A REVIEW OF THE SAFETY OF TRANSCRANIAL MAGNETIC STIMULATION

by

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The Safety of Transcranial Magnetic Stimulation

Acknowledgement and Overview of Report

Acknowledgement

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The Safety of Transcranial Magnetic Stimulation

Acknowledgement and Overview of Report
**Overview of Report**

The benefits of transcranial magnetic stimulation were first demonstrated in 1985. Recent developments mean that the technique is now moving out of the research laboratory and into the clinical setting. This report provides an overview of the evidence for the safety of transcranial magnetic stimulation as a medical technique.

A literature search was undertaken using Pubmed and Google Scholar as the search engines. Parameters included the use of ‘transcranial magnetic stimulation’ with or without ‘safety’. The resultant report sets out some of the most common side effects of transcranial magnetic stimulation and evaluates their incidence and their comparative seriousness.

The literature up to late 2006 suggests that unintentional seizure induction using single pulse TMS is a rare event. The intensity of stimulation required to reliably induce seizure is many times that used routinely in TMS and rTMS.

Furthermore, the commonest side effect of TMS is headache. Research has also shown that single-pulse TMS is safe to administer in children and adolescents. All available evidence points to the conclusion that the use of TMS within previously published safety guidelines is a safe diagnostic procedure, and an FDA expert panel concluded in January 2007 that rTMS is safe for use in humans.
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# Abbreviations and Style

## Abbreviations

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Abbreviations and Style

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**Style conventions for text**

‘TMS’ refers to both TMS and rTMS.
‘single-/paired-pulse TMS’ refers to single-/paired-pulse TMS procedures.
‘rTMS’ refers to repetitive TMS procedures.
CHAPTER 1: AN INTRODUCTION TO TRANSCRANIAL MAGNETIC STIMULATION

Although the concept of using magnets to stimulate neural tissue has been known since Jacques-Arsène d’Arsonval detailed the use of magnets to stimulate a retina in 1896 [6], transcranial magnetic stimulation (TMS) was first described in the mid-1980s by a team from the University of Sheffield [11]. For over twenty-one years, the technique has been used in fields as diverse as neurological and cognitive research, diagnosis and active treatment. TMS has since become an important tool for researchers and clinicians alike, with over four thousand papers to date describing the technique and its applications.

1.1 The stimulating equipment

The stimulators used today usually consist of capacitor discharge systems coupled with switching elements and a coil [41].

The strength of the electric field and therefore of the electrical current induced by the stimulator within the brain, is affected by the rate of change of the magnetic field generated, which then affects the current flowing around the coil. In order to excite the neurons with reasonable efficiency within the brain, the current passing through the coil must reach its peak over the course of a few tens of microseconds. Transcranial magnetic stimulation is non-invasive and no electrodes are used, though surface electrodes are often a part of the monitoring equipment used in conjunction with the technique [66]. The intensity of the magnetic field produced decreases with the distance from the coil; the strength of stimuli at depth is therefore always less intense than those closer to the surface.

1.2 The stimulation process

Unlike other techniques, such as electroconvulsive therapy (ECT), which involve passing current through the skull, the spatial resolution characteristic of TMS allows specific areas of the cortex to be selectively pinpointed for stimulation and, since temporal resolution is also high, any disruption created within the brain by a single pulse is brief and reversible.

When administering TMS, the operator places a stimulating coil upon the scalp. The coil is then energised by a powerful current that changes rapidly, thus creating a time-varying magnetic field. In contrast to transcranial electrical currents, this magnetic field is unimpeded by the bones and tissues of the head and brain and can therefore pass to the stimulation site unaffected by the presence (or absence) of these structures. The direction of the magnetic field pulse is parallel to the central axis of the coil and its strength depends both on the magnitude of the current, the number of turns of wire within the coil and its dimensions. The ‘eddy currents’ induced within the brain are perpendicular to the
original magnetic field and therefore parallel to the primary current originally applied to the coil.

The intensity of the magnetic field needed to induce motor movement due to cortical magnetic stimulation varies from individual to individual and is known as the Motor Threshold (MT). It has been proven that coil orientation affects the stimulation of the brain 68. For example, holding a large circular coil so that the current, when viewed from above, flows in a clockwise direction leads to preferential excitation of the left hemisphere, while holding the coil so that the current as viewed from above flows in an anticlockwise direction leads to preferential excitation of the right hemisphere 7.

Transcranial magnetic stimulation can be used to temporarily disrupt or stimulate brain activity depending on the intensity, duration and frequency of the stimulation used. It can also be used to modulate neuronal networks that are functionally connected. Slow TMS (≤ 1Hz) tends to be inhibitory, while fast TMS (> 1Hz) tends to be excitatory 58. Stimuli can be administered singly, in pairs, or in series or trains of varying durations. When administered singly the process is known as single-pulse TMS and in pairs as paired-pulse TMS, but when administered several times a second in trains, the process is known as repetitive TMS (rTMS). In general, single and paired TMS pulses are used for neurodiagnosis, whilst trains of rTMS are used in clinical settings for research and therapeutic purposes.
CHAPTER 2: AN INTRODUCTION TO THE SAFETY OF TRANSCRANIAL MAGNETIC STIMULATION

According to most sources, single-pulse TMS is both safe and useful for investigating the neurophysiological aspects of human health and disease. Repetitive TMS also appears in general to be safe and well tolerated. In support of this, 35% of subjects in a recent study reported no side effects or discomfort either during the procedure itself, or for one month following completion, while 53% of the subjects reported some mild discomfort during the procedures and a further 11% some mild annoyance by the procedure. Meanwhile, Hirshberg et al. have concluded that use of both single- and paired-pulse TMS in children is of minimal risk, and research into the use of rTMS in child and adolescent populations is underway. All the data available at present suggest that the long-term risks of single-pulse TMS and rTMS in adults are not significant.

Significantly, there have been no cases to date of investigators who work with TMS developing epilepsy, cognitive impairment, cancer, or any other adverse side effect, despite repeated exposure to as many as 100 pulses a day over many years.

When compared with environmental sources, exposure to rTMS is extremely brief, even though the local field strength is great and exposure can be repeated many times. Fields produced by TMS procedures have an approximate strength of 2 Tesla and are therefore similar to the static field strength used in magnetic resonance imaging (MRI) scanners. In contrast with exposure to clinical MRI fields, the total time of exposure to a TMS field during a procedure is brief, typically less than 1ms. Despite this, since clinical staff working with single-pulse TMS or rTMS can be exposed to levels exceeding the EU Directive 2004/40/EC on The Minimum Health and Safety Requirements Regarding the Exposure of Workers to the Risks Arising from Physical Agents (Electromagnetic Fields), and the International Commission on Non-Ionizing Radiation Protection guidelines, it is recommended that unnecessary exposure is limited and that staff should not work at a distance of less than 0.7m from the transducer. It should however be borne in mind that these standards are designed in this context to avoid unwanted neuromuscular stimulation. This has not been reported in practice by users of magnetic stimulation and, in general, is not dangerous.

Despite their apparent safety, it is recommended that TMS procedures should always be administered under the supervision of a trained physician and medical assistance should always be to hand. A supervision plan that covers screening for risk factors, assessment of risks and benefits, informed consent, stimulation parameters and monitoring is also recommended to be conducted prior to administering the procedure.

2.1 Strength and configuration

According to Wassermann, the United States Food and Drug Administration (FDA) states that there is always significant risk involved in the use of stimulation frequencies.
greater than 1 Hz, but that significant risk may not be involved with using frequencies of 1 Hz or less. The FDA currently decides investigational device exemptions for trials involving low frequency magnetic stimulators and makes its decisions on a case-by-case basis depending on the protocols of use and the population toward which these protocols are aimed.

2.2 Precautions and guidelines

Following research into TMS and the realisation that adverse effects linked with TMS procedures can be mitigated or eliminated through careful choice of pulse frequencies, burst durations and amplitudes, and through the careful vetting of individuals intended to receive the treatment, protocols for the safe use of TMS procedures now exist and are continually adapted as more information comes to light. Pascual-Leone et al. give a comprehensive list of guidelines to follow when undertaking rTMS and single-pulse TMS procedures. These guidelines include:

- Wearing of earplugs by all subjects and investigators/therapeutic staff when frequencies of ≥1Hz are used;
- Subjects undergoing high frequency rTMS should be made aware that there is a risk of seizure induction, especially in those with familial history of epileptic convulsions;
- Procedures should always take place in appropriate surroundings in the presence of staff capable of managing convulsions should they occur;
- Procedures that minimize the risk of any electrodes used burning the scalp should always be applied; and
- During stimulation of the motor cortex, the detection of any signs of spread of excitability should be considered as the earliest indication of an rTMS epileptogenic effect.

The International Society for Transcranial Stimulation Consensus Statement on rTMS has since added to this. It recommends that: licensed physicians must approve and supervise all rTMS procedures; that risk factors should be screened for prior to the procedure taking place; that an informed consent form is signed; that rTMS is only undertaken according to recommended published parameters; that subjects are monitored both during and after the procedure; and that rTMS should only be undertaken within a medical setting and in the presence of trained “first responders”.

Since the accuracy of information received from the proposed subjects is important, Keel et al. have created a Transcranial Magnetic Stimulation Adult Safety Screen (TASS) questionnaire, which asks fourteen questions of the subjects. A positive answer to one of the questions would in all likelihood preclude the subject’s undergoing a procedure, although the final decision would of course rest with the investigator/clinician. On application to the authors, it is possible to receive copies of the TASS questions free of charge.
Since 1993, the list of contraindications to TMS has grown considerably. Several authors have added to this list, and some of their recommendations are included here:

- Hömberg & Netz noted that those with large ischaemic scars should not undertake TMS procedures, for fear of seizure induction.
- Tredget et al considered any of the following conditions inimical to TMS – metal implants within the head; implantation of cardiac pacemakers; pregnancy (because of the unknown effects of TMS on the unborn foetus); uncontrolled migraines; a past major injury to the head; a past cerebrovascular accident; a family history of convulsions (including febrile convulsions in childhood); and any previous neurosurgery.
- Prikryl and Kucerova added sleep deprived individuals to this list.
- Anand & Hotson included individuals with unstable major medical conditions, major psychiatric conditions and neurological conditions that predispose the individual to epilepsy or which lower the seizure threshold, and those who are on medications that could lower the seizure threshold.
CHAPTER 3: ADVERSE EFFECTS ASSOCIATED WITH TRANSCRANIAL MAGNETIC STIMULATION

3.1 Methodology

Seventy-four papers and statements were identified using the PubMed and Google Scholar databases. The search criteria used the following terms: ‘TMS’ or ‘transcranial magnetic stimulation’ with ‘safety’ and/or ‘effects’.

3.2 Adverse effects

Although it is well established that single-pulse TMS has practically no known adverse effects in adults or children \(^{15, 31, 49}\) and that the risk from rTMS is greater \(^{37}\), most adults generally suffer no adverse effects from either single-pulse TMS or rTMS \(^{33, 50, 54}\). Those who do experience adverse effects find that they resolve themselves immediately upon cessation of the procedures or within three weeks of procedure completion \(^{9}\). There is very little data available on the safety of rTMS in children as yet, but research in this field is ongoing \(^{49}\) and no significant adverse effects have been seen to date.

The following sections discuss the adverse effects associated with TMS and the likelihood of occurrence. For convenience, a table showing the side effects reported in the papers mentioned within this review may be found in Appendix 1.

3.2.1 Seizure and syncope

Although single-pulse TMS has been known to induce generalized or partial seizures in individuals predisposed to epilepsy or those with central nervous system (CNS) lesions or diseases (e.g. lesions induced by stroke), it is not considered to be high-risk for seizures \(^{17, 24, 31, 49, 60, 73}\). Indeed, only one case of repeated convulsions induced by single-pulse TMS has ever been reported in one subject, a 17-year-old with focal epilepsy and an abnormality on the left frontal lobe \(^{18, 64}\). It has been recommended that care should be taken when using any kind of TMS on children aged between 6 months and 5 years with a high risk of febrile seizure, however, although no seizures caused by single- or paired-pulse TMS have ever been reported in children \(^{34}\).

Although low-frequency rTMS stimulation appears to reduce seizure activity \(^{28}\) and has never induced a seizure \(^{31}\), high-frequency rTMS is considered a significant potential risk for seizure induction as it is liable to decrease seizure threshold in susceptible individuals \(^{35, 74}\). For example, Pascual-Leone \(et al\) \(^{60}\) reported that high-intensity rTMS induced a seizure in an otherwise healthy individual, whose only risk factor was familial epilepsy. Because of this, a consensus has emerged that the following high-risk individuals should not undergo diagnostic rTMS procedures:

- Epileptic individuals \(^{49}\);
Those with a history or family history of seizures;  
Individuals with brain lesions that could affect seizure threshold;  
Individuals suffering from multiple sclerosis;  
Those taking tricyclic antidepressants, neuroleptic agents or any other drug that could lower seizure threshold, unless the potential benefits of receiving the therapy outweigh the increased risk of seizure;  
Individuals suffering from sleep deprivation during rTMS procedures, as Prikryl and Kucerova witnessed the first rTMS induced seizure since 1997 in a sleep deprived patient;  
Individuals with a heavy consumption of alcohol or those using epileptogenic drugs;  
Those with severe heart disease or with increased intracranial pressure.

Sometimes, seizures are reported in the weeks following a TMS investigation. Kandler surveyed 218 subjects with a variety of diseases, including multiple sclerosis and Parkinson’s disease. A small number of adverse incidences were reported during the 3-21 month post-investigation period surveyed. The number of seizures reported was described by Kandler as being consistent with normal expectancy for the particular group. It is as well, however, to be aware of the increased risk of seizure amongst those with multiple sclerosis, and not to subject them to single-pulse TMS and/or rTMS procedures unnecessarily.

Should an individual have one or more seizures induced, whether by ECT or rTMS, this does not increase the likelihood of an otherwise healthy person suffering an unprovoked seizure; and seizures induced by TMS of any kind are self-limiting with no permanent sequelae. In addition, rTMS does not seem to affect the frequency or types of seizure in epileptic individuals and has no damaging effects on the structure of the temporal lobe.

It is possible to deliberately use rTMS procedures to induce seizures in a manner equivalent to ECT. It should always be borne in mind, however, that deliberate use of rTMS to induce seizures involves the use of non-standard stimulation equipment capable of creating stimulation parameters at power settings (100Hz at 100%) that are vastly in excess of the parameters generally used in rTMS protocols. The numbers of seizures reported given the amount of people who have received rTMS treatment suggests that the risk of inadvertent seizure is very small. Overall, the risk of inadvertently induced seizures would appear to be less than 1 in every 1,000 rTMS procedures. This figure compares favourably with the risk of inadvertent seizures induced through commonly prescribed antidepressant use. In support of this, increased levels of adrenocorticotropic hormone have not been found following rTMS procedures, whilst a transient surge of luteinizing hormone and of prolactin has only been seen in one individual following the induction of a complex partial seizure.
Following early incidences of seizures associated with rTMS procedures, safety limits and stimulation parameters have been established (see Section 2.2) and, provided these guidelines are adhered to, the risk of unintentional seizures is considerably lowered, although incidences have occurred. For example, intensity of the field delivered by the rTMS procedure is tailored to the individual’s MT, based on the assumption that the threshold for depolarizing pyramidal neurons via a single pulse is a predictor for seizure risk within the brain. This technique lessens the likelihood of TMS being given to a person susceptible to seizures. Combining this procedure with screening for underlying neurologic conditions (e.g. use of the TASS screen proposed by Keel et al) further decreases the risk of inadvertently inducing a seizure.

Occasionally, a normal subject will suffer syncope – a temporary faint or swoon brought on by generalized cerebral ischaemia – and this can be mistaken for, or accompanied by, a seizure. Despite being observed in individuals undergoing rTMS, syncope is, however, unlikely to have been caused by the procedure. The rTMS procedure can also generate pseudoseizures which can, again, be misdiagnosed as a true seizure in the absence of encephalogram (EEG) monitoring. The EEG will change following a true seizure, thus allowing correct diagnosis to take place.

### 3.2.2 Tissue damage, memory, cognitive function and reaction times

It has been proven that continuous direct electrical stimulation of the cortex for 24 hours at 50Hz and with a charge density of $\leq 20\mu$Coulombs/cm$^2$ does not cause detectable damage within the feline cortex. The actual threshold for neuronal injury falls in the 40-100µCoulombs/cm$^2$ range. Since most magnetic stimulators only yield a charge density of 1-3µCoulombs/cm$^2$ per pulse, a large safety margin exists before histologically detectable damage may be expected to arise after rTMS procedures. In rats, histological analysis of brain structures and measurement of brain metabolites showed no evidence for an adverse effect of low-frequency rTMS in daily trains of 1,000 supra-threshold stimuli over 5 days.

According to Abler et al, a correlation exists between the amount of discomfort experienced at the stimulation site and the amount of errors produced in cognitive tests immediately following stimulation, where the greater the pain, the greater is the likelihood of producing errors. It has also been discovered that high-dose rTMS causes no structural damage discernible by MRI scans, and that rTMS has no effect upon the hypothalamus. According to Fitzgerald, rTMS does not affect the blood brain barrier or the output of recorded EEGs or electrocardiograms (ECGs). Even if TMS were to have adverse effects on cognition, its ameliorative effect in neuropsychiatric diseases could well mean that its use outweighs the risk of developing any side effects. Additionally, rTMS compares favourably with ECT with regards to long-term anterograde, retrograde and subjective memory problems, making TMS a more favourable treatment in patient perception. Most authors are agreed that stimulation with both kinds of TMS does not have an adverse effect on cognitive function, despite its ability to disrupt brain processing, however transiently.
There are suggestions that rTMS could have a positive but transient effect on cognitive function, enhancing verbal memory, psychomotor speed and concentration. Higher frequency stimuli seem to have greater effects on reduced motor reaction times and increased verbal memory. There is, however, a pulse strength threshold above which stimuli may have a transient adverse effect on memory.

3.2.3 Noise and hearing

Although exposure to the clicking noise made by rTMS devices (when the energized stimulating coil undergoes rapid mechanical deformation) can cause temporary instances of tinnitus and transient increases in auditory thresholds, the use of earplugs is successful in preventing these changes. Although increased auditory thresholds in animals following single-pulse TMS has been described, there has been no permanent hearing loss reported in humans, despite transient increases in the auditory threshold, even after exposure to repeated trains of stimulation over several years. Barker & Stevens showed that the number of daily stimuli necessary to approach or exceed a daily exposure level of 85 dB(A) is ‘large’, and according to Angel et al, exposing 18 children, 2 doctors and 2 technicians to 48 TMS procedures at 50-75% Tesla intensity did not cause significant differences in auditory function. Significantly, the 22 individuals of the Angel et al study did not use ear protectors during the procedures. However, Machii et al reported that rTMS to non-cortical areas of the brain exacerbated already existing tinnitus in two patients, while Loo et al told of one patient who showed a rise in auditory threshold after 6 weeks of rTMS. It is therefore important that both individuals undergoing rTMS procedures, and those administering it, wear earplugs or earmuffs at all times.

3.2.4 Headaches, pain and nausea

Repeated stimulation of the peripheral muscles in the scalp and face can result in the mild, tension headaches that are one of the most common adverse effects of rTMS. These headaches are experienced by around 5-25% of individuals who undergo rTMS. Interestingly, Anderson et al could find no association between active rTMS and an increase in headaches when compared with sham rTMS, although the noise produced by the stimulation and the enforced immobility required for the procedures might have influenced these results. These headaches, which usually start at least 20 minutes after treatment but sometimes as much as three hours after treatment, are usually transient, lasting for no longer than 10 minutes and respond well to analgesics such as acetaminophen (paracetamol) or ibuprofen when it is felt that intercession is necessary. Pascual-Leone et al noted that frequencies of up to 25Hz and trains that lasted for 10 seconds or less were most likely to induce these tension headaches. In several instances, no medication was given to individuals suffering rTMS-induced headaches. In some cases, these are the only reported side effects suffered by individuals in a trial.
Chapter 3: Adverse Effects Associated with TMS

Very occasionally, some individuals suffer a migraine attack following rTMS. Padberg et al. found that one of their volunteers suffered a migraine attack within four hours of undergoing sham rTMS. The induction of migraine by rTMS is, however, rare and, indeed, rTMS to the left dorsolateral prefrontal cortex seems to reduce migraine pain.

In some cases, individuals have reported experiencing feelings of nausea following rTMS procedures, but this is fairly rare and does not last long, and is usually associated with frequencies of less than 1 Hz and intensities of below the MT given to the cerebellum. Anderson et al. withdrew one subject from their study following completion of the second procedure after he suffered from nausea associated with vomiting and dizziness. The subject later stated that he felt that these symptoms were the consequence of a cold he had suffered from at the time, and his partner developed similar symptoms without undergoing rTMS a week later.

Another frequent side effect is pain induced during the procedure. During rTMS, muscles and nerves proximate to the coil are activated, causing discomfort at the point of stimulation or in the neck. There appears to be a direct relationship between the frequency and intensity of the stimulation and pain perception, and it is thought that varying the intensity and frequency of stimuli could minimize discomfort. Low-frequency rTMS is more associated with headaches and pain at the stimulation site than high-frequency rTMS. Although this discomfort is rarely troublesome during single-pulse TMS, some individuals find the pain very uncomfortable during rTMS. Most individuals cope well with this particular side effect and it does not affect treatment for these people. Others find that the pain is so acute it precludes their receiving treatment with rTMS. The pain usually disappears immediately upon ceasing rTMS treatment and analgesics can also be given, but not in all instances.

Occasionally, certain individuals experience dysesthesia, an unpleasant abnormal sensation of burning or crawling. Figiel et al. report on a 45-year old woman whose dysesthesia, which developed 10 minutes following the first rTMS procedure, lasted for 48 hours before resolving itself. In Janicak et al.’s study, six of their subjects presented with erythema – a reddening of the skin because of capillary inflammation – at the site of coil placement, probably because of individual sensitivity to the magnetic force concentrated there, whilst another reported moderate pain at this site. Application of a topical anaesthetic at the placement site overcame this problem, and could eventually be dispensed with altogether.

3.2.5 Burns

Metal objects placed upon the surface of the skin during rTMS can rapidly heat to levels capable of causing burns. This occurs when the currents induced in objects (e.g. EEG electrodes) placed in close proximity to a stimulating coil cause metal within the objects to heat to dangerous levels, according to the principles of I^2R heating. Electrode size and electrical conductivity also play a part in this process. Since the conductivity of most metals is over a million times more than that of tissue, the currents created within the
metal electrodes are much greater than those induced in the body and skin. If a high-frequency train is used and as a consequence the electrode does not have time to cool between pulses, this heating is exacerbated. Experimental data has shown that if the tissue temperature is raised to 50°C for 100 seconds or to 55°C for 10 seconds, then the skin will burn. These temperatures and durations occurred when rapid-rate rTMS was undertaken in proximity with silver electrodes. The situation may be remedied by not using gold or silver electrodes (because of their high electrical conductivity) in conjunction with rTMS procedures, and by notching or slotting the electrodes prior to placement. This last technique is particularly effective because it interrupts the concentric circumference around which the induced current flows. Making sure wires situated near the stimulating coil are kept loop-free can also help reduce induced currents.

Another thermal problem is heating of the actual coil itself during procedures because of the currents passing through it. This problem is overcome by equipping the coil with temperature sensors that will disable the device if coil temperature ever exceeds a threshold level. To date, there has never been a report of a coil-induced burn in humans.

3.2.6 Toxicity, histotoxicity and cancers

According to Wassermann, most instances of histotoxicity (the poisoning of the respiratory enzymes found within tissues) associated with TMS potentially happen because of mass hyperexcitation of neurons. Incidences of toxicity are therefore directly related to the efficiency of the stimulation given. There are no reported instances of histotoxic side effects occurring in children.

Although some epidemiological studies have shown an association between long term exposure to 50/60 Hz fields and, in particular, childhood leukaemia, there is no evidence that exposure to the short-lived magnetic fields created by TMS equipment has much effect. It is also significant that technicians who work with MRI machines, and therefore have prolonged exposure to magnetic fields similar to those associated with TMS, do not have an increased risk of developing cancer.

3.2.7 Ohmic heating

Another possible source of injury to body tissues through rTMS procedures is Ohmic heating of the tissue by the induced currents. The likelihood of this happening, although theoretically possible in tissues with poor perfusion (e.g. cysts and infarctions), is very slight and it is therefore not considered a significant hazard.

3.2.8 Mechanical forces on implants

The magnetic field created by single-pulse TMS and by rTMS procedures can cause forces to be exerted on metallic or paramagnetic hardware that comes within range. In general, the stimulating coil will have very little effect on small objects (e.g.
aneurysm clips located approximately five centimetres away from the stimulating equipment), but larger objects placed within 20cm of the coil will be subject to much more significant physical forces. The object’s size, conductivity and its ferromagnetic properties will all affect the amount of force exerted upon it by the magnetic field. Individuals, therefore, who have any sort of metal in the head (apart from the mouth) are generally contraindicated against undergoing single-pulse TMS or rTMS procedures, as a precaution against the magnetic field causing dislodgement of the metal. For the same reason, individuals fitted with cardiac pacemakers, implanted medication pumps, cochlear devices or other electronic implants must also be excluded from single-pulse TMS or rTMS procedures, in case of dislodgement or interference with and inactivation of the equipment.

3.2.9 Heart rate, blood pressure and secretions

Transcranial magnetic stimulation can have an effect on blood pressure and heart rate in some individuals. Andoh et al. showed that strong pulsed magnetic fields, when applied with the centre of the coil approximately above the left ventricle, can cause arrhythmia, but the pulse levels used in their study far exceeds those generally used in any kind of TMS procedures. On the whole, TMS is not believed to adversely affect blood pressure and is unlikely to result in adverse cardiovascular effects. It has been reported, however, that left-sided stimulation may reduce mean arterial pressure and cause blood pressure problems, although the patient in whom this complication was noted was mildly hypertensive. It should also be noted that the blood pressure at the time of complaint was not markedly different from the base rate.

Transcranial magnetic stimulation has no adverse effects on prolactin secretion, suggesting that the induction of seizures is not directly linked to the procedure (see also Section 3.2.1). Bridgers even found that prolactin levels dropped slightly in some individuals during TMS procedures, though he could give no explanation for this fact.

3.2.10 Muscular problems and motor movements

Muscular contractions and involuntary movements can arise from rTMS procedures. For example, contraction of the facial and eye muscles that are in proximity to the coil can cause tingling and occasional mild spasms. These tend only to be seen during the actual stimulus trains. Occasionally, the nose will itch when the stimulus is applied. Sometimes, the contractions and movements are a little more serious. Figiel et al. terminated treatment in a 66-year-old man following development of brisk muscular contractions in the right upper extremities. Once treatment had ceased the contractions stopped. Another individual in the same study, a woman with pre-existing motor tics in the right upper and lower extremities, found that the first rTMS treatment caused them to recur. Limb flexion occurred periodically for 20 minutes without affecting speech or alertness. Gentle, repeated pressure to the arm or leg caused it to stop. The administration of intravenous lorazepam terminated these movements, and no subsequent complications.
were seen. In some cases, moving the coil until the contractions lessen, or the reduction of the magnetic field, can help terminate these problems.

### 3.2.11 Mania

There have been several cases of manic symptoms being induced by rTMS procedures in depressed patients and it is possible that this is a corollary of using rTMS for depression in bipolar disorder, as pharmacological treatment of depression in patients with bipolar disorder can also result in mania. However, George et al. and Janicak et al. used rTMS in patients with bipolar disorder without inducing mania. Cohen et al. described the switch to mania in two patients suffering post-traumatic stress disorder following three rTMS sessions. In all cases these individuals were not psychotic nor a real or immediate danger to themselves or others. The symptoms of mania ceased following withdrawal of rTMS. It is still unknown, however, whether the inducement of mania was intrinsically linked to the rTMS, to a certain disorder, or to the individuals themselves. In most cases, however, there have been no instances of induced mania, and most individuals on medication for psychiatric disease that have received rTMS have tolerated it without any adverse effects.

### 3.2.12 Pregnancy

There is some difference of opinion as to the effects of exposure to single-pulse TMS or rTMS fields on pregnant women and their developing foetuses. For example, George et al. reported that a female in the second trimester of pregnancy was unaffected by exposure to rTMS, but despite this, most recommend that pregnant women be contraindicated against undergoing single-pulse TMS or rTMS for fear of foetal damage, for example, during an rTMS-induced seizure.

### 3.2.13 Sleep

It has been noted that one individual with sleep difficulties found that rTMS gave them daytime drowsiness, although this becomes progressively less and ceased after the sixth session, and that their night-time sleep improved. Sleep deprivation can, however, be an indicator for increased seizure risk, therefore care should be taken with those having difficulty sleeping.

### 3.2.14 Children and adolescents

Several studies have been undertaken to decide whether TMS is safe to use in children and adolescents. Generally, they have all found that single-pulse TMS is safe, although extra care should be taken when administering rTMS. Loo et al. concluded that rTMS appeared to be safe to use, with no adverse effects reported, but it is strongly recommended that rTMS should never be undertaken in children and adolescents without a very strong medical reason. Only two subjects were used in this study, however, indicating that further research is needed. A study conducted into children’s perceptions...
Chapter 3: Adverse Effects Associated with TMS

of single-pulse TMS found that although they did not think it very enjoyable, it was far more interesting than long car journeys. A study into treating children with Tourette’s syndrome with single- and paired-pulse TMS found that transient hand weakness, headache and pain, hearing changes and tiredness were the only adverse effects, and that these all resolved themselves by the next day.

3.3 Conclusions

Perhaps the most serious risk side effect reported for TMS is the accidental causing of seizures, but such episodes have been very rare. The levels of TMS that are necessary to cause deliberate seizures and syncope in individuals that are not predisposed to these episodes are many times greater than levels routinely used. The commonest side effect of TMS is headache which, should it prove necessary, may be mitigated by administration of commonly available analgesics. Research has also shown that single-pulse TMS is safe to administer in children and adolescents, and although great care should be taken in administering rTMS to these age groups, all the evidence thus far points towards it being safe to do so. In conclusion, the consensus of available evidence points to TMS being, within the published guidelines, a safe diagnostic and treatment method.
REFERENCES


15. Direct communication with the FDA.


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<table>
<thead>
<tr>
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<th>Headache</th>
<th>Nausea</th>
<th>Pain</th>
<th>Cognitive Effects</th>
<th>Manic Episodes</th>
<th>Motor Effects/Weakness</th>
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<th>Auditory Effects</th>
<th>N° in Trial</th>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10</td>
</tr>
<tr>
<td>Hömberg &amp; Netz 1989</td>
<td>Single-pulse TMS</td>
<td>–</td>
<td>1+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>?</td>
</tr>
<tr>
<td>Kandler 1990</td>
<td>Single-pulse TMS</td>
<td>–</td>
<td>2+ (1%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>Gates et al 1992</td>
<td>rTMS</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>?</td>
</tr>
<tr>
<td>Pascual-Leone et al 1993</td>
<td>rTMS</td>
<td>–</td>
<td>1+ (5%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1 (5%)</td>
<td>–</td>
<td>–</td>
<td>2 (11%)</td>
<td>19</td>
</tr>
<tr>
<td>Classen et al 1995</td>
<td>Single-pulse TMS</td>
<td>–</td>
<td>1+</td>
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<th>Pain</th>
<th>Cognitive Effects</th>
<th>Manic Episodes</th>
<th>Motor Effects/Weakness</th>
<th>Sleep/Tiredness</th>
<th>Auditory Effects</th>
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<td>–</td>
<td>–</td>
<td>–</td>
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<td>rTMS</td>
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<td>2</td>
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<td>–</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
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<td>George et al 1997</td>
<td>rTMS</td>
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<td>–</td>
<td>4 (33%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>–</td>
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</tr>
<tr>
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<td>rTMS</td>
<td>12 (92%)</td>
<td>–</td>
<td>1 (8%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Figiel et al 1998</td>
<td>rTMS</td>
<td>–</td>
<td>1 (2%)</td>
<td>10 (18%)</td>
<td>–</td>
<td>3 (5%)</td>
<td>–</td>
<td>–</td>
<td>3 (5%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Loo et al 1999</td>
<td>rTMS</td>
<td>–</td>
<td>–</td>
<td>3 (17%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>1 (6%)</td>
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## Appendix 1: Table of Side Effects Seen in Human Participants of the Included Papers

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<tr>
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<th>Total No. of Participants</th>
<th>Seizure / Syncopae</th>
<th>Headache</th>
<th>Nausea</th>
<th>Pain</th>
<th>Cognitive Effects</th>
<th>Manic Episodes</th>
<th>Motor Effects/Weakness</th>
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<th>Auditory Effects</th>
<th>No. in Trial</th>
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<tr>
<td>Menkes et al</td>
<td>1999</td>
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<td>14</td>
<td>7 (50%)</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>14</td>
</tr>
<tr>
<td>Pridmore et al</td>
<td>1999</td>
<td>rTMS</td>
<td>22</td>
<td>–</td>
<td>1 (5%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1 (5%)</td>
<td>–</td>
<td>22</td>
</tr>
<tr>
<td>Triggs et al</td>
<td>1999</td>
<td>rTMS</td>
<td>10</td>
<td>–</td>
<td>3 (30%)</td>
<td>–</td>
<td>5</td>
<td>(50%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10</td>
</tr>
<tr>
<td>George et al</td>
<td>2000</td>
<td>rTMS</td>
<td>32</td>
<td>30 (94%)</td>
<td>10 (31%)</td>
<td>–</td>
<td>2 (6%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>32</td>
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<tr>
<td>Mosimann et al</td>
<td>2000</td>
<td>rTMS</td>
<td>25</td>
<td>25 (100%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>25</td>
</tr>
<tr>
<td>Niehaus et al</td>
<td>2000</td>
<td>rTMS</td>
<td>11</td>
<td>11 (100%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>–</td>
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<th>Seizure / Syncope</th>
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<th>Nausea</th>
<th>Pain</th>
<th>Cognitive Effects</th>
<th>Manic Episodes</th>
<th>Motor Effects / Weakness</th>
<th>Sleep / Tiredness</th>
<th>Auditory Effects</th>
<th>Nº in Trial</th>
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<tr>
<td><strong>Rossi et al.</strong> 2000</td>
<td>rTMS</td>
<td>5 (100%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td><strong>Dolberg et al.</strong> 2001</td>
<td>rTMS</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>?</td>
</tr>
<tr>
<td><strong>d’Alfonso et al.</strong> 2002</td>
<td>Single-pulse TMS</td>
<td>8 (100%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>8</td>
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<tr>
<td><strong>Dragoševic et al.</strong> 2002</td>
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<td>–</td>
<td>–</td>
<td>3 (30%)</td>
<td>–</td>
<td>4 (40%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td><strong>Janicak et al.</strong> 2002</td>
<td>rTMS</td>
<td>–</td>
<td>–</td>
<td>1 (7%)</td>
<td>–</td>
<td>6 (40%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>6 (40%)</td>
<td>15</td>
</tr>
<tr>
<td><strong>Jenkins et al.</strong> 2002</td>
<td>rTMS</td>
<td>25 (100%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<th>Auditory Effects</th>
<th>Nº in Trial</th>
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<tbody>
<tr>
<td>Padberg <em>et al</em> 2002</td>
<td>rTMS</td>
<td>–</td>
<td>3 (10%)</td>
<td>–</td>
<td>5 (16%)</td>
<td>–</td>
<td>–</td>
<td>5 (16%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>31</td>
</tr>
<tr>
<td>Gilbert <em>et al</em> 2004</td>
<td>Single-/paired-pulse TMS</td>
<td>23 (68%)</td>
<td>–</td>
<td>–</td>
<td>6 (18%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>~4 (~12%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>34</td>
</tr>
<tr>
<td>Abler <em>et al</em> 2005</td>
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<td>–</td>
<td>–</td>
<td>7 (2.5%)</td>
<td>10 (36%)</td>
<td>–</td>
<td>–</td>
<td>3 (11%)</td>
<td>1 (4%)</td>
<td>2 (7%)</td>
<td>–</td>
<td>6</td>
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<tr>
<td>Isenberg <em>et al</em> 2005</td>
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<td>–</td>
<td>1+ (100%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>28</td>
</tr>
<tr>
<td>Prikryl &amp; Kucerova 2005</td>
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<td>–</td>
<td>16 (100%)</td>
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<td>–</td>
<td>–</td>
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<td>Schulze-Rauschenbach <em>et al</em> 2005</td>
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<td>Seyal et al 2005</td>
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<td>9 (100%)</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>9</td>
</tr>
<tr>
<td>Anderson et al 2006</td>
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<td>22 (35%)</td>
<td>12 (19%)</td>
<td>2 (3%)</td>
<td>33 (52%)</td>
<td>–</td>
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<td>–</td>
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<td>–</td>
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<tr>
<td>Fitzgerald et al 2006</td>
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<td>–</td>
<td>5 (12%)</td>
<td>3 (7%)</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>43</td>
</tr>
<tr>
<td>Loo et al 2006</td>
<td>rTMS</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>?</td>
</tr>
</tbody>
</table>

Where ✓ (?) = these adverse effects were recorded, but the number suffering from them is unknown.
Where *= an underlying condition that made these side effects more likely existed in those suffering from them.
Where ? = the full number of individuals in the trial is unknown.
All percentage values are rounded to the nearest round figure.