



## Report of seizure induced by intermittent theta burst stimulation



To the Editor

We report the following TMS-related seizure. The subject was a 23-year-old woman with no medical diagnoses who was participating in a research study as a healthy volunteer. Her only medication was ethinyl estradiol/norethindrone (Nortrel), a birth control medication. She had been advised prior to the visit to avoid any substances (e.g., caffeine) or activities that could affect seizure risk, and reported compliance. She slept 7 h the night before the event and had no history of seizures.

Our study was attempting to replicate the protocol of Iseger and colleagues [1,2] which involves serial rTMS at either 10 Hz or theta burst over several prefrontal cortical locations. We were delivering the TMS in the following manner – MagVenture Cool-B65-A/P figure eight coil positioned over five different cortical locations (F3, F5, FC3, FZ, FP1) at either 10 Hz rTMS at 100% of resting motor threshold (rMT) or iTBS pulses at 120% of rMT. The 10 Hz rTMS settings were as follows: 5 second trains with 10 pulses per second (50 pulses per train) and an inter-train interval of 30 seconds. The iTBS settings were as follows: 50 Hz-triplets at 5 Hz for 5 s (i.e., 75 pulses per train) with an inter-train interval of 30 s. On this machine, the subject's rMT was 70% machine output. The subject wore an EEG cap for locating cortical locations during stimulation. The cap was also worn during the determination of motor threshold and during the procedure but there was no electrode gel or electrodes.

The study involved a single visit involving two sections—15 total trains of 10 Hz rTMS delivered over the five different cortical locations in random order (each location receiving a total of three trains) and 15 total trains of iTBS over the same locations in random order (each location also receiving a total of three trains). The 10 Hz rTMS and iTBS sections were separated by a fifteen-minute break, and the order in which a subject receives the sections (i.e., 10 Hz followed by iTBS, or vice versa) was randomized. (See Table 1). This subject received her 10 Hz rTMS section first (which she tolerated without issue), followed by the 15-min break, and progressed uneventfully through the first 3 min of the iTBS section before seizing while the coil was positioned over F5.

The first “round” of the iTBS section had ended with FC3, and we noted hand twitching here as soon as the train began. Once noted, the coil was immediately removed from FC3. This twitching was self-limited. Given that this was our most posterior location, close to motor cortex, and that subsequent locations, being more frontal, were less likely to stimulate the motor cortex, a decision was made to continue the protocol. The 4.8 seconds of that train passed, as did an inter-train interval of 30 seconds, before we began the second stimulation at F5. This was when the seizure occurred. Therefore, about 34.8 seconds of rest (no stimulation) had elapsed between the brief stimulation at FC3—which, again, was aborted due to

hand twitching—and seizure onset with stimulation over F5. MagVenture settings for the iTBS section were as follows: 5 pulses per second, each train 4.8 seconds in duration, 24 pulses in a train, 30 second inter-train interval, 15 trains per section.

The subject was seated during the event. The setting was a research lab in a large academic center that specializes in noninvasive brain stimulation. The TMS operator first noted right-sided facial grimacing, then head turning to the right side, upward eye roll, extension and rigidity of both arms and legs, and drooling. We immediately dialed emergency services and passively supported the patient in a lateral decubitus position while awaiting arrival of emergency services. The subject was monitored closely throughout the seizure, which lasted about 1 min before spontaneously resolving.

After the seizure resolved, the subject was breathing spontaneously and, though disoriented, began speaking to us. She later endorsed post-ictal confusion for about 15 min after the event. She can recall the moments immediately preceding seizure onset—she remembers trying to speak and move her right arm but not being able to do so—and her first memory thereafter is arrival at the emergency department (ED) (about 15 min after seizure onset).

A general neurologic exam and mental status exam were both normal. She had normal vital signs, complete blood count, metabolic panel and a brain CT scan. The subject did not receive an EEG. There were no sequelae. The clinical diagnosis of this event was TMS related seizure.

Seizure is a rare but known risk of TMS [3,4]. Though our subject had none of the risk factors known to decrease seizure threshold [5], it has been observed that “seizures can occur within safety guidelines, even in patients who present with no known risk factors.” [6] There is at least one reported case of seizure induced by theta burst in a patient without risk factors—though this was continuous stimulation rather than intermittent, as was used on our subject [7].

The risk of TMS-induced seizure is difficult to quantify given the lack of a requirement to report them [8], but a recent review of 24 seizures out of 318,560 TMS sessions concluded that TMS applied within published guidelines to those without risk factors “appears to cause fewer than one seizure per 60,000 sessions.” [9] These authors provided a risk of 0.08/1000 for the conventional figure-8 coil, as was used on our subject [9]. Oberman et al. estimate theta-burst-induced seizure risk at 0.02% [10].

We wonder if the design of this protocol caused progressive excitation of the prefrontal cortex. A limitation of this case report is lack of EEG recording during the session. For this subject, the 10 Hz rTMS section could have increased prefrontal cortex excitability in a way that did not resolve even after the fifteen-minute

**Table 1**  
Visit example, with location of seizure onset highlighted in red.

10 Hz rTMS			iTBS		
Round 1	Round 2	Round 3	Round 1	Round 2	Round 3
FC3	F5	F3	F3	F5	FP1
F5	F3	FC3	FZ	FC3	FC3
FZ	FC3	FP1	FP1	FZ	F3
F3	FZ	FZ	F5	F3	F5
FP1	FP1	F5	FC3	FP1	FZ

Rest Period (15 mins)

100% MT:	70 % of maximum stimulator output
120% of MT:	84% of maximum stimulator output

break, increasing the likelihood of a seizure during the iTBS section. Alternatively, we wonder if moving the coil between different nodes was tapping into different brain networks, or if combining two different styles of brain stimulation in close succession contributed to this event.

This event highlights the need for rigorous reporting of adverse events associated with neuromodulation technologies and for dosing studies to assess the seizure risk associated with theta-burst parameters.

**Location**

30 Bee Street, Charleston, SC, Medical University of South Carolina.

**Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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