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Safety of different inter-train intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters

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Abstract

Induction of a seizure in a normal subject with trains of repetitive transcranial magnetic stimulation (rTMS) applied in close succession suggested that short inter-train intervals, a parameter not considered in our previous safety studies, may not be safe. Here, we evaluate the safety of different inter-train intervals for rTMS in 10 healthy volunteers. Ten rTMS trains at 20 Hz for 1.6 s and a stimulus intensity of 110% of motor threshold (MT) were found to be safe at the inter-train interval of 5 s. However, inter-train intervals of 1 s or less were unsafe for trains of 20 Hz for 1.6 s and stimulus intensities higher than 100% of MT. Based on these results, we propose safety guidelines for inter-train intervals at different stimulus intensities. We also analyzed the stimulus parameters, used in 3 studies, that led to seizures in normal subjects. One seizure was due to short inter-train intervals, one was likely related to intense individual rTMS trains close to the limit of our previous safety recommendations, and one was likely due to a combination of these two factors. To provide an additional safety margin, we suggest reducing the duration for individual rTMS trains by 25% from our previous recommendations. Updated safety tables currently in use at our institution are provided. Published by Elsevier Science Ireland Ltd.

Keywords: Transcranial magnetic stimulation; Safety; Seizure

1. Introduction

High-frequency repetitive transcranial magnetic stimulation (rTMS) refers to regularly repeated TMS delivered to a single scalp site at frequencies of more than 1 Hz. It provides a noninvasive means of transiently blocking cortical neuronal networks and is a useful technique for studying human cortical physiology (Pascual-Leone et al., 1991; Grafman et al., 1994; Chen et al., 1997b). It may also have applications in treating neurological and psychiatric disorders. For example, rTMS can improve akinesia in Parkinson's disease (Pascual-Leone et al., 1994a), alter the mood in normal subjects (George et al., 1996; Pascual-Leone et al., 1996a) and improve the mood in depressed patients (George et al., 1995; Pascual-Leone et al., 1996b).

The most serious documented side effect of rTMS is the induction of epileptic seizures, caused by rTMS trains of high stimulus intensities and frequencies (Pascual-Leone et al., 1993, 1994b). Our previously reported seizure was preceded by spread of excitation to muscles not targeted for stimulation, which can be regarded as a warning sign for seizures and may be due to breakdown of cortical inhibition (Pascual-Leone et al., 1993, 1994b). The stimulus parameters that may be important in determining the likelihood of adverse effects of rTMS include stimulus intensity, frequency, train duration and number of pulses for individual trains, inter-train interval and total number of trains delivered (Fig. 1). For single trains of rTMS, we previously reported the different combinations of stimulus intensities, frequencies and durations necessary to induce spread of excitation (Pascual-Leone et al., 1993, 1994b). Based on these results, we suggested sets of stimulation parameters that are unlikely to cause spread of excitation and are, therefore, considered safe (Pascual-Leone et al., 1993).

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We followed the reported guidelines for rTMS studies in our laboratory for more than 3 years without inducing further seizures. However, in September 1995, a normal volunteer had a seizure during a rTMS study, even when the parameters for individual trains of stimuli were well within these guidelines (Wassermann et al., 1996a). It is likely that the seizure was due to short inter-train intervals. a factor not included in our previous safety study (Pascual-Leone et al., 1993).

It seemed obvious that new safety guidelines for rTMS were necessary and should include limitations on inter-train intervals, since almost all rTMS studies require multiple trains. Here, we report a study of the safety of different inter-train intervals. One subject had a seizure during this study (Wassermann et al., 1996a), and shortly afterwards a different rTMS study in our laboratory led to another seizure (Chen et al., 1997b). Therefore, we also analyzed the stimulus parameters used at the time these 3 seizures occurred in an attempt to understand why they occurred, and to devise possible ways to prevent future occurrence. Based on these findings, we report new safety guidelines for rTMS that are presently used in our laboratory.

2. Methods

2.1. Safety of different inter-train intervals

We studied 10 right-handed healthy volunteers (4 men and 6 women, mean age 45.5 years, range 28–64 years). All subjects gave their written informed consent; the study was approved by the Institutional Review Board.

We used a Cadwell rapid-rate magnetic stimulator (Cadwell Laboratories Inc., Kennewick, WA) and water-cooled 8-shaped coil, each loop of which measures 7.5 cm at its inner diameter. The coil was flat, and the position of closest contact with the scalp was the intersection of the two loops where the induced magnetic field was strongest (Cohen et al., 1990). The technical details of the magnetic stimulator and the figure-of-8-shaped water-cooled coil were described previously (Pascual-Leone et al., 1993). A specially designed coil holder kept the coil in a constant position with reference to the subject's head. The coil holder consisted of an aluminium frame with adjustable plastic joints. The coil was attached by metal screws to a ball and socket joint with adjustable clamps. The position of the coil can be freely adjusted and then secured. After the subject was seated in a comfortable position, a head restraint was applied to prevent movements. The coil was placed at the optimal position over the left motor cortex for eliciting motor-evoked potentials (MEPs) in the right abductor pollicis brevis (APB) muscle and was fixed for the remainder of the experiment. The positions of the head restraint and the stimulating coil were also marked on the scalp and monitored throughout the experiment.

The motor threshold (MT) was defined as the minimum percentage of the stimulator output that evoked an MEP of 50 μV in at least 5 out of 10 trials. Surface EMG was recorded from the right APB, biceps and deltoid muscles. Subjects were instructed to maintain relaxation throughout the study. The signals were filtered (bandpass 50 Hz to 2 kHz), amplified, displayed (Dantec Counterpoint Electromyograph; Dantec Electronics, Skovlunde, Denmark), and stored in a laboratory computer for off-line analysis.

EMG was continuously monitored for spread of excitation to proximal muscles and post-TMS EMG activity, which may be warning signs for seizures. Spread of excitation occurred if there was no MEP in the biceps or deltoid muscles with the first train of stimulation but MEP appeared with later trains. In some subjects, it was not possible to evoke MEPs from the APB muscle at the desired stimulus intensity without inducing small MEPs in the biceps or deltoid muscles. In these situations, spread of excitation was regarded as an increase in the deltoid MEP amplitude by more than 100% of the baseline. Post-TMS EMG activity referred to continuation of EMG activity after cessation of rTMS and may be the EMG correlate of EEG after-discharges. As a safety precaution, we considered any EMG activity following rTMS that was not clearly due to poor muscle relaxation as post-TMS EMG activity. The stimulation was terminated if either spread of excitation or post-TMS EMG activity occurred. A neurologist trained to recognize these warning signs and to manage seizures was always present during the experiments.

All subjects had rTMS trains at 20 Hz and 110% MT for 1.6 s (32 pulses). The train duration was the maximum duration of a single train at this frequency and intensity that did not lead to spread of excitation in our previous study (Pascual-Leone et al., 1993). The inter-train intervals of 5 s, 1 s or 0.25 s were tested and 10 trains were administered at each interval. Spread of excitation, post-TMS EMG activities or seizures were considered as adverse events. The inter-train interval for a particular set of stimulus parameters is considered unsafe if any adverse event occurred in any subject. In the first 4 subjects, the inter-train interval of 5 s was tested first, followed by 1 s and then 0.25 s. Since the inter-train interval of 5 s was safe in the first 4 subjects, the next 6 subjects were first tested with an inter-train interval of 1 s. The longer inter-train interval of 5 s was tested only if spread of excitation or after-discharges occurred at an inter-train intervals of 1 s.

In addition to the stimulus intensity of 110% MT, we studied some subjects at stimulus intensities of 100% (3 subjects), 105% (4 subjects) or 120% (8 subjects) of MT at 20 Hz with inter-train intervals of 5 s, 1 s or 0.25 s. The train duration for 100% and 105% MT stimulation was 1.6 s. It was reduced to 1 s (20 pulses) for 120% MT stimulation, which was the maximum recommended duration (Pascual-Leone et al., 1993). We also tested 3 subjects at the higher rTMS frequency of 25 Hz, 120% of MT and 0.4 s duration (maximum recommended duration at this intensity) (Pascual-Leone et al., 1993) with inter-train intervals of 1 s or

0.25 s, and one subject at 25 Hz, 110% of MT and 0.8 s duration with an inter-train interval of 1 s. One subject was tested with 10 Hz, 110% of MT and 1 s duration with an inter-train interval of 1 s.

3. Results

3.1. Safety of different inter-train intervals

The results of the inter-train intervals study are shown in Table 1. Spread of excitation or post-TMS EMG activity was observed in 13 studies. MEP amplitudes in the target muscle (APB) increased with successive trains in 11 of these studies and were unchanged in the other two studies. Examples of spread of excitation and post-TMS EMG activity are shown in Figs. 2 and 3.

rTMS at 120% MT and 1 s train duration with an inter-train interval of 1 s was unsafe since spread of excitation or post-TMS EMG activity occurred in 3 of 8 subjects tested. With rTMS at 110% MT and 1.6 s duration, spread of excitation or post-TMS EMG activity occurred in two of 10 subjects at an inter-train interval of 1 s and in 3 of 10 subjects at an inter-train interval of 0.25 s. We consider these inter-train intervals unsafe. Inter-train intervals of 5 s can be considered safe because none of the 10 subjects had adverse events either at this inter-train interval (5 subjects, two of whom had spread of excitation at an inter-train interval of 1 s) or at the shorter inter-train interval of 1 s (5 subjects) (Table 1).

At stimulus intensities of 105% and 100% of MT (20 Hz, 1.6 s), inter-train intervals of less than 1 s are unsafe since spread of excitation occurred in one subject (Table 1). With a frequency of 25 Hz, stimulation at 120% MT with inter-train intervals of 1 or 0.25 s were unsafe (Table 1). Since a seizure occurred at 25 Hz, 110% MT with an inter-train interval of 1 s (Table 1; subject 2, Table 2), we also consider this set of parameters unsafe.

3.2. Stimulus parameters of rTMS studies that induced seizures

The rTMS parameters used at the time the seizures occurred in the 3 normal subjects are shown in Table 2. All seizures were of focal onset, began on the side being stimulated and then secondarily generalized. All subjects fully recovered. The clinical descriptions of these seizures have been reported (Wassermann et al., 1996a; Chen et al., 1997b).

In subject 1, the train duration of 0.75 s was only 47% of the duration required for induction of spread of excitation for single rTMS trains at that intensity and frequency (Table 2). Therefore, the seizure was unlikely to be due to the excessive stimulation for individual trains and was probably related to the short inter-train interval of 0.25 s. In subject 2, the train duration of 0.8 s was close to the duration that may induce spread of excitation (0.84 s) (Table 2). This seizure was probably due to a combination of the strong individual trains and the short inter-train interval (1 s). EMG monitoring was performed and spread of excitation occurred at the end of the third train. Because of the short inter-train inter-

Table 1
Results of inter-train interval safety study

Frequency (Hz)	Stimulus intensity (% of MT)	Train duration (s)	Inter-train interval (s)	No. of subjects	No. of subjects without adverse events	No. of subjects with spread of excitation, PTEA or seizure
10	110	1	1	1	1	1
20	120	1	5	1	1[a]	0
20	120	1	1	8	5	2 spread and PTEA; 1 PTEA
20	120	1	0.25	1	1	0
20	110	1.6	5	5	5[b]	0
20	110	1.6	1	10	8	2 spread
20	110	1.6	0.25	10	7	2 spread; 1 PTEA
20	105	1.6	5	4	4	0
20	105	1.6	1	4	4	0
20	105	1.6	0.25	4	4	0
20	100	1.6	5	1	1	0
20	100	1.6	1	1	0	1 spread
20	100	1.6	0.25	1	1	0
25	120	0.4	1	2	0	2 spread and PTEA
25	120	0.4	0.25	3	2	1 PTEA
25	110	0.8	1	1	0	1 seizure[c]

Up to 10 trains were applied in each study. PTEA, post-TMS EMG activity; MT, motor threshold; spread, spread of excitation; adverse events are spread of excitation, post-TMS EMG discharges or seizure.
[a]Four other subjects had no adverse event at inter-train interval of 1 s; the inter-train interval of 5 s was not tested.
[b]Five other subjects had no adverse event at inter-train interval of l s; the inter-train interval of 5 s was not tested.
[c]Subject 2 in Table 2.

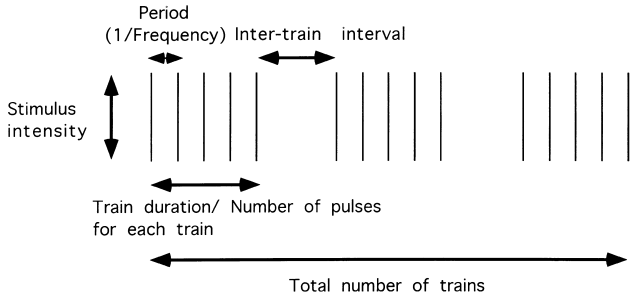

Fig. 1. Parameters that may influence the occurrence of adverse effects in rTMS studies. Each line represents one TMS pulse.

val (1 s), we were unable to stop the stimulation before the fourth train was delivered which caused the seizure. The inter-train interval in subject 3 was long (>1 min) and unlikely to have contributed to the seizure. However, the stimulus parameters for individual trains were at the edge of the original safety guidelines and likely caused the seizure.

4. Discussion

4.1. Parameters for single trains of rTMS

The occurrence of seizures in subjects 2 and 3 (Table 2) showed that rTMS parameters at the edge of our previous recommendations (Pascual-Leone et al., 1993) are not safe under some circumstances. However, the risk appears to be small as we have studied over 130 subjects following these guidelines during a 4 year period without complications. Moreover, 10 other subjects were studied with the same parameters as used in subject 3 without adverse effects (Chen et al., 1997b). A likely explanation for the occurrence of these two seizures is that our previous safety guidelines were based on the minimum number of pulses necessary to cause spread of excitation in 10 subjects (Pascual-Leone et al., 1993). When more subjects are tested, it is likely that spread of excitation may be more easily induced in some subjects than in any of the subjects previously studied. However, the individual variability in number of pulses required to cause spread of excitation among the 10 subjects previously studied was small, and was never more than 5 pulses (Pascual-Leone et al., 1993). In addition, there is some variability in determining MT, and the finding of a higher threshold would lead to using a higher stimulus intensity. In 6 subjects, we found that the coefficient of variation for MT determined at two different days was 5.8%, with a maximum difference of 12% between the two MT measurements (unpublished observations). To account for these variables, extra safety margins from our original safety recommendations are necessary. We suggest reducing the safe train duration for each combination of stimulus frequency and intensity by 25% of the original recommendation, which should be adequate to account for individual variability in susceptibility to seizures in normal volunteers and the margin of error in the determination of MT.

Our recommendations for stimulation parameters for single trains are shown in Table 3. Our suggestions for 1 Hz and intensities of 100 and 110% of MT were based on our recent study of 0.9 Hz stimulation for 15 min at 115% of MT in 9 subjects (Chen et al., 1997a). Eight subjects completed the study without complications, but one subject had spread of excitation after 360 stimuli. The safe train duration and number of pulses for 1 Hz stimulation at 100 and 110% of MT is therefore more than 270 (75% of 360). It is likely that 1800 pulses are safe for 1 Hz stimulation at 100 and 110%

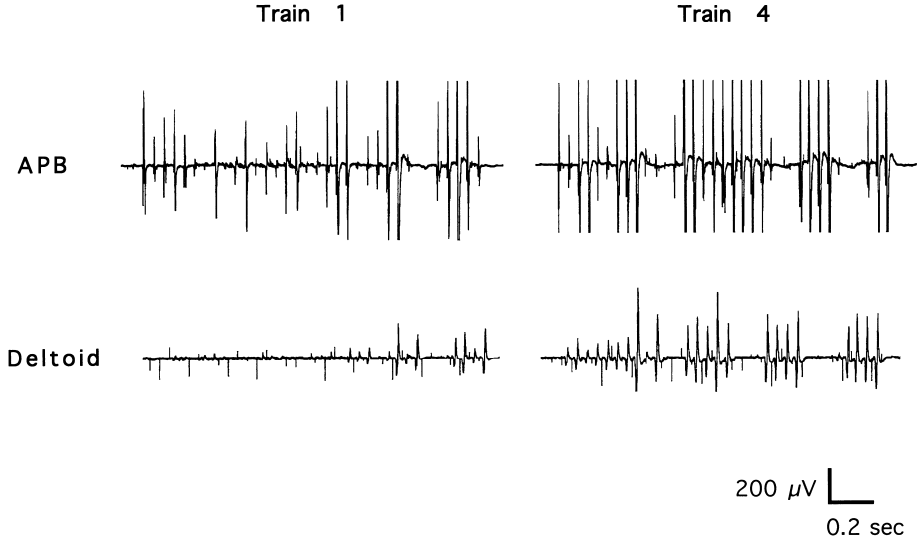

Fig. 2. Example of spread of excitation. The subject (a 39 year old woman) received rTMS at 20 Hz, 110% of motor threshold, train duration of 1.6 s and inter-train interval of 1 s. MEPs in the deltoid became evident towards the end of train 1. By train 4, the deltoid MEPs occurred near the onset of the train and amplitudes were much higher (increased by more than 100% of the baseline). The MEP amplitude of the APB muscle was also higher in train 4 compared to train 1. Although spread of excitation occurred in train 1, it was not recognized until train 4. The stimulation was then immediately terminated. This underscores the risk of short inter-train intervals.

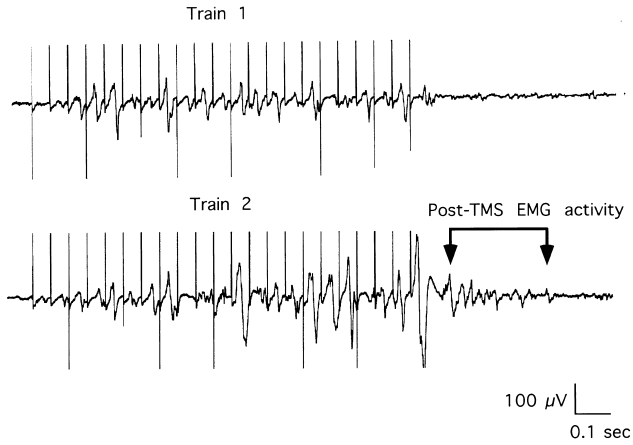

Fig. 3. Example of possible post-TMS EMG activity. EMG recordings from the biceps muscle are shown. The subject (a 58 year old man) received rTMS at 20 Hz, 120% of motor threshold, train duration of 1 s and inter-train interval of 1 s. With train 1, most pulses elicited an MEP but there was no further EMG activity following the last stimulus. Following train 2, there was EMG activity of declining amplitude for about 0.3 s.

of MT, since several subjects (Wassermann et al., 1997) had stimulation between 100 and 110% of MT for 30 min (1800 pulses) with no change in MEP amplitude although monitoring for spread of excitation was not performed. The recommendation for 1 Hz and 120% of MT was based on our previous study (Wassermann et al., 1996b) which found no spread of excitation or post-TMS EMG activity in 6 subjects with stimulation at 1 Hz and 125% of MT for 180 s.

4.2. Safe inter-train intervals for rTMS

Since rTMS may be associated with potential adverse effects, it is imperative that the potential benefit in advancement of knowledge or therapeutic benefit outweighs the inherent risk. For these reasons, we only tested a limited range of rTMS parameters out of a large number of possible combinations in normal volunteers. We chose stimulus parameters that we believe are adequate for most rTMS studies. Although we stimulated only the dominant (left) motor cortex, the results should be applicable to the non-dominant motor cortex since we found no significant difference between the stimuli that induced spread of excitation on the dominant and non-dominant motor cortices. (Pascual-Leone et al., 1993) Our main safety concern was increased cortical excitability and potential for induction of seizures. We did not systemically test for other potential side effects of rTMS, such as headaches, changes in cognition or hormone levels.

The seizures in subjects 1 and 2 suggested that individual rTMS trains that are safe when delivered with long inter-train intervals may cause seizures if the inter-train intervals are short. We found that at an inter-train interval of 1 s or less, facilitation of subsequent trains may lead to increased MEP amplitudes, spread of excitation, post-TMS EMG activities or seizures. However, we found no evidence of facilitation at the inter-train interval of 5 s. Stimulation at high intensities is more likely to cause facilitation of later trains than stimulation at lower intensities (Table 1). These findings are consistent with the much earlier observations of Graham Brown that the response to a second train of unipolar electrical stimulation of the monkey cortex was increased if the first and second trains were close together (Graham Brown, 1915a,b). Pascual-Leone et al. (1994b) also found an increased probability of producing MEPs and increased MEP amplitudes immediately following rTMS trains. However, there was no cumulative effect when the rTMS trains were delivered 1 min apart.

Post-tetanic potentiation may be a mechanism for facilitation at short inter-train intervals. It is of presynaptic origin and likely due to elevated calcium in the presynaptic terminals (Zucker, 1989). Post-tetanic potentiation may last up to 1 min. and its decay is slower following tetani of long durations or high frequencies (Schlapfer et al., 1975; Malenka, 1991). Another potential mechanism is short-term potentiation (STP), which originates postsynaptically and requires activation of *N*-methyl-D-aspartate (NMDA) receptors. However, STP declines over 5–40 min (Malenka,

Table 2
Stimulus parameters in rTMS studies that induced seizures

Subject	Age (years)	Sex	Site of stimulation	Stimulus intensity (% of MT)	Frequency (Hz)	Train duration (s)	No. of pulses	Previously recommended maximum train duration (s)[a]	Train duration that induced seizure expressed as a percentage of previously recommended maximum train duration[a]	Inter-train interval (s)
1	27	F	Left prefrontal cortex	105	15	0.75	11	1.6	47	0.25
2	39	F	Left motor cortex	110	25	0.8	20	0.84	95	1
3	26	F	Left motor cortex	120	15	2.7	41	2.7	100	>60

MT, motor threshold.
[a]The minimum duration required for spread of excitation at the stimulus intensity and frequency used (based on Pascual-Leone et al., 1993).

Table 3

Table of safe train duration (s)/number of pulses for single trains of rTMS in normal volunteers currently in use at NINDS

Frequency (Hz)	rTMS intensity (% of motor threshold)												
	100	110	120	130	140	150	160	170	180	190	200	210	220
1	>270/270[a]	>270/270[a]	180/180[b]	50/50[c]	50/50[c]	50/50[c]	50/50[c]	20/20	8/8	8/8	6/6	5/5	4/4
5	10/50[c]	10/50[c]	10/50[c]	10/50[c]	5.7/28	3.9/19	2.7/13	1.95/9	1.8/9	1.2/6	1.1/5	1.2/6	0.9/4
10	5/50[c]	5/50[c]	3.2/32	2.2/22	1.0/10	0.6/6	0.7/7	0.6/6	0.4/4	0.5/5	0.3/3	0.2/2	0.2/2
20	1.5/30	1.2/24	0.8/16	0.4/8	0.3/6	0.2/4	0.2/4	0.1/2	0.2/4	0.2/4	0.2/4	0.1/2	0.1/2
25	1.0/25	0.7/17	0.3/7	0.2/5	0.2/5	0.2/5	0.2/5	0.1/2	0.1/2	0.1/2	0.1/2	0.1/2	0.1/2

The maximum safe train duration (s) is shown followed by the number of pulses. See also Wassermann (1997).
[a]Based on Chen et al. (1997a).
[b]Based on Wassermann et al. (1996b).
[c]No spread of excitation or post-TMS EMG activity was observed at these train durations. Based on Pascual-Leone et al. (1993).

1991), and differs from the time course of facilitation at short inter-train intervals.

The post-TMS EMG activity we observed could be the correlates of EEG after-discharges. We could not confirm this with EEG recordings immediately after TMS because of the technical problems of large stimulus artifacts and overloading the amplifiers with our experimental set-up. EEG after-discharges are observed after strong electrical brain stimulation which often precedes seizure development (Racine, 1972). After-discharge involves synchronous firing of a population of neurons and may be related to enhanced excitatory pathways and reduced efficacy of recurrent inhibitory circuits following tetanic stimulation (Miles and Wong, 1987; Rafiq et al., 1993; Traub and Jefferys, 1994). In many instances, it was difficult to distinguish between post-TMS EMG activity and poor muscle relaxation. Post-TMS EMG activity that is due to an after-discharge is likely to be rhythmic and occur simultaneously in more than one muscle. For the purpose of safety monitoring, we adopted the conservative approach that any EMG activity after rTMS that was not clearly due to voluntary muscle activation was considered as post-TMS EMG activity, although no example was seen that was clearly a correlate of an EEG after-discharge. Spread of excitation likely occurs in the motor cortex and may be due to breakdown of intracortical inhibition (Pascual-Leone et al., 1994b). With single trains of rTMS, it is more likely to occur at high frequencies and stimulus intensities and is often accompanied by increased MEP amplitudes in the target muscle (Pascual-Leone et al., 1994b). Spread of excitation or after-discharges with short inter-train intervals may be a consequence of potentiation of responses to subsequent trains. This then leads to reduced intracortical inhibition, similar to the effects of more intense rTMS stimulations.

4.3. Safety recommendations for inter-train intervals

The inter-train intervals we propose to be in the safe range are shown in Table 4. The stimulus parameter for each individual train should not exceed that listed in Table 3. An inter-train interval of 5 s at 110% of MT or lower appears to be safe. Combinations produced by reducing any of the stimulating parameters should also be safe (e.g. rTMS trains with stimulus intensities less than 110% MT and train duration less than 1.6 s at inter-train intervals of 5 s or more). rTMS studies with less than 10 trains should also follow these guidelines for inter-train intervals, because there was spread of excitation in some subjects even with two trains (Table 4). Since our inter-train interval study used the maximum allowed duration for each train from our previous safety recommendation (Pascual-Leone et al., 1993), a 25% reduction of the individual train duration adds an additional margin of safety. For stimulus intensities of 120% MT or higher, the inter-train interval should be longer than 1 min as no potentiation was observed at the inter-train interval of 1 min (Pascual-Leone et al., 1994b).

It should be noted that our guidelines have several limitations. (1) We only studied 10 rTMS trains for each set of stimulus parameter. Caution should be exercised when extrapolating the data for rTMS studies involving more

Table 4

Safety recommendations for inter-train intervals for 10 trains of rTMS at < 20 Hz

Inter-train interval (s)	Stimulus intensity (% of MT)			
	100%	105%	110%	120%
5	Safe	Safe	Safe	Insufficient data
1	Unsafe (3)	Unsafe[a]	Unsafe (2)	Unsafe (2)
0.25	Unsafe[a]	Unsafe[a]	Unsafe (2)	Unsafe (3)

The minimum number of trains that caused spread of excitation or post-TMS EMG activity are indicated in the parentheses. The maximum duration/number of pulses for individual rTMS trains at each stimulus intensity should not exceed that listed in Table 3. Stimulus parameters produced by reducing a set of parameters that is considered safe (reduction in stimulus intensity, train duration, or increase in inter-train interval) is also considered safe. rTMS at 25 Hz, 120% of MT (0.4 s duration) is unsafe at inter-train intervals of 1 s or less. The safety of longer inter-train intervals at 25 Hz has not been determined.
[a]These stimulus parameters are considered unsafe because adverse events occurred with stimulation of lower intensity or longer inter-train interval, but no adverse event was observed with these parameters.

than 10 trains. (2) We only examined the potential for rTMS-induced seizures in the motor cortex. Since the threshold for induction of after-discharges with electrical cortical stimulation is lowest in the motor cortex compared to other cortical areas (Penfield and Jasper, 1954), the above recommendations are likely to be safe in rTMS studies of cortical areas other than the motor cortex. Nevertheless, caution should be exercised when stimulating these other cortical areas. (3) Adverse effects other than increased cortical excitability or seizure were not studied, although none of our subjects had any complaints. (4) These guidelines will need to be continually updated based on the results of ongoing studies at our institution and internationally (Wassermann, 1997).

These guidelines are intended for use in most rTMS studies with a reasonable degree of safety. However, the balance between risk and benefit should be individually assessed for each study. Spread of excitation with low frequencies of TMS (such as 1 Hz) may be less dangerous than that with high frequencies of stimulation. The number of pulses delivered in the time required to recognize the spread of excitation to termination of stimulation is likely to be less for lower frequencies of stimulation, and it is more likely that stimulation can be stopped before spread of excitation evolves into an epileptic seizure. In some circumstances, as, for example, when therapeutic benefit may be expected from rTMS, parameters exceeding our current recommendations may also be considered (Wassermann, 1997).

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