

Title:

Report of one confirmed generalized seizure and one suspected partial seizure induced by deep continuous theta burst stimulation of the right operculo-insular cortex

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Dear Editor,

We report one confirmed generalized epileptic seizure and one suspected partial epileptic seizure that occurred during short (20s) continuous theta burst stimulation (cTBS) over the right operculo-insular cortex. Combined with psychophysics performed before and after cTBS, the aim of the procedure was to test whether modulation of the operculo-insular cortex affects the perception of thermal, nociceptive and tactile stimuli delivered to the ipsilateral and contralateral hands.

Our report is the second describing epileptic seizures triggered by cTBS [7]. Case 1 was a 25-year-old healthy woman with no medical history other than the fact that, two days before the event, she took 150 mg fluconazole and 3x500 mg ornidazole to treat a benign, acute and local non-neurological infection. Case 2 was a 23-year-old healthy man with no medical history. He was not under any medication. The two participants had no risk factor for epilepsy and no contraindication to cTBS [8].

The study was approved by the ethical committee of the Université catholique de Louvain (B403201316436). All participants provided written informed consent. In both cases, cTBS was delivered with a MagPro X100 stimulator. Biphasic pulses – with an anterior-posterior eddy current direction – were delivered using a 70-mm double-cone coil (Model D-B80) designed for deep stimulation. The coil was positioned tangentially over the scalp covering the right Sylvian fissure with the handle pointing occipitally. The exact position of the coil over the dorsal-posterior operculo-insular cortex was achieved by means of a MRI-guided neuronavigation system. The stimulation intensity was set to 80% of the average of the left and right tibialis anterior resting motor thresholds (rMT; 52% of the maximal stimulator output (MSO) in case 1 and 39% MSO in case 2). This intensity of stimulation was chosen based on a report of repetitive TMS (rTMS) of the insula [2]. The rMT was determined

following the guidelines of the International Federation of Clinical Neurophysiology [9]. A short cTBS protocol was used, comprised of 100 trains of 3 biphasic pulses delivered at 50Hz with a 200ms inter-train interval (total of 300 pulses). The experiments took place in the Université catholique de Louvain (Brussels, Belgium) under the supervision of a neurologist. During stimulation, the participants were comfortably positioned in left lateral decubitus. To reduce the scalp discomfort associated with the delivery of cTBS, 45 minutes before cTBS, the skin area located under the TMS coil was treated with 2.5 g of topical lidocaine/prilocaine cream (EMLA, AstraZeneca). The participants were provided with earplugs and a mouth-guard to reduce discomfort due to the sound and the peripheral muscular activation induced by TMS.

Case 1. The event occurred approximately 15 seconds after the beginning of cTBS. The stimulation was interrupted during the 93rd train of pulses. During the first 10 seconds of cTBS the participant had euphoric thoughts immediately followed by mild bilateral paraesthesias at the fingertips, which progressively increased in the left (contralateral to cTBS) upper limb. A dystonic attitude started in the left hemibody followed by clonic movements of the upper and lower limbs and eyes rotation. The participant then tried to sit with a feeling of panic. She recovered within one minute after the onset of the episode. The participant reported afterward that she was not able to speak or move especially the left upper and lower limbs during the incident. She also described dyspnea associated with sensations of laryngeal constriction and thoracic oppression. The neurologist and experimenters confirmed these manifestations (dyspnea, dysarthria and tonic contraction with a striking facial asymmetry). The participant remained conscious. She had no post-ictal confusion. Within 20 minutes, she was admitted to the Department of Neurology of Saint-Luc University Hospital where an electroencephalogram (EEG) examination was performed and did not reveal any epileptic

activity nor post-ictal signs. Neurological examination was normal. A T1 structural MRI did not reveal any lesion or structural abnormality. A 24-hours EEG performed a few weeks after the event was normal.

Case 2. The event occurred approximately 10 seconds after the beginning of cTBS. The stimulation was stopped during the 65th train of pulses. As in case 1, during the first seconds of cTBS the participant had euphoric thoughts immediately followed by grunts and a dystonic attitude predominantly of the right (ipsilateral) hemibody, which tended to become bilateral and followed by generalized clonic movements during approximately 2 minutes. TMS was interrupted as soon as the experimenters noted the change in behaviour. The participant became unresponsive and presented a stertorous respiration. He had post-ictal confusion during approximately 30 minutes. He was admitted to the Emergency Department of Saint-Luc University Hospital. Neurological examination was normal. A T1 structural MRI did not reveal any lesion or structural abnormality. Both subjects recovered fully.

Our observations suggest that deep cTBS of the operculo-insular cortex triggered two epileptic seizures with an operculo-insular onset. In case 1, the seizure was very short lasting and remained focal. In case 2, the seizure was also short lasting, initially focal, but with secondary generalization. Supporting an operculo-insular onset is the fact that the clinical manifestations and their sequence are highly like the manifestations of insular lobe seizures [4; 10].

In healthy volunteers, the seizure risk associated with TBS appears to be extremely low. Seizure occurrences after TBS and other high-frequency rTMS protocols are respectively estimated to 0.02% and less than 0.1% [6; 8]. The fact that deep cTBS of the operculo-insular cortex triggered two seizures out of only 18 participants suggests that this specific protocol is associated with a higher risk of TMS-induced seizures. Two potential factors could have

1 contributed to this increased risk. First, as compared to standard figure-of-eight coils, the
2 double-cone coil can achieve significantly deeper field penetration, but at the expense of
3 more intense and widespread electrical fields [3]. Therefore, the volume of cortex that is
4 synchronously stimulated by each TMS pulse is probably markedly increased as well as the
5 electric field affecting the superficial cortex. These two factors potentially increase the risk of
6 TMS-induced seizures. Current safety guidelines for rTMS have been proposed only for
7 standard figure-of-eight coils [6; 8] and may not be fully applicable to other coil designs [3].
8 Nevertheless, it is important to stress that numerous previous studies have delivered deep
9 rTMS using double cone coils at comparable or even higher intensities to what was delivered
10 here without any report of TMS-induced seizure [1; 5]. This suggests that deep cTBS of the
11 operculo-insular cortex could be associated with a higher seizure risk than deep cTBS of other
12 deep regions, e.g. cingulate or lower limb motor cortices.

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