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Report of Seizure Induced by Continuous Theta Burst Stimulation

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Dear 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 prior to the event the subject had flown Trans-Atlantic from London to Boston, and his sleep pattern may have still been altered, though he reported restful nights and no signs of jetlag.

We were delivering TMS with a MagPro X100 stimulator delivering biphasic pulses via a figure 8 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 deg to the mid-sagital 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 determined by the method of limits following the guidelines approved by the International Federation of Clinical Neurophysiology (Rossini et al., 1994). Continuous TBS was applied as 3 pulses at 50Hz with 200ms 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 ‘ok’ at that point, he answered ‘no’. The following 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 became then 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 s. The responsible physician was rapidly alerted and was on site before the convulsion terminated. The subject had post-ictal 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, BP 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 exam, detailed neurologic exam and mental status exam were normal starting 45 minutes after the event and remained normal later in the day and the following morning. Vital signs were stable,

the subject was afebrile. Routine blood tests (blood counts and electrolytes) were normal. An EEG was not done, but a brain MRI (including perfusion and diffusion images) was done and revealed no abnormalities. Within 60 min 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. CTBS 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 (see for example Gangitano et al, 2002). Furthermore, there has been one report where under specific conditions in which the subject is relaxed for several minutes prior to cTBS with less than 300 pulses, the net effect is excitatory (Gentner et al., 2008). Since we used resting motor threshold to define the cTBS intensity, and the subject was at rest prior to 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 cortico-spinal excitability. It should also be noted that most of the published reports of TBS use an intensity of 80% of Active Motor Threshold while the current protocol used an intensity of 100% of Resting Motor Threshold (which is approximately equal to 120% of 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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