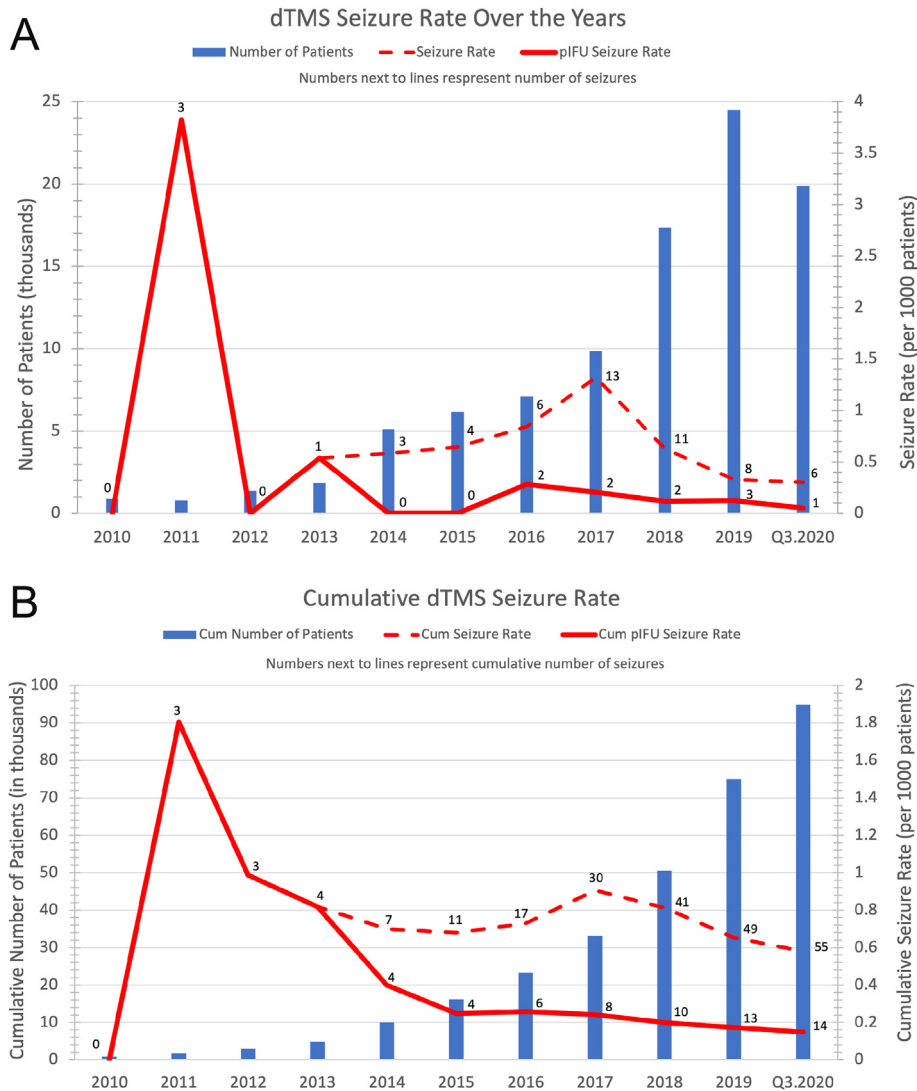


## Seizures provoked by H-coils from 2010 to 2020

Introduction: As part of ongoing quality assurance, the manufacturer of H-coil deep-TMS (Transcranial Magnetic Stimulation) systems continuously surveys customers and the literature for the occurrence of device related adverse events. The most serious acute

TMS device related adverse event is a TMS-provoked seizure, which occurs when the synchronized neuronal firing induced by the coil persists beyond the TMS train duration and spreads beyond the area of stimulation. As these are rare events, their exact frequency



**Fig. 1.** Annual and cumulative dTMS seizure rates. Annual (A) and cumulative (B) seizure rates from 2010 through October 2020 (red dashed line) and per instructions for use (pIFU) seizure rates (red line) are shown along with number of patients treated (blue bars) and number of seizures (numbers next to lines). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and cause are difficult to figure out, but it is important to give patients an estimate of the risk.

**Background:** We previously reported the seizure rate [1,4], but since that publication the number of patients who received deep TMS has nearly tripled with the H1 coil in 567 locations and H7 coil in 185 locations, stressing the need for this updated report.

**Methods:** Seizures: All H-coil customers are instructed to report adverse events to the chief medical officer. Additionally, all customers are orally surveyed by their account manager every quarter and in writing once a year. A specific written request for information about seizures was sent from the chief medical officer to all customers on June 15th, 2020. All events with potential harm to a patient are reviewed by the chief medical officer (AT) who discusses the events with the treating clinician. Questionable psychogenic non epileptic seizures (pseudo-seizures) and events with unclear causation are discussed with a TMS epilepsy specialist. **Patients:** The number of patients treated is estimated from individualized head caps. Each cap costs the treating provider money, and they are ordered in increments of five so they are presumably used though they may be reusing head caps amongst patients or using an alternative. The newer stimulators which log patient and treatment data confirm that the cap data is accurate.

**Results:** From 2010 to October 2020, 55 seizures were reported, of which 14 seizures occurred when the instructions for use were followed (pIFU). The number of patients treated from 2010 to October 2020 was 94,857 for an overall seizure frequency of 0.00058 and pIFU seizure frequency of 0.00015. The annual seizure rate and cumulative seizure rate along with the number of patients treated are shown in Fig. 1. All fifty-five seizures and nine pseudo-seizures with reporting dates or previous publication references are detailed in the supplementary material. This suggests, for patient education, an overall seizure frequency of 6:10,000 patients and 2:10,000 patients pIFU.

**Discussion:** This comprehensive listing of every seizure provoked by an H-coil reaffirms the safety of H-coil deep-TMS. When seizures did occur, all self-terminated without pharmacological intervention and no injuries were sustained by the patients. None of the seizures occurred on the first day of treatment, in contrast to the results of a survey which included very few deep TMS clinics [2] and was emphasized in the TMS safety guidelines [3]. Potential multifactorial causes for the seizures included not rechecking the motor threshold once a week, medication changes since the last motor threshold was checked, substance use in the 24 h before the seizure and poor sleep the night before the seizure. Lack of compliance with the instructions for use (IFU) was not due to a lack of clarity or comprehension. Clinicians chose to not recheck the MT every week because they believed it had a low risk of variability and it was not reimbursed by insurance. Patients perceive substance use and medication changes as low risk as well. Frankly, as seizures are rare events causation and risk are hard to ascribe and quantify. Practically, it is difficult to know which coils were used on patients who did not have seizures, and some patients used multiple coils. From the more informative newer stimulators (104 systems) we can conclude that 3000 patients used the H7 coil, which stimulates a significantly deeper and larger volume than the H1 (75cm<sup>3</sup> vs 17cm<sup>3</sup>). The only seizure that occurred with the H7 coil occurred when it was used over the left temporo-parietal junction after lowering Lorazepam from 6mg to 3mg. Either not enough treatments have been done with the H7 to detect the seizure rate or the medial and symmetrical stimulation with the H7 is less likely to induce seizures than the asymmetric stimulation

of the H1 coil or both are true. As this is all observational and hidden covariates may play a factor, we point out that the frequency of seizures from 2010 to 2018 was published online (September 7, 2018) as 0.00087 and since then (September 2018–October 2020), there has been a 1.7-fold increase in the number of patients treated (59,423) and a 3-fold decrease in the overall seizure rate to 0.00027. This may reflect increased awareness since the last publication on seizures, improved manufacturer training practices on this subject, and clinics following the IFU more rigorously. For TMS seizure prevention and effective treatment it is essential to recheck the motor threshold at least once a week, more often if medications that affect the motor threshold were adjusted or if the patient has a history of substance use. Fluctuations in the motor threshold (MT) should prompt more detailed questioning about missed or increased medication doses, substance use and sleep disruption. We continue to advise in the IFU against voluntary movements during TMS, and six seizures (11%) may have been provoked by large voluntary patient movements. Further investigation may reveal a correlation between temporary increases in motor cortex excitability and prefrontal cortex excitability. Alternatively, prefrontal cortex stimulation at 120%MT of the resting motor threshold does not induce seizures in a resting motor cortex but it may be sufficient to overly excite it following voluntary motor activation.

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Potential conflicts of interest: Aron Tendler is the chief medical officer of BrainsWay (H-coil manufacturer) has a financial interest in BrainsWay as well as a commercial clinical and research TMS center. He has received speaking fees from BrainsWay, Neuronetics and the Clinical TMS Society. Tal Harmelech and Roman Gersner are BrainsWay employees. Yiftach Roth is an inventor of the H-coils, chief scientist at BrainsWay and has a financial interest in BrainsWay.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2020.11.006>.

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