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Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996

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Abstract

Single-pulse transcranial magnetic stimulation (TMS) is a safe and useful tool for investigating various aspects of human neurophysiology, particularly corticospinal function, in health and disease. Repetitive TMS (rTMS), however, is a more powerful and potentially dangerous modality, capable of regionally blocking or facilitating cortical processes. Although there is evidence that rTMS is useful for treating clinical depression, and possibly other brain disorders, it had caused 7 known seizures by 1996 and could have other undesirable effects. In June 1996 a workshop was organized to review the available data on the safety of rTMS and to develop guidelines for its safe use. This article summarizes the workshop's deliberations. In addition to issues of risk and safety, it also addresses the principles and applications of rTMS, nomenclature, and potential therapeutic effects of rTMS. The guidelines for the use of rTMS, which are summarized in an appendix, cover the ethical issues, recommended limits on stimulation parameters, monitoring of subjects (both physiologically and neuropsychologically), expertise and function of the rTMS team, medical and psychosocial management of induced seizures, and contraindications to rTMS. © 1998 Elsevier Science Ireland Ltd.

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1. Introduction

From its introduction in 1989 until recently, repetitive transcranial magnetic stimulation (rTMS) was a little known experimental means of stimulating the human brain non-invasively. Its inherent riskiness and the need for expertise in clinical neurophysiology for its use kept it in a few specialized laboratories and out of general scientific and medical awareness. In 1995, with the demonstration of possible therapeutic effects of rTMS on depression, there was a marked increase in interest among psychiatrists, neurologists, basic scientists, and the public. Coincidently, rTMS induced seizures in several subjects who were participating in research studies at the National Institute of Neurological Disorders and Stroke (NINDS) and elsewhere. Although the safety of rTMS had been explored (Hufnagel et al., 1993; Pascual-Leone et al., 1993; Wassermann et al., 1996c) and guidelines for its safe use were promulgated (Pascual-Leone et al., 1993), it became clear that additional information was needed. To this end, an international workshop on the risk and safety of rTMS was held in June 1996 in Bethesda, Maryland. The workshop brought together some of the leading researchers in the fields of neurophysiology and psychiatry who are currently using the technique, along with several basic and applied scientists and clinicians whose work has bearing on decisions regarding the safe and ethical use of rTMS. Other scientists and clinicians who are involved in projects using rTMS were also in attendance. The workshop participants catalogued the known and potential risks of rTMS, and reached consensus on guidelines for its safe and ethical use. They also agreed on a nomenclature for TMS. This paper summarizes the workshop's deliberations.

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2. Nomenclature

In a universal system of referring to the different types of TMS, the term 'repetitive TMS' should replace the terms 'rapid TMS' and 'rapid-rate TMS' and should be used to refer to regularly repeated TMS delivered to a single scalp site. The term 'fast' or 'high-frequency' rTMS should be used to refer to stimulus rates of more than 1 Hz, and the term 'slow' or 'low-frequency' rTMS should be used to refer to stimulus rates of 1 Hz or less. This division is based on the different physiological effects and degrees of risk associated with low- and high-frequency stimulation. According to the U.S. Food and Drug Administration (FDA), stimulation frequencies of more than 1 Hz always carry significant risk, whereas certain studies using lower frequencies may not carry significant risk. In the present paper, the term 'single-pulse TMS' is used to refer to arrhythmical stimulation with conventional magnetic stimulators capable of delivering pulses not more than once every few seconds.

3. Principles of TMS

TMS uses the principle of inductance to get electrical energy across the scalp and skull without the pain of direct percutaneous electrical stimulation. It involves placing a small coil of wire on the scalp and passing a powerful and rapidly changing current through it. This produces a magnetic field that passes unimpeded and relatively painlessly through the tissues of the head. The peak strength of the magnetic field is related to the magnitude of the current and the number of turns of wire in the coil. The magnetic field, in turn, induces a much weaker electrical current in the brain. The strength of the induced current is a function of the rate of change of the magnetic field, which is determined by the rate of change of the current in the coil. In order to produce enough current to excite neurons in the brain, the current passed through the coil must change within a few hundred microseconds.

The stimulators and coils currently in production develop about 1.5–2 tesla (T) at the face of the coil and are thought to be able to activate cortical neurons at a depth of 1.5–2 cm beneath the scalp (Epstein et al., 1990; Rudiak and Marg, 1994). Even though TMS with conventional equipment appears to penetrate no deeper than the cortex, it may affect cells trans-synaptically at some distance from the site of stimulation, as evidenced by its effect on distant cortical and subcortical sites detected with positron emission tomography (Kimbrell et al., 1997; Paus et al., 1997; Wassermann et al., 1997).

Single-pulse magnetic stimulators repeat pulses no faster than once every few seconds. Faster cycling is prevented by the charging time of the capacitors, which store the electrical charge that generates the current in the coil. In the last 10 years, stimulators using multiple capacitors and capable of generating pulses at up to 60 Hz have been introduced. High-frequency stimulation can also be produced by multiple stimulators that discharge through a single coil and are triggered in sequence by a microprocessor. The number of pulses that these systems can deliver in a single train may be limited by the number of stimulators, but very high pulse frequencies are possible. Heating of the coil is a problem that potentially endangers subjects as well as equipment and limits the duration of stimulation at high intensities and frequencies. To deal with this problem, one manufacturer has developed a water-cooled coil that can be energized at high stimulus rates and intensities for extended periods.

4. TMS of the corticospinal system

In classic TMS experiments, stimulation is delivered to the primary motor cortex (M1), and motor evoked potentials (MEPs) from a muscle or set of muscles are recorded with surface EMG electrodes. The intensity of TMS is typically given as a multiple or percentage of the threshold intensity for evoking MEPs of a certain amplitude in a specified fraction of a series of consecutive trials in a hand muscle. Because thresholds to TMS vary greatly in the population, measures of intensity that take into account the biological efficacy of the stimulus in the individual subject rather than the output of the stimulator are critical. The multiple of the threshold for eliciting MEPs in a muscle with a low threshold is most often used as the unit of stimulus intensity. However, this is problematic for studies involving stimulation of regions other than the M1, where the threshold for the target effect and other unintended effects of TMS may differ from that for MEPs with stimulation of the M1. For instance, speech arrest can be produced at a moderate stimulus intensity in some patients receiving anti-epileptic drugs even though they have very high MEP thresholds. The relation between the MEP threshold determined with single pulses and the safety of rTMS trains at the same nominal stimulus intensity may also be influenced by technical factors. Users of a prototype of one stimulator model (Amassian et al., 1993) found that at high stimulus intensities the amplitude of the second pulse in a pair was reduced when the interval between the pulses was as long as 100 ms, and others (Valls-Solé et al., 1992) found significant attenuation at intervals shorter than 50 ms. Since its introduction, this stimulator's reliability appears to have been substantially improved. Manufacturers specify various degrees of reduction of stimulus intensity at different frequencies, and one model provides a read-out of realized peak current change (di/dt). However, to avoid errors in estimating the intensity of rTMS, investigators are urged to calibrate their devices using precise physical measurements of output.

The motor cortex is said to be among the most epileptogenic of brain areas (Gottesfeld et al., 1944; Penfield and Jasper, 1954; Ajmone-Marsan, 1972; Prince, 1987). If this is

true, the MEP threshold may provide a reasonable reference with respect to an individual's susceptibility to seizure induction. On the other hand, an absence of systematic differences in the after discharge threshold in different cortical areas has been reported (Lesser et al., 1984). The relation between the MEP threshold and the seizure threshold is also uncertain because the MEP threshold has always been tested with single stimuli, whereas rTMS induces seizures by the cumulative effect of trains of pulses, and the MEP threshold may change over the course of a train of rTMS. The relation between the MEP and seizure thresholds needs to be explored systematically, which may require experimental studies on animals.

MEPs have the lowest threshold in the muscles of the hand (Wassermann et al., 1992), probably because of the richness of the corticospinal projection that impinges on their spinal motor neurons. Pascual-Leone et al. (1993) found that rTMS trains of low frequency and intensity delivered to the hand area of the M1 produced series of uniform MEPs, which were restricted to hand muscles. However, as the stimulus frequency and intensity increased, excitation, as evidenced by the production of MEPs, spread to more proximal muscles in the arm in an orderly somatotopic fashion. As they spread, the central latency of the MEPs increased, suggesting activation of increasingly distant and/or higher threshold areas of the M1 via intracortical conduction. This was interpreted as evidence that high-frequency and high-intensity rTMS can overcome the intrinsic neural inhibition in the M1, allowing the apparent intracortical spread of excitation and creating a necessary condition for epileptogenesis. This theory was borne out by the observation of such spread of excitation immediately before the occurrence of a seizure induced by rTMS (Pascual-Leone et al., 1993).

High-frequency rTMS may also cause rhythmic series of MEPs that persist briefly after stimulation ends. This is considered to be the EMG equivalent of an EEG afterdischarge. The phenomena of intracortical spread of excitation and afterdischarge in a study of 9 subjects at NINDS, one of whom had a seizure, were used as the basis on which the maximum safe combinations of stimulus intensity, frequency, and duration for single trains of rTMS were defined (Pascual-Leone et al., 1993). Later, as more subjects were studied, more combinations of parameter settings were included (see Table 3).

Pascual-Leone et al. (1994c) found that at stimulus intensities exceeding the MEP threshold, the frequency of an rTMS train had a strong effect on the pattern of MEPs elicited by the individual stimuli comprising the train. For instance, at 10 Hz, a pattern emerged wherein every second stimulus induced a very large MEP and the intervening stimuli produced little or no response. This phenomenon appears to be caused by the interaction of the stimulus frequency with the cycle of excitatory and inhibitory activity induced by TMS, which produces inhibition in the period approximately 30–200 ms after the stimulus (Valls-Solé et al., 1992). Higher stimulus frequencies, particularly at high intensities, could theoretically deliver pulses during an earlier excitatory phase that occurs approximately 10 ms after the conditioning stimulus (Valls-Solé et al., 1992).

In addition to producing different patterns of MEPs at different stimulus intensities and frequencies (Pascual-Leone et al., 1994c), rTMS can produce longer lasting or 'conditioning' effects on the excitability of the M1, as reflected in the MEP threshold and amplitude. For instance, stimulation of the M1 at supra-threshold intensities and a frequency of 1 Hz produces inhibition of MEPs that occurs within a few seconds and lasts minutes (Wassermann et al., 1996c). When 0.9 Hz rTMS was delivered for 15 min at an intensity of 1.1× the MEP threshold and the excitability of the M1 was measured before and after a conditioning stimulus (15 min of 0.1 Hz stimulation), significant inhibition usually occurred (Chen et al., 1997). However, in one subject, intracortical spread of excitation appeared to develop after several minutes of stimulation without any increase in the amplitude of the MEP elicited from the target muscle. This effect may have been caused by shifting the position of the coil or some other extrinsic factor, but it also may be that not all regimens of stimulation tending to produce enhanced inhibition are free of epileptogenic potential. The stimulus frequency appears to have critical effects on the type of conditioning induced in the M1 by rTMS. In studies by Pascual-Leone et al. (1994c and unpublished data), the MEP threshold was lowered for minutes after 10 Hz rTMS at intensities below the MEP threshold, with no emergence of MEPs or other indications of epileptogenic activity. Both of these effects of rTMS have actual and potential experimental and therapeutic applications.

5. Applications of rTMS

5.1. Language localization and other cognitive studies

Aside from the attempted activation of epileptogenic foci, the earliest application of rTMS was as a non-invasive means of producing speech arrest with stimulation of the motor speech area of the dominant frontal lobe (Pascual-Leone et al., 1991). This important work demonstrated that unlike single-pulse TMS, rTMS could produce sustained and spatially selective interruptions of organized neural activity, which allowed the non-invasive mapping of cognitive and perceptual processes on the human cortex. The accuracy of rTMS-induced speech arrest in determining language laterality was borne out in a larger study (Jennum et al., 1994a), and the technique has been improved for optimal comfort and safety in normal subjects (Epstein et al., 1996). During left hemisphere stimulation, there may be transient deficits in the recall of verbal stimuli (Grafman et al., 1994), and stimulation of the language-dominant temporal lobe disrupts the ability of subjects to name objects presented

visually (Wassermann et al., 1996a). Selective effects on the mnemonic encoding of words and pictures have also been found with stimulation at sites in the temporal and frontal lobes (Blaxton et al., 1996). rTMS has also been used to map cortical areas involved in other processes, such as working memory (Pascual-Leone and Hallett, 1994), visual perception and attention (Pascual-Leone et al., 1994a), and motor learning (Pascual-Leone et al., 1996c).

5.2. Parkinson's disease

In medicated patients with Parkinson's disease, continuous rTMS of the M1 with an intensity just below motor threshold improved their reaction time and performance on the grooved pegboard task (Pascual-Leone et al., 1994b). The physiological basis of this effect is uncertain, but it appears that rTMS has the effect of increasing the sensitivity of the M1 or replacing the excitatory drive from the ventral thalamus on the motor cortex, which is deficient in Parkinson's disease.

5.3. Psychiatric disorders and mood

George et al. (1996) and Pascual-Leone et al. (1996a) found that rTMS of the prefrontal cortex of healthy subjects affected their mood. These studies, and unpublished observations from the same laboratories, showed small but significant increases in self-rated happiness and alertness with stimulation of the right prefrontal area, and the opposite effect (generally increases in sadness) with stimulation of the left prefrontal area. Further, clinical improvement was found in severely depressed subjects after daily rTMS of the left prefrontal region (George et al., 1995; Pascual-Leone et al., 1996b; George et al., 1997). In one subject, this change was accompanied by normalization of decreased glucose metabolism in the prefrontal area (George et al., 1995). This work was the first indication of a potential therapeutic role for non-invasive brain stimulation. The use of rTMS for the treatment of obsessive-compulsive disorder (Greenberg et al., 1997) and other psychiatric disturbances is currently being tested, with encouraging preliminary results.

5.4. Epilepsy

Physiological and safety studies of rTMS show inhibition of the motor cortex after low-frequency stimulation, which suggests that such stimulation may be useful for suppressing the development or spread of epileptogenic activity (Wassermann et al., 1996c; Chen et al., 1997). Weiss et al. (1995) showed that in rats whose seizure thresholds were lowered (kindled) with high-frequency amygdala stimulation, 15 min of 1 Hz stimulation daily for 1 week produced a marked and long-lasting increase in the seizure threshold. Similar but less dramatic effects were also present at frequencies of up to 20 Hz (S.R.B.Weiss, unpublished data). The investigators called this phenomenon 'quenching' in contrast with kindling, and it may be analogous in some respects to associative long-term depression.

5.5. Activation of epileptogenic foci

The non-invasive activation of epileptogenic foci has been a goal of researchers and clinicians interested in epilepsy ever since transcranial stimulation was introduced. Using single TMS pulses spaced seconds apart, Hufnagel et al. (1990) were unable to produce seizures in 5/6 medicated patients with temporal lobe epilepsy. Steinhoff et al. (1992) found dramatic suppression of epileptiform spikes on the EEG with a similar paradigm. Schüler et al. (1993) observed that single-pulse TMS activated epileptogenic foci in 3/10 patients with epilepsy, whereas hyperventilation produced epileptiform EEG activity in 6 patients. Classen et al. (1995) reported that TMS of a patient with epilepsy activated an epileptogenic focus in the supplementary motor area, resulting in a generalized convulsion. Dhuna et al. (1991), the first to use rTMS as a provocative procedure in focal epilepsy, failed to activate foci in 8 patients despite high stimulus intensities and frequencies. They did, however, produce a secondarily generalized seizure by stimulating the unaffected hemisphere of a patient with temporal lobe epilepsy (see Table 2). Jennum et al. (1994b), attempting to activate seizure foci in 10 unmedicated patients with temporal lobe foci, used high-intensity and high-frequency stimulation and not only failed to produce seizures but also caused significant, if transient, reductions in epileptiform EEG activity.

Tassinari and colleagues, who have used rTMS in more than 60 patients with various types of epilepsy, observed apparently rTMS-induced seizures in 2/10 patients with progressive myoclonus epilepsy and in 1/4 patients with epilepsia partialis continua (unpublished data). These events occurred 5–10 min after the cessation of stimulation. It is notable that, in contrast with other types of epilepsy, the seizures in these disorders can be readily evoked by external stimuli. Michelucci et al. (1994), from this same group of investigators, reported the occurrence of an ipsilateral homonymous hemianopia lasting 5 min without 'positive' symptoms, such as hallucinations, in a medicated patient undergoing temporal rTMS. No EEG recording was made. They also mentioned two patients who experienced persistent jerking of the contralateral arm after rTMS of the M1 was stopped, indicating the presence of afterdischarges. In a study of language and memory by Wassermann et al. (1996a), no seizures occurred with rTMS, at parameter values within the safe zone (see Table 3), of the prefrontal and temporal areas of 14 patients with epilepsy. In view of the induction of seizures by rTMS in normal subjects, the difficulty of producing seizures in patients with epilepsy seems paradoxical, especially given that all of the studies, except those at the NINDS, used combinations of stimulus parameters exceeding the guidelines for safety, at least for

Table 1

Potential adverse effects of rTMS

Known	Theoretical
Seizure induction	Histotoxicity
Effects on cognition	Kindling
Effects on mood	Long-term potentiation
Transient effects on hormones	Long-term depression
Transient effects on lymphocytes	Social consequences of induced seizure
Transient auditory threshold shift	
Pain and headache	
Burns from scalp electrodes	
Psychological consequences of induced seizure	

stimulation of the M1. A likely explanation is that the patients with epilepsy were taking anti-convulsant medications when rTMS was performed.

5.6. Cerebral blood flow

Transcranial Doppler measurements of cerebral blood flow velocity showed a significant increase in the middle cerebral artery on both sides with rTMS of the M1 (Sander et al., 1995). The increase was similar to that observed with physiological activation of the M1 by voluntary hand movement. A similar increase in blood flow velocity in the posterior cerebral artery occurred with occipital rTMS (frequency, 3 and 6 Hz; intensity, MEP threshold) (Sander et al., 1996). The greatest increases occurred in subjects who experienced phosphenes during stimulation. These studies provide additional evidence that physiologically significant cortical activation can occur in the absence of subjective effects.

6. Adverse effects of rTMS

Aside from its potentially beneficial clinical and research applications, rTMS is not only known to produce certain adverse cerebral and extracerebral effects, but also theoretically may be capable of eliciting other unintended or undesirable effects (Table 1).

6.1. Accidental seizures and their sequelae

Secondarily generalized or partial motor seizures have been induced by single-pulse TMS in several patients with stroke or other disorders involving the central nervous system (Hömberg and Netz, 1989; Kandler, 1990; Fauth et al., 1992). It is worth noting that some of these events took place several minutes after the stimulation ended. Epilepsy developed in at least one of these patients, presumably as a result of the underlying lesion. At least 3 unreported seizures have been caused by single-pulse TMS in patients with brain lesions (A. Eisen, U. Ziemann and H. Topka, pers. commun.).

To our knowledge, as of June 1996, 7 seizures have been produced by high-frequency rTMS in 6 different studies worldwide (Table 2). In addition to a secondarily generalized seizure elicited by Dhuna et al. (1991) in a patient with temporal lobe epilepsy (Table 2, seizure 1), accidental seizures have occurred in 5 normal volunteers and in one patient with depression. At the NINDS, 4 seizures have been produced in approximately 250 subjects studied so far, many of whom were stimulated on multiple occasions. The first of those seizures (Table 2, seizure 2) occurred during a study on the safety of rTMS (Pascual-Leone et al., 1993), and was produced in a woman by rTMS of the left M1 for approximately 10 s at a frequency of 25 Hz and an intensity of 2.5 × the MEP threshold. The seizure had a focal onset in the right arm with proximal spread and rapid generalization. Subsequently, it was learned that this woman had a first-degree relative who had a history of seizures.

Later, 3 seizures occurred in the same NINDS laboratory, and all were in women despite a predominance of men in the study group. Two of these three seizures occurred in studies in which the intensity, frequency, and duration of the rTMS trains were within the original safety guidelines (Pascual-Leone et al., 1993), but the interval between trains was very

Table 2

Seizures induced by rTMS: summary of world experience as of June 1996

Source	Subject/seizure type	rTMS train			
		Intensity (% threshold)	Frequency (Hz)	Duration (s)	Intertrain interval (s)
Dhuna et al., 1991	Temporal lobe epilepsy[b]/2° generalized	>>100	16	10	Long[a]
Pascual-Leone et al., 1993	Normal/2° generalized	250	25	10	Long[a]
Wassermann et al., 1996b	Normal/2° generalized	105	15	0.75	0.25
	Normal/2° generalized	110	25	0.8	1
NINDS, unpublished	Normal/2° generalized	120	15	2.5	Long[a]
B. Mercuri, unpublished	Normal/partial motor	130	3	7	Long[a]
A. Pascual-Leone, unpublished	Depression, on medication/2° generalized	90	10	10	60

[a]The intertrain interval did not appear to be a factor in seizure induction.
[b]The hemisphere contralateral to the side of the seizure focus was stimulated.

short (Wassermann et al., 1996b). One seizure (Table 2, seizure 3) occurred when 3 750 ms trains of rTMS, at a frequency of 15 Hz, an intensity of 105% of the MEP threshold, and an intertrain interval of 250 ms, were delivered to the left prefrontal area. The seizure started with the emergence of twitches in the right hand that were initially time-locked to the stimulus but became spontaneous, spread proximally, and became generalized within seconds. The other seizure (Table 2, seizure 4) occurred during a study designed to find the minimum safe intertrain interval by monitoring for afterdischarges and intracortical spread of excitation when 800 ms trains of rTMS, at a frequency of 25 Hz, an intensity of 1.1 × the MEP threshold, and an intertrain interval of 1 s, were delivered to the M1. Another seizure (Table 2, seizure 5) occurred in the NINDS laboratory (unpublished data) when 2500 ms trains of rTMS, at a frequency of 15 Hz, an intensity of 1.2 × the MEP threshold, and an intertrain interval of approximately 2 min, were delivered to the M1.

A partial motor seizure (Table 2, seizure 6) occurred in a healthy man after a 7 s train of rTMS, at a frequency of 3 Hz and an intensity of 1.3 × the MEP threshold, was delivered to the M1 (B. Mercuri, unpublished data).

Finally, a woman with psychotic depression who was participating in a treatment trial of rTMS had a seizure (Table 2, seizure 7) when 10 s trains of rTMS, at a frequency of 10 Hz, an intensity of 0.9 × the MEP threshold, and an intertrain interval of 1 min, were delivered to the prefrontal area (A. Pascual-Leone, unpublished data). She had received rTMS to this area several times before without mishap. The seizure occurred after the subject began taking amitriptyline and haloperidol without the investigators' knowledge (A. Pascual-Leone, unpublished data).

None of these subjects has suffered lasting physical sequelae. In most of them, EEGs obtained immediately after the seizure showed slowing, but normalized within 1 or 2 days. Two subjects had neuropsychological testing before and after the seizures (Pascual-Leone et al., 1993; Wassermann et al., 1996b). Both subjects had mild recall deficits, which disappeared within 24 h. However, the subject reported by Pascual-Leone et al. (1993) experienced some degree of anxiety about the possibility of a recurrent seizure. She reported becoming acutely anxious whenever she experienced any sort of muscular cramping or discomfort in the right arm. After being told by the technologist that epileptic activity could be provoked by the photic activation procedure performed during the EEG, she said she actively avoided flashing lights, believing that they would cause another seizure. There is no evidence to suggest that a single provoked seizure, or even a series of induced seizures, as in electroconvulsive therapy (ECT) for depression, makes another seizure more likely in an otherwise healthy individual (Devinsky and Duchowny, 1983).

Syncope, which occasionally occurs in normal subjects, can be mistaken for, or accompanied by, seizures. Syncope has been observed in a few subjects undergoing TMS, but is unlikely to be caused by brain stimulation. When loss of consciousness occurs in the TMS laboratory, its cause should always be investigated. Pseudoseizures can also occur during rTMS, particularly in patients with epilepsy, and occasionally can be difficult to distinguish from true seizures without EEG monitoring.

6.2. Neuropsychological and motor effects

Although several studies have examined the transient effects of focal rTMS on various cognitive, perceptual, or motor functions, very few have considered its longer-lasting, unintended effects. Pascual-Leone et al. (1993) screened for various types of deficits in 9 normal subjects before and after stimulation of several scalp positions at maximum stimulus intensity and in a range of frequencies. Neuropsychological tests included the immediate and 20 min delayed story recall tests from the Wechsler Memory Scale-Revised (WMS-R), selective reminding, word fluency, Boston naming test, serial reaction-time test, and letter identification task (Posner paradigm). Neurological examinations were performed before and after stimulation. There was no significant effect of rTMS on any of these tests, except in one subject who had a seizure (Table 2, seizure 2). However, there was a trend toward shortening of motor reaction time and improved verbal memory in the subjects who received the greatest number of stimuli at the highest frequencies. The effect on recall was most pronounced in those subjects who had received the most stimulation.

Wassermann et al. (1996c) examined the delayed (1–2 h post-rTMS) effects of exposure to two different frequencies and intensities of rTMS (1 Hz and 1.25 × MEP threshold; 20 Hz and 1.0 × MEP threshold) delivered to multiple scalp positions in the same subjects. Increases in finger tapping frequency were most pronounced after 1 Hz stimulation contralateral to the tapping finger. A neuropsychological test battery, consisting of the immediate and delayed tests of story recall from the WMS-R and a verbal fluency task requiring generation of words based on a semantic category and a letter, was administered. As in the earlier study (Pascual-Leone et al., 1993), the only notable cognitive finding was a trend toward enhanced delayed story recall with 20 Hz stimulation.

In another study (J. Grafman and E.M. Wassermann, unpublished data), subjects were tested for finger tapping frequency, completion time for the grooved pegboard task, and WMS-R logical memory subtest scores before and after exposure to 150 trains of rTMS (train duration, 750 ms; frequency, 15 Hz; intensity, 1.2 × MEP threshold) at each of four scalp positions (study time, approximately 3 h). There was a significant decrease in the scores on the WMS-R logical memory subtest when subjects were tested within 1 h after rTMS. These subjects have not yet been reexamined, so the time course of their recovery is

unknown. However, for the adverse effects of rTMS on memory, there is apparently a threshold below which enhancement of certain functions may occur.

6.3. Effects on mood

Crying has been observed in some subjects receiving intense left prefrontal rTMS in studies of speech arrest (Pascual-Leone et al., 1991; Michelucci et al., 1994) and in a subject receiving intense stimulation of the motor speech area who also had a seizure shortly afterward (Table 2, seizure 3) (Wassermann et al., 1996b). The crying episodes are consistent with reports of dysphoria with milder left-sided stimulation in normal subjects (George et al., 1996; Pascual-Leone et al., 1996a), although one subject (Wassermann et al., 1996b) noted that the crying was out of proportion to the degree of emotion or pain that was experienced. In contrast, in another rTMS study (Epstein et al., 1996) that was performed on the investigators themselves, speech arrest was accompanied by laughter. The coexistence of speech arrest and laughter has also been observed in epileptic, hemiparetic, and normal subjects who were relaxed and well-prepared for the experiment. These subjects usually described the experience of speech arrest as 'weird' but not necessarily unpleasant (A. Pascual-Leone and E.M. Wassermann, unpublished data).

6.4. Effects on hormones

Pascual-Leone et al. (1993) tested serum levels of hormones, including prolactin, adrenocorticotropic hormone, thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone. No hormonal changes were found, except in the subject who had a seizure (Table 2, seizure 2). Wassermann et al. (1996c) found no changes in prolactin levels with rTMS at a frequency of either 1 Hz or 20 Hz. George et al. (1996) found consistent increases in thyroid-stimulating hormone that paralleled subjective decreases in sadness after 5 Hz rTMS of the right prefrontal area. In an earlier study on mood (M.S. George and E.M. Wassermann, unpublished data), one of the subjects had an increase in the serum prolactin level accompanied by acute dysphoria after midfrontal rTMS.

6.5. Immunological effects

Amassian et al. (1994) reported lateralized effects of single-pulse stimulation on T lymphocyte subsets. For instance, the number of CD8 + cells increased as much as 100% with left-sided stimulation, but decreased with stimulation on the right. The increases, which appeared to be consistent across individuals, resolved within 48 h. Comparable changes in lymphocyte subpopulations can occur with mild stress (Dhabhar et al., 1994, 1995), the normal circadian cycle (Fukuda et al., 1994), and the menstrual cycle (Northern et al., 1994).

6.6. Effects on hearing

Rapid mechanical deformation of the stimulating coil when it is energized produces an intense, but deceptively mild-sounding click. After exposure to single-pulse TMS, animals have had permanent increases of the auditory threshold (Counter et al., 1990) and humans transient increases (Pascual-Leone et al., 1992). Foam earplugs were useful in avoiding changes in the auditory threshold of volunteers participating in the safety study of rTMS (Pascual-Leone et al., 1993).

6.7. Local pain and headache

Muscles and nerves near the stimulating coil are activated by TMS. The resulting discomfort is rarely a problem with single-pulse TMS, but rTMS can be quite uncomfortable for some subjects, particularly with stimulation over frontal areas, where there is more muscle overlying the skull. The discomfort apparently is related to the intensity and frequency of the stimulation. Varying the stimulus intensity and frequency may minimize the pain. For instance, Epstein et al. (1996) found that by lowering the frequency and increasing the intensity, they could produce marked effects on speech without excessive pain.

In susceptible individuals, rTMS may cause persistent muscle tension-type headaches. The headaches usually respond well to mild analgesics. In a depressed subject, rTMS produced rapid relief of migraine headache and relief of depressed mood and psychomotor retardation (M.S. George, pers. commun.). On the other hand, in a subject with migraine, occipital stimulation caused typical scotoma and the subsequent development of headache. (B.D. Greenberg, pers. commun.).

6.8. Scalp burns from electrodes

Eddy currents induced in metal surface EEG electrodes located near a stimulating coil can cause heating and skin burns during rTMS (Roth et al., 1992). Heating is related to the size and conductivity of the electrode as well as the stimulation parameters. Radial notching of electrodes can reduce their tendency to heat by interrupting the current path. Induced currents in wires can also be reduced by keeping them free of loops near the stimulating coil.

6.9. Histotoxicity

The main source of histotoxicity potentially occurring with TMS results from mass hyperexcitation of neurons and is related directly to the efficacy of the stimulation. With cortical electrical stimulation, the co-factors in neural injury are 'charge per phase' and 'charge density.' Charge per phase is the amount of charge (in microcoulombs, μC) passed across the electrode face during each phase of the stimulus waveform, and charge density is the charge per

phase divided by the active surface area of the electrode (in cm^2). McCreery et al. (1990) examined the effect of various combinations of charge per phase and charge density on animals stimulated for 7 h with cortical surface electrodes at 50 Hz with a phase duration of 400 μs. The parameter space in which there was no detectable histological damage was roughly bounded by a straight line connecting a charge per phase of 10 μC and a charge density of 100 $\mu C/cm^2$. No detectable histopathological effects could be produced with up to 24 h of 20 Hz stimulation with any attempted combination of charge per phase and charge density (Agnew and McCreery, 1987). In the one comparable study performed on humans (Gordon et al., 1990), two patients with epilepsy received 50 Hz subdural stimulation of the anterior temporal lobe for fairly brief periods with a maximum charge per phase of 4.5 μC and a charge density of 57 $\mu C/cm^2$ before resection of the temporal lobe. Light microscopy showed no evidence of histological damage to the stimulated tissue. It should be noted that this combination of parameters yields a combination of charge density and charge per phase that would have been unsafe in the study of McCreery et al. (1990). Manufacturers' estimates of the maximal charge density of currently available TMS devices are on the order of 2–3 $\mu C/cm^2$ and continuous 50 Hz stimulation is beyond the effective operating range of most magnetic stimulators. Therefore, the chance of producing excitotoxicity with rTMS seems to be remote.

The only other known potential source of tissue injury from rTMS is ohmic heating of tissue by induced currents. Although, theoretically, such heating is possible in poorly perfused volumes, such as infarctions and cysts, it is not considered to be a significant hazard of rTMS.

Fifty high-intensity pulses of TMS had no behavioral or histopathological effect on rats (Mano et al., 1988). However, dopamine and serotonin turnover increased 60 min after stimulation ended, but disappeared by 4 days. Other studies of the effect of rTMS on rats showed biochemical evidence of increased noradrenergic activity (R.H. Belmaker, unpublished data) and enhancement of apomorphine-induced stereotypy and reduction of immobility on the Porsolt swim test (Fleischmann et al., 1995). The existing reliable studies of animals' brains have failed to show any pathological changes after rTMS at a frequency of 7 Hz (Sgro et al., 1991) or higher (R.H. Belmaker and A. Pascual-Leone, unpublished data). A study in rats (Matsumiya et al., 1989) showed vacuolization of brain tissue after exposure to TMS, but this finding is generally regarded as an artifact. A study of a resected human temporal lobe that had been exposed to rTMS revealed no histopathological changes (Gates et al., 1992).

When rTMS was used in mice at intensities and frequencies that usually do not cause seizures, the expression of glial fibrillary acid protein was increased in the hippocampus and dentate gyrus, a phenomenon similar to that which occurs after the induction of seizures with electrical stimulation (M. Fujiki, unpublished data). This response may be mediated by a transient increase in extracellular potassium released by activated neurons, which has no intrinsic pathological significance (McCreery and Agnew, 1990). However, it could provide a marker for changes in gene expression, which might underlie behavioral effects.

6.10. Effects of magnetic fields

The peak field strength of conventional TMS coils is 2 T or less, which falls off very rapidly with distance from the surface of the coil, so that exposure to strong, rapidly changing magnetic fields occurs only in the head. The National Research Council (1996) has concluded that, at least for chronic household exposure, there are no proven health risks of electromagnetic fields. While the local field strength is strong, the exposure to rTMS is extremely brief, even with repeated stimulation, in comparison with exposure to common environmental sources. Prolonged exposure to TMS has not occurred except in a few investigators and others who have been habitual experimental subjects. If rTMS becomes an established therapeutic modality, this aspect of its safety may have to be investigated.

Early concerns about the effects of TMS on magnetic media in the laboratory, but distant from the coil, have not been substantiated. However, discharge of the coil near computer monitors can cause temporary color distortions, which can be corrected by degaussing. There are also various anecdotal reports of damaged watches, pagers, and credit cards.

6.11. Kindling

Kindling is a process occurring in animals wherein the repeated administration of an initially subconvulsive stimulus results in progressive intensification of induced neuroelectrical activity, culminating in a seizure. Classic kindling occurs with repeated stimulation at regular intervals with stimuli of specific combinations of intensity, frequency, and pulse duration (Goddard et al., 1969). Although kindling can be produced with frequencies in the single-hertz range (Cain and Corcoran, 1981; Minabe et al., 1986), the most effective frequency for kindling is in the range around 60 Hz, which is outside the effective range of the commercially available repetitive magnetic stimulators. Kindling also generally requires pulse durations of 1 ms, which is longer than the current pulse produced by these magnetic stimulators. Kindling is usually produced in the amygdala and hippocampus in rodents, and the neocortex is relatively resistant to kindling (Engel, 1989; Racine et al., 1989). Secondary epileptogenesis is an allied process in which ongoing epileptogenic activity at a single site appears to induce the emergence of a mirror-image focus in the opposite hemisphere (Morrell, 1989). Conceivably, repeated rTMS could act as an inducer of epileptogenesis at distant sites. Kindling may be a factor in the genesis of human epilepsy, and there is a report of a phenomenon resembling

kindling occurring in a single subject with chronic thalamic stimulation for phantom pain (Sramka et al., 1977). However, it has not been observed in humans, who have received even prolonged cortical stimulation (Goldensohn, 1984) or frequent ECT over many years (Devinsky and Duchowny, 1983). While kindling and secondary epileptogenesis are unlikely to occur with the rTMS protocols currently in use, they must remain safety considerations, especially with repeated stimulation near the threshold for afterdischarge and in long-term treatment regimens. Animal studies in this area may be helpful.

A related concern is long-term potentiation (LTP), where repetitive electrical brain stimulation at high frequencies results in long-lasting physiological potentiation (Sastry et al., 1986; Gustafsson and Wigstrom, 1988; Iriki et al., 1991; Sil'kis et al., 1994) and ultrastructural changes (Geinisman et al., 1993) in central synapses. The mechanisms underlying LTP and the kindling processes may be related (Matsuura et al., 1993). It is conceivable that LTP, which is believed to underlie some types of behavioral conditioning and learning, could be induced by intense rTMS, with resultant behavioral changes. Brain stimulation appears to be more effective in inducing synaptic changes in younger animals (Geinisman et al., 1994), which suggests that children might be more vulnerable to such changes if they can be induced with rTMS.

While stimulation in the single-hertz range can result in kindling under some conditions, it can also produce long-term depression (LTD) of synaptic transmission (Stanton and Sejnowsky, 1989; Artola et al., 1990; Christie et al., 1994; Linden, 1994) and prevent and partially reverse kindling (Weiss et al., 1995). As mentioned earlier, rTMS at a frequency of 1 Hz also decreases the excitability of the M1. This type of functional change is also a theoretical concern with rTMS because, as with high-frequency stimulation, repeated exposure could result in long-lasting changes. However, it also suggests the possible therapeutic application of rTMS in conditions of abnormally high cortical excitability, such as epilepsy and cortical myoclonus.

7. Relevance of animal models in TMS

Although animal models have been used to great advantage in studies of the safety of direct electrical stimulation of the brain, the implications of animal work for the safety of TMS in humans must be interpreted with great caution. Differences in the size of the head and brain, as well as in the cortical topology, between animals and humans could have pronounced influences on the efficacy of TMS. For instance, despite intensive efforts, no investigator has succeeded in producing seizures in rodents (R.H. Belmaker and P. Jennum, unpublished data) or non-human primates (H. Sackheim, unpublished data) with TMS. For ethical and logistical reasons, non-human primates must be anesthetized in studies designed to produce seizures with TMS. The non-human primate may be a poor model, even for studying the genesis of the human MEP, because TMS in anesthetized primates appears to produce a preponderance of direct activation of corticospinal cells (Edgley et al., 1990) rather than transsynaptic activation, as is apparently the case in unmedicated humans (Amassian et al., 1989).

Ideally, the safety and mechanisms of action of rTMS would be investigated in animals, where invasive monitoring techniques can provide highly specific and accurate information. However, the development of realistic models will probably require the production of stimulating coils of a size proportionate to the brain to which they are applied and, because small coils heat rapidly, of active cooling systems. Efforts in these areas are already underway in some laboratories.

8. Guidelines for the use of rTMS

Guidelines for the use of rTMS bear on ethical and legal considerations, selection of safe and appropriate stimulation parameters, physiological monitoring of data, neuropsychological analysis of subjects, composition and expertise of the rTMS team, management of the medical and psychosocial consequences of rTMS-induced seizures, and contraindications to rTMS. The guidelines are also summarized in the appendix.

8.1. Ethical requirements

Research on rTMS must be governed by three basic ethical and legal requirements pertaining to all research on human subjects. The first requirement is for informed consent, which demands that the subject's decision to participate must be voluntary and based on the provision of all relevant information. When a procedure is novel or experimental, as is rTMS, informed consent requires disclosure of all significant risks. The second prerequisite is that the potential benefit of the research must be found by an independent assessment to outweigh the risk. It is not sufficient merely that the subject be willing to accept the risk involved, and there must be no means of obtaining the desired data without placing subjects at risk. The third stipulation is for equal distribution of the burdens and benefits of research. This requirement is violated when research is conducted on categories of patients made vulnerable by economic, social, or physical conditions and who are likely to bear only its burdens.

Permissible rTMS studies may be divided into three classes in the order of their demand for protection of the subjects. Class 1 consists of studies where direct clinical benefit to the subject may be reasonably anticipated. An example of this type of study is research on the use of rTMS for the treatment of depression. Class 2 consists of studies in patients where the potential clinical benefit is

more speculative or where no clinical benefit is expected, but the study is anticipated to yield valuable data for the development of therapies for or improved understanding of disabling conditions, such as Parkinson's disease. Normal subjects may participate in these studies as control subjects. Class 3 consists of studies in normal subjects and patients that are expected to yield important data on the function of the brain, but have no immediate relevance to clinical problems.

In class 1 studies, as in all rTMS studies, all appropriate and feasible safety measures must be instituted, but stimulation parameters and schedules must be chosen with clinical goals and considerations in mind. Such regimens may pose significant risks in some cases, and, indeed, there could be instances where adverse effects (e.g., seizures) would be expected and prepared for. Nevertheless, the risks should be outweighed by the potential benefit in serious disorders where alternative therapies also have significant risks (e.g., ECT for depression). In class 2 studies, regimens that will place subjects at significant risk of seizures or other serious adverse effects should not be used, because exposure to adverse effects is unacceptable when clinical benefit is questionable or nonexistent.

The risks of seizures and other adverse effects of rTMS are significant enough to raise strong concerns about the use of normal volunteers in rTMS research. However, rTMS appears to hold the promise of important advances in the understanding of normal and abnormal brain functioning and in the treatment of psychiatric and neurological disorders. Therefore, normal volunteers should be permitted to participate in rTMS research when it is likely to produce data that are of outstanding scientific or clinical value. This does not include information that is merely of interest to a few researchers or that is likely to provide only incremental expansion of the knowledge base. Safety studies of new rTMS devices must continue to be performed in normal subjects in a manner analogous to toxicity studies of new drugs. Therefore, in class 3 studies, where normal subjects are exposed to the high risks of rTMS, the responsibility rests on the investigator to prove how the participation of normal subjects will enhance the understanding of brain function or advance the understanding or treatment of a disease, in an important way, and why there is no less risky means of obtaining such data. All studies, including safety studies, in normal subjects and patients for whom there is no potential benefit should proceed only with maximally stringent safety measures and limits on stimulation parameters. Exhaustive disclosure of known and potential risks, including the psychological and social risks of having a seizure, is mandatory in all rTMS studies.

8.2. Stimulation parameters

The maximum safe durations of single trains of rTMS at various frequencies and intensities as determined from the NINDS experience are shown in Table 3. When a seizure was induced by rTMS for which the combination of parameter settings was determined by interpolation to lie on the edge of the safe area of the parameter space (Table 2, seizure 5), the NINDS researchers reduced the allowable duration of a train by 25% in all class 2 and class 3 studies in order to increase the margin of safety. (This reduction is not reflected in Table 3.) This experience suggests that the edge of the parameter space defined by Table 3 may not be safe in all subjects and also that linear interpolation may not be a valid means of predicting the safety of combinations of settings that have not been tested.

No stimulation parameters have been promulgated for trains of pulses at an intensity below the MEP threshold or with a frequency of less than 1 Hz. Although subthreshold trains of pulses and stimulus rates of less than 1 Hz have been used without incident, as, for example, in studies of Parkinson's disease (Pascual-Leone et al., 1994b) and mood (Pascual-Leone et al., 1996a), caution is urged, because the seizure occurring in a depressed patient treated with tricyclic antidepressants and neuroleptics (Table 2, seizure 7) was caused by stimulation below the MEP threshold, as determined with single pulses. However, several subjects have been stimulated with rTMS for 30 min at a frequency of 1 Hz and an intensity just above the MEP threshold without any evidence of increased cortical excitability (Wassermann et al., 1997). Experience with 15-min trains of rTMS at a frequency of 0.9 Hz and an intensity of 1.15× the MEP threshold (Chen et al., 1997) suggests that,

Table 3
Maximum safe duration (s) of single trains of rTMS based on the NINDS experience

Frequency (Hz)	Intensity (% of MEP threshold)												
	100	110	120	130	140	150	160	170	180	190	200	210	220
1	>1800	>1800	360	>50	>50	>50	>50	27	11	11	8	7	6
5	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2
10	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4	0.3	0.3
20	2.05	1.6	1.0	0.55	0.35	0.25	0.25	0.15	0.2	0.25	0.2	0.1	0.1
25	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12	0.08	0.08

Numbers preceded by > are the longest durations tested. No after discharge or spread of excitation has been encountered with single trains of rTMS at these combinations of stimulus frequency and intensity.

under these conditions, the risk is low but that subjects should be monitored for spread of EMG activity.

When repeated trains of rTMS are used, the intertrain interval adds another dimension to the stimulation parameters. The only study designed to explore this dimension (R. Chen, unpublished data) was discontinued after a subject experienced a seizure (Table 2, seizure 4), demonstrating both the riskiness and the importance of this work. Data from this limited work suggest that with rTMS at a frequency of 20 Hz and intensities of 1.0–1.1× the MEP threshold, an interval of 5 s between trains of maximal allowable duration prevented a cumulative increase in cortical excitability when the trains were delivered in sets of ten. The only other information on the issue of the safe intertrain interval comes from Pascual-Leone et al. (1994c), who found no interaction between high-intensity trains of rTMS at frequencies of up to 25 Hz delivered at 1-min intervals.

These data should provide investigators with the basis for constructing tables with margins of safety appropriate to various types of rTMS studies. Safety margins should be conservative for the protection of subjects in class 2 and class 3 studies. In class 1 studies, which are of potential clinical benefit to the subjects, higher degrees of risk are clearly tolerable. It is also probable that the values in this set of guidelines may be safely exceeded in subjects receiving anticonvulsant medications.

8.3. Physiological monitoring

Afterdischarges following the cessation of cortical stimulation are traditionally considered the first indicator of induced epileptic activity (Ajmone-Marsan, 1972). Therefore, monitoring of the EEG from the cortex directly under the coil during rTMS would provide the most sensitive indication that the threshold for epileptogenesis had been exceeded. However, afterdischarges, while readily recorded subdurally, may not be apparent on the scalp-recorded EEG. In addition, technical difficulties prevent the recording of the EEG during rTMS in most laboratories. Most conventional amplifiers recover too slowly from the large inductive artifact of the stimulating pulse, and some stimulators emit continuous electrical noise through the coil even when not stimulating, which obscures the weaker EEG signal. The EEG electrodes may also become hot during rTMS and may cause scalp burns. These problems should be surmountable in the future, but alternative means of monitoring will be required until then.

In studies where rTMS is not expected to elicit MEPs (e.g., stimulation of the M1 below threshold), the EMG should be monitored continuously from a hand muscle, such as the abductor pollicis brevis or the first dorsal interosseous muscle, on the side contralateral to rTMS. These muscles have a low threshold for the production of MEPs, and the appearance of MEPs during an experiment may indicate the spread of excitation from neighboring areas to the M1. In a study by Wassermann et al. (1996b), this phenomenon occurred before a seizure during stimulation of the prefrontal cortex (Table 2, seizure 3). In experiments where the stimulation is expected to produce MEPs, at least two muscles in the arm contralateral to the stimulation site should be monitored. For example, if the stimulation is intended to produce isolated MEPs in the abductor pollicis brevis muscle, the appearance of MEPs in a forearm muscle, such as the extensor carpi radialis, would indicate the intracortical spread of excitation or lowering of the motor threshold. The wrist and finger extensors and the biceps and lateral deltoid muscles are convenient sites for recording MEPs.

Visual monitoring of subjects during rTMS is also important. Muscle twitching time-locked to the stimulus provides a less sensitive but potentially important indication of evoked motor activity. It might be advisable to use video monitoring in high-risk studies. In the safety study of Pascual-Leone et al. (1993), video recording was helpful in describing the afterdischarges and spread of excitation and in reconstructing the clinical events preceding the seizure. Subjects should be observed by a qualified individual at all times during rTMS.

8.4. Neuropsychological monitoring

Given the uncertain safety of rTMS and the very small region of the parameter space that has been explored in safety studies, it is important for investigators to probe for unintended, potentially adverse effects of rTMS whenever feasible, regardless of the primary goal of a particular experiment. Objective tests should be used because subjects' self-reports, while important, are not sufficiently sensitive or reliable to rule out adverse effects when the stimulation may have altered judgment and perception. These tests will help to define the safe limits of rTMS with respect to not only seizures but also other adverse effects, and may uncover potentially useful effects of rTMS or produce other valuable information.

Tests of cognitive function appear to be the most sensitive means of detecting any lasting effects of rTMS. Batteries of cognitive tests should be short and easy to administer, but sensitive enough to detect subtle deficits. In addition to a subject's self-report of mood state, a fairly comprehensive battery might contain tests of simple and choice reaction time, the ability to inhibit automatic responses (e.g., a Stroop-type task), the ability to retrieve and express symbols (e.g., word fluency test), verbal and non-verbal working and episodic memory, retrieval of information (presented before rTMS), executive functions (e.g., judgement, insight, reasoning), and overall functional state (observer rating scale for mood and various other factors). Each laboratory should institute a policy on the action to be taken in the event of significant changes in neuropsychological function after rTMS, especially in the domains of reaction time, perception, and executive function in situations where subjects might be at increased risk of injury (e.g., driving a vehicle).

8.5. The rTMS team

Repetitive TMS should be performed only in a medical setting where a skilled medical team and life-support equipment are available. The rTMS team should include a qualified clinical neurophysiologist to supervise the recording and interpretation of electrophysiological data. A physician or nurse who has experience with rTMS and is skilled in the management of seizures should be present in the rTMS laboratory whenever a subject is being studied.

8.6. Medical management of seizures

Each rTMS laboratory must institute an explicit plan for dealing with seizures, and everyone on the rTMS team must be familiar with it. There must be a place where the subject can lie in the event of a medical emergency. The team must be familiar with the location of life-support equipment and the means of summoning help. As with seizures in general, the seizures induced by TMS are usually brief and without serious physical sequelae. Thus, efforts should be focused on preventing complications of the seizure rather than starting anti-epileptic treatment. Seizure management proceeds according to the rule of A-B-C: airway-breathing-circulation, which is also common to the management of other medical emergencies. The airway should be maintained by placing the subject on his or her side. In the event of vomiting, the pharynx should be cleared with suction. Breathing should be assessed, and in the rare event of respiratory arrest, artificial respiration should be applied. Oxygen should be administered. Cardiac and circulatory status should be assessed and blood pressure measured. Cardiac arrest or circulatory failure must be treated according to local protocols. Venous access should be obtained as soon as possible, but the administration of large amounts of fluid is usually not indicated. The use of anti-epileptic drugs should be reserved for seizures lasting more than several minutes, seizures resulting in significant hypoxia or acidosis, or repeated seizures, and should be used under the guidance of an experienced physician.

8.7. Management of psychosocial consequences of seizures

Subjects who experience seizures with rTMS should be informed of the fact that they are not at a greater risk for further seizures than before. For some individuals, however, the potential psychological effects of having a seizure can be significant and should not be ignored or minimized. Informed consent documents should clearly discuss the possibility of a seizure, and investigators must ensure that the subjects understand its implications. Both medical and psychological support must be provided to patients and normal subjects who have rTMS-induced seizures.

It is readily imaginable that the report of a seizure in the medical record of a normal volunteer or certain patients could be misinterpreted or deliberately used as a pretext for the denial of employment or medical insurance. Subjects of research studies must be informed of this possibility, and investigators must make certain that documentation of seizures is done in such a way that jeopardizes subjects to the minimum extent possible. Additional documentary support of a healthy subject's claim that a provoked seizure carries no adverse prognosis must be provided when appropriate.

8.8. Contraindications to rTMS

Metallic hardware near the coil can be moved or heated by TMS. Therefore, the presence of metal anywhere in the head, excluding the mouth, is generally a contraindication to TMS. Exceptions may be made in circumstances where the physical properties of the metal object are known and there is a compelling reason for using TMS. For example, TMS studies have been carried out safely in patients with implanted brain stimulators (A. Pascual-Leone, unpublished data).

Individuals with cardiac pacemakers and implanted medication pumps should not participate in rTMS studies without a clear potential benefit (e.g., treatment of severe and refractory depression). In these cases, the manufacturer of the device should be consulted about the potential effect of the magnetic pulse on the control circuitry. TMS should not be performed in patients with intracardiac lines. Persons with serious heart disease are at increased risk in the event of a seizure, and unless the potential clinical benefit outweighs the risk, they should not participate in rTMS studies. Persons with increased intracranial pressure, such as after large infarctions or trauma, are also at increased risk in the event of a seizure, and should not receive rTMS.

Children should not be used as subjects for rTMS without compelling clinical reasons, such as the treatment of refractory epilepsy or depression. Women of childbearing age must be questioned about the possibility of pregnancy before participating in rTMS studies, and excluded if there is a chance that they may be pregnant. However, exceptions may be made if the potential benefit of rTMS is more significant than the risk.

Tricyclic anti-depressants, neuroleptic agents, and other drugs that lower the seizure threshold are contraindications to rTMS, except in extraordinary circumstances where the potential benefit outweighs the increased risk of a seizure. In all cases, even where there is substantial potential benefit, efforts must be made to withdraw such medications before rTMS is performed.

Investigators should consider using a standard questionnaire to screen rTMS candidates for a history of head trauma or head surgery, seizures, implanted hardware, medications, neurological and medical illnesses and a family history of epilepsy.

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[1]Invited participants (all of whom approved the report).
[2]Deceased.

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Appendix A. Summary of guidelines for rTMS

1. Ethical requirements. (a) Obtain subjects' informed consent, disclosing all known and potential risks of rTMS. (b) Ensure that the potential benefit of rTMS outweighs the risk. (c) Demand equal distribution of the burdens and benefits of rTMS among study populations. (d) Stratify rTMS studies according to the following criteria: Class 1. Experimental treatment of disease in patients, with potential direct clinical benefit and subject protection determined by well-defined clinical goals and risks of alternative treatments. Class 2. Development of treatment, safety studies, or improved understanding of disease in patients or normal subjects, with outstanding potential clinical value and maximum subject protection. Class 3. Basic research in patients or normal subjects, with outstanding potential scientific value and maximum subject protection. (e) Observe all reasonable safety precautions in all studies, but some significant adverse effects are acceptable in class 1 studies, and must be anticipated.
2. Stimulation parameters. (a) For class 2 and class 3 studies, base stimulation parameter limits on data shown in Table 3 and other relevant considerations. (b) Use subthreshold rTMS with caution; its safety has not been systematically investigated. (c) For class 2 and class 3 studies, allow intervals of at least 5 s between 20 Hz trains with intensities of up to 1.1× the MEP threshold. Longer intervals are required for higher intensities and frequencies.
3. Physiological monitoring. (a) Continuously monitor the EMG from hand muscles contralateral to the stimulation site for elicited MEPs when areas other than the M1 are stimulated or when the M1 receives subthreshold stimulation. Under these conditions, the presence of MEPs indicates intracortical spread of excitation or a decrease in the threshold. For rTMS stimulation of the M1 at intensities above the threshold, monitor sets of contralateral arm muscles for evidence of the intracortical spread of excitation. (b) Monitor the EEG when and if it becomes if feasible, and if electrode heating can be avoided. (c) During stimulation, have the subject observed by a physician who is experienced in the use of rTMS. (d) Consider videotaping high-risk studies.
4. Neuropsychological monitoring. (a) In all classes of rTMS studies, monitor subjects for neuropsychological effects whenever possible until the safety of the specific regimen is established. The following domains are suggested for testing: simple and choice reaction time, ability to inhibit automatic responses (e.g., a Stroop-type task), ability to retrieve and express symbols (e.g., word fluency tests) verbal and nonverbal working and episodic memory, retrieval of pre-rTMS information, executive functions (e.g., judgment, insight, reasoning), mood state (subject's self-report),and overall functional state (observer rating scale for mood and various other factors). (b) Establish a policy on protection of subjects

who might experience significant neuropsychological changes after rTMS.

5. The rTMS team. (a) Perform rTMS only in a medical setting where a skilled medical team and life-support equipment are available. (b) Have a qualified clinical neurophysiologist to monitor the recording and interpret rTMS data. (c) Make certain that a physician or nurse skilled in seizure management is present in the rTMS laboratory during and immediately after rTMS.
6. Medical management of seizures. (a) Ensure that the rTMS laboratory has a place where the subject can lie in the event of a seizure or other medical emergency. (b) Familiarize persons in the rTMS laboratory with the location of life-support equipment and the means of summoning help. (c) Manage seizures according to the A-B-C rule: airway-breathing-circulation. (d) Obtain venous access as soon as possible. (e) Use anti-epileptic drugs only under the guidance of an experienced physician and only to treat seizures lasting more than several minutes, seizures resulting in hypoxia or acidosis, or repeated seizures.
7. Management of psychosocial consequences of seizures. (a) Provide medical and psychological support to patients and normal subjects who have rTMS-induced seizures, and counsel them that they are not at a greater risk than before for further seizures. (b) Minimize the potential social impact of a seizure by medical documentation. (c) Inform appropriate subjects that a seizure induced by rTMS may affect employability and insurability. (d) When appropriate, provide additional documentary support of a healthy subject's claim that a provoked seizure carries no adverse prognosis.
8. Contraindications to rTMS. (a) Absolute: metal in cranium, intracardiac lines, increased intracranial pressure. (b) Relative: pregnancy, childhood, heart disease, cardiac pacemaker, medication pump, tricyclic anti-depressants, neuroleptics, family history of epilepsy.

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