

Seizure incidence during single- and paired-pulse transcranial magnetic stimulation (TMS) in individuals with epilepsy

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Abstract

Objective: We reviewed published data and our own data to determine a quantitative incidence of seizure in subjects with epilepsy undergoing single- and paired-pulse transcranial magnetic stimulation (spTMS and ppTMS) and to explore conditions that may increase this risk.

Methods: A PubMed literature search was performed, and articles from this search were reviewed. Subjects from our institution also were included.

Results: The crude risk of a TMS-associated seizure ranges from 0.0 to 2.8% for spTMS and 0.0–3.6% for ppTMS. Medically intractable epilepsy and lowering antiepileptic drugs were associated with increased incidence. There was significant center-to-center variability that could not be explained by differences in patient population or by differences in reported stimulation parameters. In all cases, seizures were similar to each subject's typical seizure and without long-term adverse outcome. In most cases, doubt was expressed in the original reports as to whether the seizures were induced by TMS or merely coincidental.

Conclusions: The incidence of seizure in a subject with epilepsy during spTMS and ppTMS appears to be small and not associated with long-term adverse outcome. The incidence is higher under the specific conditions mentioned above.

Significance: These findings may enable researchers to more accurately inform subjects of seizure risk during TMS.

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1. Introduction

Transcranial magnetic stimulation (TMS) is an emerging experimental tool that can measure cerebral cortex excitability non-invasively. Because of case reports of seizures during single-pulse TMS (spTMS) performed on individuals with and without epilepsy (Homberg and Netz, 1989; Hufnagel and Elger, 1991a), concern exists about the safety of performing such studies in individuals with epilepsy (Wassermann, 1998).

Some of the earliest reports of *TMS-associated seizures* (defined in this article as seizures occurring during or within 4 min of cessation of single- or paired-pulse TMS) in individuals with epilepsy were from the TMS laboratory of Hufnagel and Elger (Hufnagel et al., 1990a–c; Hufnagel and Elger, 1991a,b). These investigators identified five conditions that may be associated with an increased likelihood of a TMS-associated seizure which are summarized in Table 1 (Hufnagel and Elger, 1991a).

Early reports of seizures in individuals with epilepsy undergoing spTMS (Hufnagel et al., 1990a–c; Hufnagel and Elger, 1991a,b) were followed by many subsequent studies that did not report seizures, and single- and paired-pulse TMS (ppTMS) are generally considered safe in individuals

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Table 1

Conditions associated with an increased likelihood of a TMS-associated seizure, as previously reported (Hufnagel and Elger, 1991a)

1. Low antiepileptic drug serum concentration
2. Frequent ($\geq 10/\text{min}$) interictal epileptiform discharges on electrocorticography immediately before TMS
3. Frequent ($\geq 4/\text{month}$) spontaneous complex partial seizures of temporal lobe origin
4. Recent (within 48 h of TMS) spontaneous seizures, and
5. TMS to the region over the epileptogenic region

with epilepsy (Tassinari et al., 1990). In our recent experience with five subjects with epilepsy, two had a typical seizure during TMS (one during spTMS and the other during ppTMS) and one had a typical seizure within 2 min of cessation of ppTMS. This high incidence contrasts strongly with the paucity of reports of seizures occurring in the many subjects with epilepsy that have undergone spTMS and ppTMS.

To reconcile this discrepancy, we performed a systematic search for all published reports of spTMS and ppTMS studies that used subjects with epilepsy and addressed the risk of seizure with an examination of factors that may increase the likelihood of seizure occurrence. Such a search or an analysis has not yet been published. This risk estimate and analysis of features also includes the five subjects with epilepsy who underwent spTMS and ppTMS at our institution.

2. Methods

2.1. Literature review

A PubMed literature search of ‘transcranial magnetic stimulation’ and ‘epilepsy’ produced 112 references. An additional article was included after being identified among the references of several of the articles (Hufnagel et al., 1990c). Of these 113 articles, 64 were excluded for the following reasons: 31 were review articles without original research data, 14 did not test subjects with epilepsy, six described animal experiments, three were letters to the editor without original research data, one was an editorial, five reported data that possibly overlapped with data that was published in other articles and four did not include single-pulse or paired-pulse studies. To the best of our abilities, we eliminated data that were republished. The remaining 49 articles (listed in Appendix A) were original research experiments that utilized single- and paired-pulse TMS during all or a portion of their protocol on human subjects with epilepsy.

The 49 articles were reviewed and the following was recorded: the number of subjects with epilepsy exposed to spTMS technique, the number of patients with epilepsy exposed to ppTMS technique, the number of subjects with medically intractable epilepsy, the number of individuals

who experienced a seizure and whether AEDs were tapered prior to TMS. For each seizure, we recorded its type and severity, its timing in relationship to the TMS stimulation, the subject’s baseline seizure frequency and type of epilepsy, the TMS stimulation parameters at the time of the seizure, the number of stimuli given prior to the seizure’s onset and the scalp location of stimulation. To assess the possibility that some seizures may not have been reported, we noted the number of articles that specifically included in their reports whether seizures or side effects occurred. For each seizure during TMS, we examined each case with regard to the five above-mentioned conditions that may increase likelihood of seizure occurrence (Table 1) (Hufnagel and Elger, 1991a). To address whether certain stimulation conditions may be associated with an increased likelihood of seizure occurrence, we recorded the following TMS parameters from each article: brand and model of stimulator, coil shape and size, intensity of TMS stimulation, duration of TMS session, time interval between stimulations, total number of TMS pulses, duration of TMS pulse and pulse configuration. To address whether certain patient populations are at increased risk of a TMS-associated seizure, we also noted the whether subjects were undergoing video-EEG monitoring as part of an epilepsy surgery evaluation at the time of TMS.

An additional PubMed literature search of ‘transcranial magnetic stimulation’ and ‘seizures’ produced 81 references. All of the 81 articles were excluded for the following reasons: 58 were duplications of the ‘transcranial magnetic stimulation’ and ‘epilepsy’ PubMed search, 10 did not test subjects with epilepsy, nine were review articles without original research data, three described animal experiments and one was not a TMS study.

2.2. UCLA TMS methods

Single- ($N=5$) and paired-pulse ($N=2$) TMS was administered to five subjects (age 31–56, one male, four female) with intractable partial onset seizures who were hospitalized for scalp video-EEG monitoring as part of an epilepsy surgery evaluation. The doses of AEDs were lowered and subjects were sleep-deprived every other night as part of a standard protocol for eliciting seizures.

TMS was performed using two Magstim model 220s (The Magstim Company Ltd, Wales, UK) configured for single- and paired-pulse. This configuration provides biphasic stimulation with a rise time of approximately 80 μs and total pulse duration of 250 μs . At maximal output, the stimulator’s 70 mm figure-of-eight coil generates a 1.75 T field. The University of California Los Angeles Institutional Review Board approved the protocol, and informed consent was obtained from all subjects.

Each of four subjects underwent 2 or 3 separate 20–180 min sessions on different days, for a total of 10 TMS sessions among these four subjects. A fifth subject

underwent 20–35 min sessions over two days for a total of seven TMS sessions. The first hemisphere stimulated during each subject's first TMS session was alternated from subject to subject. In addition, the first hemisphere stimulated for subsequent TMS sessions was alternated within each individual subject. All single-pulse and paired-pulse studies were completed for one hemisphere before the same studies were repeated for the contralateral hemisphere.

For each hemisphere, spTMS was used to determine the scalp location that produced the most reliable and highest amplitude motor evoked potential (MEP) for the first dorsal interosseus muscle. The resting motor threshold (RMT) for each hemisphere then was determined by reducing stimulator intensity in step-wise decrements of 2% to find the intensity that produced an MEP of at least 50 μ V peak-to-peak amplitude for at least five of 10 stimulations. Silent period was determined with spTMS using intensities of 130% RMT. If this intensity exceeded the maximum stimulator output (MSO), intensity was set at 100% MSO. Paired-pulse TMS was done using interstimulus intervals (ISIs): 1, 3, 6, 8, 10, 12, 50, 100, 150, 200, 250, and 300 ms. The intensity of the conditioning stimulus was 75% of RMT. The intensity of the test stimulus (TS) was adjusted such that MEPs of 1–2 mV amplitude were reliably evoked. If 100% MSO was not sufficient to evoke 1–2 mV MEPs, 100% MSO was used for the TS intensity. The order of ISIs was the same for each hemisphere within one TMS session, but randomized for each session. There was at least a 5 s interval between each single-pulse TMS stimulation and each pair of paired-pulse stimuli.

The duration of the TMS sessions was affected by several factors. In most subjects, the RMT was either near or greater than 100% MSO, and this shortened the sessions by limiting the number of possible TMS studies. In addition, two subjects' sessions were terminated early because of a seizure. In another subject, postictal TMS data was collected.

2.3. Statistical analysis

Statistical analysis was done using only those studies that reported whether or not adverse events occurred. The UCLA data was considered a separate study. Single-pulse and paired-pulse data were analyzed separately. For each study, the crude rate of seizure occurrence was calculated by dividing the total number of subjects who had a seizure during TMS by the total number of subjects in the study. The weighted rate was computed by weighing the rate in each study inversely to the study variance (StatXact version 5.0, Cytel Software Inc.) and therefore accounts for both random within and between study variability. The upper 95% confidence limit for true mean rate across studies and homogeneity p value were also calculated. The homogeneity p value tested the null hypothesis that seizure occurrence rates are homogeneous across studies.

Separate average rates were calculated for the literature review data and the pooled data.

3. Results

3.1. Literature review

In the 49 publications reporting original research, 712 subjects with epilepsy were reported to have undergone spTMS, and of these subjects had clinical seizures during stimulation (Classen et al., 1995; Hufnagel and Elger, 1991a,b; Hufnagel et al., 1990a–c; Tassinari et al., 1990). Interestingly, five of these subjects were from one lab (Hufnagel and Elger, 1991a,b; Hufnagel et al., 1990–c). If one assumes that all seizures during spTMS have been reported, the crude risk of seizure during spTMS is 7 in 712 (1.0%). However, only 22 articles, comprising 458 subjects, specifically reported whether adverse side effects or seizures occurred during the TMS study. Twenty-seven articles, comprising 254 subjects, reported results without commenting upon whether seizures or other side effects occurred. Thus, it is possible that there may have been seizures that occurred in these 254 subjects that were not reported. If these 254 subjects are not included in the risk assessment, the risk of a seizure during spTMS is 7 in 458 (1.5%, crude mean rate). For these 458 subjects, the weighted mean rate of seizure occurrence during spTMS is 1.8% with an upper 95% confidence limit for true mean rate of 3.2% and a homogeneity p value of 0.0435. All of the seizures that occurred during spTMS were similar to each individual subject's habitual seizures in both seizure type and severity, and all were followed by the subject's typical postictal recovery. The data collected for each subject who experienced a seizure are in Table 2.

In addition to the seven seizures that occurred during spTMS, three more occurred within 2–4 min after spTMS cessation (Hufnagel and Elger, 1991a,b). All three of these subjects were from the same lab that reported seizures in five subjects during spTMS. Two of these three seizures were complex partial, and one was an aura. The association between these seizures and TMS is unclear because all three subjects had highly frequent spontaneous seizures, and AEDs had been almost completely stopped prior to TMS. All three of these seizures also were similar to each subject's habitual seizure.

None of the 118 subjects with epilepsy who underwent ppTMS were reported to have had a seizure. Thirteen articles reported performing ppTMS. Three articles, comprising 54 subjects, specifically reported whether adverse side effects or seizures occurred. Ten articles comprising 64 subjects, reported data without specifically mentioning whether there were seizures or side effects.

Antiepileptic drugs were tapered prior to TMS in 208 subjects exposed to spTMS. Five of these 208 spTMS subjects had a seizure during spTMS, resulting in a crude

Table 2
Epilepsy subjects who had a seizure during single-pulse transcranial magnetic stimulation (TMS)

	Subject 1 ^{a,b}	Subject 2 ^c	Subject 3 ^{d,e,f,g,h}	Subject 4 ^{e,f,g,i}	Subject 5 ^{e,f,g,j}	Subject 6 ^{f,k}	Subject 7 ^{f,k}
Epilepsy type	Left frontal (SMA ^l)	Localization-related	Right mesial temporal	Temporal lobe	Temporal lobe	Not reported	Not reported
Typical seizure type	CPS ^m with secondary generalization	CPS	CPS	CPS	CPS	CPS	CPS
Baseline seizure frequency	5–9 per month	5–10 per day	Not reported specifically. Patients with a seizure during TMS had from 4 to 28 per month	8–10 per month	Not reported specifically. Patients with a seizure during TMS had from 4–28 per month	Average of 3–5 seizures per day	Average of 3–5 seizures per day
Typical seizure during TMS?	Yes. CPS	Yes. CPS	Yes. CPS	Yes. CPS	Yes. Typical aura	Yes	Yes
Timing of seizure	Immediately after a stimulation	20 s after the 12th stimulus	Between two pulses that were 2–3 s apart	During TMS	During TMS	During TMS	During TMS
Intensity of stimulation at time of seizure	Seizure 1: first 30 stimuli were 25% MSO ⁿ (2T ^o maximum) above MT ^p . The 31st and 32nd pulses were 5% MSO below MT. Seizure 2: No seizures occurred during MT determination. A seizure occurred after the first pulse at 150% MT	Specific intensity at time of seizure not reported. Intensities were 50–90% MSO (2.3T maximum) throughout the study	Specific intensity not reported. Intensities were 5–30% above MT intensities throughout the study	80% MSO (1.5 T maximum)	5–40% above MT intensities	130% MT	130% MT
Coil type	Angular figure-of-8 (14-cm one wing)	9-cm circular	7-cm or 14-cm circular	7-cm or 14-cm circular	7-cm or 14-cm circular	14-cm circular	14-cm circular
Number of stimuli given before seizure	Seizure 1: 32, Seizure 2: not reported	12	56	174	71	61	78
Location of stimulation	Primary motor cortex	Primary motor cortex	Right temporal seizure focus	Seizure focus	Seizure focus	Primary motor cortex	Primary motor cortex
Typical recovery?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

^a Classen et al. (1995).

^b Two separate seizures occurred at two separate TMS sessions one day apart.

^c Tassinari et al. (1990).

^d Hufnagel et al. (1990a).

^e Hufnagel and Elger (1991b).

^f Hufnagel and Elger (1991a).

^g Subject had bilateral implanted subdural strip electrodes.

^h Phenobarbital was lowered, blood level 5.4 µg/ml.

ⁱ Anticonvulsants were lowered, resulting in phenobarbitone level of 5.1 µg/ml and carbamazepine level of 1.1 µg/ml.

^j Anticonvulsants were lowered, resulting in valproic acid level of 3.1 µg/ml and carbamazepine level of 2.0 µg/ml.

^k Hufnagel et al. (1990c).

^l SMA, supplementary motor area.

^m CPS, complex partial seizure.

ⁿ MSO, maximal stimulator output.

^o T, telsa.

^p MT, motor threshold.

seizure risk of 2.4% for subjects in whom AEDs were tapered prior to spTMS. All five of these subjects were from one lab. In contrast, 2 of 500 subjects exposed to spTMS whose AEDs remained constant had a seizure. This results in a crude seizure risk during spTMS of 0.4% when AEDs

were not changed prior to spTMS. The reports did not mention whether there was a change in AED dosage for four spTMS subjects. Of the 118 subjects who underwent ppTMS, 34 subjects underwent AED taper prior to TMS. None of the subjects had a seizure during ppTMS.

Of the 712 individuals with epilepsy studied with spTMS, seizures were medically intractable in 520 and well-controlled in 74. The reports did not mention seizure control for 118 subjects. Since all seizures occurred in individuals with intractable epilepsy the crude risk of a seizure during spTMS is 7 in 520 (1.3%) for individuals with medically refractory seizures. No seizure has occurred in individuals with well-controlled epilepsy. Of the 118 ppTMS subjects, there were 79 with intractable epilepsy, 31 with well-controlled epilepsy and eight for whom it was not clear from the report. None of the subjects had a seizure during ppTMS.

Of the 712 subjects studied with spTMS, 203 were undergoing video-EEG monitoring as part of a surgical evaluation. Five of these 203 (2.5%, crude mean rate) had a TMS-associated seizure. Of the 712 subjects who underwent spTMS, 509 were not undergoing video-EEG monitoring. Two of these 509 (0.4%, crude mean rate) had a TMS-associated seizure during spTMS. Of the 34 ppTMS subjects undergoing video-EEG monitoring and the 84 ppTMS subjects who were not undergoing video-EEG monitoring, none had a TMS-associated seizure with ppTMS.

Of the seven subjects in the literature that have had seizures during single-pulse TMS, two (Classen et al., 1995; Tassinari et al., 1990) were not subjects from the TMS lab of Hufnagel and Elger. Thus, we reviewed their reports with regard to the five conditions in Table 1 (Hufnagel and Elger, 1991a). Upon reviewing the description of these cases, subject 1 clearly met only condition 3 (highly frequent seizures). Conditions 1 and 4 (low serum AED concentrations and recent seizures) were not met. Condition 2 (frequent ECoG discharges) could not be assessed because electroencephalography/ECoG was not done during TMS. It is unclear whether this subject met condition 5 (TMS over the epileptogenic region) because the authors questioned whether the TMS field was broad enough to include the epileptogenic region. Subject 2 met conditions 3 and 4, and not condition 1. Conditions 2 and 5 could not be assessed because electroencephalography/ECoG was not performed during TMS and the localization of the subject's epileptogenic region was not provided.

No long-lasting adverse consequences of a TMS-associated seizure were reported. In fact, Hufnagel and Elger specifically reported that none of their eight subjects who had a TMS-associated seizure experienced an increase in seizure frequency or any other 'deleterious effect' after the investigation was completed (Hufnagel and Elger, 1991a).

There was variable reporting of TMS parameters in the literature. The stimulator model and the shape and size of the stimulating coil were reported in almost all papers (96 and 92%, respectively). Some measure of stimulation intensity was reported in 82% of the papers, but the unit of measure varied and many papers reported an average intensity across subjects. Most papers reported stimulation intensity as a proportion of the resting or active motor threshold (66%)

although a substantial percentage of papers (26%) used percentage of maximum stimulator output. Only 33% of papers reported the time interval between single pulses or pairs of pulses and only 20% reported the total number of pulses delivered to each patient. Pulse configuration, pulse rise time and pulse duration were included in only three reports (6%). However, the manufacturer and specific model of machine was usually reported (92%), and thus the pulse configuration, rise time and duration usually could be inferred from this information (71%). Only 20% of the papers commented upon the total number of TMS pulses given per subject, and all but one of these papers reported ranges or averages rather than a specific number.

3.2. UCLA TMS data

The data from each subject is summarized in Table 3. One subject had a seizure during spTMS. Another subject had a seizure during ppTMS. A third subject had a seizure 2 min after the last paired-pulse stimulation. For all seizures, the semiology and electroencephalographic characteristics were similar to their typical seizures. In all cases, the seizure was followed by the subjects' typical postictal recovery. In all three instances of TMS-associated seizures, the subjects were on their lowest doses of AEDs and had high baseline seizure frequencies. None of the three subjects had any long-term adverse consequences from experiencing a TMS-associated seizure.

We examined the data on our five subjects with regard to the five conditions in Table 1 (Hufnagel and Elger, 1991a). AED blood levels were not monitored daily. However, all three TMS-associated seizures likely met the condition 1 because all three subjects were on significantly lowered AED doses (<25% admission doses) on the day of the TMS-associated seizure. In contrast, one subject who did not have a TMS-associated seizure was on high doses of AEDs on both days that he underwent TMS while the other subject who did not have a TMS-associated seizure was on approximately 50% of her admission AED dose on both days she underwent TMS. Condition 3 was met by all three subjects, as each of them had a baseline seizure frequency of at least 4 per month. One subject without a TMS-associated seizure had less frequent seizures at baseline while the other subject who did not experience a TMS-associated seizure had nearly daily seizures at baseline. With regard to condition 4, a seizure within 48 h of TMS was present for all three TMS sessions associated with a seizure. However, 10 TMS sessions not associated with a seizure also took place within 48 h of the last seizure. The other four TMS sessions not associated with a seizure occurred >48 h after the last seizure. It is unclear whether our subjects met condition 5. In all three cases of a TMS-associated seizure, the seizure occurred when TMS was being administered to the hemisphere ipsilateral to the seizure focus, but not necessarily over the seizure focus. The two individuals that had a seizure during TMS stimulation had mesial temporal

Table 3
UCLA data

	Subject 1 ^a	Subject 2 ^b	Subject 3	Subject 4	Subject 5 ^a
Epilepsy etiology	Left MTLE	Right hemisphere large cortical dysplasia	Right MTLE	Left MTLE	Left mesial temporal tumor
Typical seizure type	CPS	CPS	CPS	CPS	CPS
Baseline seizure frequency	3 per month	6–15 per month	10 per month	25–30 per month	> 30 per month
Baseline AED dose	LEV 500 mg BID, Ativan 0.5 mg BID, PHT 200 BID, TPX 200 BID	Gabapril 8 mg BID, CBZ 400 mg TID	PHT 500 mg QD, TPX 400 mg BID, ZNS 100 mg QHS	VPA 500 mg BID	LEV 1000 mg BID
AED dose on day of seizure	Not applicable	No AED	TPX 100 mg BID	No AED	Not applicable
Duration of TMS session during which TMS occurred	Not applicable	40 min	90 min	20 min	Not applicable
Typical seizure during TMS?	Not applicable	Yes	Yes	Yes	Not applicable
Intensity of stimulation at time of seizure	Not applicable	Paired-pulse with CS 46% MSO/TS 76% MSO. RMT 62% MSO	Paired-pulse with CS 67% MSO/TS 100% MSO. RMT 89% MSO	Single-pulse at 100% MSO. AMT > 100% MSO	Not applicable
Number of stimuli given before seizure	Not applicable	Exact number unknown, but at least 232	Exact number unknown, but at least 369	98	Not applicable
Location of stimulation	Not applicable	Right primary motor cortex	Right primary motor cortex	Left primary motor cortex	Not applicable
Typical recovery?	Not applicable	Yes	Yes	Yes	Not applicable

AED, antiepileptic drug; TMS, transcranial magnetic stimulation; MTLE, mesial temporal lobe epilepsy; CPS, complex partial seizure; LEV, levetiracetam; PHT, phenytoin; TPX, topiramate; CBZ, carbamazepine; ZNS, zonisamide; VPA, valproic acid; BID, twice per day; TID, thrice per day; QD, per day; QHS, each night; MSO, maximal stimulator output; RMT, resting motor threshold; AMT, active motor threshold; CS, conditioning stimulus; TS; test stimulus.

^a Did not experience a TMS-associated seizure.

^b Seizure occurred 2 min after last TMS stimulation.

lobe seizure foci but were being stimulated over the ipsilateral hand primary motor cortex. The subject who had a seizure 2 min after the last stimulation had a large hemispheric cortical dysplasia and was stimulated over the ipsilateral primary motor cortex just prior to the seizure occurrence. Condition 2 could not be assessed because ECoG was not performed on our subjects. However, none of the subjects had a high frequency of EEG epileptiform discharges prior to their TMS-associated seizure. There were two subjects with no epileptiform discharges in 8–9 min and one subject with < 1 discharge per minute in 6 min immediately preceding the TMS-induced seizure.

3.3. Risk of a typical seizure during spTMS and ppTMS: pooling the data

By combining data from the literature review and our own data, we have determined the risk of a seizure during TMS under different sets of circumstances (Table 4). A total of 717 individuals with epilepsy have undergone spTMS. Of these, eight had typical seizures during spTMS. If we assume that all authors reported the occurrence of seizures during TMS, the calculated crude risk of a typical seizure occurring during spTMS is 8 in 717 (1.1%). If we include

the seizures that occurred within 2–4 min of spTMS cessation, the crude risk increases to 11 in 717 (1.5%). However, if we eliminate the 254 subjects from articles that did not specifically report whether seizures or side effects

Table 4
Crude risk of a seizure occurring in association with TMS in epilepsy subjects: a pooling of published data and UCLA experience

Condition	Single-pulse TMS	Paired-pulse TMS
Risk of seizure during TMS	8 in 717 (1.1%)	1 in 120 (0.8%)
	8 in 463 (1.7%) ^a	1 in 56 (1.8%) ^a
Risk if seizure during or within 4 min of TMS cessation	11 in 717 (1.5%)	2 in 120 (1.7%)
	11 in 463 (2.4%) ^a	2 in 56 (3.6%) ^a
Risk of seizure during TMS if AEDs were lowered	6 in 213 (2.8%)	1 in 36 (2.8%)
Risk of seizure during TMS if no change in AEDs	2 in 500 (0.4%)	0 in 84 (0.0%)
Risk of seizure during TMS if medically intractable epilepsy	8 in 525 (1.5%)	1 in 81 (1.2%)
Risk of seizure during TMS in well-controlled epilepsy	0 in 74 (0.0%)	0 in 31 (0.0%)

AED, antiepileptic drug; TMS, transcranial magnetic stimulation.

^a Excludes subjects from articles that did not specifically comment upon seizures or side effects.

occurred, the risk is 8 in 463 (1.7%, crude mean rate) for seizures occurring during spTMS and 11 in 463 (2.4%, crude mean rate) if seizures occurring within 2 min of cessation of TMS are included. For these 463 subjects, the weighted mean rate of seizure occurrence during spTMS is 2.1% with an upper 95% confidence limit for true mean rate of 3.4% and a homogeneity p value of 0.0346.

A total of 120 subjects with epilepsy have undergone ppTMS. Of these, one had a typical seizure during ppTMS. If all subjects are included, the crude risk of a typical seizure occurring during ppTMS in an individual with epilepsy is 1 in 120 (0.8%). There were 64 subjects from articles that did not specifically comment upon seizures or side effects. If these 64 subjects are removed from the calculation the risk of a typical seizure is 1 in 56 (1.8%, crude mean rate). For these 56 subjects, the weighted mean rate of seizure occurrence during ppTMS is 5.0% with an upper 95% confidence limit for true mean rate of 9.95% and a homogeneity p value of 0.0357. If we include seizures that occurred within 2–4 min of TMS cessation, the crude risk of inducing a typical seizure increases to 2 in 120 (1.7%) or 2 in 56 (3.6%), depending which subjects are included in the calculation (Table 4).

The risk of a typical seizure during spTMS or ppTMS is very low in individuals who have not had their AEDs tapered prior to TMS and in individuals with well-controlled epilepsy. The crude risk of a seizure occurring during spTMS and ppTMS in individuals whose AEDs were lowered is 2.8 and 2.8%, respectively, compared to 0.4 and 0.0%, respectively, for those whose AEDs were not lowered. The crude risk of a seizure during spTMS and ppTMS is 1.5 and 1.2%, respectively, for individuals with medically intractable epilepsy. In contrast, there have been no reported seizures during spTMS and ppTMS in individuals with well-controlled epilepsy.

Not surprisingly, subjects who were undergoing video-EEG monitoring as part of a surgical evaluation had incidence rates that were nearly identical to those who underwent AED tapering prior to TMS. This was due to a high correlation between subjects who were admitted for video-EEG monitoring and the occurrence of AED taper prior to TMS. Of the 717 subjects who underwent spTMS, 208 were undergoing video-EEG monitoring as part of a presurgical evaluation. Six of these 208 (2.9%, crude mean rate) had a TMS-associated seizure with spTMS. Of the 717 subjects who underwent spTMS, 509 were not undergoing video-EEG monitoring. Two of these 509 (0.4%, crude mean rate) had a TMS-associated seizure during spTMS. Of the 36 ppTMS subjects undergoing video-EEG monitoring, one (2.8%, crude mean rate) had a TMS associated seizure. Of the 84 ppTMS subjects who were not undergoing video-EEG monitoring, none (0.0%) had a TMS-associated seizure with ppTMS.

As mentioned above, there was variability in the reporting of TMS parameters in the literature, allowing no firm conclusions to be made regarding whether certain TMS

conditions might increase the likelihood of seizure occurrence. TMS-associated seizures occurred with the use of three different machines. Of the three papers reporting one or more seizures, two of these used the Magstim 200 system (Classen et al., 1995; Hufnagel and Elger, 1991a). The other paper that reported a TMS-associated seizure used a Cadwell MES-10 (Tassinari et al., 1990) and our laboratory used two Magstim 220s combined with a Magstim Bistim unit. The occurrence of TMS-associated seizures did not appear to correlate with pulse configuration, as seizures occurred with the use of monophasic, biphasic and polyphasic pulse configurations. Likewise, there was also no clear association with pulse duration. Pulse durations ranged from 70 to 1000 μ s, and TMS-associated seizures occurred with pulse durations of 70, 250, and 1000 μ s. Different coil sizes and shapes were used in each of the studies in which seizures were documented. The two laboratories in which several subjects experienced a TMS-associated seizure used less than 10 s between single pulses or pulse-pairs. Of the two papers in which a single subject experienced TMS-associated seizure(s), one used an interval of 10–20 s (Tassinari et al., 1990) and the other did not report the interval (Classen et al., 1995). There was also no clear association between total number of pulses per subject and incidence of a TMS-associated seizure. Of the 10 articles that commented upon the number of pulses given per subject, seven did not report a seizure and reported a total number of pulses per subject ranged from >20 to >260. The other three articles reported TMS-associated seizures and reported the total number of pulses per subject ranged from 20 to 450. Interestingly, the group who reported the highest number of TMS-associated seizures reported that the total number of stimuli per subject in their protocol ranged from 80 to 450 (Hufnagel et al., 1990a–c; Hufnagel and Elger, 1991a,b). All but one of their subjects had a TMS-associated seizure after <80 stimuli. This contrasts with the UCLA data which shows that seizures generally occurred after a relatively higher number of stimuli were given.

4. Discussion

4.1. Variability between laboratories

The small homogeneity p values support the observation that there is large center-to-center variability in the occurrence of seizures in individuals with epilepsy undergoing spTMS and ppTMS. Of the 13 TMS-associated seizures, 11 occurred in two TMS labs. In particular, our center had an atypically high incidence of TMS-associated seizures. Despite a comprehensive literature review, we found no explanation for this center-to-center variability. To the best of our abilities, we made note of all possible experimental conditions and patient population characteristics that might contribute to such variability and were unable to find an association. However, the data

obtained from the literature search were incomplete due to inconsistencies in reporting, allowing no firm conclusions to be made. Thus, the center-to-center variability may still be due to differences in experimental conditions and/or patient populations that were not findable from a literature review.

It is possible that seizures have occurred in some laboratories but have not been reported. As noted above, only 22 of the 49 articles reviewed specifically commented upon whether side effects or seizures occurred in their study. The remaining articles simply reported their results without commenting upon side effects. Thus, it is possible that seizures have occurred at some centers but have not been reported.

4.2. The significance of a TMS-associated seizure in an individual with epilepsy

The occurrence of a TMS-associated seizure does not appear to result in any long-lasting adverse consequences. All subjects had their typical seizure during TMS followed by their typical postictal recovery. Because most of the subjects who had seizures during TMS also had histories of frequent seizures, doubt was expressed in some of the original reports as to whether the seizures were actually induced by TMS or a mere coincidence (Hufnagel and Elger, 1991a,b; Hufnagel et al., 1990a,c; Tassinari et al., 1990). This doubt is supported by the similarity between the TMS-associated seizures and the typical seizures. To further address the possibility of coincidence, Hufnagel and Elger reviewed the seizure occurrence rate during baseline memory testing performed immediately prior to the TMS in individuals whose antiepileptic drugs were lowered as part of their epilepsy evaluation (Hufnagel and Elger, 1991b). The memory testing required almost exactly the same amount of time as the TMS session. Within the subgroup of 17 subjects who underwent the memory testing, five subjects had seizures during memory testing (29.4%). Thus, the seizure rate was actually higher during memory testing than during TMS. This lends greater support to the possibility of coincidence; however, establishing whether the seizures were induced or coincidental is impossible with the limited data that currently exist.

4.3. Conditions that may increase the likelihood of a seizure occurring during TMS

The sensitivity and specificity of the five conditions in Table 1 cannot be adequately assessed because specific details of the 712 individuals with epilepsy reported in the literature to have undergone spTMS cannot be thoroughly addressed with a literature review. Thus, firm conclusions could not be drawn due to incomplete data. From our review, we could find no other conditions that occurred commonly among those with seizures.

As previously discussed by Hufnagel and Elger (1991a) and as noted in Table 4, the tapering of AEDs and

medically intractable seizures appear to be risk factors for TMS-associated seizures. In addition, stimulating ipsilateral to or near the epileptogenic region may be an additional risk factor. Patients who are undergoing video-EEG monitoring as part of an epilepsy surgery evaluation are at increased risk for a TMS-associated seizure. This may be because these patients typically undergo concurrent AED withdrawal and have intractable seizures. However, it is also possible that there is something specific to the seizure disorders in these patients that may place them at increased risk.

It remains unclear whether certain single- and paired-pulse TMS parameters may increase the likelihood of seizure occurrence. The diversity in reporting methods, not to mention a complete absence of reporting for many of these variables, prevent a determination of their potential contribution to seizure risk. It would be helpful for future studies to report as much information as possible about the stimulation parameters, at the very least in those cases where seizures occurred. Whenever possible, stimulation intensity should be reported relative to both motor threshold and maximum stimulator output. When a seizure occurs, the intensity, frequency, pulse width, pulse configuration, and number of pulses delivered should be reported.

5. Conclusion

Despite the safety concerns, the risk of spTMS and ppTMS causing a seizure in individuals with epilepsy appears small. The lowering of AEDs and the presence of medically intractable epilepsy increases the likelihood of a typical seizure occurring during spTMS or ppTMS. In all cases of a seizure during spTMS and ppTMS, the subject had their typical seizure followed by their typical recovery after the seizure. In most cases, it was not clear if the seizure was actually induced by TMS or was merely a coincidence. Furthermore, there have been no clear long-term adverse consequences in any individuals with epilepsy who have experienced a TMS-associated seizure. The numerical risk assessment from this study may enable TMS epilepsy researchers to more accurately inform their research subjects with epilepsy of the risk of seizure during spTMS and ppTMS.

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