Chapter 2

Transcranial Magnetic Stimulation (TMS) Safety Considerations and Recommendations

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Abstract

Ensuring patient and participant safety during transcranial magnetic stimulation (TMS) is of paramount importance. In this chapter, we begin by exploring a number of general safety concerns and the prevalence of reported side-effects in the TMS literature. Next, we outline contraindications and the recommended safety parameters for each of the major stimulation paradigms (including single and repetitive pulse patterns). Finally, we offer several practical tips to ensure TMS is delivered in the safest and most ethical manner.

Key words Transcranial magnetic stimulation, Safety, Ethics, Side-effects, Contraindications

1 Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive neuromodulatory and neurostimulatory technique increasingly utilized in clinics and research laboratories around the world. Exploiting the properties of electromagnetic induction, TMS can transiently or lastingly modulate cortical excitability via the application of localized, time-varying magnetic field pulses.

TMS has been used in a growing number of laboratories and clinics worldwide since 1984. Since then, a number of adverse events have been reported and thoroughly reviewed. In 1996 and 2008, consensus conferences were held to establish safe-use recommendations for both clinical and academic TMS. The resulting publications were, and remain today, the mainstay safety guidelines for TMS therapeutics and research [1, 2]. In this chapter, we will outline the major issues and recommendations set forth by the TMS Safety Consensus Group and we will also briefly examine TMS-related ethical concerns.

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2 Safety Concerns

Heating—Brain tissue heating caused by single-pulse TMS has been shown to be less than 0.1 °C [3]. To put this into context, estimated heating in the tissue surrounding deep brain stimulatory electrodes can reach as high as 0.8 °C [4]. When TMS is combined with electrode recording/imaging devices, induced eddy currents can cause heating of the electrode surface. The temperature increase depends on the shape, size, orientation, conductivity, and surrounding tissue properties of the electrode or implant as well as the TMS coil type, position, and stimulation parameters. As can be intuited, excessive electrode heating can lead to skin burns. To avoid this possible risk, it is recommended low-conductivity plastic electrodes be used whenever possible. Radial notching of electrodes and skull plates can also reduce heating by interrupting the eddy current path [2].

In addition to surface heating, implanted metallic devices—such as aneurysm clips or titanium skull plates—can theoretically generate temperature increases; although, recent evidence suggests these increases are negligible [5, 6]. Even so, when confronted with this scenario, it is recommended ex vivo heating be examined before commencing TMS.

Magnetization—As the magnetic field generated by TMS exerts an attractive/repellant force on all point charges (due to the Lorentz force: [7]), any implanted medical or therapeutic device sensitive to these fields may shift during treatment. Implanted devices, including aneurysm clips, implanted electrodes, and cochlear implants, could potentially suffer movement or demagnetization during stimulation. Again, whenever possible, it is recommended ex vivo effects be measured prior to TMS and that watches, jewelry, glasses, and other potentially conductive or magnetic objects worn on or close to the head be removed to prevent interactions with the magnetic field [2].

Induced Voltages—Any wires or electronic devices near the discharging TMS coil may suffer deleterious induced voltages. To avoid this, it is recommended all proximal wires be kept free of loops and bound in a twisted fashion [8]. In addition, induced voltages may occur in any implanted device containing circuitry, such as cochlear implants, deep brain stimulation (DBS) systems, and epidural electrode arrays for cortical stimulation. TMS can induce voltages in the electrode wires whether the implant is turned ON or OFF, and this can result in unintended brain stimulation at the electrode site. TMS pulses can also damage the internal circuitry of electronic implants near the coil, causing them to malfunction or permanently break down [9, 10]. The same recommendations outlined above apply here.

Implanted Electrodes—Based on several ex- and in vivo studies, TMS appears to be safe for patients with implanted stimulators as long as the "internal pulse generator" systems are not in close proximity to the TMS coil [8–11]. However, exact parameters for "close proximity" have not yet been determined (see [10, 12]). As such, TMS should *only* be applied in patients with implanted stimulators if there are sound medical justifications, with appropriate oversight by the Institutional Review Board or Ethic Committee. With regard to peripheral devices (vagal nerve stimulators, pacemakers, spinal cord stimulators, etc.), TMS is considered safe so long as coil discharge is not initiated near said device components [2, 8].

3 Side Effects (Table 1)

3.1 Common

Headache/Neck Pain—Headache and/or neck pain have been reported in an estimated 20–40 % of subjects undergoing TMS [13, 14]. This is the most commonly reported side effect of TMS (Table 1). The intensity of pain experienced varies from subject to subject, depending on individual susceptibility, coil design, stimulation location, intensity, and frequency. Reported head/neck pains are largely believed to occur due to muscle tension, generated either by the stimulation itself or the posture assumed during longer protocols [13]. A single dose of acetaminophen or aspirin may be recommended if pain persists beyond stimulation duration. No migraine attacks have been described following TMS, either in healthy controls or in migraine patients who underwent rTMS applications as treatment [15]. It has also been reported that the local painfulness of prefrontal rTMS declines over the first few days of daily treatment [16]. To take advantage of this finding, ramping algorithms (where investigators intentionally start below target dose and gradually increase over the first week of treatment) are used by some practitioners.

Acoustic Trauma—During discharge, the TMS coil produces a deceptively loud clicking noise (on the order of 120–140 dB: [17]). This exceeds the recommended safety levels for the auditory system (OSHA). Although seemingly innocuous, repeated exposure to this intense sound can lead to acoustic trauma. To date, several reports of a shift in auditory threshold following stimulation have occurred [18, 19] and one report of a permanent threshold shift following H-Coil stimulation without the use of ear protection has been published [20]. In order to prevent these potential adverse effects, it is recommended subjects and operators wear earplugs during the full duration of treatment. Furthermore, prompt referral for auditory assessment of individuals who complain of hearing loss, tinnitus, or aural fullness following completion of

Table 1
Possible side effects from TMS according to protocol

Side effect	Single-pulse	Paired-pulse	Low frequency rTMS	High frequency rTMS	Theta-burst
Transient headache/neck pain	Possible/rare	Not reported	20–40 %	20–40 %	Possible
Transient hearing change	Possible	Not reported	Possible	Possible	Not reported
Seizure induction	Rare	Not reported	Rare	<1 % in healthy subjects	1 reported
Syncope	Possible as epiphenomenon	Possible as epiphenomenon	Possible as epiphenomenon	Possible as epiphenomenon	Not reported
Transient hypomania	No	No	Rare	Possible (following left PFC stimulation)	Not reported
Transient cognitive changes	Not reported	Not reported	Rare/negligible	Rare/negligible	Transient WM impairment reported
Induced current in electrical circuits	Theoretically possible	Theoretically possible	Theoretically possible	Theoretically possible	Theoretically possible

TMS is advised. Patients with known preexisting noise-induced hearing loss or concurrent treatment with ototoxic medications (Aminoglycosides, Cisplatin) should only receive TMS in cases of a favorable risk/benefit ratio, as when rTMS is used for the treatment of tinnitus [2].

3.2 Rare

Seizure—The induction of seizure, although exceedingly rare, is of major concern when utilizing TMS. Seizures can be induced by rTMS when pulses are applied with relatively high-frequencies and short interval periods between trains of stimulation. rTMS can theoretically induce seizures during two different periods of stimulation: (a) during or immediately after rTMS trains and (b) post-stimulation due to the modulation of cortical excitability (i.e., kindling effect: [21]). Although the first has been seen, there is no evidence that the latter has ever occurred. From the several thousands of TMS studies reported to date, a total of 16 seizures had been reported through 2008 [2]. Since then, four reports of seizures have been reported [22–25]. Based on this data, the reported risk of seizure stands conservatively at 1 in 1,000 applications. It is important a plan be established prior to treatment to deal with any induced seizure. In the case of a seizure, treatment should be ceased immediately and the subject should be treated as any other patient with a witnessed seizure.

Syncope/Fainting—Syncope during TMS can occur for several reasons in addition to the stimulation: anxiety, physical discomfort, psychological discomfort, etc. Syncope has been reported less frequently than seizure; however, the true number of occurrences is not known. It is recommended all subjects be monitored closely for any signs of syncope (dizziness, light-headedness, faint feelings). In the event of syncope, stimulation should be ceased immediately, assistance offered, and a full neurological evaluation undertaken.

Mood—Acute mania emergence during rTMS over the left prefrontal cortex in patients with uni- and bipolar depression has been reported. However, the prevalence of this occurrence (13 reports in 53 RCTs) appears to be below natural switch rates of bipolar patients taking mood stabilizers (0.84 % with rTMS vs. 2.3–3.45 % with mood stabilizers: [26]). In addition, transient psychotic symptoms, anxiety, insomnia, suicidal ideation, and extreme agitation have all been reported following rTMS in psychiatric patient populations, but it remains to be established whether these symptoms occur at a higher rate than during the natural course of each disease state [27, 28]. Although psychotic symptoms and suicidal ideation have never been reported in healthy subjects, it is important to inform all potential subjects of these possible acute side effects. Should acute mood shifts occur, cease stimulation immediately, monitor the subject closely until normal function returns, and administer a full neurological exam.

Dental Pain—Although rare, several instances of induced dental pain during TMS have been reported [2]. If this occurs, it will happen during stimulation and may be the sign of a tooth cavity or loose cap/filling. If dental pain is reported, cease stimulation immediately and encourage the subject to seek a dental evaluation.

4 Contraindications

Decisions regarding TMS treatment should be made on a case-by-case basis. Contraindication guidelines should be followed closely and deviations made only under extremely compelling medical conditions.

- *Implanted Cranial Electrodes*—As discussed above, TMS may cause heating or induced voltages within ferro-magnetic electrodes or medical devices implanted in the cranium. The presence of such metallic hardware in close contact to the discharging coil is therefore an absolute contraindication to TMS/rTMS. Accordingly, it is recommended TMS treatment be avoided in these cases.
- *Cochlear Implants*—Again, as TMS can cause heating and induced voltages within the electronics of cochlear implants, it is recommended TMS treatment be avoided under this circumstance.
- *Personal History of Syncope or Seizure*—Subjects with a history of syncope/seizure may be at higher risk for seizure induction. Currently, TMS is under investigation for seizure treatment. Accordingly, under circumstances of treatment, seizure history may not be considered a contraindication. However, under "non-treatment" circumstances, it is recommended treatment be avoided.
- *Patients with epilepsy*—As seizure induction is a real, if rare, possible side effect of TMS, it is typically not recommended to utilize TMS on subjects with a history of epilepsy. With this said, several studies have suggested beneficial effects of low-frequency TMS on intractable epilepsy (for review: [29]). Again, possible benefit must be weighed against the likely risk before treatment is recommended.
- *Cerebral Lesion*—Due to issues of induced current shunting, it is recommended any patient suffering from a vascular, traumatic, tumoral, infectious, or metabolic lesion—even without a history of seizure—avoid TMS unless medically compelling reasons exist.
- *Drug/Medication Interactions*—Because active or recent intake of several drug classes may lower a subject's seizure threshold, it is recommended a full and detailed medication history be obtained (Table 2). Treatment decisions should

Table 2
Drugs with potential Hazards for rTMS

Strong potential hazard	Relative hazard
Alcohol	Ampicillin
Amitriptyline	Anticholinergics
Amphetamines	Antihistamines
Chlorpromazine	Aripiprazole
Clozapine	BCNU
Cocaine	Bupropion
Doxepine	Cephalosporins
Ecstasy	Chlorambucil
Foscarnet	Chloroquine
Gamma-hydroxybutyrate (GHB)	Citalopram
Ganciclovir	Cyclosporine
Imipramine	Cytosine arabinoside
Ketamine	Duloxetine
Maprotiline	Fluoxetine
MDMA	Fluphenazine
Nortriptyline	Fluvoxamine
Phencyclidine (PCP)	Haloperidol
Ritonavir	Imipenem
Theophylline	Isoniazid
	Levofloxacin
	Lithium
	Mefloquine
	Methotrexate
	Metronidazole
	Mianserin
	Mirtazapine
	Olanzapine
	Paroxetine
	Penicillin
	Pimozide

(continued)

Table 2
(continued)

Strong potential hazard	Relative hazard
	Quetiapine
	Reboxetine
	Risperidone
	Sertraline
	Sympathomimetics
	Venlafaxine
	Vincristine
	Ziprasidone

only be made following a careful and medically responsible evaluation.

- *Recent Drug Withdrawal*—Recent withdrawal from alcohol, barbiturates, benzodiazepines, meprobamate, and/or chloral hydrate may significantly reduce a subject's seizure threshold. Accordingly, treatment is not recommended until a suitable time following drug cessation.
- *Pregnancy*—As the magnetic field generated by TMS decays rapidly with distance, any fetal exposure to TMS effects is very unlikely. However, under this circumstance it is arguably best to take a conservative stance and avoid treatment for women of term. In addition, any TMS operators should maintain a 0.8 m distance (conservative) from the discharging coil [2].
- *Children*—To date, there have been nearly 100 studies reporting TMS application to pediatric populations (for review: [30]). Although no serious adverse effects have been reported, special consideration should be taken when considering TMS in children [31]. It has been *cautiously* concluded that single- and paired-pulse TMS is safe in children above the age of two [2]. For children younger than 2 years, data about risk for acoustic injury are not available, and therefore specialized hearing protection may be required. In absence of an appreciable volume of data on the potential for adverse effects with rTMS, children should not be used as subjects for rTMS without compelling clinical reasons, such as the treatment of refractory epilepsy or particular psychiatric conditions.
- *Illness*—Since the effects of TMS are dependent upon the baseline activation state of the targeted cortical region, it is important to monitor and consider the effects of both physical

Table 3
Example of TMS screening questionnaire

	Yes	No	Notes
Have you ever had TMS before?			
Have you ever had an adverse reaction to TMS?			
Have you ever had a seizure?			
Is there any family history of epilepsy?			
Have you ever had an unexplained loss of consciousness?			
Do you suffer from chronic or severe headaches?			
Have you ever had a stroke?			
Do you have any brain-related neurological illness?			
Have you ever had any serious head injury or concussion?			
Have you ever had any surgery to your head?			
Have you ever had any illness that may cause brain damage?			
Do you have any metal in your head outside of your mouth?			
Do you have any implanted medical devices?			
Are you taking any medications (including OTCs)?			
Are you pregnant or potentially pregnant?			

and mental illness on this basal activity. For instance, Fitzgerald and colleagues [32] found that schizophrenic patients show a decreased response to low-frequency TMS while Oberman and colleagues [33] found that autistic patients show a prolonged response to theta-burst stimulation. Accordingly, it is important to monitor subject condition and consider the neural effects prior to treatment (Table 3).

5 Stimulation Parameters

The low number of severe side effects reported with the use of TMS is due, in large part, to the exacting stimulation guidelines first laid out by Wassermann et al. in 1998 [1] and refined by Rossi et al. in 2009 [2]. Strict adherence to the guidelines will help ensure subject safety and maintain the strong track record of TMS as a safe form of noninvasive treatment.

When considering issues of parameter safety, there are four important quantities to consider: intensity, frequency, train duration, and inter-train interval (Tables 4 and 5). Although these

Table 4
Parameter safety issues: maximum recommended stimulation duration of single TMS trains (in seconds)

Freq (Hz)	90 % MT	100 % MT	110 % MT	120 % MT	130 % MT	140 % MT	150 % MT	160 % MT	170 % MT	180 % MT	190 % MT	200 % MT
1	>1,800	>1,800	>1,800	360	>50	>50	>50	>50	27	11	11	8
5	>10	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4
10	>5	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4
20	2.05	2.05	1.6	1.0	0.55	0.36	0.25	0.25	0.15	0.2	0.25	0.2
25	1.28	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12

Table 5
Parameter safety issues: commonly employed stimulation parameters

rTMS Frequency	No. of studies	Average train duration	Average inter-train interval	Average no. of trials
4–9 Hz	>10	Variable	Variable	Variable
10 Hz	>50	5–6 pulse-trains for 400–500 ms	3.2 s	250
20–25 Hz	>20	10 pulse-trains for 400–500 ms	17.1 s	80

values will necessarily differ across varied circumstances, it is important to remain conservative when constructing a paradigm so as to maintain maximum subject safety.

rTMS for Cognitive Research—rTMS applied shortly preceding or during a cognitive task has been shown to modulate subject performance [34]. Although low-frequency TMS typically inhibits neural activity and high frequency excites neural activity, investigations of cognitive nature see a wide variation in neural response across subjects. Furthermore, in several studies, certain cognitive tasks have been demonstrated to be enhanced by inhibitory rTMS, revealing the potential of TMS-induced paradoxical functional facilitation (for review: [35, 36]). As such, when determining TMS parameters for a cognitive study, it is important that intensity, train duration, and inter-train interval be established before study commencement and not amended simply to evoke a desired effect in non-responding subjects.

rTMS for Therapeutics—The cumulative effects of repeated rTMS sessions can be at once beneficial and detrimental. Whereas many studies have shown an ameliorative effect of TMS on numerous neurological symptoms, several side-effects—including fatigue, difficulty concentrating, and neck pain—have been reported. It is important that determined treatment parameters remain within recommended safety boundaries and patient status be assessed both before and following each treatment.

rTMS of the Motor Cortex—It is recommended rTMS of the motor cortex not exceed 130 % resting motor threshold [2]. If a subject's motor threshold cannot be determined, it is recommended an intensity corresponding to the lower 95 % confidence interval of the average MT of the other subjects be used.

Theta-Burst Stimulation—The use of TBS protocols in both therapeutics and research is increasing rapidly. Although there have been no formal safety guidelines issued from the TMS Safety Consensus Group, it is strongly recommended TBS intensity be derived from a subject's *active* motor threshold (rather than the

resting motor threshold). This lower number will increase overall safety during the rapid stimulation paradigm. Also, until further research is conducted exploring safe inter-TBS session durations, it is recommended subjects not undergo TBS more than once during a 7-day period [37].

6 Physical and Neuropsychological Monitoring

It is strongly recommended that practitioners administer both pre- and post-stimulation physical and neuropsychological evaluations. These evaluations should be short and easy to administer yet sensitive enough to detect subtle deficits possibly brought on due to TMS. Possible evaluations include (but are not limited to) the Mini-Mental State Examination [38], the Montreal Cognitive Assessment [39], the Beck Depression Inventory [40], the Autism Diagnostic Interview—Revised [41], and any standardized IQ test. Although points of interest will vary according to utilized paradigms, it is important that issues regarding both physical and cognitive status be examined (Table 6).

7 The TMS Lab/Clinic

Space—For diagnostic and therapeutic applications of TMS, a medical setting with attending physicians is required [2]. However, for studies with normal subjects utilizing the prescribed parameters, a medical setting may not be necessary. Each institution's IRB

Table 6
Example physical/mental status questionnaire

	Severity (1–5)	Relationship	Notes
Headache			
Neck pain			
Scalp pain			
Seizure			
Scalp burn (if EEG utilized)			
Hearing impairment			
Impaired cognition			
Trouble concentrating			
Acute mood change			
Other			

should be the final decider regarding this issue. It is suggested that, regardless of setting, appropriate life-support equipment be available onsite at each TMS clinic/lab.

Practitioners—The TMS Consensus Group is currently working on recommendations for practitioner training and certification. Although work is ongoing, several suggestions regarding the practitioner team are relevant. First, any clinical application of TMS should be overseen by a trained and certified neurologist. On the other hand medical assistants, including nurses and nurse practitioners, are also highly recommended during any clinical utilization of TMS [2].

All technicians administering stimulation should be BLS certified and well trained in both stimulation techniques and patient assessment. Although there are no official certification classes, it is recommended each center adheres to a strict "internal" certification system for new technicians, which includes ample observation and supervised treatments. In addition, a well-defined plan of action in the event of a seizure or syncope should be developed and well learned by each practitioner.

8 General Ethical Concerns

Informed Consent—Subjects must be provided with all information regarding procedure, risks, and/or any possible discomfort associated with treatment in order to supply the practitioner with informed consent. This information must be presented in easy-to-understand language without equivocation [42].

Risk-to-Benefit Ratio—When considering treatment options, informed consent does not constitute sufficient reason to forge ahead. Instead, a careful analysis of the possible benefits of therapy must be undertaken and shown to clearly outweigh the possible risks. The same risk-to-benefit ratio assessment stands in matters regarding research and data collection [42].

9 Conclusion

The use of TMS has grown dramatically in the past decade. New protocols of TMS have been developed and changes in the devices have been implemented. Furthermore, TMS is being increasingly combined with other brain imaging and neurophysiologic techniques including fMRI and EEG, and a growing number of subjects and patients are being studied with expanding numbers of longer stimulation sessions. A further increase in the widespread use of TMS in medical therapeutic applications and research is expected. This makes the need for clear and updated safety guidelines and recommendations of proper practice of application critical.

Over the years, safety and ethical considerations have been generally guided by the consensus statements [1, 2]. This chapter reflects not only on safety guidelines, including the appropriate training of TMS personnel, but also many other ethical issues raised in both clinical and research applications of TMS. As in any evolving field, the most essential are the questions we're still trying to answer.

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