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Seizure risk with repetitive TMS: Survey results from over a half-million treatment sessions

Joseph J. Taylor [a, b, *], Noam G. Newberger [c], Adam P. Stern [d, e], Angela Phillips [f, g], David Feifel [h, i], Rebecca A. Betensky [j], Daniel Z. Press [d, k]

[a] Center for Brain Circuit Therapeutics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[b] Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[c] National Center for PTSD at VA Boston Healthcare System, USA
[d] Berenson Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
[e] Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA, USA
[f] Department of Veterans Affairs, Palo Alto, CA, USA
[g] Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, CA, USA
[h] Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA
[i] Kadima Neuropsychiatry Institute, La Jolla, CA, USA
[j] Department of Biostatistics, School of Global Public Health, New York University, New York, NY, USA
[k] Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Background: Seizures are rare during repetitive transcranial magnetic stimulation (rTMS) treatment, but estimating risk is difficult because of study heterogeneity and sampling limitations. Moreover, there are few studies comparing rates between device manufacturers.
Objective: The objective of this study was to calculate rTMS seizure rates across various FDA-cleared devices in naturalistic clinical settings.
Methods: In July and August 2018, approximately 500 members of the Clinical TMS Society (CTMSS) were electronically surveyed about seizures in their practices. Seizures were distinguished from non-seizures by a remote semi-structured interview with a Board-certified neurologist and Co-Chair of the CTMSS Standards Committee. Exact Poisson calculations were used to estimate seizure rates and confidence intervals across the four most widely used manufacturers.
Results: The survey was completed by 134 members, with 9 responses excluded because of data inconsistencies. In total, 18 seizures were reported in 586,656 sessions and 25,526 patients across all device manufacturers. The overall seizure rate was 0.31 (95% CI: 0.18, 0.48) per 10,000 sessions, and 0.71 (95% CI: 0.42, 1.11) per 1000 patients. The Brainsway H-coil seizure rate of 5.56 per 1000 patients (95% CI: 2.77,9.95) was significantly higher ($p < 0.001$) than the three most widely used figure- 8 coil devices' combined seizure rate of 0.14 per 1000 patients (95% CI: 0.01, 0.51).
Conclusion: The absolute risk of a seizure with rTMS is low, but generic Brainsway H-coil treatment appears to be associated with a higher relative risk than generic figure- 8 coil treatment. Well-designed prospective studies are warranted to further investigate this risk.

Introduction

Seizures have been recognized as adverse events of transcranial magnetic stimulation (TMS) since the corticospinal tract experiments of the 1980s [1–5]. These foundational studies documented TMS-related seizures in patients with epileptic foci [6–9]. In 1993, a safety study reported the first TMS-related seizure in a healthy volunteer [10]. This seizure occurred during 10 Hz motor cortex stimulation at 208% resting motor threshold (rMT), an unfavorable protocol that highlights improved safety guidelines since that era. In 1995, the first TMS-induced focal motor seizure was documented by electromyography [11].

* Corresponding author. Center for Brain Circuit Therapeutics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.
E-mail address: jtaylor61@bwh.harvard.edu (J.J. Taylor).

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Consensus safety guidelines for TMS were first published in 1998 [12], approximately three years after the first pilot study of repetitive TMS (rTMS) for depression [13]. Updates in 2009 [1] and 2020 [14] covered a notably larger body of literature [15]. As the field of TMS has expanded, so too has the challenge of estimating seizure risk. Confounds such as pulse sequence, stimulus waveform, rMT accuracy and frequency, stimulation site, targeting method, coil geometry, and patient factors are difficult to address. The most recent systematic review identified 41 events as TMS-related seizures. Out of these 41 seizures, 13 occurred in healthy adults and 28 occurred in patients with at least a dozen different neuropsychiatric diagnoses [16]. Approximately half of all seizures occurred during motor cortex stimulation, but the rest were distributed across four stimulation sites and a group of unspecified sites. Surprisingly, 20% of seizures occurred during single pulse TMS [16]. This systematic review could not provide new insights into whether these events should be classified as seizures versus clonic activity associated with syncope or other phenomena [1,14].

Another challenge in estimating TMS seizure risk is contextualizing a rare event in a large estimate of total treatments or patients. Case reports typically provide a numerator (i.e., seizures) without a denominator (i.e., sessions or patients). Multisite trials provide a numerator and a denominator, but they are limited by heterogeneity, sample size, and other design features. Out of six multisite trials, there was one seizure in approximately 805 patients reaching the primary endpoint of an active treatment arm [17–22]. This lone seizure occurred after alcohol consumption the evening prior to Brainsway H-coil treatment for depression [22]. From 2008 to 2012, the seizure rate for the Neuronetics FDA-cleared figure- 8 coil was estimated to be 0.0003% per treatment exposure [23]. This rate is still commonly cited as the best estimate of seizure risk with figure- 8 coil clinical treatment [2,3].

Surveys and manufacturer databases are alternative ways to estimate TMS seizure risk. A recent survey of research labs and clinics capturing 318,560 treatments from 2012 to 2016 estimated the TMS seizure rate to be 0.8 per 10,000 sessions, which drops to 0.2 seizures per 10,000 sessions if guidelines are followed and patients have no identifiable seizure risk factors [24]. These numbers may have limited clinical generalizability because of sample characteristics; only 50% of the sample delivered TMS in a clinical setting, and only 2% delivered H-coil treatment. A recent study by Tendler et al. capturing 94,857 patients from 2010 to 2020 estimated H-coil treatment seizure risk to be 0.6 in 1000 patients, which drops to 0.2 in 1000 patients when instructions for use are followed [25]. This estimate is derived from head caps purchased through Brainsway, a technique that limits insight into session count and limits comparisons to data obtained with different methodology.

In this study, we surveyed Clinical TMS Society members about seizures in their practices. The goal was to capture retrospective, observational data on TMS seizure rates per session and per patient in naturalistic clinical settings across the four most widely used device manufacturers (Brainsway, Magstim, MagVenture, and Neuronetics).

Methods

Survey

An electronic survey was sent to all members of the Clinical TMS Society (CTMSS) in July and August of 2018. At that time, there were approximately 500 CTMSS members. Follow-up reminders included an e-mail message and a short message in the CTMSS e-mail newsletter. The survey was designed to be brief in order to facilitate participation (Supplemental Material). The four most widely used device manufacturers were explicitly listed on the form (Brainsway, Magstim, MagVenture, and Neuronetics), but the "Other" category provided space for alternative device manufacturers. Targeted questions about device name, coil type, and other variables were not asked on this form. Identifying information was not required, but the final question asked if members were willing to be contacted for follow-up questions in the form of a semi-structured interview.

Semi-structured interview

Members who reported seizures and consented to follow-up contact were scheduled for a remote semi-structured interview with a Board-certified neurologist who also served as Co-Chair of CTMSS Standards Committee at that time. During the scheduling process, members were asked to ensure that the person who either witnessed the seizure or knows the most about it would be available for questions. Similar to the original questionnaire, the interview was designed to be brief and focused in order to facilitate participation (Supplemental Material). Questions primarily focused on qualitative descriptions of the seizure-like episode as well as the response to it.

Data processing

Survey responses were collated for all devices, but the *a priori* focus was on the four most widely used device manufacturers (Brainsway, Magstim, MagVenture, and Neuronetics). Data were reviewed for inconsistencies and errors such as missing information, duplicate entries from the same site, or patients equaling or exceeding sessions in a single response. Any inconsistencies that were flagged on initial review were addressed with follow-up calls and messages to identified survey responders. Data inconsistencies that could not be reconciled were excluded from primary analyses but included in supplementary analyses.

Data analysis

Seizure rates were calculated per 10,000 sessions and per 1000 patients with exact Poisson 95% confidence intervals for all manufacturers separately and combined. Exact Poisson tests were conducted to compare the four most widely used manufacturers (Brainsway, Magstim, MagVenture, and Neuronetics) per *a priori* survey design. Additionally, each of the four widely used devices was compared to the remaining three combined. Confidence intervals and p-values are Bonferroni-adjusted to correct for multiple comparisons.

All analyses were conducted in R 4.0.2 (https://www.r-project.org/). The pois. exact function from the epitools package was used to calculate Poisson rates (CRAN: https://cran.r-project.org/web/packages/epitools/epitools.pdf), and the poisson. test function from the stats package was used for pairwise comparisons (https://stat.ethz.ch/R-manual/R-devel/library/stats/html/00Index.html).

Results

Information about devices and coil types was not collected in this survey. As such, data are referenced by device manufacturer. Eight manufacturers were represented at 143 sites, with a wide range of manufacturer distribution across sites. Nine responses were excluded because patients exceeded sessions, resulting in a total of 134 sites (Table 1). A sensitivity analysis included these nine responses (Supplementary Table 1).

The majority of sites were private practice (87), based in the United States (81), and identified rather than anonymous (100). The most commonly used device manufacturers were Neuronetics (57 sites), MagVenture (25 sites), Brainsway (22 sites), and Magstim (17 sites). A limited number of sites reported data on Neurosoft (8 sites), MAG & More (2 sites), Deymed (2 sites), and Nexstim (1 site). On average, there were 4378 treatment sessions per manufacturer per site (SD = 6071) and 190 patients per manufacturer per site (SD = 539). A total of 18 seizures were captured by the survey, 14 of which occurred in the four most widely used device manufacturers (Table 1, Fig. 1). On average, there were 0.13 seizures per manufacturer per site (SD = 0.53). Follow-up interview verified 6/18 reported seizures. The remainder were unable to be verified, but they were still included in this analysis.

Seizure rates were calculated (Table 2) and plotted (Fig. 2) per 10,000 sessions and per 1000 patients across the four most widely used manufacturers. For example, the estimated risk with MagVenture was 0.24 seizures per 10,000 sessions (95% CI: 0.03, 0.88) and 0.73 seizures per 1000 patients (95% CI: 0.09, 2.62). Combining data from all four of the most widely used manufacturers yielded an estimated seizure rate of 0.25 per 10,000 sessions (95% CI: 0.14, 0.42) and 0.61 per 1000 patients (95% CI: 0.33, 1.02). A sensitivity analysis including the nine sites that were excluded for data inconsistencies showed similar results across the four most widely used manufacturers, with an increased estimated seizure rate of 0.30 (95% CI: 0.17, 0.47) per 10,000 sessions and a decreased estimated seizure rate of 0.43 per 1000 patients (95% CI: 0.25, 0.69). Analyses that included all manufacturers regardless of site representation were also calculated (Supplementary Material).

Pairwise comparisons of seizure rates per session and per patient were calculated for the four most widely used manufacturers (Table 3). Significant per session differences were found when Brainsway was compared to Magstim ($p = 0.024$) and Neuronetics ($p < 0.001$). Of note, the per session difference between Brainsway and MagVenture approached significance ($p = 0.054$). Similarly, significant per patient differences were found when Brainsway was compared to Magstim ($p = 0.002$), MagVenture ($p = 0.017$), and Neuronetics ($p < 0.001$). No significant differences were detected between other pairwise comparisons. Bonferroni adjusted (for six comparisons) confidence levels were set at 99.2%, and p-values were multiplied by six to correct for multiple comparisons.

Finally, each of the four most widely used manufacturers was compared to the other three combined (Table 4). Relative to all others, Brainsway had significantly higher seizure rates per session ($p < 0.001$) and per patient ($p < 0.001$), and Neuronetics had significantly lower seizure rates per session ($p < 0.001$) and per patient ($p < 0.001$). Of note, Neuronetics had only one reported seizure in the largest number of patients and treatments. Bonferroni adjusted confidence levels were set at 98.75%, and p-values were multiplied by four to correct for multiple comparisons.

Discussion

Summary

TMS is generally considered to be safe, but the rapid evolution and expansion of the field has generated new opportunities and challenges for seizure risk estimation. Contextualizing the rare event of a seizure in a large denominator of patients or sessions has been difficult; case reports typically provide a numerator without a denominator and extrapolating a denominator from clinical trials has limitations. Device manufacturers have started collecting and sharing data, but between-manufacturer comparisons are limited. In this study, we captured retrospective, observational data on TMS seizure in naturalistic clinical settings across the four most widely used device manufacturers (Brainsway, Magstim, MagVenuture, Neuronetics). In total, 18 seizures were reported in 586,656 sessions across 25,526 patients. The overall seizure rate was 0.31 (95% CI: 0.18, 0.48) per 10,000 sessions, and 0.71 (95% CI: 0.42, 1.11) per 1000 patients. The Brainsway seizure rate of 5.56 per 1000 patients (95% CI: 2.77,9.95) was significantly higher ($p < 0.001$) than the remaining three manufacturers' combined figure- 8 seizure rate of 0.14 per 1000 patients (95% CI: 0.01–0.51).

This study has several strengths worth noting. First, the study provides the largest survey denominator with which to estimate seizure risk across device manufacturers. Second, data were collected from a wide range of clinical programs, providing a means by which to estimate average TMS seizure risk for treatment-seeking patients independent of individual variables. Third, lack of industry funding diminishes potential conflicts of interest and bias. Fourth, seizure risk was estimated with the same methodology across device manufacturers, and calculations were exact rather than approximate. Fifth, seizures were reported exclusively in the context of clinical treatment, with data on sessions and patients. Sixth, a Board-certified neurologist attempted to verify seizures with a follow-up interview. This approach falls short of electrophysiological confirmation, but it could diminish the possibility of counting events such as clonic activity associated with syncope [1,14]. Lastly, the study used conservative statistical analyses with Bonferroni-adjusted corrections for multiple comparisons.

Table 1
Survey Summary. The survey was completed by 143 CTMSS members, with 9 responses excluded because of data inconsistencies. In total, 18 seizures were reported across 586,656 sessions and 25,526 patients.

	All	Neuronetics	MagVenture	Brainsway	Magstim	Neurosoft	MAG & More	Deymed	Nexstim
Sites	134	57	25	22	17	8	2	2	1
Academic	14	4	4	1	3	0	0	1	1
Private	87	38	15	15	11	5	2	1	0
Unreported	33	15	6	6	3	3	0	0	0
US	81	41	15	14	6	3	0	1	1
Non-US	18	1	4	2	6	2	2	1	0
Unreported	35	15	6	6	5	3	0	0	0
Identified	100	42	20	16	12	5	2	2	1
Anonymous	34	15	5	6	5	3	0	0	0
Sessions	586,656	333,657	82,382	70,358	72,588	7011	12,300	8000	360
Sessions per device, per site, Mean (SD)	4378 (6071)	5854 (7263)	3295 (4238)	3198 (4005)	4270 (7220)	876 (919)	6150 (1626)	4000 (5657)	360 (NA)
Patients	25,526	16,097	2752	1979	2103	320	1065	1200	10
Patients per device, per site, Mean (SD)	190 (539)	282 (797)	110 (132)	90 (83)	124 (187)	40 [43]	533 (237)	600 (283)	10 (NA)
Seizures	18	1	2	11	0	0	4	0	0
Seizures per device, per site, Mean (SD)	0.13 (0.53)	0.02 (0.13)	0.08 (0.28)	0.50 (0.86)	0	0	2 (2.83)	0	0

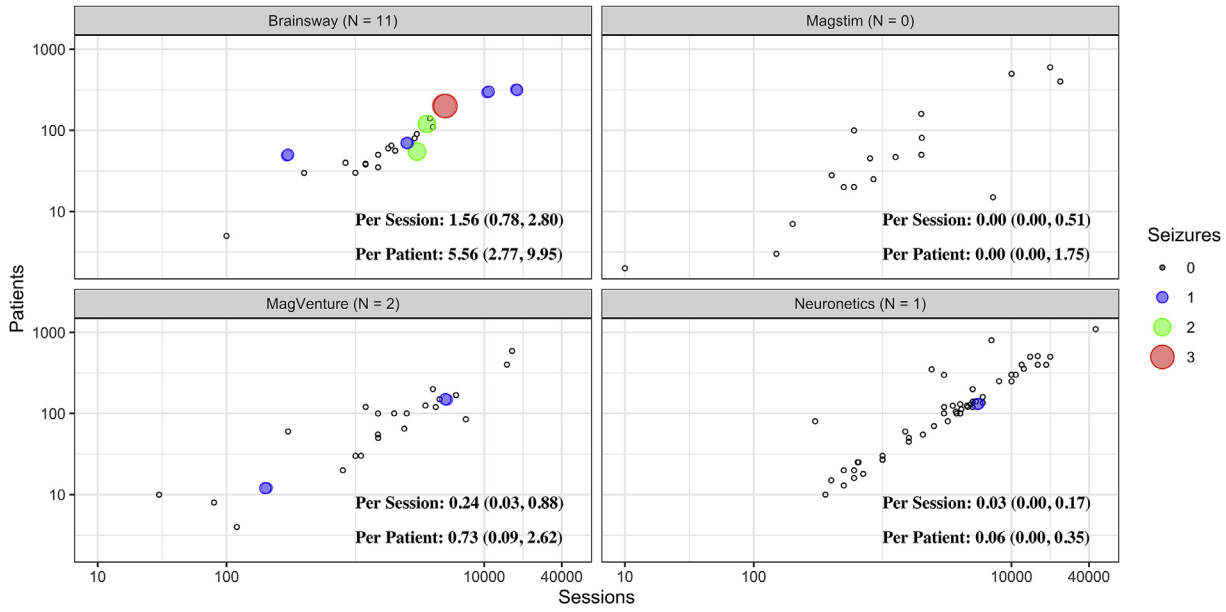

Fig. 1. Seizures by site. This scatterplot visualizes seizures at each site as a logarithmic function of patients and sessions across the four most commonly used manufacturers. Note that four sites that omitted either patient or session count were excluded from this visualization despite being included in primary analyses.

Expanding the denominator

The results of this study largely corroborate seizure risk estimates from smaller sample sizes in the literature. A seizure rate of 0.31 per 10,000 sessions is equivalent to 1 seizure per 32,258 sessions, which is comparable to the rate of 1 seizure per 30,000 session estimate from the 2008–2012 Neuronetics post-marketing period [23]. The results of this study also fit between the 1 in 12,500 (off-label use or patients with risk factors) and the 1 in 50,000 (on-label use and patients without risk factors) estimates from a from a 2012–2016 survey of TMS research labs and clinics by Lerner et al. [24].

There are several important differences to note between the Lerner et al. study [24] and present study. The Lerner et al. study captured a smaller sample size (318,560 vs. 586,656 sessions) over a shorter amount of time (2012–2016 vs. up to 2018). The Lerner et al. sample was also different in that it included research labs; only 50% of the sample reported on TMS in clinical settings, and approximately 2% reported using H-coil devices. The hybrid clinical and research sample in Lerner et al. is likely more heterogeneous than the clinical sample in this study, which complicates comparisons. Including healthy volunteers would theoretically diminish the seizure rate in Lerner et al. relative to the present study, but Lerner et al. also included high-risk populations less likely to be treated clinically. For example, the highest seizure rate in Lerner et al. occurred in the single- and paired-pulse protocol category; most of these seizures were in patients with epilepsy, tumor, stroke, and arteriovenous malformation. These data potentially explain by Lerner et al. concluded that rTMS (within published guidelines) is no more likely to cause seizures than single-pulse TMS [24]. One final difference to note is that Lerner et al. had no information on seizure verification. Despite these important differences, it is reassuring to see some alignment between seizure estimates.

Elevated seizure risk with generic H-coil vs. Figure- 8 coil treatment

The results of this study suggest that the relative risk of a seizure with generic H-coil treatment is significantly higher than it is with generic figure- 8 coil treatment, both in terms of most pairwise comparisons and in terms of Brainsway versus all others. The term "generic" is used because the data do not capture specific information about coil types, treatment indications, stimulation parameters, and other confounding factors.

There are relatively few studies directly comparing the safety and efficacy of H-coils versus figure- 8 coils, although it is conceivable that an increased relative seizure risk might be tolerated if it translates into a larger probability of response or remission. The only published head-to-head trial showed significantly better response rates with H1-coil treatment relative to figure- 8 coil treatment in 228 patients with major depressive disorder, though the study found no differences in remission rates [26]. Moreover, the study used an outdated and less effective targeting method for the figure- 8 coil treatment ("5 cm rule") [27–31], and it examined outcomes at 20 sessions rather than the 30–36 sessions commonly used in clinical treatment. No seizure differences were noted in this sample. In the Lerner et al. study, H-coils had a higher

Table 2
Seizure rate by device. Seizure rates were estimated per 10,000 sessions and per 1000 patients across the four most widely used manufacturers.

	Per 10,000 Sessions		Per 1000 Patients	
Manufacturer	Estimated Seizure Rate	95% CI	Estimated Seizure Rate	95% CI
All	0.25	(0.14, 0.42)	0.61	(0.33, 1.02)
Brainsway	1.56	(0.78, 2.80)	5.56	(2.77, 9.95)
Magstim	0.00	(0.00, 0.51)	0.00	(0.00, 1.75)
MagVenture	0.24	(0.03, 0.88)	0.73	(0.09, 2.62)
Neuronetics	0.03	(0.00, 0.17)	0.06	(0.00, 0.35)

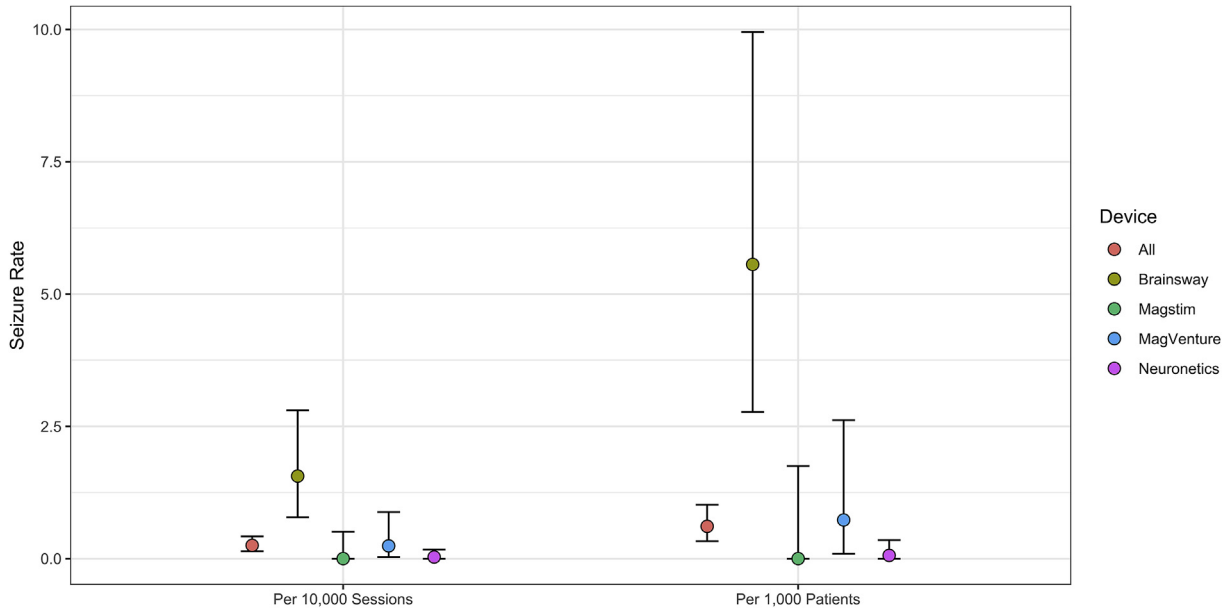

Fig. 2. Visualization of seizure rate by device. Plot showing seizure rates per 10,000 sessions and per 1000 patients across the four most widely used manufacturers.

relative seizure risk than figure- 8 coils, but this conclusion was tempered by a small H-coil sample size [24].

Most published H-coil safety data are from Brainsway-sponsored studies that calculate seizure risk per patient with head caps purchased from the company. These studies do not include figure- 8 coils, nor do they provide direct information about seizure risk per treatment session. The most recent report capturing 94,857 patients over the last decade estimated seizure risk to be 0.6 in 1000 patients, or 0.2 in 1000 patients when instructions for use are followed [25]. Cap methodology notwithstanding, these rates are an order of magnitude lower than our estimate of 5.56 per 1000 patients (with no information about instructions for use). H-coil seizures were reported in 7 different clinics, diminishing the probability that a single outlier site was driving our results.

It is difficult to reconcile the large discrepancy between estimated H-coil seizure risk in this study and in Tendler et al. [25]. One possible explanation is that this study captured practice sites that were not represented in Tendler et al. either because they chose not to participate in that study or because they do not purchase Brainsway headcaps. A second possibility is that Tendler et al. reflects a shorter and more recent timeframe in which safety has improved. The majority of seizures reported in Tendler et al. occurred in 2010–2013, but the majority of their patient volume appears to be from 2018 to 2020. Capping their analysis in 2018 (the year that this survey ended) would increase their seizure rate, although the magnitude of this increase is difficult to estimate. This observation highlights the possibility that seizure rate is decreasing as more patients are treated and more experience is gained.

A seizure can be thought of as a dynamic process in which locally synchronous ictal discharges propagate through a wider cortical network. Some authors caution against describing seizures in the context of a hypersynchronous state, noting definitional discrepancies and highlighting that 'state' implies stasis [32,33]. TMS-associated seizures occur during or seconds after stimulation; there is no direct evidence that TMS is associated with a kindling phenomenon that might increase seizure risk minutes or longer after stimulation [12,14]. The precise manner in which TMS-associated seizures occur is likely multifactorial, but coil placement is one factor. For example, one third of patients in the OPT-TMS trial required coil adjustments because stimulating 5 cm anterior to the motor hotspot would have targeted premotor cortex instead of dorsolateral prefrontal cortex [21]. Stimulating premotor cortex would theoretically increase seizure risk and decrease response and remission rates [34].

Another factor to consider is magnetic field breadth. By design, H-coils are less focal and more penetrative than traditional figure- 8 coils [14,35–37]. Studies suggest that H-coils more robustly activate motor cortical regions during rMT assessment relative to figure- 8 coils [38], and modeling data suggest that wider H-coil

Table 3
Seizure rate ratios. Pairwise comparisons of seizure rates per session and per patient among the four most widely used manufacturers. *P*-values and confidence intervals are adjusted for multiple comparisons.

Contrast	Per Session			Per Patient		
	Rate Ratio	Adjusted 95% CI	Adjusted p-value	Rate Ratio	Adjusted 95% CI	Adjusted p-value
Brainsway/Magstim	Inf	(1.6, Inf)	0.024	Inf	(1.6, Inf)	0.002
Brainsway/MagVenture	6.4	(1.0, 157.9)	0.054	7.6	(1.1, 187.6)	0.017
Brainsway/Neuronetics	52.2	(4.9, 14195.9)	<0.001	89.5	(8.5, 24348.8)	<0.001
Magstim/MagVenture	0.0	(0.0, 16.8)	1.00	0.00	(0.0, 19.4)	1.00
Magstim/Neuronetics	0.0	(0.0, 1144.6)	1.00	0.00	(0.0, 1905.9)	1.00
MagVenture/Neuronetics	8.1	(0.2, 3029.5)	0.61	11.7	(0.2, 4375.2)	0.35

Note: Confidence Intervals and p values are adjusted for 6 multiple comparisons.

Table 4
Grouped Comparisons. Each of the four most widely used manufacturers were compared to the other three combined. *P*-values and confidence intervals are adjusted for multiple comparisons.

Contrast	Per Session			Per Patient		
	Rate Ratio	Adjusted 95% CI	Adjusted p-value	Rate Ratio	Adjusted 95% CI	Adjusted p-value
Brainsway/Other	25.5	(5.0, 242.3)	<0.001	38.8	(7.7, 369.4)	<0.001
Magstim/Other	0.0	(0.0, 2.9)	0.96	0.0	(0.0, 4.3)	1.00
Magventure/Other	1.0	(0.1, 5.8)	1.00	1.2	(0.1, 7.4)	1.00
Neuronetics/Other	0.1	(0.0, 0.5)	<0.001	0.0	(0.0, 0.3)	<0.001

Note: Confidence Intervals and p values are adjusted for 4 multiple comparisons.

fields are more likely to incidentally stimulate cortical motor regions than figure- 8 coils when the prefrontal cortex is being targeted [35]. A different possibility relates to parameter differences, most notably the higher frequency of stimulation with the Brainsway device (18 HZ) relative to traditional figure- 8 protocols (10 HZ). It is critical to note the speculative nature of these explanations as well as the limitations of the current study.

Limitations

There are several reasons to interpret the current results with caution, starting with sampling bias and generalizability. This survey was designed and conducted exclusively within the CTMSS. Moreover, there was a relatively low survey response rate, even after our efforts to increase it (approximately 27%). As such, our sample is largely comprised of private practices in the United States, even if all unreported sites are counted as academic. There are limited published data with which to explore the implications of this sample composition on TMS seizure risk. Other generalizability questions arise because of the speed with which the field evolves. For example, the pivotal non-inferiority trial for theta burst stimulation (TBS) [17] was published as this study was being designed and implemented. Since that time, TBS has likely become more prevalent in routine clinical practice as well as in clinical trials offering accelerated protocols [39,40]. Indeed, the most recent systematic review identified three seizures associated with TBS, including two with intermittent TBS and one with continuous TBS [16]. More information is needed to assess how these protocols and other new additions to the field (e.g., new coils, protocols, imaging-guided treatment, etc.) might influence seizure risk.

Data processing limitations should also be considered. We were unable to verify all reported seizures with follow-up interviews. Also, there were some irreconcilable data inconsistencies (e.g., patients exceeding sessions, percentages without actual numbers, etc.) that prompted post-hoc decisions about inclusion and exclusion. It was difficult to balance the desire for an inclusive, realistic clinical sample with the desire for data consistency. The additional analyses run (supplementary material) were an attempt to ensure that these decisions did not substantially affect our results. Furthermore, there could be a case made against the *a priori* decision to focus on the four most widely used manufacturers, although one of two sites reporting four seizures with MAG & More illustrates the risks of drawing conclusions from less represented and distributed manufacturers.

Another limitation is the broad but nonspecific scope of the survey, which did not collect information on diagnosis, protocol, device settings, coil geometries, targeting strategies, etc. These factors are difficult to track and share, especially in clinical contexts. For example, there are four treatment protocols (Traditional, Dash, Intermittent Theta Burst, Brainsway) across at least eight device manufacturers cleared by the Food and Drug Administration for "treatment-resistant" or difficult-to-treat depression in the United States alone. Even if these variables were tracked across sites, the data would still be missing information on off-label protocols (e.g., 1 Hz right, bilateral stimulation, etc.), coil geometries (e.g., traditional vs. theta burst figure- 8 coil angle), and treatment of other indications on- (e.g., migraine headache, obsessive-compulsive disorder, nicotine craving, etc.) or off-label (e.g., bipolar depression, etc.). This information would also need to be collected for all treatments and patients, regardless of whether the patient had a seizure. Requiring this information would have likely limited participation and thus sample size, opposing the goal of assessing average risk for patients seeking treatment in a wide range of naturalistic clinical settings. Nevertheless, it is critically important to investigate these and other factors in follow-up studies that can more effectively evaluate individualized seizure risk.

One of the most important limitations to discuss is the absence of patient-specific seizure risk factors, which can be considered either static or dynamic. The list of medications, medical conditions, genetic predispositions, and behaviors that may affect seizure threshold is often extrapolated from animal models of seizures or epilepsy [41–43], human studies of electroconvulsive therapy [44,45], or miscellaneous retrospective studies [46–48]. The degree to which these data should inform TMS practice remains underexplored. For example, some established static risk factors have never been associated with TMS-related seizures [14,49]. Dynamic risk factors such as stress, fatigue, caffeine, and sleep deprivation are even more difficult to contextualize [14,50,51], particularly when there are conflicting reports on how they impact cortical excitability [52–57]. There is also evidence that psychiatric disorders are generally associated with non-specific cortical excitability changes, further complicating risk assessment [58].

Seizure risk factors are widely considered to be relative rather than absolute contraindications for TMS [2,12,14,51]. Studies rarely report these risk factors in patients who did not have a TMS-related seizure; they are typically reported after a seizure has occurred, raising the possibility of a post-hoc fallacy. Furthermore, there are no published guidelines about actionable steps to take when certain combinations of static or dynamic risk factors are identified or measured before or during a course of treatment. For example, the lone seizure in the Brainsway pivotal multisite trial for depression was noted to have occurred the evening after "excessive" alcohol consumption [22], but there are no specific *a priori* guidelines about how much alcohol (or sleep deprivation, caffeine, etc.) should warrant rMT reassessment or treatment postponement [14]. There are also limited data directly demonstrating the logical presumption that frequent rMT reassessment diminishes seizure risk. It is for these and other reasons that statements about seizure risk factors in TMS should be made with caution.

One final limitation to note is the assumptions of the statistical analyses used in this study. It is challenging to statistically assess the distribution of a rare event, particularly in groups where none occurred. The Poisson distribution was used for the analyses because of the availability of software for exact probability

calculations based upon it, which are necessary in this context of extremely rare events. However, as it has only one parameter, it is constrained both with regard to the observations with zero seizures and the variability of the counts.

Conclusion

This study appears to provide the largest real-world sample size estimation of TMS seizure risk across device manufacturers. The absolute risk of a seizure with rTMS is low, but generic H-coil treatment appears to be associated with a higher relative risk than generic figure- 8 coil treatment. Investigations of comparative efficacy and safety across devices are needed to replicate and contextualize these findings.

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Data statement

This survey did not include a statement consenting to data sharing.

CRediT authorship contribution statement

Joseph J. Taylor: Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Supervision. **Noam G. Newberger:** Software, Formal analysis, Writing – review & editing, Visualization. **Adam P. Stern:** Conceptualization, Data curation, Writing – review & editing. **Angela Phillips:** Investigation, Data curation, Writing – review & editing. **David Feifel:** Conceptualization, Writing – review & editing. **Rebecca A. Betensky:** Software, Formal analysis, Writing – review & editing, Visualization. **Daniel Z. Press:** Conceptualization, Data curation, Writing – review & editing, Supervision.

Declaration of competing interest

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AP: I have no conflicts of interest.

DF: I serve on the Scientific Advisory Board for Brainsway.

RB: I have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.05.012.

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