Epilepsy & Behavior 57 (2016) 167–176

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Safety of repetitive transcranial magnetic stimulation in patients with epilepsy: A systematic review

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ARTICLE INFO

Article history:
Received 3 December 2015
Revised 13 January 2016
Accepted 15 January 2016
Available online 10 March 2016

Keywords:
Repetitive transcranial magnetic stimulation
Epilepsy
Seizure
Safety
Adverse events

ABSTRACT

Approximately one-third of patients with epilepsy remain with pharmacologically intractable seizures. An emerging therapeutic modality for seizure suppression is repetitive transcranial magnetic stimulation (rTMS). Despite being considered a safe technique, rTMS carries the risk of inducing seizures, among other milder adverse events, and thus, its safety in the population with epilepsy should be continuously assessed. We performed an updated systematic review on the safety and tolerability of rTMS in patients with epilepsy, similar to a previous report published in 2007 (Bae EH, Schrader LM, Machii K, Alonso-Alonso M, Riviello JJ, Pascual-Leone A, Rotenberg A. Safety and tolerability of repetitive transcranial magnetic stimulation in patients with epilepsy: a review of the literature. Epilepsy Behav. 2007; 10 (4): 521–8), and estimated the risk of seizures and other adverse events during or shortly after rTMS application. We searched the literature for reports of rTMS being applied on patients with epilepsy, with no time or language restrictions, and obtained studies published from January 1990 to August 2015. A total of 46 publications were identified, of which 16 were new studies published after the previous safety review of 2007. We noted the total number of subjects with epilepsy undergoing rTMS, medication usage, incidence of adverse events, and rTMS protocol parameters: frequency, intensity, total number of stimuli, train duration, intertrain intervals, coil type, and stimulation site. Our main data analysis included separate calculations for crude per subject risk of seizure and other adverse events, as well as risk per 1000 stimuli. We also performed an exploratory, secondary analysis on the risk of seizure and other adverse events according to the type of coil used (figure-of-8 or circular), stimulation frequency (≤1 Hz or >1 Hz), pulse intensity in terms of motor threshold (<100% or ≥100%), and number of stimuli per session (<500 or ≥500). Presence or absence of adverse events was reported in 40 studies (n = 426 subjects). A total of 78 (18.3%) subjects reported adverse events, of which 85% were mild. Headache or dizziness was the most common one, occurring in 8.9%. We found a crude per subject seizure risk of 2.9% (95% CI: 1.3–4.5), given that 12 subjects reported seizures out of 410 subjects included in the analysis after data of patients with epilepsia partialis continua or status epilepticus were excluded from the estimate. Only one of the reported seizures was considered atypical in terms of the clinical characteristics of the patients' baseline seizures. The atypical seizure happened during high-frequency rTMS with maximum stimulator output for speech arrest, clinically arising from the region of stimulation. Although we estimated a larger crude per subject seizure risk compared with the previous safety review, the corresponding confidence intervals contained both risks. Furthermore, the exclusive case of atypical seizure was the same as reported in the previous report. We conclude that the risk of seizure induction in patients with epilepsy undergoing rTMS is small and that the risk of other adverse events is similar to that of rTMS applied to other conditions and to healthy subjects. Our results should be interpreted with caution, given the need for adjusted analysis controlling for potential confounders, such as baseline seizure frequency. The similarity between the safety profiles of rTMS applied to the population with epilepsy and to individuals without epilepsy supports further investigation of rTMS as a therapy for seizure suppression.

1. Introduction

Epilepsy is an enduring alteration in the brain, which predisposes the patient to seizures, occurring as a consequence of abnormal excessive or enhanced synchronous neuronal activity [1]. Despite the

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http://dx.doi.org/10.1016/j.yebeh.2016.01.015
1525-5050/

development and availability of more than 15 new antiepileptic drugs within the last 25 years, about one-third of patients with epilepsy remain with pharmacologically intractable seizures [2]. Nonpharmacologic methods, including noninvasive brain stimulation and modulation techniques, are thus emerging as a therapeutic option for seizure control. Among these techniques is transcranial magnetic stimulation (TMS), a safe and well-tolerated method for focal electrical brain stimulation where small intracranial electric currents are induced by strong and fluctuating extracranial magnetic fields [3,4].

In general, TMS protocols may be divided into single-pulse TMS (spTMS), paired-pulse TMS (ppTMS), and repetitive TMS (rTMS). In day-to-day care of patients with epilepsy, spTMS and ppTMS can be useful for presurgical mapping of cortical function and for detecting abnormalities in the cortical excitation:inhibition ratio [5], and rTMS (particularly low-frequency rTMS) has been tested as a means to induce lasting reductions in cortical excitability and thus reduce seizure frequency [6]. The rTMS effects are highly variable across individuals [3] and depend on parameters such as frequency (Hz), number of stimuli within a train [7], stimulation intensity, type of coil, coil position, duration of stimulation, and intertrain interval. However, in general, low-frequency (≤1 Hz) rTMS reduces cortical excitability, while higher frequencies (conventionally standardized as ≥1 Hz) enhance cortical excitability [8]. These effects are analogous to those of long-term depression (LTD) and long-term potentiation (LTP) phenomena, and it is the LTD-like depression induced by low-frequency rTMS that has interested the epilepsy community as a potential therapeutic tool for seizure suppression.

Since 2008, rTMS has been approved for use in mild treatment-resistant depression [9], but it is still under investigation for neurologic and psychiatric conditions, such as mood disorders (major depression, bipolar disorder, posttraumatic stress disorder, obsessive–compulsive disorder, borderline personality disorder, and schizophrenia), Parkinson's disease, chronic pain, and epilepsy [3,4,10]. Overall, open-label studies and case reports show a reduction of seizure frequency and/or epileptic discharges after rTMS applications [11–15]. Patients with refractory epilepsy showed a significant decrease in the number of seizures in a randomized sham-controlled clinical trial of low-frequency rTMS [16,17]. However, well-designed, multiparametric rTMS studies, with strict inclusion criteria, are needed to increase data consistency and to ascertain reproducibility of effects. Such studies should also account for different underlying epileptogenic mechanisms.

While rTMS is generally safe, some of the potential and most frequent side effects are transient headache, pain at the site of stimulation, discomfort due to muscular contraction, and transient tinnitus [18]. Although very rare, induced seizure is the most severe adverse effect of rTMS, and therefore, it is especially important given the seizure-prone profile of patients with epilepsy. Reports have been published about epileptic foci activation by rTMS in patients with medically intractable complex partial seizures [19], as well as seizure induction in patients with epilepsy and in healthy volunteers [6,7,18].

Safety guidelines and recent reviews by the International Federation of Clinical Neurophysiology define the limits of safe rTMS protocols [18]. The observance of these safety guidelines has contributed to maintain the number of convulsive complications and side effects low. However, since rTMS is more likely to induce seizure, compared with single- or paired-pulse TMS [3], and ongoing research on rTMS supports it as a valuable potential therapeutic modality because of its longer lasting effects, it is crucial to continuously assess its safety. Bae et al. [6] reviewed the safety and tolerability of rTMS applied to patients with epilepsy, which included 30 studies published from 1990 to 2007 and reported a crude per subject seizure risk of 1.4% (95% CI: 0.04–2.82) among 280 subjects. Accordingly, the primary goal of this study was to perform an updated systematic review of the available data in order to further estimate the risk and tolerability of rTMS in epilepsy.

2. Methods

2.1. Literature search

We performed a comprehensive literature search of articles describing rTMS application in patients with epilepsy in PubMed, Embase, Web of Science, PsycINFO, and Cochrane Central Register of Controlled Trials. Our search was slightly different from that of the previous review [6], which obtained articles exclusively from PubMed. We used the following keywords: “rTMS”, “repetitive transcranial magnetic stimulation”, “low frequency rTMS”, “TMS”, “transcranial magnetic stimulation”, “epilepsy”, “seizure”, and “myoclonus”. In PubMed, our primary source of articles, the search was performed in the following manner: (“Epilepsy”[mesh] OR epilep*[tiab] OR seizure*[tiab] OR myoclon*[tiab]) AND (“Transcranial Magnetic Stimulation”[mesh] OR Transcranial Magnetic Stimulation[tiab] OR rtms[tiab] OR repetitive tms[tiab] OR low frequency tms[tiab]). We also searched for relevant studies in the references of articles describing noninvasive brain stimulation in the context of epilepsy. Using EndNote X5, we screened all obtained reports by reading their titles and abstracts. We reviewed the reports that were potentially eligible and selected those that described the application of rTMS in patients with epilepsy.

2.2. Study selection

The research process considered papers published until August 7th, 2015. To reduce the probability of selection bias, no language or time restrictions were applied. We included studies that met the following criteria: (1) involved human subjects only, (2) reported original research, and (3) described rTMS application in patients with epilepsy.

2.3. Data extraction

We noted the total number of relevant subjects, age range, usage of anticonvulsant medication during rTMS, incidence and type of adverse events, and rTMS parameters: stimulation intensity, stimulus frequency, train duration, intertrain interval, session schedule, type of coil, and coil position or stimulation site. Corresponding authors were contacted by e-mail when relevant information was not found in the manuscript.

2.4. Data analysis

2.4.1. Per person crude risk assessment

As this study is an update of the safety review performed by Bae et al. [6], we limited our analysis to crude per person risk and crude risk per 1000 rTMS stimuli, given the infrequency of adverse events and the variability in sample size (1–60 subjects per study) and in rTMS protocols. Crude risk averages were calculated along with their corresponding 95% confidence intervals. The crude risks of seizure and other adverse events were calculated separately. Only seizures reportedly occurring during or shortly after rTMS were included in the risk estimates. Data from patients with epilepsia partialis continua (EPC) or status epilepticus at the time of rTMS administration were excluded from these estimates, and only data from full-length papers were included.

2.4.2. Exploratory, secondary analysis on the risk according to coil, intensity, frequency, and stimuli per session

We included unadjusted estimates of relative risks of adverse events according to stimulation intensity (<100% motor threshold (MT) or ≥100% MT), frequency (≤1 Hz or >1 Hz), type of coil (figure-of-8 or circular), and number of stimuli per session (<500 or ≥500). Confidence intervals were computed for each estimate, and Fisher's exact test (two-sided) was used for comparison of proportions, considering that there were cases of expected frequencies <5%. Relative risks of seizures and other adverse events were also computed separately. Reported

p-values were not adjusted for multiple comparisons (total of 8) considering that, as it is a safety review, we were less stringent on committing a type I error than a type II error.

3. Results

3.1. Literature review

Using the search criteria previously mentioned, we retrieved 1802 references after duplicate exclusion using EndNote X5. After screening titles and abstracts, we excluded studies that were clearly unrelated to rTMS being applied in patients with epilepsy (n = 1469) and selected potentially relevant studies (n = 333) for whole text review. After revision, 287 studies were excluded because of the reasons summarized in Fig. 1. Finally, 46 articles of rTMS application in patients with epilepsy were included in our review, of which 16 were published after 2007 and, therefore, were not part of the review performed by Bae et al. Despite performing a broader search in more databases, we did not identify any additional studies published within the time period that was accounted by the previous review. Three articles [20–22] reporting and analyzing duplicate data from two other studies [23,24] were excluded from the analysis.

The rTMS parameters, adverse events, and subject characteristics are summarized in Table 1. Of the 43 articles with original data (n = 434 subjects), 36 (n = 372 subjects) reported continued use of anticonvulsant medication during rTMS; in 5 of them (n = 44 subjects), this information was not found; one study (n = 8 subjects) reported tapering of antiepileptic drugs (AEDs) 1 to 3 weeks prior to the rTMS study for the purpose of localizing epileptic foci and determining hemispheric dominance for language [23]; and one study (n = 10 subjects) reported discontinuation of the antiepileptic treatment as part of presurgical evaluation where ictal video-EEG scalp recordings were performed [27].

Of all studies reporting rTMS intensity according to motor threshold (n = 30 studies), 144 subjects received rTMS at and/or above MT (range, 100–150%), and 143 subjects received exclusively sub-MT rTMS (range: 20% for placebo, 90–95% for active treatment). Low-frequency (≤1 Hz) rTMS was exclusively applied in 306 subjects, and high-frequency (>1 Hz) rTMS exclusively or concurrently with low-frequency rTMS was applied in 110 subjects.

3.2. Adverse events

Adverse events, or lack thereof, were reported in 40 out of 43 articles reporting original data; however, we also present a sensitivity analysis for the main assessment of crude risk per subject including these three studies and considering that no adverse events happened. Although our sensitivity analysis accounts for a best-case scenario, it is conceivable to assume that the absence of reporting of adverse events, particularly seizures, is more likely to represent their lack than their presence. Among the 426 subjects in the 40 studies, a total of 78 subjects (18.3%) reported adverse events; 85% were mild. The reported adverse events were: (1) seizures in 12 subjects, (2) headache or dizziness in 38 — one event of headache was accompanied by ear pain and another one by leg pain, (3) nonspecific discomfort during stimulation in 18, (4) tinnitus in 2, (5) skin irritation in 1, (6) jerking of one arm in 2, (7) nausea or vomiting in 1, (8) resting tremor of hand in 1, (9) scalp, arm, and leg pain together during 20 Hz stimulation with an intensity of 100% MT during 4 s in 1 subject, (10) transient visual defect in 1, which occurred after a stimulation with an intensity of 70% motor output (MO) and 20 Hz, over the right temporal region, characterized as a "left homonymous hemianopia, which subsided completely in about 5 minutes", and (11) difficulty in sleeping after rTMS in 1 patient. These findings are summarized in Fig. 2.

3.3. Risk assessment

We estimated the crude risk of side effects other than seizure per subject to be 15.5% (95% CI: 12.1–18.9). Seizures occurring during or

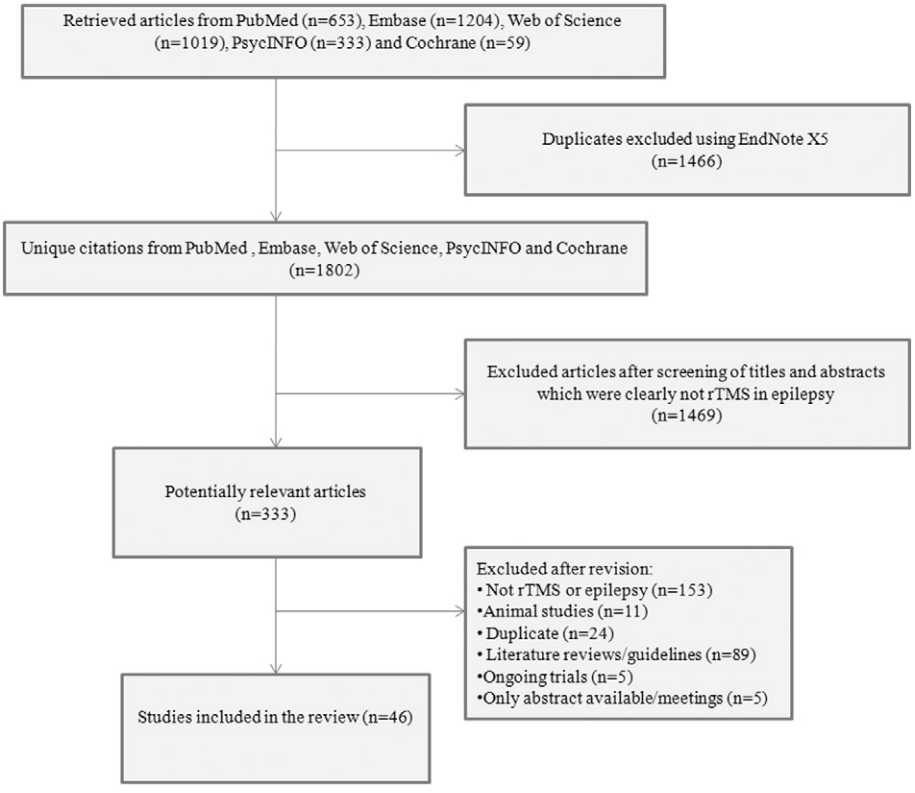

Fig. 1. The process of trial extraction and selection.

Table 1
Summary of reviewed rTMS studies.

Author	Year	No. of Subjects	Age	AEDs[a]	Frequency (Hz)	No. of stimuli	Intensity	Coil	Duration	Intertrain interval	Session schedule	Coil position	Adverse event
Hufnagel et al. [19]	1990	13	16–35	Y	0.33–0.5	25/train	105–130% MT	C	NR	≥1 min	≤10 trains repeatedly in one sessions	Vertex, central, parietal, temporal, occipital, frontal	None
Pascual-Leone et al. [20]	1991	6	24–49	N	≤25	NR	40–50% MO	C	10 s	NR	NR	D5, D7	Seizure (n = 1)
Dhuna et al. [23]	1991	8	23–49	N	8–25	490–1060 total	40–100% MO	C	NR	NR	NR	Epileptic focus (frontal, temporal, central)	Seizure (n = 1), Skin irritation (n = 1)
Gates et al. [21]	1992	2	32, 49	N	≤25	1200 total (n = 1), 1040 total (n = 1)	40–80% MO	C	NR	NR	NR	Frontal, temporal, central, parietal	Seizure (n = 1)
Schuler et al. [25]	1993	2	25, 26	Y	3–5	80, 150 total	70–100% MO	C	16–50 s	N/A	1 session	Vertex	None
Michelluci et al. [26]	1994	14	19–58	Y	16–25	NR	55–100% MO	C	6–10 s	NR	NR	Frontal, central, parietal, temporal	Pain/discomfort (n = 10); Jerking of one arm (n = 2); Left visual defect (n = 1)
Jennum et al. [27]	1994	10	20–60	N	30, 50	340 total	120% MT	C	1 s	1 min	8 trains	Temporal, frontal	None
Jennum et al. [28]	1994	21	18–44	Y	18–44	≤1680 total	75–100% MO	C	1 s	NR	NR	Temporal, frontal	Headache (n = 5), Unpleasant muscle contractions (n = 2)
Wedegaertner et al. [29]	1997	3	NR	NR	1	1800 total	110% MT	C	30 min	N/A	1 train/day for 5 days (n = 2), for 3 days (n = 1)	LM1	None
Tergau et al. [30]	1999	9	21–48	Y	0.33	500/train	NR	C	25 min	NR	2 trains daily, for 5 days	Vertex	Seizures (n = 2)
Wasserman et al. [31]	1999	14	22–54	Y	5–15	20/train	100–150% MT	Fig8	2–3 s	12	1 session of 12 trains	Frontal, temporal	Discomfort (n = 4)
Epstein et al. [32]	2000	17	NR	NR	4	NR	NR	Fig8	NR	NR	NR	Lateral frontal	None
Menkes et al. [12]	2000	1	38	Y	0.5	20/train	95% MT	C	40 s	1 min	5 trains biweekly for 4 weeks	Area of cortical dysplasia	None
Theodore et al. [33]	2002	12	40 ± 14 years	Y	1	900/train	120% MT	Fig8	15 min	N/A	2 daily sessions for 1 week	Ictal focus	Discomfort (n = 1); Typical CPS on two occasions (n = 1)
Daniele et al. [13]	2003	4	27–33	Y	0.5	100/train	90% MT	Fig8	200 s	N/A	1 session biweekly, for 4 weeks	Vertex (multifocal epilepsy); seizure focus (single focus epilepsy)	None
Tergau et al. [34]	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
Brasil-Neto et al. [14]	2004	5	6, 19, 30, 32, 50	Y	0.3	20/train	95% MT	C	66 s	1 min	5 trains/day biweekly for 3 months	Vertex	NR
Graff-Guerrero et al. [35]	2004	2	7, 11	Y	20	40/train	50% MO (n = 1); 128% MT (n = 1)	Fig8	2 s	58 s	1 session of 15 trains	Left frontal	NR
Rossi et al. [36]	2004	1	34	Y	1	900 total	90% MT	Fig8	15 min	N/A	1 session	R M1	None
Fregni et al. [11]	2005	8	14–38	Y	0.5	600 total	65% MO	Fig8	20 min	N/A	1 session	Areas of cortical malformation: Cz (n = 2), temporal (n = 5), other (n = 1)	None
Misawa et al. [15]	2005	1	31	Y	0.5	100 total	90% MT	Fig8	200 s	N/A	2 sessions separated by 3 months	Left hand motor area (5 cm lateral to Cz)	None
Morales et al. [37]	2005	2	8, 16	Y	1, 6	≤600/train (n = 1); ≤900/train (n = 1)	100% MO (n = 1); 68–76% MO (n = 1)	C, Fig8	10 min, 15 min	25 s	2 days of stimulation	L M1 (n = 1); Left parietal (n = 1)	Headache and leg pain (n = 1)
Kinoshita et al. [38]	2005	7	16–33	Y	0.9	810/train	90% rMT or 100% aMT (when rMT was higher than MO)	C	15 min	5 min	2 trains/day for 5 days	FCz or PCz	Headache (n = 2); SPS and CPS during stimulation (n = 1)
Schrader et al. [39]	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. [40]	2006	6	28–44	Y	5	50/train	90% MT	Fig8	10 s	50 s	1 session of 2 trains daily for 20 days, excluding weekends	Cerebellum (2 cm below and lateral to the inion)	None

Fregni et al. [41]	2006	15	>12	Y	1	900 total	90% MT	Fig8	15 min	N/A	1 session	L M1	None
Mecarelli et al. [42]	2006	1	22	Y	0.33	500/train	100% MT	C	25 min	NR	2 trains daily, for 5 days	Vertex	None
Fregni et al. [16]	2006	12	13–30	Y	1	1200/train	70% MO	Fig8	20 min	N/A	1 train/day, for 5 days	Cz (n = 3); Seizure focus (n = 9)	Headache (n = 5); Difficulty sleeping after rTMS (n = 1)
Joo et al. [43]	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. [44]	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	Dizziness or headache (n = 7)
Löscher et al. [45]	2007	8	19–49	Y	1	300/train	90% MT	Fig8	300 s	N/A	1 train/day for 2 days (1 hemisphere/day)	Premotor cortex of both hemispheres	CPS after rTMS (n = 1); Headache (n = 2)
Conte et al. [46]	2007	1	25	Y	5	10/train	120% MT	C	2 s	60 s	1 session of 10 trains	Vertex, cervical region	NR
Rotenberg et al. [22]	2007	1	14	NR	1	1800/train	100% MT	Fig8	30 min	N/A	1 train/day, for 9 days	Seizure focus (central, frontal)	None
Santiago-Rodríguez et al. [47]	2008	12	14–54	Y	0.5	900 total	120% MT	Fig8	15 min	N/A	1 daily session, for 2 weeks	Frontal, temporal	Seizure (n = 1); Headache (n = 1); Rest tremor in the hands (n = 1)
Wang et al. [48]	2008	15	27.9 ± 4.1	Y	1	500/train	90% MT	Fig8	8 min, 3 min	N/A	1 train/day, for 7 days	Seizure focus (temporal)	Headache (n = 5)
Rotenberg et al. [24]	2009	5	12–22	Y	1	1800/session	100% MT, 70% M0	C, Fig8	30 min	N/A	Blocks of 10–15 consecutive weekdays (total number of session per subject: 11, 10, 152, 35, 10)	Dominant seizure focus	Seizures (n = 5); Headache and ear pain (n = 1)
Wu et al. [49]	2009	3	18, 25, 32	Y	1	20/train	90% MO	C	20 s	10 s	25 trains per session, 1 session every 3 days for 1 month	L temporal	Headache (n = 1)
Rotenberg et al. [50]	2009	7	11–79	Y	1 Hz (n = 3); 1 Hz, 20 Hz (n = 2); 6 Hz, 1 Hz (n = 1); 100 Hz, 1 Hz (n = 1)	≤1800 total	100% MT (n = 6); 90–100% MO (n = 1)	Fig8	2 s–30 min	NR	1 session of 3 trains (n = 1), 1 train (n = 1), 2 trains (n = 1); 9 trains (n = 1); 2 sessions (n = 3)	Seizure focus	Scalp, arm and leg pain (n = 1)
Brodbeck et al. [51]	2010	5	18–35	Y	6, 1	1200 total	90% MT and 110% MT	Fig8	10 min	25 s	1 session of 2 blocks	Frontal or Cz (n = 2); Parietal (n = 2); Temporal (n = 1)	None
Notghi et al. [52]	2011	18	5–15	NF*	Low frequency	NF	NF	Fig8	20 min	N/A	1 daily session for 5 days	NF	Nausea and vomiting (n = 1)
Wang et al. [53]	2011	4	11, 19, 22, 64	Y	0.5	100/train	45% MO	C	200 s	30 s	15 trains/day, for 10 days	Seizure focus (right temporal n = 2; right frontal = 1; left frontal n = 1)	None
Sun et al. [17]	2012	60	14–42	Y	0.5	500/train	90% MT (n = 31), 20% MT (n = 29)	Fig8	17 min	600 s	3 sessions daily, for 2 weeks	Epileptogenic focus: Temporal (n = 6); Frontal (n = 21); Parietal (n = 26); Occipital (n = 7)	Headache (n = 2); Tinnitus (n = 1)
Liu et al. [54]	2013	2	46, 51	Y	1	1200/train	70% MO (n = 1); 100% MT (n = 1)	Fig8	20 min (n = 1); 30 min (n = 1)	N/A	1 train	C4/T4 (n = 1); Left sensorimotor cortex (n = 1)	None
Thordstein et al. [55]	2013	2	2, 6	Y	0.5	1800 total	NF	NF	60 min	N/A	1 train/day for ≤2 weeks	Seizure focus according to EEG (n = 1), R M1 (n = 1)	None
Vitikainen et al. [56]	2015	4	12–17	NR	5 (n = 3); 5,7 (n = 1)	NR	71–100% MT	Fig8	NR	NR	NR	Frontal, temporal, parietal	Discomfort (n = 1)
Van Haerents et al. [57]	2015	1	24	Y	1	600/train	95–100% MT	Fig8	10 min	1 min	11 3-train sessions, 10 days	Left occipital focus	None

NR, not reported; N/A, not applicable; MT, motor threshold; MO, machine output; C, circular coil; Fig8, figure-of-eight; M1, primary motor cortex; Y, yes; N, no; L, left; R, right. References of the 10–20 International System for EEG electrode placement were used to indicate the stimulation site. Otherwise, author's description of stimulation site was used.

[a] Continued use of anticonvulsant medication during rTMS.

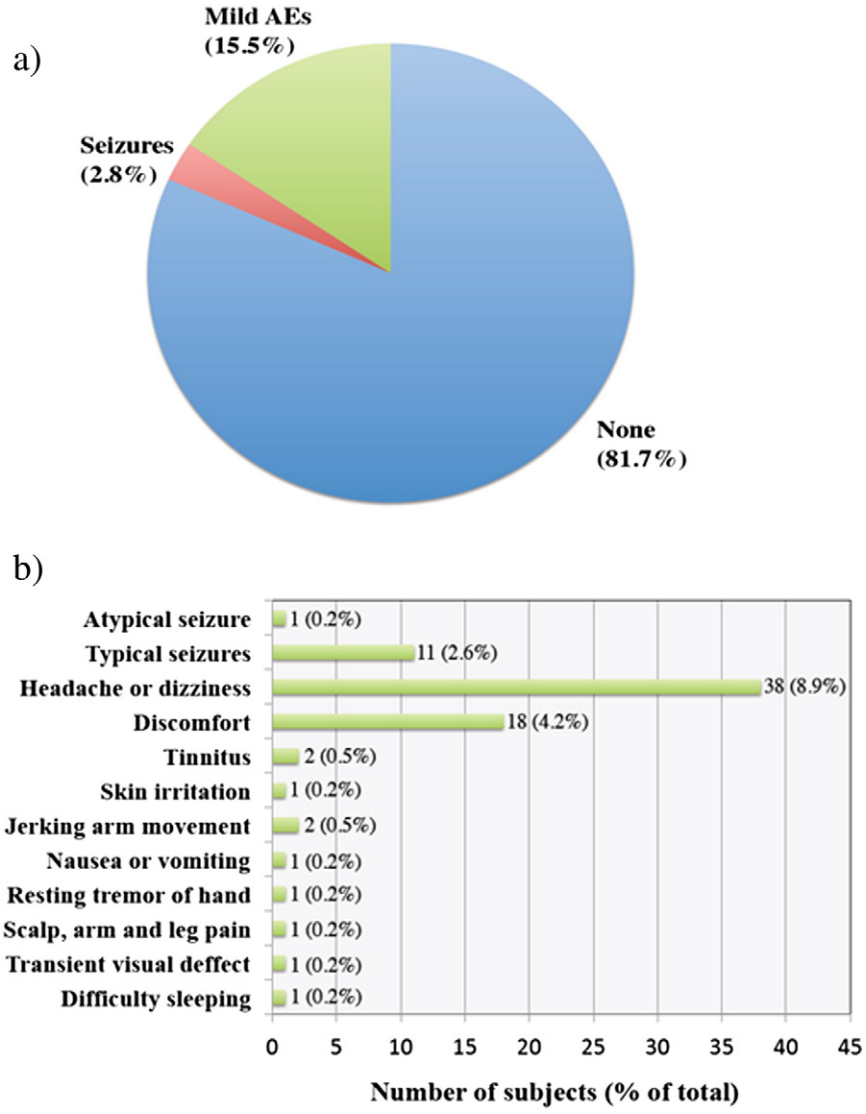

Fig. 2. Distribution of adverse events (AEs). (a) General distribution dividing AEs in mild, seizures and none. (b) Specific events occurring in total sample of subjects (n = 426) from studies reporting AEs.

shortly after rTMS were reported in 12 out of 410 subjects. Thus, we estimate the crude risk per subject to be 2.9% (95% CI: 1.3–4.5). In our sensitivity analysis, which included the subjects (n = 6 subjects) pertaining to studies that did not report presence or absence of adverse events, we estimated the crude risk per subject of side effects other than seizure to be 15% (95% CI: 11.6–18.4) and of seizures to be 2.8% (95% CI: 1.2–4.4). Patients with EPC or status epilepticus [15,35,37,39,50,54] were excluded from the assessment of risk of seizure.

For our analysis of risk of seizure per 1000 rTMS stimuli, of the 40 studies presenting original data and reporting presence or lack of adverse events, one study [51] did not report total number of stimuli and was excluded from this analysis. We estimated an incidence of 0.04 seizures per 1000 stimuli.

The stimulation parameters and characteristics of the patients who reported seizures during or shortly after rTMS are summarized in Table 2. Only 1 of the 12 patients who reported seizures was being tapered off AEDs for the purpose of preoperative characterization of the ictal focus [23]; all other patients were on their regular medication during stimulation. The same patient who was tapering AEDs was the only one to report an atypical seizure, clinically arising from the opposite side of her usual seizures, after a second train of stimulation at 100% MO, with 16 Hz. In this case, rTMS was being used to determine hemispheric dominance for language by induction of speech arrest and counting errors, prior to surgical treatment for epilepsy. Following a second train with the coil applied over the P4 EEG electrode location over the right hemisphere, the patient experienced a left-body simple motor seizure with Jacksonian march. The patient had a well-documented left mesial temporal epileptic focus, with spontaneous complex partial seizures arising exclusively from the left temporal lobe. She was the only patient in the study who received rTMS at 100% MO. Data during 25 days after this event showed that there was no increase in her typical left hemisphere seizure frequency, and no further right-hemispheric (atypical) seizures. All other reported seizures were typical, and patients had high baseline seizure frequencies (range of 5 seizures per week to 40 seizures per day).

3.4. Secondary exploratory analysis: risk according to coil, intensity, frequency, and stimuli per session

Of all the characteristics being compared, the only one that showed a significant difference in the univariate analysis was the proportion of mild adverse events according to frequency of stimulation (>1 Hz versus ≤1 Hz): Fisher's exact test: p = 0.005 [Fig. 3]. For this analysis, we excluded 2 studies (n = 11 subjects) [27,41] because of their

Table 2
Summary of reported seizures during or shortly after rTMS.

Authors reporting seizure during or shortly after rTMS	N. of subjects reporting seizures	Age/gender	Diagnosis/baseline seizure type	Epileptic focus	AEDs	Adverse event	rTMS protocol
Dhuna et al. [23][a] Pascual-Leone et al. [20][a] Gates et al. [21][a]	1	32/F	Partial complex seizures (PC), (PC-2o GTC) Partial complex seizures, secondarily generalized tonic–clonic seizures	Left mesial temporal epileptic focus	Y	After a second train of stimulation, the patient experienced a clinical right simple motor seizure with Jacksonian march, which secondarily generalized on EEG (seizure duration according to Bae: 90 s).	100% MO (0.2 mJ), 16 Hz, circular coil centered over P4 (right parietal region)
Tergau et al. [30]	2	Adult (age between 21 and 48)	Refractory focal epilepsy	NR	Y	Partial seizure occurred directly after rTMS; patients had, on average, more than seven seizures per week prior to the study (seizure duration: NR).	100% MT, 0.33 Hz, circular coil over vertex
Theodore et al. [33]	1	Adult/NR	NR (CPS or secondarily generalized seizure)	NR	Y	Typical CPS on two occasions during rTMS; the patient had a baseline mean of 5 seizures per week.	120% MT, 1 Hz, Fig8 coil over ictal focus
Rotenberg et al. [50]	5	12/M	Cortical dysplasia; Simple motor 15–30 min 2/day	R frontal	Y	Simple motor seizure (L thumb clonic adduction; Seizure duration: 5 min; during 4th session of rTMS). Seizure was typical relative to baseline and seizure frequency reduced after first follow-up.	1 Hz, 70% MO 30 min Fig8 over dominant seizure focus (11 sessions)
		12/M	Unknown; Simple motor seizures of 15–20 s 2–4 times per day	R frontal	Y	Simple motor seizure (tonic L arm abduction; seizure duration: 3–4 s, during sessions 4 and 7 of rTMS). Seizure was typical relative to baseline and seizure frequency remained unchanged after first follow-up.	1 Hz, 100% MT, 30 min, Fig8 over dominant seizure focus (10 sessions total)
		19/F	Unknown; complex partial seizures of 10 s–20 min 8 times per week	L, R, and bifrontal	Y	Complex partial or primary generalized (unresponsive forward stare; seizure duration: 10 s, during session 5). Seizure was typical relative to baseline and reduced frequency during 1st follow up.	1 Hz, 100% MT 30 min circular coil over broad dominant seizure focus (152 sessions total)
		21/M	Cortical dysplasia; complex partial seizures of 20–60 s, 10–>30 times per day	R frontal	Y	Complex partial (R leg or R arm shaking, then secondary generalization; seizure duration: 10–30 s, during sessions 1 and >5 between sessions 2 and 33). Seizure was typical relative to baseline and reduced frequency during 1st follow up.	1 Hz 70% MO 30 min Fig8 over dominant seizure focus (35 sessions total)
		23/F	Unknown; simple motor seizure 10–15 times per day	L fronto–parietal	Y	Simple motor seizure (R hand clenching; seizure duration: 2–4 s, during sessions 2, 8, 10). Seizure was typical relative to baseline and seizure frequency remained unchanged after first follow-up.	1 Hz 70% MO 30 min Fig8 over dominant seizure focus
Kinoshita et al. [38]	1	27/F	Frontal lobe epilepsy	SPSs, CPSs; F3 focus	Y	Patient had SPSs and CPSs. Seizures were of the same semiology and severity as her habitual ones during stimulation, which was considered not to be evoked by rTMS. Were not convulsive seizures.	0.9 Hz, 90% MT, 15 min, circular coil over FCz
Santiago-Rodrigues et al. [47]	1	NR	CPSGS (complex partial secondarily generalized seizures)	NR	Y	Seizure at the beginning of the rTMS session. According to authors, "it was not related to stimulation because this patient suffered frequently of seizures even before the initiation of rTMS sessions."	0.5 Hz, 110% MT, 15 min, Fig8 coil over epileptogenic focus
Löscher et al. [45]	1	22/F	NR. Up to 40 seizures daily	RF (F4); right or bitofrontal	Y	Complex partial seizure immediately after the experiment. Seizure semiology was typical for this patient.	1 Hz, 90% aMT, 5 min, Fig8 coil over premotor cortex

M, male; F, female; NR, not reported; Y, yes; R, right; L, left; MT, motor threshold; aMT, active motor threshold; MO, machine output; Fig8, figure-of-eight; SPSs, simple partial seizures; CPSs, complex partial seizures. References of the 10–20 International System for EEG electrode placement were used to indicate the stimulation site. Otherwise, author's description of stimulation site was used.

[a] Three publications reported data of the same patient.

reporting of the concurrent use of >1 Hz and ≤1 Hz frequencies during rTMS. We estimated the relative risk of mild adverse events during stimulation with intensity >1 Hz versus ≤1 Hz to be 2.34 (95% CI: 1.50–3.66). All other comparisons were not statistically significant. All obtained results are summarized in Table 3.

4. Discussion

We found a small crude risk of seizures per subject during rTMS of 2.9% (95% CI: 1.3–4.5). Although the risk is twice as high as the one reported by Bae et al. [6], who found a per subject crude risk of seizure

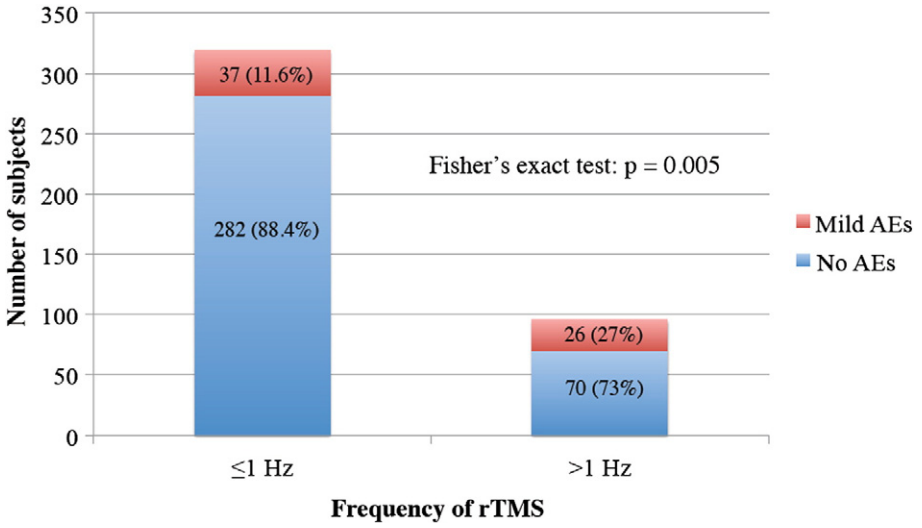

Fig. 3. Distribution of mild adverse events according to frequency of stimulation (≤1 Hz or >1 Hz).

of 1.43% (95% CI: 0.04–2.82), it should be noted that the confidence intervals contain both risk values. The risk of all adverse events other than seizures that we reported (15.5%) was also approximately the same as the one identified by Bae et al. (15.7%), which did not differ from the risk reported during rTMS application in other conditions [6]. Studies showing no seizure occurrence during low-frequency rTMS and similar frequency and complexity of mild adverse events in healthy individuals also support the safe profile of rTMS [7,10].

The fact that 12 out of 410 patients with epilepsy reported seizures occurring during or shortly after rTMS does not, however, ensure that the cause of these seizures was the stimulation itself, since the majority of patients had refractory epilepsy, some with as many as 40 seizures per day. Interestingly, the single case (1 of 410 subjects) of atypical seizure [23] was the same as the one reported by Bae et al. [6]. This patient presented a seizure appearing to clinically originate from the opposite side of where her usual seizures arose and from the site of high frequency (16 Hz) and maximum intensity (100% MO) stimulation. Out of all reported seizures, this was the exclusive case that indicated causality rather than possible coincidence between the event and rTMS.

The other reported seizures, mostly in patients with severe epilepsy, had a seemingly coincidental relationship with rTMS application. It is nonetheless important to include the risk of seizures in these patients, given that they are the most likely to receive rTMS as an off-label treatment. Interestingly, we estimated an incidence of 0.04 seizures per 1000 stimuli; a risk 10 times smaller than the one reported by Bae et al. While this finding supports the safety of rTMS, given that we included 5 subjects who underwent long off-label treatment, with one patient having up to 152 sessions of rTMS [24], it should also be interpreted with caution, considering the heterogeneity of rTMS application duration among included subjects.

Although we conducted a secondary and exploratory assessment to identify risk factors associated with the risk of seizure following rTMS application, the results from this analysis are limited because of the possibility of confounding factors. Given the goals of this report and the available data for the analysis, adjusted analysis was not possible to be performed. We identified baseline seizure frequency as the most important potential confounder, given that low-frequency rTMS is most probably administered to patients with severe epilepsy. Future studies controlling for baseline seizure frequency are therefore required to obtain more data on risk factors for seizures associated with rTMS application. Furthermore, although we regard the lack of adjustment for multiple comparisons as a potential limitation, it is important to note that this was mainly a hypothesis-generating analysis. Adjusting for multiple comparisons would increase significantly the probability of committing a type II error and, therefore, decrease the value of this secondary analysis. Besides this, since we were exploring potential risk factors in rTMS protocols that could lead to seizure induction in a particularly seizure-prone population, we decided to be less stringent on committing a type I error.

Our risk assessments during rTMS are still limited by the significant variation in rTMS protocols with respect to parameters (intensity, frequency, train duration, coil position, session schedule) and to application

Table 3
Relative risks and p-values for Fisher's exact test for comparisons between frequency of adverse events according to pre-specified rTMS parameters: type of coil (Fig8 vs. circular), stimulation intensity (≥100% MT vs. <100% MT), and number of stimuli per session (≥500 vs. <500 stimuli).

Parameter	AE	RR (95% CI)	p-Value	Number of AEs reported/n. of subjects included
Fig8 vs. circular	Mild AEs	0.64 (0.40–1.01)	0.06	29 MAEs/230 Fig8 31 MAEs/157 Circ.
Fig8 vs. circular	Seizures	2.04 (0.58–7.22)	0.37	9 Seiz/230 Fig8 3 Seiz/157 Circ.
≥100% MT vs. <100%MT	Mild AEs	1.43 (0.75–2.74)	0.36	21 MAEs/152 ≥ 100% MT 13 MAEs/135 < 100%MT
≥100% MT vs. <100%MT	Seizures	1.77 (0.38–9.34)	0.69	4 Seiz /152 ≥ 100% MT 2 Seiz/135 < 100%MT
≥500 vs. <500 stimuli/session	Mild AEs	1.41 (0.64–3.11)	0.53	44 MAEs/306 ≥ 500 stimuli 6 MAEs/59 < 500 stimuli
≥500 vs. <500 stimuli/session	Seizures	1.93 (0.26–14.12)	1.0	10 Seiz/306 ≥ 500 stimuli 1 Seiz/59 < 500 stimuli

AEs: adverse events; RR: relative risks; CI: confidence interval; Fig8: figure-of-eight; Circ: circular; MAEs: mild adverse events; Seiz: seizures; MT: motor threshold.

(for research or clinical purposes); by the heterogeneity of the clinical aspects of epilepsy; and by the small number of reported seizures. The absence of a control group was also a methodological limitation, without which the significance of identified results is still questionable.

Furthermore, as described by Bae et al. [6], taking into account the nature of our data, we limited our analysis to crude risk estimates and recommend that future analyses – particularly meta-analyses of RCTs – should be performed when more data are available, providing more accurate risk assessments, controlling for the limitations we previously disclosed, especially for patient and protocol variations.

Present safety guidelines for rhythmic stimulation suggest applying ≤1 Hz rTMS continuously in one single train but ≥5 Hz rTMS in short repeated trains separated by intertrain intervals with no stimulation [18]. The 2009 guidelines published by Rossi et al. compare seizure incidence in patient populations during stimulation with parameters within and outside the 1998 safety guidelines [18]. There were 4 seizures occurring in protocols considered to be safe according to the 1998 safety guidelines and 4 in protocols outside of the safety guidelines. Within the safe protocols, one seizure occurred during stimulation at a frequency of 10 Hz of frequency [22], one occurred during low-frequency stimulation [58], and the other two frequencies were not reported [59,60].

It is also relevant to assess whether other factors can increase the risk of seizures associated with rTMS. One potential risk factor is the use of antidepressants. Interestingly, Rossi et al. reported in the 2009 safety TMS guidelines that a total of 6 out of the 8 seizures among individuals without epilepsy after the publication of the 1998 safety guidelines occurred in patients that were taking antidepressant, proepileptogenic medications [18]. However, a meta-analysis of randomized, double-blind, and sham-controlled studies of rTMS combined with antidepressants for treatment-resistant depression published in 2014 did not report any seizures during rTMS [61]. The fact that rTMS protocols for depression generally use high-frequency stimulation also warrants the need of assessing the safety of rTMS depression protocols applied to patients with concurrent epilepsy. As per our data, only 1 out of 102 (0.98%) subjects undergoing high-frequency rTMS reported a seizure. We did not, however, include studies on the efficacy of rTMS in the treatment of depression or other conditions in patients with epilepsy. Considering that it is common for patients with epilepsy to have psychiatric comorbidities [56], especially depression, further studies comparing risk of seizures in patients with epilepsy exclusively and concurrently with depression are required for a greater understanding of both the protective effects of anticonvulsant medications and the proepileptogenic mechanisms of antidepressants on seizure induction during rTMS.

Further research controlling for the limitations we describe is needed in order to obtain more accurate risk assessments. Although our results indicate a primarily safe risk profile for rTMS in patients with epilepsy, especially for protocols abiding to previously established safety guidelines, the risk we identified should be interpreted with caution. Furthermore, reviews assessing the efficacy of rTMS in epilepsy will provide a more precise assessment of the risk–benefit ratio of the technique. As TMS is a potentially valuable treatment modality, we anticipate future studies involving rTMS for patients with epilepsy with regular reporting of any adverse events and seizures occurring during or shortly after stimulation.

Conflict of interest

Authors reported no biomedical financial interests or potential conflicts of interests with the prese.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2016.01.015.

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