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LETTER TO THE EDITOR

Report of seizure induced by continuous theta burst stimulation

To the Editor: We report the first-ever seizure induced by continuous theta burst (cTBS) transcranial magnetic stimulation (TMS). The subject was a 33-year-old man, healthy control without any risk factors for epilepsy. He was not taking any medications. Two days before the event, the subject had flown transAtlantic from London to Boston, and his sleep pattern may have still been altered, although he reported restful nights and no signs of jetlag.

We were delivering TMS with a MagPro X100 stimulator that delivered biphasic pulses via a figure-of-eight coil (Model MCF-B65) with each wing measuring 8.5 cm. The coil was held tangential to the scalp with the handle pointing occipitally at approximately 45 degrees to the midsagittal plane. We were targeting the left motor cortex defined by the optimal scalp location for induction of motor potentials in the right first dorsal interosseus muscle. Stimulation intensity was set at 100% of resting motor threshold (RMT) determined by the method of limits according to the guidelines approved by the International Federation of Clinical Neurophysiology.[1] Continuous TBS was applied as three pulses at 50 Hz with 200-millisecond intertrain interval for 50 trains (total of 150 pulses). The TMS operator had ample prior experience with TMS in general and cTBS in particular. She had completed a training in the recognition and acute care of seizures and syncopal episodes at the Harvard Intensive Course in Transcranial Stimulation.

The subject was sitting in a chair in a fully equipped research laboratory within the Berenson-Allen Center for Noninvasive Brain Stimulation at Beth Israel Deaconess Medical Center. The event occurred approximately 5-10 seconds after the completion of the final train of stimulation. The TMS operator first noted a contraction of the hand and wrist muscles, which spread up the arm and eventually also involved facial muscle contractions. Asked whether he was feeling "okay" at that point, he answered "no." The next day, recalling the events, he reported having felt that the movements were out of his control and he had experienced a surge of fear and anxiety. He then became unresponsive, was quickly laid down in a left lateral supine position to minimize the risk of aspirations, his head was padded, and he was observed to experience tonic, then clonic movements of all extremities synchronously for 40 seconds. The responsible physician was rapidly alerted and was on site before the convulsion terminated. The subject had postictal confusion lasting for approximately 25 minutes. The seizure self-terminated. There was no tongue bite or sphincter incontinence. During the event the pulse was regular and 140. After the event the pulse slowly decreased to 62, blood pressure was 110/50, respiratory rate was 18, and all blood sugar was normal. The subject was admitted to the Harvard-Thorndike Clinical Research Center for close observation and stayed overnight. Physical examination, detailed neurologic examination, and mental status examination were normal starting 45 minutes after the event and remained normal later in the day and the next morning. Vital signs were stable, the subject was afebrile. Routine blood tests (blood counts and electrolytes) were normal. An electroencephalogram was not performed, but brain magnetic resonance imaging (including perfusion and diffusion images) was performed and revealed no abnormalities. Within 60 minutes of the event, the subject reported feeling completely back to baseline.

The clinical diagnosis of this event was TMS-related seizure. To our knowledge this is the first seizure triggered by cTBS. Continuous TBS is traditionally thought to suppress cortical activity. However, it is possible that in some individuals cTBS may lead to facilitatory effects. Such paradoxical modulations have been reported for some subjects undergoing slow rTMS as well.[2] Furthermore, there has been one report in which it was reported that under specific conditions in which the subject is relaxed for several minutes before cTBS with less than 300 pulses, the net effect is excitatory.[3] Because we used RMT to define the cTBS intensity and the subject was at rest before the stimulation, it is possible that the delivered stimulation protocol may have increased the subject's cortical excitability rather than decreasing it. However, we have used this same protocol in a cohort of normal subjects, as well as a group of patients with autism spectrum disorder, and found this form of cTBS to consistently lead to a suppression of corticospinal excitability. It should also be noted that most of the published reports of TBS use an intensity of 80% of active motor threshold, whereas the current protocol used an intensity of 100% of RMT (which is approximately equal to 120% of

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active motor threshold). Currently, there are no safety guidelines for TBS; however, in light of this event, it is reasonable to conclude that TBS should be applied at $< 90\%$ RMT intensity. This event also highlights the need for an intensity-dosing study with TBS protocols to assess the seizure risk. Until then, TBS, both continuous and intermittent, should be applied with caution and appropriate precautions even in subjects with no predisposing factors for seizures should be taken, including appropriate physician supervision and emergency medical care access.

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