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Review

Safety and tolerability of repetitive transcranial magnetic stimulation in patients with epilepsy: a review of the literature

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is emerging as a new therapeutic tool in epilepsy, where it can be used to suppress seizures or treat comorbid conditions such as mood disorder. However, as rTMS carries a risk of inducing seizures among other adverse events, its safety and tolerability in the population with epilepsy warrant distinct consideration, as this group is especially seizure-prone. Accordingly, we performed a review of the literature to estimate the risk of seizures and other adverse events associated with rTMS in patients with epilepsy. We performed an English-language literature search, and reviewed all studies published from January 1990 to February 2007 in which patients with epilepsy were treated with rTMS, and complemented the literature search with personal correspondence with authors when necessary. We identified 30 publications that described patients with epilepsy who underwent rTMS, and noted total number of relevant subjects, medication usage, incidence of adverse events, and rTMS parameters including stimulus frequency, number of stimuli, train duration, intertrain interval, coil type, and stimulation sites. The data were analyzed for adverse events related to rTMS. Crude per-subject risk, as well as per-subject mean risk weighted by sample size and risk per 1000 stimuli weighted by number of stimuli in each study, were computed for seizures and for other adverse events. Adverse events or lack thereof was reported in 26 studies ($n = 280$ subjects). Adverse events attributed to rTMS were generally mild and occurred in 17.1% of subjects. Headache was most common, occurring in 9.6%. The most serious adverse event was seizure during treatment, which occurred in four patients (1.4% crude per-subject risk). All but one case were the patients' typical seizures with respect to duration and semiology, and were associated with low-frequency rTMS. A single case of an atypical seizure appearing to arise from the region of stimulation during high-frequency rTMS is reported. No rTMS-related episodes of status epilepticus were reported. We cautiously conclude that the risk of seizure in patients with epilepsy undergoing rTMS is small, and the risk of other mild adverse events is comparable to that seen when rTMS is used to treat other diseases. Status epilepticus or life-threatening seizures have not been reported in patients undergoing rTMS treatment. rTMS thus appears to be nearly as safe in patients with epilepsy as in nonepileptic individuals, and warrants further investigation as a therapy in this population.

Keywords: Repetitive transcranial magnetic stimulation; Epilepsy; Safety; Seizure; Adverse event

1. Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive, generally well-tolerated method for cortical stimulation that is based on principles of electromagnetic induction, where small intracranial electric currents are generated by a strong fluctuating extracranial magnetic field [1]. Single-pulse TMS and paired-pulse TMS are safe and useful tools

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for investigating various aspects of human neurophysiology [2], including measures of cortical excitability in epilepsy [3]. In contrast to single-pulse and paired-pulse TMS, repetitive transcranial magnetic stimulation (rTMS) can induce a lasting change in neural activity [4], where the effects outlast the duration of the rTMS train itself. This durable effect is best seen as a change in cortical excitability that is reduced with low-frequency ($\leqslant$1 Hz) rTMS and enhanced with high-frequency ($\geqslant$10 Hz) rTMS [5]. The presumed mechanisms underlying these lasting changes in cortical excitability are similar to those of long-term depression (LTD) and long-term potentiation (LTP) of synaptic strength, which are seen with low- and high-frequency electrical brain stimulation, respectively [6,7].

The capacity of rTMS to induce lasting changes in cortical excitability has been applied in recent years to treatment of various neurological and psychiatric diseases, particularly mood disorders, parkinsonism, chronic pain, and epilepsy [1,8,9]. For patients with epilepsy, low-frequency rTMS, by reducing cortical excitability in or near the epileptic focus, holds therapeutic promise [9,10]. Additionally, for patients with epilepsy and accompanying psychiatric diseases, such as depression, rTMS may be useful in the treatment of either seizures or the psychiatric symptoms [11].

The risk profile of rTMS is more extensive than that of single- or paired-pulse TMS. Notably, the most serious reported side effect of rTMS is a seizure occurring at the time of treatment. Repetitive TMS-induced seizures are thought to arise from excessive activation of pyramidal cells, spread of excitation to neighboring neurons, and/or overwhelming of inhibitory mechanisms [12]. In patients with epilepsy, rTMS has been reported to activate a seizure focus [13], and thus the risks of rTMS might be greater than in nonepileptic individuals. The less serious and more common side effects of rTMS in adults include headache and scalp pain that result from direct activation of the scalp pericranial muscles [2,14,15].

The crude per-subject risk of a seizure in patients with epilepsy during single- and paired-pulse TMS is estimated at 1.7 and 1.8%, respectively, and has not been associated with a long-term adverse outcome [16]. However, the incidence of seizures in patients with epilepsy undergoing rTMS has not been investigated. As this population is by definition seizure-prone, rTMS-triggered seizure risk, if high, could have practical implications that potentially limit its use. Accordingly, we examined all published reports on the use of rTMS in patients with epilepsy for seizures and other side effects.

2. Methods

2.1. Literature review

Using PubMed, we identified 30 English-language publications describing rTMS application in patients with epilepsy published from January 1990 to February 2007. The search criteria relied on the following keywords: *TMS*, *transcranial magnetic stimulation*, *rTMS*, *repetitive transcranial magnetic stimulation*, *epilepsy*, *seizure*. We reviewed all reports and noted article references, total number of relevant subjects, medication usage during rTMS, incidence of adverse events, and rTMS parameters including stimulation intensity, stimulus frequency, train duration, intertrain interval, magnetic coil type, and stimulation sites. When not explicitly stated in the article, we obtained the relevant information by personal communication with the corresponding authors.

2.2. Statistical analysis

The crude risks of seizure and other mild adverse events were computed separately. Each case of reported seizure occurring during or directly after an rTMS session was considered in the risk estimates, although seizures in patients with epilepsia partialis continua (EPC) were excluded from the count.

We limited our statistical analysis to crude per-person risk and crude risk per 1000 rTMS stimuli. Our rationales for doing so were the small number of reported seizures and inconsistency in sample size (1–43 subjects per study) and rTMS protocol (0.3–50 Hz, 20–3000 stimuli per train) between studies. Accordingly, we calculated crude risk averages with 95% confidence intervals weighted by sample size and by stimulus number (total stimuli per patient).

To estimate the potential antiseizure benefit of rTMS, we grouped all reports in which change in seizure frequency relative to baseline was stated for individual patients after rTMS. From these data, we calculated the median change in seizure frequency in intervals after rTMS. We opted to use median rather than mean values, as averages of percentage change from baseline can be confounded by vastly different limits for improvement (maximum 100% reduction) and worsening (limitless percentage increase from baseline).

3. Results

3.1. Literature review

The subject characteristics and rTMS settings used in the reviewed papers are summarized in Table 1. Of 30 studies applying rTMS to patients with epilepsy, 2 publications [17,18] with data derived from another study [19] were excluded from the analysis. Of 28 remaining studies ($n = 287$ subjects), 22 studies reported the value of motor threshold (MT) and 6 studies reported only the value of motor output (MO). Of 22 studies with reported MT, 12 studies ($n = 145$ subjects) applied rTMS at or above MT (range, 100–150%), whereas 77 subjects were treated exclusively with sub-MT rTMS (range, 90–95% of MT). One hundred ninety-two subjects received exclusively low-frequency ($\leqslant$1 Hz) rTMS and 95 subjects received high-frequency (>1 Hz) rTMS exclusively or concurrently with low-frequency rTMS.

Of 28 articles reporting original research with rTMS in patients with epilepsy, adverse events or lack thereof was reported in 26. Accordingly, data from two articles [20,21] ($n = 7$ subjects) were excluded from analysis of adverse events. Of the subjects ($n = 280$) in the 26 remaining articles, the reported adverse events were: (1) seizures in 4 patients—2 during rTMS and 2 after an rTMS session, (2) headache or dizziness in 27 subjects (one with headache and leg pain), (3) nonspecific discomfort in 13, (4) skin irritation in 1, (5) jerking arm movement during treatment in 2, and (6) transient visual defect (a transient left

Table 1
Summary of reviewed rTMS studies (January 1990–February 2007)

Author	Year	No. of subjects	Age	AEDs[a]	rTMS frequency (Hz)	No. of stimuli	Intensity	Coil	Duration	Intertrain interval	Session schedule	Coil position	Adverse event
Hufnagel et al. [13]	1990	13	16–35	Y	0.33–0.5	25/train	105–130% MT	C	NR	⩾1 min	⩽10 trains repeatedly in one session	Central, temporal, parietal	None
Pascual-Leone et al. [17]	1991	6	24–49	N	⩽25	NR	60–80% MO	C	10 s	NR[b]	NR	D5, D7	Seizure ($n = 1$) Headache ($n = 3$) Skin irritation ($n = 1$)
Dhuna et al. [19]	1991	8	23–49	Y	⩽25	490–1060 total	40–80% MO ($n = 7$) 40–100% MO ($n = 1$)	C	NR	NR	NR	Frontal, temporal, central	Seizure ($n = 1$), Skin irritation ($n = 1$)
Gates et al. [18]	1992	2	32, 49	N	⩽25	2000 total	40–80% MO	C	NR	NR	NR	Temporal, frontal, central, parietal	Seizure ($n = 1$)
Schuler et al. [42]	1993	2	25, 26	Y	3–5	80, 150 total	70–100% MO	C	16–50 s	N/A	1 session	Vertex	None
Michelucci et al. [24]	1994	14	20–47	Y	16–20	NR	55–100% MO	C	8–10 s	NR	NR	Frontal, central, parietal, temporal	Pain/discomfort ($n = 10$) Jerking of one arm ($n = 2$) L visual defect ($n = 1$)
Jennum et al. [43]	1994	21	18–44	NR	30	750–2295 total	75–100% MO	C	1 s	NR	NR	Temporal, frontal	Headache ($n = 5$), Discomfort ($n = 2$)
Jennum et al. [44]	1994	10	20–60	N	30, 50	340 total	120% MT	C	1 s	60 s	8 trains	Temporal, frontal	None
Wedegaertner et al. [45]	1997	3	NR	NR	1	1800 total	110% MT	C	30 min	N/A	1 train/day for 3 days ($n = 1$), for 5 days ($n = 2$)	L M1	None
Tergau et al. [26]	1999	9	19–47	Y	0.33	500/train	100% MT	C	25 min	NR	2 trains/day for 5 days	Vertex	Partial seizure directly after rTMS ($n = 2$)
Wasserman et al. [15]	1999	14	22–54	Y	5–15	20/train	100–150% MT	Fig8	2–3 s, NR*	>12 s	12 trains in one session	Temporal, frontal	None
Epstein et al. [25]	2000	17	Adult	NR	4	NR	<100% MT	Fig8	NR	NR	NR	Lateral frontal	None
Menkes et al. [27]	2000	1	38	Y	0.5	20/train	95% MT	C	40 s	1 min	5 trains biweekly for 4 weeks	Midline parietal (area of cortical dysplasia)	None
Theodore et al. [28]	2002	12	26–54	Y	1	900/train	120% MT	Fig8	15 min	NR	Twice daily for 1 week	Seizure focus	Discomfort ($n = 1$), Typical CPS on two occasions ($n = 1$)
Daniele et al. [29]	2003	4	27–33	Y	0.5	100/train	90% MT	Fig8	200 s	N/A	Biweekly, 4 weeks	Seizure focus, Cz	None
Tergau et al. [30]	2003	17	21–50	Y	1, 0.333	1000/train	Slightly below MT	C	17 min, 50 min	N/A	1 train/day for 5 days	Vertex	None

(*continued on next page*)

Table 1 (*continued*)

Author	Year	No. of subjects	Age	AEDs[a]	rTMS frequency (Hz)	No. of stimuli	Intensity	Coil	Duration	Intertrain interval	Session schedule	Coil position	Adverse event
Fregni et al. [31]	2004	8	14–38	Y	0.5	600 total	65% MO	Fig8	20 min	N/A	1 session	Midcentral ($n = 2$), temporal ($n = 5$), other ($n = 1$); areas of cortical malformation	None
Brazil-Neto et al. [20]	2004	5	6, 19, 30, 32, 50	Y	0.3	20/train	95% MT	C	1 min	1 min	5 trains/day biweekly for 3 months	Cz	NR
Graff-Guerrero et al. [21]	2004	2	7, 11	Y	20	40/train	50% MO ($n = 1$) 128% MT ($n = 1$)	Fig8	2 s	58 s	1 session with 15 trains	L frontal	NR
Rossi et al. [46]	2004	1	34	Y	1	900 total	90% MT	Fig8	15 min	N/A	1 session	R M1	None
Misawa et al. [22]	2005	1	31	Y	0.5	100 total	90% MT	Fig8	200 s	N/A	1 session	Lateral to midcentral	None
Morales et al. [14]	2005	2	8, 16	Y	1, 6	20/train	100% MO ($n = 1$) 76% MO ($n = 1$)	C	10 min, 15 min	25 s	2 sessions	L M1 ($n = 1$) Seizure focus ($n = 1$)	Headache and leg pain (n = 1)
Kinoshita et al. [32]	2005	7	16–33	Y	0.9	810/train	90% MT	C	15 min	5 min	2 trains/day for 5 days/week for 2 weeks	FCz or PCz	Headache ($n = 2$)
Schrader et al. [23]	2005	4	37–48	Y	0.5	450/train	95% MT ($n = 3$), 100% MT ($n = 1$)	Fig8	15 min	3 min	2 trains biweekly for 4 weeks	Seizure focus	Seizure ($n = 1$) Headache ($n = 1$)
Brighina et al. [33]	2006	6	28–44	Y	5	50/train	90% MT	Fig8	10 s	50 s	2 trains for a total 20 sessions for 4 weeks	Cerebellum	None
Fregni et al. [35]	2006	15	>12	Y	1	900 total	90% MT	Fig8	15 min	N/A	1 session	L M1	None
Mecarelli et al. [47]	2006	1	22	Y	0.33	500/train	100% MT	C	25 min	NR	2 trains/day for 5 days	Vertex	None
Fregni et al. [10]	2006	12	13–30	Y	1	1200/train	>100% MT	Fig8	20 min	N/A	1 train/day for 5 days	Cz ($n = 3$) Seizure focus ($n = 9$)	Headache ($n = 3$)
Joo et al. [34]	2007	35	18–46	Y	0.5	3000/train ($n = 19$) 1500/train ($n = 16$)	100% MT	C, Fig8	100 min ($n = 19$) 50 min ($n = 16$)	N/A	1 train/day for 5 days	Cz ($n = 17$) Temporal ($n = 12$) L frontal ($n = 3$) R parietal ($n = 3$)	Headache ($n = 5$)
Cantello et al. [48]	2007	43	36.9 ± 13	Y	0.3	500/train	100% MT ($n = 34$) 65% MO ($n = 9$)	C	30 min	30 s	2 trains/day for 5 days	Vertex	Headache ($n = 7$)

[a] Continued use of anticonvulsant medication during rTMS.

[b] NR, not reported in publication; N/A, not applicable; MT, motor threshold; MO, machine output; C, circular coil; Fig8, figure-of-eight coil; M1, primary motor cortex. Where available in the reference, 10–20 International System for EEG electrode placement was used to indicate coil position (note intermediate scalp position (D5, D7) coordinates in Pascual-Leone et al., 1991). Otherwise, the authors' description of coil position is provided.

homonymous hemianopia after receiving a high-frequency rTMS train (70% intensity, 20 Hz) over the right temporal region, which subsided completely in 5 minutes) in 1. These findings are summarized in Fig. 1.

The 30 reviewed articles contain seven reports of seizures in four subjects, although one patient who had a single seizure during rTMS is described in three publications [17–19]. Thus, distinctive reported seizure cases are counted as five seizures in four subjects with an adjusted total number of subjects of 280. Six cases of EPC [14,21–23] were excluded from this count.

3.2. Risk assessment

Seizures starting during or shortly after rTMS were reported in 4 of 280 subjects. Thus, we estimate the crude risk per subject to be $1.43 \pm 1.39\%$ ($1.43 \pm 0.65\%$ per-subject mean risk weighted by sample size). Excluding two studies [17,24] in which total number of stimuli was not reported, we estimate the risk of seizure per 1000 stimuli to be $0.41 \pm 0.08\%$. The reported crude risk of side effects per subject other than a seizure is 44 in 280 ($15.7 \pm 4.27\%$ crude per-subject risk and $15.7 \pm 3.09\%$ per-subject mean risk weighted by sample size). The stimulation parameters and characteristics of the rTMS-induced seizures are summarized in Table 2.

All four patients who experienced a seizure during or shortly after rTMS were adults (age 18 or older), and all were on their regular medication during rTMS session.

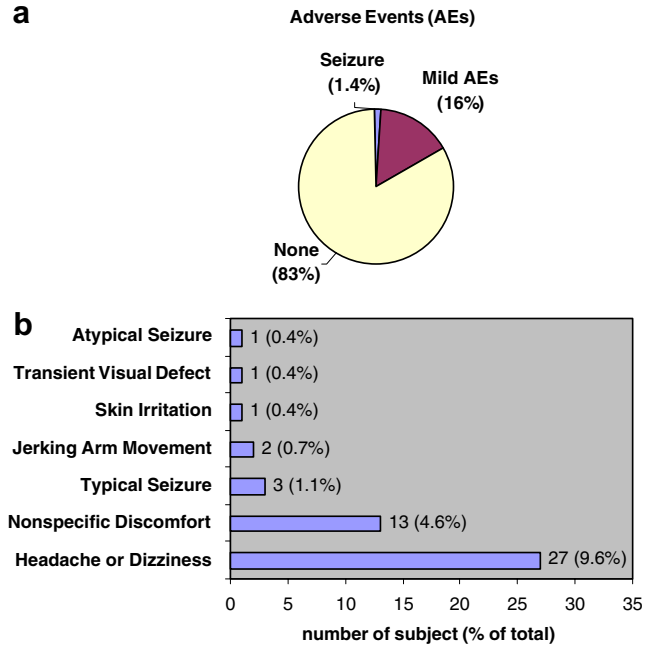

Fig. 1. Distribution of reported adverse events. (a) Adverse events categorized by seizure (1.4%) versus mild events (16%). (b) The reported adverse events during rTMS sessions are atypical seizure [17, 18, 19 (same patient)], transient visual defect [24], skin irritation [17, 19 (same patient)], jerking arm movement [24], typical seizure [26,28], nonspecific discomfort [21,28,43], and headache [10, 14 (with leg pain), 17, 23, 32, 34, 43, 48].

Table 2
Summary of patients with seizures induced during rTMS

	Age/gender	Diagnosis	AEDs	Adverse event	rTMS protocol at time of seizure
Dhuna et al., 1991 [19][a] Pascual-Leone et al., 1991 [17][a] Gates et al., 1992 [18][a]	32/F	CPS,[b] CPS–2°GTCS	Yes	Following a second train of stimulation, patient experienced a clinical right simple motor seizure with Jacksonian march, which secondarily generalized on EEG Seizure duration: about 90 s	100% MT, 16 Hz at R parietal region, circular coil
Theodore et al., 2002 [28]	Adult/NR	CPS, 2°GTCS	Yes	Patient with baseline five seizures per week had a typical CPS on two occasions during rTMS sessions Seizure duration: NR	120% MT, 1 Hz, Fig8 coil
Tergau et al., 1999 [26]	Adult/NR ($n = 2$)	Refractory focal epilepsy	Yes	Both patients with baseline more than seven seizures per week had a partial seizure directly after rTMS Seizure duration: NR	100% MT, 0.33 Hz over vertex, circular coil

[a] A single patient was discussed in three publications.
[b] CPS, complex partial seizures; 2°GTCS, secondary generalized tonic–clonic seizures; AEDs, continued use of medications during rTMS; Fig8, figure-of-eight coil; MT, motor threshold; NR, not reported in publication.

Two patients had a seizure shortly after a 1000-stimulus rTMS session, one patient had a seizure after 800 stimuli, and another patient had two seizures in one session of 900 stimuli. Notably, the two patients who experienced a seizure after 1000 stimuli each had frequent (more than seven per week) seizures [26], and thus, a causal relationship between their clinical event and the rTMS session is not clear. Also of note, all four subjects who had a seizure during or shortly after rTMS had medically refractory seizures at baseline.

A single patient [17–19] had an atypical seizure that appeared clinically to originate in the right hemisphere, which was the stimulation site, whereas her spontaneous seizures arose exclusively from the left temporal lobe. In contrast to the other instances of reported seizures during rTMS, this patient was treated with high-frequency (16-Hz) trains.

3.3. Therapeutic efficacy of rTMS in inpatients with epilepsy

We also reviewed the published data for a potential therapeutic benefit that may outweigh the risks associated with rTMS. With respect to its anticonvulsive application, 13 studies reported seizure frequencies before and after therapeutic rTMS [10,20,23,26–34,48]. Individual (per-subject) changes in seizure frequency were reported for 55 patients in 7 of the 13 studies [20,23,26,29,31–33]. In these reports, most patients had less frequent seizures 2 to 8 weeks after treatment. From this group, 21 subjects (38% of total) experienced a seizure frequency reduction of 50% or more. The potential antiseizure benefit of rTMS is illustrated in Fig. 2 as median change in seizure frequency, where a reduction in seizures is reported in most patients for 2 to 8 weeks after treatment.

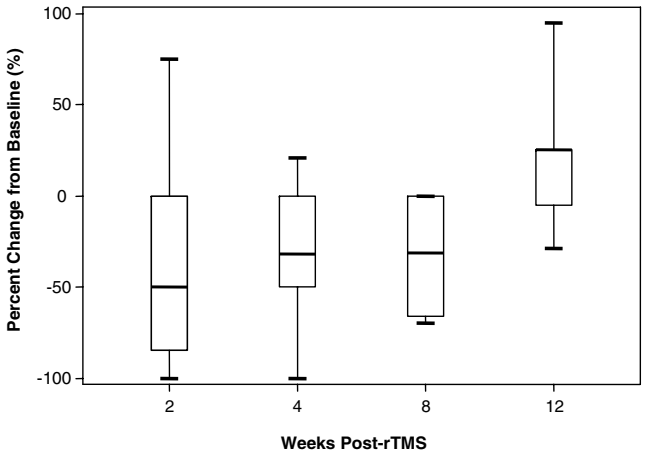

Fig. 2. Seizure reduction after rTMS. Box plot demonstrating median (center bar in each box) seizure reduction with first (bottom box margin) and third (top box margin) quartiles, as well as minima and maxima (bottom and top whiskers) for each group. (Note, median and third quartile values are equal in the 8-week group). Data for individual patient were available for 2 weeks ($n = 15$), 4 weeks ($n = 31$), 8 weeks ($n = 4$) and 12 weeks ($n = 5$). These data suggest a potential beneficial effect of rTMS with reduced seizure frequency in most subjects for 2 to 8 weeks after treatment.

In five additional studies, where grouped rather than individual responses to rTMS were reported, significant average seizure reduction was demonstrated in two controlled trials [10,30]. In these, >50% seizure reduction lasting 8 weeks was reported by Fregni et al. in patients ($n = 12$) with major cortical dysplasia [10], and a 35% reduction, by Tergau et al. for a heterogeneous patient group ($n = 17$) 2 weeks after 0.33-Hz rTMS, although not after 1-Hz rTMS [30].

The three remaining studies do not demonstrate significant seizure reduction after rTMS, although they do suggest some anticonvulsive effect. A mild and short-lived average seizure reduction in patients with mesial temporal or nonlesional neocortical epilepsy ($n = 12$) was reported by Theodore et al., and two recent studies by Joo et al. [34] and Cantello et al. [48] that did not demonstrate a significant reduction in seizure frequency did report significant reductions in interictal EEG spikes, thus suggesting a potentially beneficial biological effect.

As most published reports evaluated seizure frequency in the epileptic population, we could not evaluate the potential benefit of this technique in treatment of other neuropsychiatric diseases such as depression, although this estimate would certainly be valuable in the future.

4. Discussion

We find that the risk of seizure associated with rTMS in patients with epilepsy is small, and that rTMS-triggered status epilepticus or life-threatening seizures have not been reported. Further, the risk of adverse events other than seizure in patients with epilepsy approximates that reported when rTMS is applied in other disease conditions [8].

Seizures, the most severe reported adverse event, were associated with rTMS sessions in 4 of 280 patients with epilepsy: 2 during rTMS and 2 shortly after an rTMS session. Rounded to the nearest 0.5%, our estimated crude risk of induced seizures during a rTMS session is approximately 1–2% per subject ($1.43 \pm 0.65\%$ mean weighted by sample size of each study) and approximately 0.5% per 1000 rTMS stimuli ($0.41 \pm 0.08\%$ mean weighted by stimulus number).

Our estimate of seizure risk during rTMS is limited by the small number of reported seizures; the variation in rTMS protocols with respect to stimulus intensity; rTMS frequency, train duration, and coil position; and the heterogeneity of the subjects with epilepsy. Accordingly, given the nature of our data, we opted to report only the crude risk estimates, and anticipate that more detailed analyses of the safety and tolerability of specific rTMS protocols delivered to homogenous groups are necessary for more precise risk assessment in the future.

Assessment of the risk of rTMS-induced seizures in patients with epilepsy carries the additional limitation that these individuals already have spontaneous seizures, some more often than once daily. Thus, attributing causality to any event may prove difficult. Detailed temporal examination of cortical activity during the delivery of rTMS, for

instance, with ongoing EEG, may help to clarify the association in future studies.

Notably, only a single instance (1 of 280 subjects) of seizure atypical for the patient and appearing clinically to originate from the site of stimulation during high-frequency (16-Hz) rTMS is reported [35]. This case is distinct from the remaining seizure reports in that the relationship of this event to rTMS is more likely to be causal than coincidental, and may reflect a proconvulsive capacity of higher-frequency cortical stimulation.

Seizures related to single-pulse TMS have not been reported in normal subjects, but there are a few published cases in patients with stroke, multiple sclerosis, and bipolar disease [36–38]. With rTMS, almost all seizures reported to date occurred in normal subjects before the advent of current safety guidelines, under parameters that retrospectively fall outside these recommended criteria [2]. In this regard, we find it encouraging that rTMS safety data suggest minimal risk with low-frequency ($\leqslant$1-Hz) rTMS [39], as would be used clinically in most settings for the treatment of epilepsy.

The reviewed data suggest that antiseizure applications of rTMS may offer potential benefit with acceptable risk. Notably, a 50% or greater reduction in seizure frequency was reported in 38% of patients in reports where individual seizure frequencies are available. From these findings, we cautiously conclude that the potential benefit from rTMS may outweigh the risk for patients with intractable seizures.

In our review, we did not find reports on the efficacy of rTMS in the treatment of depression or other comorbid neuropsychiatric conditions in patients with epilepsy. Although for treatment of nonepilepsy conditions in this population, rTMS may also prove to be of benefit and acceptable risk.

Given that neuromodulation is emerging as a promising novel treatment for intractable seizures, our finding that rTMS is relatively safe in patients with epilepsy may be valuable for future applications of this technique. Further, as depression and other psychiatric diagnoses often accompany epilepsy [40,41], an acceptable risk profile of rTMS in the epileptic population could facilitate treatment of these comorbid conditions [11].

We note that the rTMS protocols and clinical pictures of the patients in the studies reviewed are heterogeneous, and it is possible that seizures have occurred in some laboratories but have not been reported. Thus, although encouraging, our findings should be interpreted with caution. We conclude that carefully controlled studies of the safety of rTMS in patients with epilepsy are warranted.

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