



Seizures from transcranial magnetic stimulation 2012–2016: Results of a survey of active laboratories and clinics



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HIGHLIGHTS

- Laboratories and clinics who conduct TMS completed a survey about the risk of seizures from TMS.
- TMS within published guidelines poses a very low seizure risk to individuals without risk factors.
- Repetitive TMS within published guidelines appears no more likely to cause seizures than single-pulse TMS.

ABSTRACT

Objective: Transcranial magnetic stimulation (TMS) can cause seizures in healthy individuals and patients. However, the rate at which this occurs is unknown. We estimated the risk of seizure and other adverse events with TMS.

Methods: We surveyed laboratories and clinics about seizures and other events observed between 2012 and 2016 (inclusive). Respondents (N = 174) reported an estimated 318,560 TMS sessions.

Results: Twenty-four seizures were reported (.08/1000 sessions). TMS delivered within published guidelines to subjects without recognized risk factors caused 4 seizures (<.02/1000 sessions). High-frequency (>1 Hz) rTMS delivered within published guidelines to individuals without known risk factors was no more likely to cause seizures than low-frequency and single/paired-pulse TMS. Subject risk factors (e.g., brain lesions and epilepsy) increased seizure risk substantially. Seizures appeared more common when safety guidelines were exceeded. Seizures were most likely to occur within the first few exposures to TMS.

Conclusions: TMS delivered within published guidelines to individuals without risk factors appears to cause fewer than 1 seizure per 60,000 sessions. The assumption that repetitive TMS is riskier than single and paired pulses under these conditions should be reevaluated.

Significance: This information should help laboratories, clinics, and regulatory authorities form updated safety policies for TMS.

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1. Introduction

Transcranial magnetic stimulation (TMS) has been commercially available for over three decades. In this time, it has become a mainstream technique in human neurophysiology, cognitive

science, and psychiatry. Like an earlier transcranial electrical brain stimulation technique (Merton and Morton, 1980), TMS went directly into human use without animal testing or more than a qualitative knowledge of its safety. Since then, there have been notable attempts to assess the safety of TMS (Rossi et al., 2009; Wassermann, 1998). However, continual re-evaluation is important, given the continuing spread of the technique to new segments of the scientific and clinical communities, and the development of new stimulation paradigms in recent years.

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The most serious safety hazard of TMS is its potential to cause epileptic seizures. Early in its history, widely spaced “single” TMS pulses were found to be capable of triggering epileptic events under rare circumstances. The first events of this kind were reported, unsurprisingly, in individuals with potentially epileptogenic cortical lesions (Hömborg and Netz, 1989). Repetitive TMS (rTMS; defined as TMS pulses delivered in consecutive trains) was first used at the University of Minnesota in pioneering attempts at non-invasive language mapping and epileptic focus activation in patients (Dhuna et al., 1991). These researchers were unable to activate epileptic foci, but they did produce a partial motor seizure from the motor cortex in one patient. Later, a seizure occurred in the first rTMS study of the motor cortex in healthy volunteers (Pascual-Leone et al., 1993). The authors also noted evoked electromyographic activity occasionally persisting after the stimulation was stopped. This was interpreted as self-sustaining cortical excitation analogous to the “afterdischarges” seen after direct cortical stimulation, a sign that the inhibitory capacity of the cortex had been saturated, and as potentially epileptic in character. Preliminary limits on the combinations of stimulation frequency, intensity, and train duration were established by researchers at the National Institute of Neurological Disorders and Stroke (NINDS) based on these data, but additional seizures occurred (Wassermann, 1998).

These researchers convened the first international workshop to address the safety of rTMS in 1996, where the limits were formalized and integrated into a comprehensive set of guidelines for conducting research with TMS (Wassermann, 1998). Following another seizure at the NINDS, additional guidelines on the inter-train interval parameter, neglected in the original recommendations, were established (Chen et al., 1997). TMS safety was reviewed again at a meeting in 2008, by which time rTMS use had expanded greatly, spreading from its base in clinical neurophysiology to cognitive neuroscience laboratories and psychiatric clinics as well. The report of this meeting (Rossi et al., 2009) addressed the safety and ethics of TMS administration, including subject-based risk, and questions about how, where, and by whom TMS should be delivered. It also noted that seizures continued to occur occasionally, even when dosing parameters were kept within the previously published guidelines.

Such efforts have made TMS safe enough for use in a wide range of applications and settings. However, there has yet to be a quantitative assessment of TMS risk since the early NINDS experience and the adoption of the 2009 guidelines. Thus, researchers have limited information on the true number of seizures and, crucially, the risk ratio (i.e., seizures per exposure). Consequently, human research ethics boards and other regulatory authorities are currently assigning TMS paradigms, studies, and devices, to risk categories in the absence of quantitative data.

This paper reports the first attempt to quantify the seizure risk of TMS, as well as the occurrence of other adverse events, in a sample of laboratories and clinics. We conducted a survey of clinicians and researchers who published on or used TMS in the years 2012 through 2016. This report of that survey offers a comprehensive assessment of the safety of TMS, and in particular, the rate at which seizures occur across a variety of stimulation protocols.

2. Methods

2.1. Distribution

We aimed to assess TMS safety from a representative set of researchers and clinicians. We recruited respondents through three routes. First, we used PubMed’s e-utilities application to obtain e-mail addresses for the corresponding authors of publications whose PubMed entries included the term “transcranial magnetic stimulation” in the title or abstract. Using Qualtrics® software, we emailed

each of these addresses with a cover letter explaining the purpose of the survey and a personalized link to the survey. This link allowed us to see whether a respondent had completed the survey, but it did not allow us to associate a survey response with the identity of the respondent. Second, we sent individualized follow-up emails to investigators who had published reports of seizures, but did not respond after our initial general email. Third, we contacted four clinical TMS associations—The Clinical TMS Society, The International Federation of Clinical Neurophysiology, The International Society for ECT and Neurostimulation, and The National Network of Depression Centers TMS Task Group—asking them to distribute a survey link to their members.

PubMed’s e-utilities application generated 3214 unique email addresses. All of these were contacted with a request to participate. Of these, 2510 were valid email addresses. Direct email requests to authors resulted in 158 survey responses. Letter appeals to TMS associations and word of mouth generated 16 survey responses. Finally, two groups who had published seizure reports (Boes et al., 2016; Cullen et al., 2016) responded to follow-up emails requesting participation. In total, we received responses from 174 respondents, comprising 318,560 TMS sessions (Table 1). We sent individualized follow-up emails to respondents to clarify any errors or ambiguities in survey responses, as necessary.

2.2. Measures

The survey covered TMS sessions conducted at the lab or clinic for the five-year period 2012–2016. The survey asked about seizures and other serious adverse effects from TMS across conditions that may influence risk and safety. Participants reported on the following seven measures:

1. The setting in which they administered TMS (clinic or research lab)
2. Whether pregnancy tests were performed for women of child-bearing potential before every rTMS session or before a course of rTMS treatment
3. Total number of TMS sessions conducted, reported separately for each coil type (round coil/figure-8 coil, double-cone coil, H-coil), and whether subjects had increased subject-risk or protocol-risk factors according to 2009 safety guidelines. We report each type of risk factor (subject-risk and protocol-risk) separately
4. Total number of seizures participants experienced while receiving TMS. In addition, details about each seizure (clinical seizure type, stimulation settings in use, coil type, stimulation site, qualifications of TMS operator), and any available medical information on the participant who experienced seizures
5. Total number of times TMS caused motor activity persisting after TMS
6. Any other serious adverse effects participants experienced during or after TMS
7. How any serious adverse events were handled by staff in non-clinical settings

Respondents were allowed to estimate their numbers of sessions, but were required to state whether their responses were based on estimates or written records. Survey responses were included only when both of the following conditions were met: (1) the responses were complete and interpretable or could be clarified by subsequent direct query, and (2) the responses did not contain data previously reported to us by others.

See [Supplementary Materials](#) for the complete list of questions and answer choices. The Institutional Review Board at Princeton University approved this research. All respondents provided informed consent prior to completing the survey.

Table 1
Seizures by TMS protocol and risk category.

TMS Protocol	Total			Elevated subject risk			Elevated protocol risk			Elevated protocol & subject risk			No elevated risk		
	Seizures	Sessions	Risk	Seizures	Sessions	Risk	Seizures	Sessions	Risk	Seizures	Sessions	Risk	Seizures	Sessions	Risk
Single/Pair-pulse	13	112,897	.12/1000	10	12,201	.82/1000	0	0	0	0	0	0	3	100,696	.03/1000
Low-frequency (rTMS ≤ 1 Hz)	3	90,631	.03/1000	3	36,258	.08/1000	0	0	0	0	0	0	0	54,373	.00/1000
High-frequency (rTMS > 1 Hz)	4	82,588	.05/1000	3	5215	.58/1000	0	1029	.00/1000	1	163	6.13/1000	0	76,181	.00/1000
Intermittent Theta Burst	1	16,952	.06/1000	1	1813	.55/1000	0	7909	.00/1000	0	4501	.00/1000	0	2729	.00/1000
Continuous Theta Burst	0	8568	.00/1000	0	826	*	0	673	*	0	2075	.00/1000	0	4994	.00/1000
H-coil high-frequency rTMS	3	6924	.43/1000	2	872	2.29/1000	0	2948	.00/1000	0	10	*	1	3094	.32/1000
Totals	24	318,560	.07/1000	19	57,185	.33/1000	0	12,559	.00/1000	1	6749	.15/1000	4	242,067	.02/1000

Number of sessions and seizures for different TMS protocols and subject and protocol risk categories. H-coil high-frequency stimulation data are listed separately from standard high-frequency (>1 Hz) data. With the exception of standard high-frequency (>1 Hz) data, other numbers include round, figure-8, "double cone," and H-Coils. Three likely spontaneous seizures (#8, #12, and #17 in Table 3) are included. Seizure #7 is not included because the number of sessions was not reported. No seizures reported; sample size < 1000 sessions.

3. Results

One hundred seventy-four respondents reported on 318,560 TMS sessions (Table 1). Some of these sessions were consecutive, as when thresholding with single pulses was performed before rTMS treatment, and, therefore, do not represent separate sessions. Of the responses on numbers of sessions, 67 respondents reported solely from written records and 107 made estimates of the number of sessions in at least one category.

3.1. Setting

Eighty-seven groups (50%) reported performing TMS in a clinical setting. Of the others, 31 (18%) reported performing TMS in a non-clinical setting with a licensed, independent health care practitioner in the room or on premises, 13 (7%) reported performing TMS in a non-clinical setting with a specific coverage arrangement with a nearby clinic. Thirty-seven groups (21%) performed TMS without clinical support, and five (3%) did not report their setting. Due to rounding, percentages here and elsewhere do not add to 100%.

3.2. Pregnancy tests

Out of the 174 responding laboratories and clinics, 17 (10%) performed pregnancy tests in female participants of childbearing potential before a course of rTMS treatment and 8 performed pregnancy tests (5%) before each rTMS session. Five groups (3%) reported treating pregnant women. One hundred forty-three groups (82%) reported not doing pregnancy tests and six (3%) did not report their policy.

3.3. Seizures

Our primary aim was to assess the seizure risk of various TMS protocols. In total, respondents reported 24 TMS-provoked seizures in 318,560 sessions (.08 seizures per 1000 sessions; see Tables 1 and 2). One seizure (#7, Table 2) was documented in a published report (Groiss et al., 2017). However, the authors of this report did not complete our survey, so we did not include this seizure in the risk analyses.

Subject factors and TMS protocol played a large role in seizure risk. Only 4 of the 24 seizures (17%) occurred in individuals without elevated seizure risk and with TMS delivery parameter values within published safety guidelines. Nineteen seizures occurred in subjects at increased risk according to the 2009 criteria (Tables 1 and 2). One additional seizure occurred in a session with both elevated subject and protocol risk. We report the seizure rates for each type of risk factor below.

3.4. Subject risk factors

The occurrence of seizure with single/paired and repetitive TMS was greater in subjects with previously identified risk factors (Rossi et al., 2009; Table 2). In subjects with elevated risk, but no elevated protocol risk, the rate of seizures was .33/1000 sessions. In comparison, the risk of seizure was .02/1000 in sessions without elevated risk of either kind. The difference between sessions with and without elevated subject risk was especially large for single/paired-pulse stimulation: for sessions with elevated subject risk, the risk of seizure was .82/1000 sessions, compared to .03/1000 for sessions without elevated risk of either kind.

Of the 24 reported seizures, 7 (29%) were experienced by patients with congenital epilepsies. All epileptic individuals were on antiepileptic medication at the time of TMS. Four additional predisposing conditions were associated with seizures: stroke

Table 2
Characteristics of reported seizures and subjects.

Seizure description	Frequency	Target	Diagnosis	Medications	Previous TMS
1. "Clinical seizure"	Single/Paired-pulse	Frontal cortex	Epilepsy	Valproate, zonisamide	None
2. Myoclonic	Single/paired-pulse	M1	Myoclonus epilepsy	Antiepileptic(s)	Some (unspecified)
3. Myoclonic	Single/paired-pulse	M1	Myoclonus epilepsy	Antiepileptic(s)	Some (unspecified)
4. Secondary generalized	Single-pulse	M1	Epilepsy	Topiramate, valproate, clobazam	None
5. Partial	Single-pulse	M1	Multiple sclerosis (possible)	None	None
6. Complex partial	Single-pulse	M1	None	None	1 session
7. Partial [†]	Single-pulse	M1	Tumor	Sertraline	2 sessions
8. Partial [*]	Single-pulse	M1	Tumor	Levetiracetam, lamotrigine	1 session
9. Partial	Single-pulse	M1	None	None	None
10. Secondary generalized	Single-pulse	IPS	None	Oral contraceptives	None
11. Generalized	Single-pulse	M1 (round coil at vertex)	Paraparesis	None	None
12. Generalized [*]	Single-pulse	M1	Epilepsy	Clobazam, pregabalin, zonisamide, levetiracetam, valproate, hydantoin	None
13. Not reported	Single pulse	M1	Stroke	Not reported	None
14. Partial	Single-pulse	M1	Arteriovenous malformation	None	None
15. Myoclonic	0.3 Hz	M1 (round coil at vertex)	Myoclonus epilepsy	Valproate, zonisamide, levetiracetam, clobazam	None
16. Generalized	1 Hz	DLPFC	Stroke	Atorvastatin, warfarin	None
17. Partial [†]	7 Hz	M1	Epilepsy	Valproate, eslicarbazepine, lacosamide, levetiracetam	None
18. Partial then generalized	10 Hz	M1	Stroke	Some (unspecified)	Some (Unspecified)
19. Secondary generalized	10 Hz	M1	Stroke	Trifluoperazine	None
20. Secondary generalized	15 Hz	DLPFC	Schizophrenia	Risperidone	4 sessions
21. Secondary generalized	18 Hz	DLPFC	Depression	None	7 sessions
22. Secondary generalized	18 Hz	DLPFC	Depression Alcoholism	None	12 sessions
23. Generalized	18 Hz	DLPFC	Depression/rheumatoid arthritis	Methotrexate	Unreported
24. Secondary generalized	20 Hz	DLPFC	Depression	Mirtazepine	None
25. Secondary generalized	iTBS	M1	Stroke	None	None

^{*} Likely spontaneous seizures (see text). Not included in [Table 1](#).

[†] Reported in [Groiss et al. \(2017\)](#) (see text). Not included in [Table 1](#).

(#13, #16, #18, #19, #25, [Table 2](#)), tumor (#7, #8), arteriovenous malformation (#14), and psychiatric disorders treated with medications known to lower the seizure threshold (#20, #23, #24). A total of 4 seizures occurred in 242,067 sessions with individuals without identifiable risk factors.

Respondents described three of the reported seizures (two in refractory epilepsy and one in a tumor patient) as spontaneous events, unrelated to the TMS procedure, since these patients had been experiencing frequent seizures during the time they received TMS. However, in order to minimize the chance of underestimating seizure risk, we include these seizures in our estimate of TMS-induced seizures for subjects with elevated risk.

Among the 24 seizures reported, 15 occurred on the first TMS exposure, two on the second session, and one on the third session ([Table 2](#)).

3.5. Stimulation parameters

The most frequent mode of stimulation was single/paired-pulse (112,897 of 318,560 sessions; 35%), followed by low-frequency rTMS (≤ 1 Hz; 90,631 sessions; 28%), high-frequency rTMS (> 1 Hz; 82,588, 26%), intermittent theta burst (iTBS; 16,952; 5%), and continuous theta burst (cTBS; 8,568, 3%).

Risk of seizure in TMS sessions conducted without elevated protocol or subject risk ranged from 0 for low-frequency (≤ 1 Hz) rTMS, iTBS, and cTBS, and conventional high-frequency (> 1 Hz) rTMS, to .03/1000 for single/paired-pulse, and .32/1000 for high-frequency rTMS conducted with an H-coil. Of 318,560 total TMS sessions, 19,308 (6%) were conducted with delivery parameter val-

ues outside the 2009 guidelines (which applied only to frequencies > 1 Hz) and thus with elevated protocol risk. These sessions resulted in one seizure, in a subject who also had risk factors (#20, [Table 2](#)). However, the numbers of TBS and H-coil sessions reported were relatively small and may not have provided a reliable estimate of risk.

3.6. Coil type

Of 318,560 reported sessions, 303,183 (95%) were conducted with conventional figure-8 or round coils. 8453 sessions (3%) were conducted with the "double cone" coil. Use of the H-coil was reported in 7577 sessions (2%), 6924 of which involved conventional high-frequency rTMS.

The risk ranged from .08/1000 for conventional figure-8 or round coils, to .12/1000 for double cone coils, and .43/1000 for H-coils. Double cone coils were associated with one seizure (#14, [Table 2](#)); H-coils were associated with three seizures (#21, #22, #23). Two of these seizures occurred in individuals with subject risk factors (concurrent pharmacological treatment for depression). As such, the risk ratio for the H-coil appears higher than for conventional coils. However, there may not have been a sufficient number of H-coil or double cone sessions in the sample to assess their risks accurately.

3.7. Stimulation site

Information about stimulation site was available only for sessions where seizures occurred. Sixteen of 24 seizures (67%) occurred

during primary motor area stimulation, 7 during prefrontal stimulation (29%), and 1 (4%) during parietal stimulation. This distribution may reflect the popularity of these regions as stimulation targets rather than the relative risk of stimulating these areas.

3.8. Persistent evoked motor activity

We received reports of 41 cases of evoked activity, such as MEPs or twitching, which persisted after the end of TMS. While we have included them for completeness (Table 3), we note that we believe that the manner in which we asked this question raises questions about how to interpret this data (see discussion).

3.9. Other adverse events

Respondents were given the opportunity to list other types of adverse events. However, unlike seizures, we did not ask for numbers of events. Syncope or presyncope was the most common adverse event, reported by 29 of 174 respondents (17%). Many respondents reported multiple such events and some mentioned that this occurred in subjects new to TMS. Headache or pain at the stimulation site was also a common adverse effect, reported by 28 respondents (16%). Nine respondents (5%) reported nausea or nausea with vomiting, but in two cases, respondents reported that this was likely caused by intercurrent illness or medication. In addition, four respondents (2%) reported hypomania or mania in patients being treated for depression. Four respondents reported persistent twitching, which lasted or occurred after the TMS session. Other rare complaints include worsening of psychotic symptoms requiring hospitalization (one respondent); anxiety, irritability, and insomnia (one respondent); temporomandibular joint pain (one respondent); and tinnitus (one respondent).

3.10. Responses to adverse events

Only four respondents reporting seizures in non-clinical settings reported how these seizures were managed.

4. Discussion

This study is the first systematic and empirical study of TMS safety since safety guidelines for rTMS were first published in 1996. Since then, there has been widespread adoption of TMS in research and clinical settings. In our estimated sample, seizures occurred at a rate of .08 per 1000 sessions. Because respondents may have misdiagnosed some events as epileptic seizures, some primarily syncopal events might have been counted among the seizures. Most of the TMS-related seizures reported to us occurred in individuals with risk factors, such as congenital epilepsies, anatomical lesions, and medications. In our sample, TMS delivered within published guidelines to subjects with no elevated seizure risk carried a risk of .02 seizures per 1000 sessions. To put these rates in context, in 2013 the mean annual risk to a member of

the US population of dying in a traffic accident was .11 in 1000 (<http://www.iii.org/fact-statistic/mortality-risk>). The annual risk of developing epilepsy in the US population is approximately .47 in 1000 (Hirtz et al., 2007). Hence, these data support the general impression that TMS is a safe intervention.

TMS was consistently safe across a range of stimulation parameter values. Notably, the risks for single/paired-pulse and rTMS at ≤ 1 Hz appear comparable to those for rTMS at > 1 Hz, when delivered within published guidelines and to subjects with no elevated seizure risk. The risk of seizure for single/paired-pulse was .03 per 1000 sessions, and no seizures were reported in either rTMS at ≤ 1 Hz or rTMS at > 1 Hz. This finding should inform the future risk stratification for TMS studies. However, the findings confirm that exceeding the 2009 guidelines for delivery parameters increases the risk of seizures. Our respondents reported 19,308 sessions of rTMS (6%) outside the 2009 stimulation parameter guidelines. These treatments were associated with an elevated risk of seizure.

Of the 10 seizures we reported occurring with rTMS at 1 Hz or above, 9 occurred in individuals with risk factors identified in the 2009 guidelines (#s 16–20 and #s 22–25, Table 2). Of these, only three (#20, #23, #24)—all in individuals being treated for psychiatric illness—had medications as the only risk factor, while the rest had epilepsy, anatomical lesions, or alcoholism. This was despite the presumably large number of medicated individuals being treated with TMS for psychiatric illness worldwide during this period. Two individuals from the psychiatric population had seizures (#21, #22) during rTMS despite being on no medications. These data do not support the common view that psychiatric medications increase risk of TMS-induced seizure.

Subject factors also elevated the risk of seizure. Of the seizures provoked by single/paired-pulse and low-frequency rTMS, 81% occurred in subjects with risk factors. Individuals with risk factors similarly accounted for 87.5% of the seizures produced by the different varieties of high-frequency and patterned rTMS. The greater number of seizures reported with single/paired-pulse and ≤ 1 Hz rTMS may have been due to the population, e.g., epilepsy patients, undergoing this protocol.

A striking finding was that over 62% of seizures occurred on the first exposure to TMS, and 75% occurred within the first three exposures. These data show that subjects who have undergone TMS safely are at much less risk than first-time participants, even in the presence of risk factors. This factor could be considered when determining the level of seizure precautions.

We asked about persistent motor activity in the survey, but we did not make it clear enough that this referred specifically to the phenomenon described by Pascual-Leone et al. (1993), and we believe our question may have been misinterpreted in some cases. For example, persistent motor activity was reported after single-pulse TMS in 6 instances. Rhythmic, afterdischarge-like activity of the type we had in mind has not been previously described after single-pulse TMS. Therefore, the data in Table 3 should be interpreted with caution.

Table 3
Persistent motor activity.

TMS Protocol	Total	Elevated subject risk	Elevated protocol risk	Elevated protocol and subject risk	No elevated risk
Single-pulse	6	5	0	0	1
Paired-pulse	3	3	0	0	0
Low-frequency (rTMS ≤ 1 Hz)	3	0	0	3	0
High-frequency (rTMS > 1 Hz)	18	4	7	0	7
Intermittent theta burst	2	0	2	0	0
Continuous theta burst	2	0	2	0	0
Other	0	0	0	0	0
H-coil high-frequency	7	2	2	0	3

Number of episodes of evoked muscle activity (MEPs or twitching) persisting after TMS. (See discussion.)

This study has three significant limitations, all of which should temper the confidence of any conclusions drawn from the data. First, the sample is small relative to the population and potentially unrepresentative. We received 174 responses to our emails and announcements from a potential population of thousands of laboratories and clinics. It is possible that those who failed to respond had more seizures or other reasons to avoid exposure. The response from non-research clinics was also sparse and it is possible the rate of seizures or other serious adverse events is different in non-research clinical settings. Finally, there were categories of stimulation (e.g., continuous theta burst in subjects with elevated risk; asterisks in Table 1) where no seizures occurred, but where the sample of sessions was so small that no conclusions about safety can be drawn. Therefore, the data must be regarded as only semi-quantitative. In addition, the small numbers of sessions reported for some protocols, notably theta burst, may be so small as to underestimate their risk in absolute terms and relative to other protocols.

Second, we allowed respondents to estimate the numbers of TMS sessions they had delivered in the last 5 years and 63% did so. We recognize the potential for bias in these estimates. Respondents reporting seizures, in particular, may have had a motivation to inflate their session numbers to reduce the apparent risk. The recordkeeping on the absolute numbers of seizures, which, as serious adverse events, are usually reported to research oversight authorities, is more likely to be accurate. Could reporting bias have contributed to the seeming risk parity of high and low frequency TMS? Yes, but this is unlikely, since regulatory requirements for record keeping are generally stricter for higher-risk procedures, particularly in clinical trials, allowing any bias toward denominator inflation to operate more on data from lower-risk studies.

Lastly, the questionnaire was designed to capture the rate of seizures per exposure, not per subject. That is, since our data show that seizures tend to occur on the first few exposures to TMS, susceptible individuals are filtered out of the subject pool and repeated sessions occur in non-susceptible individuals. However, this does not weaken the finding that, in low-risk individuals stimulated at parameter combinations within the 2009 guidelines, stimulation frequency does not affect the likelihood of seizures.

Although seizures pose the most serious acute risk from TMS, there are additional adverse effects worth noting. For example, syncope and presyncope occur far more often than seizures. While syncope is an emergency, it can be handled safely by lay personnel who are trained to recognize and treat it. Approximately 17% of respondents reported the occurrence of syncope in at least one participant, with several reporting multiple episodes. We have no measure of the rate, but, for comparison, in one large study (Bravo et al., 2011), venipuncture for blood donation caused complete syncope at a rate of .27%. A similar rate for TMS, would have resulted in over 860 cases of syncope in our study. In blood donation, as in TMS, first time donation and young age were predictors of syncope. Discomfort at the stimulation site and headache were also common side effects of TMS in our data.

Assuming they approximate the true seizure risk of TMS, how should these findings affect the community of TMS users and regulators? Our data suggest that single/paired-pulse and repetitive TMS, conducted within the published guidelines pose a very small increment over the background risks of everyday life to subjects without known risk factors. We hope that this new and reassuring information will inform policies enabling wider use of TMS.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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Appendix A. Supplementary material

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