rTMS-Associated Adverse Events, Safety and Monitoring

7

7.1 Introduction

rTMS treatment is generally very well tolerated. It is notable that the overall discontinuation rate is markedly lower than that usually seen in depression treatment trials, especially trials of medication. For example, in the two large multisite rTMS trials, the withdrawal rate in the active groups was 12 % and <10 % [1, 2]. It is often less than 5 % in single site studies (e.g. [3]). However, there are some clear contraindications to, important safety considerations for and side effects of rTMS treatment.

7.2 Contraindications

The major contraindications to rTMS treatment fall into two categories:

1. Conditions that raise the risk of seizure induction
   These conditions include epilepsy or another seizure disorder or other forms of active brain illness such as a recent cerebral vascular accident, or a medical condition that substantially raises cortical excitability. In addition, alcohol or drug withdrawal, including withdrawal from benzodiazepines, can substantially increase seizure risk.
2. The presence of material that could interact with the induced magnetic field
   rTMS may potentially interact with implanted material through the induction of currents (especially in circular wires), through heating, through the induction of movement in magnetically active material or through changing the parameters of magnetically programmed devices.

   An implanted cochlear implant, pacemaker or other form of magnetically programmable device may be affected by the magnetic field generated with rTMS treatment. Although studies have not investigated the interaction of rTMS with a cochlear implant, these implants contain looped antenna where induced currents are likely to be substantial. rTMS stimulation has been shown outside of the body to induce only small currents in deep brain stimulation electrodes (e.g. [4, 5]). However, only local currents, not currents between the electrode and the pulse-generating case, were

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investigated; these latter currents may be greater. rTMS applied close to the pulse generator can produce substantial damage to the device [4]. Researchers have concluded that TMS may be safely applied in the presence of other forms of pulse generators (such as vagal nerve stimulation, cardiac pacemakers and spinal cord stimulators) as long as a substantial distance is maintained between the implanted wires/pulse generator and where the TMS coil is discharged [6]. Padding (such as a lifejacket) may be put in place to prevent accidental stimulation close to the pulse generator [7].

rTMS could also potentially interact with medically implanted metal components in the skull or brain. Skull plates are most commonly made from titanium which is non-ferromagnetic and has low conductivity, lessening the likelihood of significant interaction [8]. Aneurysm clips are frequently cited as a contraindication to rTMS treatment, though one study has calculated that the energy imparted on aneurysm clips would move these minimally in a manner unlikely to produce clinical problems [9].

A further area of relative contraindication to rTMS treatment is the presence of medical problems that could be destabilised if a seizure induced by rTMS was to occur. For example, the presence of substantial ischaemic cardiac disease could be a concern as a patient may not have the necessary cardiac reserve to tolerate the physiological stresses associated with a seizure. However, the potential benefit of rTMS treatment needs to be weighed against this concern, especially as the risk of seizure is quite low.

7.3 Adverse Events

7.3.1 Syncope

The major safety concern with rTMS treatment has been related to the potential for seizure induction (see below). However, syncope ('fainting') is another mechanism through which patients may lose consciousness during a medical procedure such as rTMS, and it is possible that this occurs more commonly than seizure. Syncopal reactions are relatively common following medical procedures such as blood taking, and there appears to be a group of individuals susceptible to this type of reaction.

Syncopal reactions are brief and have no long-term consequences. However, it can be difficult to distinguish these from rTMS-induced seizures. This diagnostic problem arises if patients display behavioural manifestations whilst unconscious that might be attributed to seizure activity. Seizure-like activity including muscle jerks and tonic muscle activity can occur during syncopal episodes. However, tongue biting or incontinence is infrequent during syncopal episodes and is more likely to indicate seizure activity. Syncopal episodes are frequently preceded by a patient experiencing light-headedness, a need to lie down, nausea and a sensation of heat. Notably, patients will recover consciousness fully within seconds, in a much more rapid manner than would be expected following a seizure, where full consciousness may take several minutes to re-establish. There is no definitive test to permit the

delineation of these two types of episodes: prolactin may be elevated following a generalised seizure but does not have adequate specificity to be relied on clinically.

The immediate management of a patient who has lost consciousness during TMS does not depend on whether the diagnosis of syncope or seizure is made at the time. Regardless, the patient should be assisted to lie in a prone position on one side and the airway protected as required. Movement of the subject undergoing a tonic–clonic seizure should not occur until motor activity has ceased. Evaluation following the event is likely to involve neurological review, including the possibility of the conduct of an EEG.

7.3.2 Seizure Induction

The major risk with rTMS treatment is the induction of seizure activity [10, 11]. A number of seizures were reported with TMS prior to the delineation of safety guidelines defining safe stimulation parameters [11]. Since that time, rTMS use has expanded rapidly, and large numbers of subjects have undergone stimulation protocols across a variety of psychiatric and neurological disorders. Despite this marked increase in use, there have only been sporadic published reports of seizure induction and mainly in conditions other than depression. All of the reported seizures occurring with rTMS treatment have been during or immediately after stimulation trains. There is no evidence that rTMS produces changes in brain activity that predispose individuals to experience seizures some time following the end of stimulation. In addition, where seizures have occurred, there is no evidence that individuals have developed a propensity to experience seizures in the future, or have experienced ongoing adverse consequences.

Box 7.1. Stimulation Parameters and Seizure Risk

For over 15 years, it has been recognised that the likelihood of seizure induction is related to several aspects of stimulation characteristics: stimulation frequency, train duration, intensity and the duration of time between rTMS trains. Safety guidelines have been published describing what are known to be safe combinations of these parameters. For example, when stimulation is applied at 10 Hz, 5 s is considered a safe train duration when stimulation is applied at up to 110 % of the resting motor threshold (Table 7.1). This train duration is reduced to 4.2 s at 120 % of the RMT and 2.9 s 130 % of the RMT. It should be noted that the vast majority of research that has informed these guidelines has been conducted with stimulation of the primary motor cortex. It is not clear whether the same guidelines should directly translate to other non-motor brain areas. However, providing stimulation in experimental and treatment studies within these guidelines has not resulted in a substantial rate of seizures. Therefore, in the absence of alternative data, these guidelines should be followed unless a clear rationale is provided and informed consent obtained with an awareness of the novelty of stimulation parameters.

Table 7.1 Established safe stimulation parameters for individual trains

	Intensity (% of RMT)				
Frequency	90	100	110	120	130
1	>1,800	>1,800	<1,800	>360	>50
5	>10	>10	>10	>10	>10
10	>5	>5	>5	4.2	2.9
20	2.05	2.05	1.6	1.0	0.55
25	1.28	1.28	0.84	0.4	0.24

Adapted from [6]
The maximum established safe train duration for motor cortical stimulation based on varying frequencies and intensities. Stimulation in excess of the safe train duration may result in the development of seizures or seizure-like brain activity. Durations marked with a '>' are the maximal tested durations

A number of the seizures reported since the publication of safety guidelines in 1998 [11] have occurred when stimulation was provided outside of safety guidelines. For example, a generalised seizure was reported following stimulation with 10 Hz trains of 10 s duration in a patient with chronic pain (at 100 % of the RMT) [12]. A second generalised seizure occurred in a patient with major depression during 15 Hz stimulation provided via 10 s trains at 110 % of RMT [13].

However, there have been several events reported as seizures where stimulation was provided within the 1998 guidelines [11]. In one patient with bipolar disorder, a generalised seizure was induced during single-pulse TMS measurement of the RMT [14]. Notably, this patient had a family history of epilepsy and was concurrently taking chlorpromazine and lithium. A second seizure was reported during RMT assessment, but this time in a patient with multiple sclerosis [15]. A generalised seizure was reported in a patient with tinnitus receiving rTMS treatment at 1 Hz [16], although the possibility that this was syncopal has been raised [17]. A single seizure has also been reported using continuous theta burst stimulation, an experimental paradigm involving repeated application of three train pulses at 50 Hz [18].

It is notable that even in patients with a substantial risk for seizure induction, rTMS-related seizures are rare. A review of the safety of rTMS in patients with epilepsy found that less than 2 % of patients have experienced an event during rTMS (4 of 280 patients) [19].

Monitoring of EEG during rTMS treatment does not appear to provide information likely to be useful in the prevention of seizure induction. As evident in a recent review [6], multiple studies have explored the induction of transient epileptiform activity during rTMS treatment. This is occasionally detectable in patient groups but does not appear to be of use in monitoring treatment [6].

A number of conditions increase the risk of seizure induction necessitating avoidance of the rTMS procedure, or use with considerable caution. These include a past history of epilepsy or seizures or a currently active brain disorder. The presence of

unstable cardiac disease also requires caution due to the increased demands that could be placed on the cardiovascular system in the event of a seizure. A history of ongoing problematic alcohol misuse is a contraindication, especially given the increased risk of seizures during withdrawal stages of use. Patients taking benzodiazepines should be advised not to discontinue their use during treatment due to the increased risk of seizure during benzodiazepine withdrawal.

7.4 Other Potential Safety Concerns

7.4.1 Impairment of Cognition

The potential for rTMS treatment to produce cognitive impairment has been a concern since the initial development of the procedure. Given the cognitive side effects that complicate the use of ECT, it is a reasonable concern. Clearly, if rTMS is able to produce lasting brain changes sufficient to ameliorate depressive symptoms, it could potentially also produce brain changes with negative implications. Indeed, transient disruption of cognition is a well-recognised effect of stimulation at certain brain sites (e.g. [20]), though enhanced function is reported in other domains [21–23].

The main question is therefore whether deleterious effects of rTMS on cognition persist after stimulation or develop with repeated applications of rTMS during a treatment course. Fortunately, neither appear to be the case. A range of studies have investigated cognitive function in patients with depression, before and after a course of rTMS. For example, in an early study, Little et al. tested 16 cognitive measures after 1 week of 1 Hz and 1 week of 20 Hz rTMS at 80 % of the RMT in a crossover design and reported no adverse effects. No deterioration in cognitive function was also reported in an open study of 2 weeks of 20 Hz rTMS administered at 80 % of the RMT [24]. Loo et al. analysed cognitive outcomes across 39 clinical studies [10]. Although in three studies deterioration on one or more cognitive tests was reported, a substantially greater number of studies reported cognitive improvement, and no specific pattern of cognitive deterioration was apparent across the trials. An analysis of potential cognitive side effects of rTMS was also included in the pivotal Neuronetics Ltd-sponsored clinical trial [3]. In this study, up to 216,000 pulses were applied to patients, typically 3,000 pulses per day over an hour, each day, for 6–9 weeks at 120 % of the RMT. No cognitive deterioration was noted across the Mini Mental State Examination, the Autobiographical Memory Interview or the Buschke Selective Reminding Test.

The conclusion that is most appropriately drawn from these studies is that there is no current evidence that rTMS as applied in its standard clinical forms for the treatment of depression produces cognitive side effects. However, as rTMS dosing and modes of application change over time (e.g. with the introduction of theta burst stimulation), cognitive safety will require continued reappraisal. The potential capacity of rTMS to produce enduring changes in brain function should also be considered when rTMS is being used in an off-label manner.

7.4.2 Hearing Impairment

When an rTMS machine produces its magnetic field, a substantial sound is generated by the deformation of the stimulating coil. At times this sound may exceed what is considered to be safe for direct exposure to the ear, with sound levels of up to 140 dB [25]. In early studies, some changes in auditory thresholds were reported in individuals exposed to rTMS stimulation, although these reports were not of permanent changes (e.g. [26]). A persistent decrease in auditory thresholds was reported in a patient stimulated with a deep TMS (H-coil) who was not using hearing protection during the procedure [27]. A series of more recent studies have reported no changes in hearing thresholds, when rTMS is provided with appropriate hearing protection (e.g. [2]). This has led to the recommendation that therapeutic use of rTMS should be accompanied by the use of appropriate hearing protection including either earplugs or earmuffs. Hearing safety of rTMS in children has not been fully established [6].

7.4.3 Potential Histotoxicity or Other Brain Changes

It is possible that rTMS stimulation could produce damage to brain tissue either through heating effects, effects mediated through the produced magnetic field or to the effects of the induced electrical fields. In regard to the former, heating effects induced by TMS stimulation appear to be minimal and are likely to be limited by the dissemination of heat through natural brain perfusion. There are no known mechanisms through which the induced magnetic field produced during TMS stimulation could generate biological adverse effects in the absence of extraneous implanted metal in the skull or brain. Magnetic forces on ferromagnetic objects such as metallic brain implants could produce displacement of these objects. Skull plates are most commonly titanium which is non-ferromagnetic. One report has shown minimal heating of titanium skull plates with 1 Hz rTMS [8].

Studies of the effects of the induced electrical fields on brain tissue take a number of approaches. Animal studies using direct electrical stimulation have produced pathological changes in brain tissue, but only after extensive periods of stimulation at charge levels markedly in excess of that induced with rTMS stimulation [28]. Animal experiments investigating more standard TMS stimulation have failed to clearly demonstrate evidence of induced pathological changes. However, the interpretation of these studies is considerably confounded by inequities in the application of rTMS across animal and human situations [10]. One animal study reported microvacuolar changes with stimulation intensities equivalent to three times motor threshold, but this finding has not been replicated in at least four other studies that have shown no adverse changes (for review see [29]).

Studies have also looked at potential effects of rTMS on various brain parameters in human subjects. These have shown no adverse effects on the blood–brain barrier [30], no changes in gross brain structure (with MRI) [31] and no adverse effects on EEG, ECG and neurohormonal levels [32]. One human pathological study revealed

no adverse changes in the brains of two patients with epilepsy who underwent rTMS prior to surgery [33].

A further consideration is whether exposure to the magnetic field generated during rTMS has potential adverse consequences. This is especially relevant considering the ongoing debate regarding potential health and safety concerns with exposure to pulsed electromagnetic field (EMF) from mobile phones and other sources. Given the average duration of the TMS magnetic pulse and the number of pulses in treatment courses, it has been calculated that the typical treatment course would provide exposure of only short duration (e.g. 5 s) [10]. Presumably, this would increase with higher doses and longer courses of rTMS as are now currently being evaluated. However, exposure duration would still remain very short compared to other sources of EMF. The nature of the exposure also varies significantly from other sources: TMS-related exposure is high intensity and pulsed for brief duration, compared to the low-intensity but continuous exposure potentially related to other devices. The implications of this variation are unclear, but to date there has been no evidence of any safety-related concerns or complications arising in regard to EMF exposure and rTMS treatment. Although it is typically assumed that there are no direct brain effects of the magnetic field produced during TMS other than those of the secondary electrical field, it is possible that this is not the case. Neurones do contain material that is potentially magnetically manipulable [34]. However, the implications of this manipulation potential to the actions of rTMS remain completely unknown.

7.4.4 Pregnancy: Breastfeeding

As discussed in Sect. 5.5, the use of rTMS in pregnancy has only been described in a limited number of case series (e.g. [35]). No adverse events or negative foetal outcomes have been documented to date. However, the accumulated number of patients treated to date is clearly inadequate to make firm conclusions about safety. The consent of patients for treatment who are pregnant should reflect this in addition to other risk–benefit-associated issues.

A similar conclusion can be made about the use of rTMS in the treatment of patients who are postpartum and breastfeeding. Although rTMS treatment could potentially induce changes in hormonal secretion, changing breast milk composition, there is no evidence of this or associated harmful effects. In addition, hormonal fluctuations associated with breastfeeding may change cortical excitability elevating the risk of seizure induction. These risks are likely to be small.

7.4.5 Children and Adolescents

Data collected on the use of rTMS in children and adolescents has been extremely limited to date, although large numbers of subjects under 18 have participated in single-pulse and paired pulse experimental protocols. One seizure in a 16-year-old female patient has been reported with relatively low-dose stimulation parameters.

This could indicate a the possibility of a higher rate of seizure induction in this population, given that the total number of adolescent patients reported as having received treatment in the literature is very low. However, making inferences from a single case is significantly problematic. Adolescent patients may also be at a higher risk of experiencing syncopal episodes.

7.5 Safety of Operators

As rTMS becomes increasingly utilised in clinical practice, the safety of operators is likely to become the focus of increasing concern. To date, it is not an area to which substantial consideration has been addressed. One study has explored the exposure of staff applying rTMS to magnetic fields, comparing measured and extrapolated fields to European safety guidelines [36]. The authors propose that staff should maintain a distance of at least of 0.7 m from the coil whilst treatment is underway. However, testing was conducted with only one rTMS device, at a limited range of stimulation parameters.

Given that all rTMS treatment coils currently available can be held in place with a holding arm system, it seems sensible to ensure that these are always used when treatment is underway. The operator of the rTMS equipment can then be standing or seated at least 1 m from the coil during treatment, except when making brief checks of coil positioning. We would also recommend that staff administering rTMS wear appropriate ear protection due to the prolonged and repeated exposure to rTMS-related noise.

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