safety guidelines to reduce the allowable durations by 25% and to impose intertrain intervals that would minimize the possibility of a cumulative increase in cortical excitability (Chen, Gerloff et al. 1997). In conclusion, we assume that the probability of inducing a seizure in a control subject using these revised parameters to be far less than 1.6%. The relative risk of seizures caused by rTMS is thought to be less than 1 in 1000, and probably even less since many thousands of subjects and patients have been studied with TMS and rTMS in the past 5 years without any seizures being reported. An additional seizure event has been reported in a normal volunteer who received 20 Hz rTMS at 110% motor threshold for 2 seconds (Bernabeu, Orient et al. 2004). Since these parameters exceed the published recommendations for safety (Table 1, section 5.2), they emphasize their validity.

2.7.6 Potential for unforeseeable adverse events.

Even though rTMS has been used in several worldwide studies since 1985, it remains an experimental technique and there is a potential for unforeseeable complications. All subjects must be informed of this point.

2.8 Theoretical risks for transcranial magnetic stimulation

Theoretical risks for TMS influences have been raised and, in general, no evidence has been found in TMS safety studies.

These include neuropsychological and mood effects for which only transient rTMS effects have been found on specific task-related studies. Formal safety studies of cognitive function have not reported adverse or sustained changes in cognitive function after rTMS.

Kindling. This is the phenomena where if you stimulate at high frequencies, the brain becomes epileptogenic. This has not been documented in humans. Kindling is unlikely to apply in rTMS studies at current frequencies because it requires repeated applications of stimulation at high frequencies over long durations (generally 60 Hz) in mesial temporal lobe models with long pulse durations of 1 ms. In contrast, neocortex (where TMS is applied) is resistant to kindling and current rTMS parameters are much slower and briefer in

nature. Also, subjects who have received direct cortical stimulation or frequent ECT treatments have not shown kindling.

Other theoretical issues that have been raised include effects on hormonies, immunological effects, histotoxicity and long-term effects of magnetic fields. In general, no evidence for these effects after TMS or rTMS have been identified.

3 Safety guidelines for investigators

3.1 General protections against risk in our laboratory

One person certified to perform independent TMS in our laboratory must be present at every TMS session. In addition, a designated M.D. physician should be in the building when TMS is performed. In most cases, this will be either Dr. Wu or Dr. Iacoboni. The designated safety and M.D. individual responsible for each TMS session should be listed on the data collection sheets for each TMS session.

Based on the ISTS statement on managing risk of repetitive TMS (Appendix 5.1) (Belmaker, Fitzgerald et al. 2003), those who administer rTMS should be trained as "first responders" in order to render appropriate care in the event of seizure. rTMS should be performed in a medical setting with appropriate emergency facilities to manage seizures and their consequences.

In practice, this means that an investigator named on the IRB approved consent form must be on location during all TMS studies and that a neurologist is on location (or in the building) during all rTMS sessions. All subjects must be monitored continuously during the TMS session. The TMS Lab contains basic life-support equipment (oxygen, suction, blood pressure monitor and CPR equipment) and anti-seizure drugs.

Inclusion/exclusion criteria and enrollment procedures as advised by the IRB protocol are always strictly followed. For any medical questions about eligibility, please contact Dr Allan Wu or Dr Marco Iacoboni.

Under no circumstances will coercion be applied to obtain informed consent, and subjects will be thanked for their participation in the study regardless of whether they choose to continue in the research study. Volunteer subjects must know that they have the option to withdraw from TMS studies at any time without consequence. The investigators should terminate a participant from this study if they suffer a severe adverse event, do not follow study requirements, or it seems that continued participation will put the person at a greater risk than indicated. Subjects should be compensated at an hourly rate for the amount of time they participated, even if they later elect to withdraw from the study.

In addition to the informed consent form, a HIPAA "Authorization for Release of Personal Health Information and Use of Personally Unidentified Study Data for Research," standard UCLA document must also be signed by each subject. This authorization allows investigators to collect personal health information (PHI) from the subject for the purposes of screening the prospective subject for the research study (ascertaining inclusion/exclusion criteria) and for evaluation in the event of an adverse event. If the subject decides, at any time during enrollment, not to participate, their PHI will be discarded immediately.

3.1.1 TMS Lab Safety Equipment

The upper right cabinet on the south wall in the TMS Lab contains airway protection devices, ambu bag (for supporting respiration), gloves, gauze, IV access equipment, and saline for infusion. The inventory list of safety equipment and supplies is also kept in this cabinet. See Trent or Leona if supplies or equipment needs updating (some supplies have expiration dates). This cabinet is kept locked. The key (with the matching orange sticker) is kept in the back of the upper drawer of the small wheeled file cabinet where routine TMS supplies are kept.

Emergency medications for the treatment of a seizure (anticonvulsants) are kept in a locked box stored in the refrigerator upstairs on the 2nd floor. The key to the locked box is also labeled as and kept in the back of the upper drawer of the small TMS Lab file cabinet.

A fully equipped "crash cart" with further emergency medical equipment including oxygen tank is available in the vicinity of the lab (currently the cart in the fMRI room).

3.2 Medical Emergencies (Serious Adverse Events)

A medical emergency can be any situation where an unstable person needs medical support. The following guidelines are intended to assist people in responding to medical emergencies in the TMS Lab.

The physician/neurologist assigned to the TMS session will be notified immediately upon any adverse events and be available to assist in determination of a medical emergency

However, it is entirely appropriate to call a medical emergency (911) for any situation that appears unclear to the observer or responder. When in doubt, call for help, even if it turns out to be unnecessary.

The majority of seizures are not considered medical emergencies and do not require the additional medical help outlined here. However, if a person has prolonged seizure (lasting longer than 5 minutes OR repeated seizures without recovery between events OR is at risk for injuring oneself, a medical emergency should be called.

3.2.1 Procedures for Responding to Medical Emergencies

One researcher should remain with the victim at all times.

First responder

- Call 911
- State medical emergency.
- State location.
  Ahmanson Lovelace Brain Mapping Center
  660 Charles E. Young Drive South, Room 159
  Tel: 206-3576 (or ext 6-3576)
- Stay with subject. Keep away from injury.

Second responder

- Open and bring medical supplies from TMS Lab cabinet (oral airways, gloves) to first responder
- Call for BMC neurologist or TMS Lab Staff
- Bring medical supplies from refrigerator to TMS Lab
- Bring the crash cart (located next doors to the fMRI acquisition room)
- Clear room and hallways for access and transport.
- Go to BMC entrance to open door and direct response team to the emergency site.

If victim is an inpatient, researcher should have medical records available. If the victim is an outpatient, have name and number of the referring physician or other health care providers available to the medical emergency team.

3.2.2 Guidelines for Care of a Person During a Seizure

A seizure can be a complication of TMS (especially rTMS) and can occur suddenly and unpredictably. There are many different types of seizures, most of which do not require any medical intervention. We classify and recognize seizures on the basis of their onset:

- Simple partial seizure – seizure that affects a focal part of the brain and does not affect consciousness
- Complex partial seizure – seizure that affects a focal part of the brain but does affect consciousness (may be blank stare, confusion, or loss of consciousness)
- Generalized seizure – seizure that affects the whole cortex bilaterally. This often presents as a generalized convulsion with loss of consciousness.
- Partial secondarily generalized seizure – probably the most common type to be seen in TMS studies. A seizure that begins as a partial (focal onset) seizure then rapidly spreads to become generalized with loss of consciousness.

Most seizures (and all TMS induced seizures that I am aware of) have been self-limited. **Seizures become a medical emergency if they are prolonged (> 5 minutes), they occur repeatedly without recovery in between episodes, or subjects are at risk for injury from the seizure.**

Following a seizure, many subjects are often lethargic, confused, and may not recognize the situation (post-ictal state). Subjects should not be left alone until and should not be allowed to leave until fully recovered.

Proper first aid for seizures includes maintaining safety of the person during and after the seizure, and observing and recording the events. The following guidelines are intended to aid researchers doing TMS in responding to people during a seizure.

Interventions for all seizure types:

- Remain calm and reassure person and observers of safety during and after a seizure.
- Assist person to safe position and location.
  - If convulsion is generalized or consciousness is lost, lay the person down safely and turn them on their side (allows potential vomiting not be aspirated)
  - If consciousness is not lost, but the person appears confused (partial complex seizure), allow person to walk in confined area if safe. Call for help if person is wandering alone, running, or appears unsafe in a closed space. Observe but do not approach person who appears angry or combative. If responder feels unsafe, call security for assistance.
- Remove harmful objects from surrounding area.
- Loosen restrictive objects around the neck, head, or person.
- Do not restrain movements unless it is necessary to keep the person safe.
- Do NOT place anything in the person's mouth
- Keep the person on side until they are fully awake.
- After the seizure, stay with the person until they awaken and are safe to be left alone.
- Do not move the person if there is a suspicion of injury.

- Observe and record what occurred during the seizure, how long it lasted, and if any injury occurred.

- If person is having breathing difficulties, turn the person on their side and call for help or a medical emergency. Suction if available can be used to clear the airway. If respiratory distress continues, call the medical emergency, consider rescue breathing if respiration has stopped (for person trained in Basic Life Support), and bring the crash cart to the area.
- Oral airways can be used to keep an open airway, but probably best used when the seizure event is over.

- **Call a <u>Medical Emergency if a person does not awaken after the seizure, the seizure lasts loner than 5 minutes, if the person has a second seizure without regaining consciousness between seizures, or if the person appears to be injured.</u>**

- If this is a person's first seizure, further medical evaluation is warranted and the person should be sent to the Emergency Unit.
- If a subject experiences a seizure, follow up has to include serial EEGs and formal neurological evaluation. The subject cannot leave UCLA alone. The family/guardian has to be contacted, and overnight admission may be indicated.

4 TMS Laboratory General Policies

4.1 TMS Lab Certification

There are 4 steps for certification.

First, we must have a current UCLA Protection of Human Subjects certification and UCLA HIPAA certification on file.

Second, this TMS Lab Manual of Policies and Procedures must be reviewed and discussed at a TMS didactic session(s). A written-post test must be passed.

TMS didactic sessions are organized periodically by Dr Wu and are usually scheduled twice a month. Sessions include a review of TMS safety, ethics, and IRB issues. Sessions will also include an in-lab demonstration of safety issues. The written post-test covers material in the TMS Lab Manual and this didactic session.

Third, investigators are required to observe, practice, setup, conduct TMS sessions (including TMS setups and devices that are needed for a particular protocol) at least 5 times. If an investigator is using a novel protocol or setup (e.g. Brainsight, repetitive TMS, paired-pulse TMS), that particular protocol or setup must be done at least 3 times (which count toward the overall required 5 practice TMS sessions). These will always be done under supervision and provide the time needed to practice running a TMS session. It is the responsibility of each investigator to document each training session.

Investigators then must conduct a dry run of either a standard TMS session (motor threshold, hot spot determination and a standard set of TMS excitability protocols) or a planned TMS session (specific to the investigator's protocol) in the presence of (and without any help from) the TMS staff and feel confident (once).

Fourth, investigators must pass both a practical TMS safety and a practical procedural test in the laboratory. This practical TMS safety test is conducted by Dr Wu and includes what-if scenarios. The TMS protocol will be tailored to the individual protocol being conducted.

Administratively, operation of the laboratory independently also requires a review of the IRB HS-1 and informed consent documents being used and the data collection sheet to ensure uniformity of data acquired by TMS personnel. These IRB documents must be registered in the TMS Database to ensure accurate study and subject session tracking.

Each step of certification is signed off by Dr Wu with final approval with Dr Iacoboni.

4.2 Laboratory policies on collaborative projects

To implement or discuss a TMS study using the TMS Lab, contact either Dr Wu or Dr Iacoboni. All projects that use TMS Lab resources must involve both Dr Wu and Dr Iacoboni in order to coordinate administrative and practical issues with other lab activities.

TMS Lab projects must be registered with the Ahmanson-Lovelace Brain Mapping Center (ALBMC) Database (http://research.bmap.ucla.edu/). This Database tracks information about all projects that take place within the Brain Mapping Center. This is the responsibility of the investigator who will be conducting the study.

The fee for TMS Lab time is $350/hr (as of Dec 2004). Additional fees may apply if Brainsight (frameless stereotaxy) or data analysis assistance is required. Individual rates can be discussed with the Director of the TMS Lab. Pilot TMS Lab time can be provided on an individual basis. Grant applications that propose the use of the TMS Lab should budget for both TMS Lab time and subject payment.

In accordance to standard authorship publication guidelines (International Committee of Medical Journal Editors. http://www.icmje.org, updated October 2005) all studies that involve Dr Wu or Dr Iacoboni must acknowledge their contributions to TMS study design, conduct, training, implementation, data analysis with appropriate authorship. As most TMS Lab projects will involve TMS study design with Dr Iacoboni and Dr Wu, acknowledgement of Dr Wu and Dr Iacoboni's contributions should be routinely discussed in advance during the initiation of a collaborative TMS Lab project.

4.3 Logging TMS sessions

All TMS sessions **must be reported into a TMS Laboratory database** to document the IRB used and to track laboratory use. The TMS Database tracks subject demographic information, type of TMS (mode, target muscle, frequency, duration), when and which IRB informed consent was signed, and whether there were any adverse events. This information must be recorded so that the TMS Lab Director and Sponsors can prepare reports to the FDA and the IRB. Non-compliance with this requirement could lead to **shutting down the lab and federal investigations.**

All data (source documents) on forms collected from this subject, labeled with the subject's coded ID, will be placed in this folder. The guideline is that documents in this folder should be complete enough that the electronic data collected in the TMS Lab can be interpreted and re-analyzed if necessary. If data is needed for off-site analysis, copies of the source documents should be made and a copy must stay in the TMS Lab.

All files are kept in a locked cabinet within the TMS Lab, which is accessible only to authorized personnel.

4.4 Financial compensation or obligations of the subject

Financial compensation and obligations are specific to each IRB protocol. In general, subjects should not be expected to pay for participation in TMS research projects. Expenses related to patient transportation and conduct of the study are the responsibility of the investigators, not the TMS Lab.

As a guideline, the current TMS Lab supported normal subject IRB protocol compensates volunteer subjects at the rate of $25 per hour of time spent in the study plus parking expenses, where applicable. This amount is intended to compensate subjects for their time and is not considered to constitute undue coercion of the subject to participate in the research. Subject payments for individual studies are the responsibility and discretion of the principal investigator

5 Appendix A: Safety Addenda

5.1 ISTS Consensus statement on managing the risks of rTMS (2003)

The statement below was adopted by the International Society for Transcranial Magnetic Stimulation (ISTS) was published (Belmaker, Fitzgerald et al. 2003).

Repetitive transcranial magnetic stimulation (rTMS), defined as the administration of a series of magnetic stimuli to the brain for the purpose of altering brain function, is an experimental medical intervention. rTMS is currently used to probe various aspects of brain function in the context of research studies approved by local ethics committees. rTMS is also under investigation as a potential treatment for various neurological and psychiatric disorders. In light of the growing interest in using rTMS in a variety of experimental risks and potential benefits in patients, the informed consent process, setting of rTMS stimulation parameters, and monitoring of subjects during and after rTMS.

Those who administer rTMS should be trained as "first responders" in order to render appropriate care in the event of seizure. rTMS should be performed in a medical setting with appropriate emergency facilities to manage seizures and their consequences. Patients and research subjects should be continuously monitored during the administration of rTMS for signs of epileptic activity or other adverse effects by a trained individual, according to criteria established in the clinical or experimental protocol. This monitoring may include electrophysiological recording and/or visual inspection. During the informed consent process, patients and study participants should be informed of the risk of seizure and its possible medical and social consequences. The dosage of rTMS should generally be limited by published safety guidelines (e.g., Wassermann, Clin Neurophysiol, 1998;108:1 or any subsequent updates). If there is a compelling scientific or clinical reason to exceed such guidelines, the rationale for doing so should be considered carefully, documented and the patients or study participants should be informed that they may be at higher risk for seizure.

The long-term risks of rTMS are not known. However, the limited data available at this time (2002) from repeated application of high intensity, time-varying magnetic fields to humans, as in magnetic resonance imaging, do no suggest that they are significant.

The use of rTMS should comply with regulations put forward by local regulatory bodies, medical professional organizations, and medical licensing boards.

5.2 Maximum safe duration of single trains of rTMS

Table 1: Maximum safe duration (sec) of single trains of rTMS (Wassermann 1998)

frequency	Intensity (% of MEP threshold)					
(Hz)	100	110	120	130	140	150
1	>1800	>1800	360	>50	>50	>50
5	>10	>10	>10	>10	7.6	5.2
10	>5	>5	4.2	2.9	1.3	0.8
20	2.05	1.6	1.0	0.55	0.35	0.25
25	1.28	0.84	0.4	0.24	0.2	0.24

Table 2: Maximum duration (sec) of single trains of rTMS in UCLA TMS Lab

frequency	Intensity (% of MEP threshold)					
(Hz)	100	110	120	130	140	150
1	270	270	180	37.5	37.5	37.5
5	7.5	7.5	7.5	7.5	5.7	3.9
10	3.8	3.8	3.2	2.2	1.0	0.6
20	1.5	1.2	0.8	0.4	0.3	0.2

Minimum intertrain duration 5 seconds

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