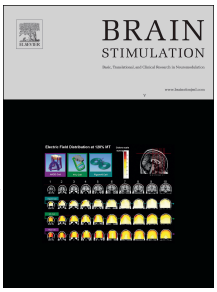
Accepted Manuscript



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

Cédric Lenoir, Maxime Algoet, Camille Vanderclausen, André Peeters, Susana Ferrao Santos, André Mouraux

PII: S1935-861X(18)30151-7

DOI: 10.1016/j.brs.2018.05.004

Reference: BRS 1252

To appear in: *Brain Stimulation*

Received Date: 24 April 2018

Revised Date: 2 May 2018

Accepted Date: 5 May 2018

Please cite this article as: Lenoir C, Algoet M, Vanderclausen C, Peeters A, Santos SF, Mouraux A, Report of one confirmed generalized seizure and one suspected partial seizure induced by deep continuous theta burst stimulation of the right operculo-insular cortex, *Brain Stimulation* (2018), doi: 10.1016/j.brs.2018.05.004.

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

Authors:

Cédric Lenoir[#1], Maxime Algoet[#1], Camille Vanderclausen[1], André Peeters[1,2], Susana Ferrao Santos[1,2], André Mouraux[1*]

[1]Institute of neuroscience, Université catholique de Louvain, Avenue Mounier 53 B-1200 Brussels Belgium
cedric.lenoir@uclouvain.be
maxime.algoet@uclouvain.be
camille.vanderclausen@uclouvain.be
andre.mouraux@uclouvain.be

[2]Department of Neurology, Saint-Luc University Hospital, Avenue Hippocrate 10 B-1200 Brussels, Belgium
andre.peeters@uclouvain.be
susana.ferrao@uclouvain.be

[#] authors contributed equally/main investigators

[*] Corresponding author

Corresponding author:
André Mouraux
andre.mouraux@uclouvain.be
Institute of Neuroscience (IONS)
Faculty of Medicine
University of Louvain
53, Avenue Mounier (B1.53.04)
B1200, Brussels, Belgium
Tel: +32.2.764.5447

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. This report is the second describing epileptic seizures triggered by cTBS [7]. Case 1 was a 25-year-old healthy woman. She had no risk factor of epilepsy. She was not taking any medication. Two days before the event, she took 150 mg of fluconazole and 3×500 mg of ornidazole. Case 2 was a 23-year-old healthy man with no risk factor of epilepsy. He was not under any medication.

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 contributed to this increased risk. First, as compared to standard figure-of-eight coils, the double-cone coil can achieve significantly deeper field penetration, but at the expense of more intense and widespread electrical fields [3]. Therefore, the volume of cortex that is synchronously stimulated by each TMS pulse is probably markedly increased as well as the electric field affecting the superficial cortex. These two factors potentially increase the risk

of TMS-induced seizures. Current safety guidelines for rTMS have been proposed only for standard figure-of-eight coils [6; 8] and may not be fully applicable to other coil designs [3]. Nevertheless, it is important to stress that numerous previous studies have delivered deep rTMS using double cone coils at comparable or even higher intensities to what was delivered here without any report of TMS-induced seizure [1; 5]. This suggests that deep cTBS of the operculo-insular cortex could be associated with a higher seizure risk than deep cTBS of other deep regions, e.g. cingulate or lower limb motor cortices.

Acknowledgments

Funding

CL, MA, MA are supported by the European Research Council (ERC Starting Grant PROBING PAIN 336130).

Declaration of interest: none.

References

[1] Benito J, Kumru H, Murillo N, Costa U, Medina J, Tormos JM, Pascual-Leone A, Vidal J. Motor and gait improvement in patients with incomplete spinal cord injury induced by high-frequency repetitive transcranial magnetic stimulation. Top Spinal Cord Inj Rehabil 2012;18(2):106-112.

[2] Ciampi de Andrade D, Galhardoni R, Pinto LF, Lancelotti R, Rosi J, Jr., Marcolin MA, Teixeira MJ. Into the island: a new technique of non-invasive cortical stimulation of the insula. Neurophysiol Clin 2012;42(6):363-368.

[3] Deng ZD, Lisanby SH, Peterchev AV. Coil design considerations for deep transcranial magnetic stimulation. Clin Neurophysiol 2014;125(6):1202-1212.

[4] Isnard J, Guenot M, Sindou M, Mauguiere F. Clinical manifestations of insular lobe seizures: a stereo-electroencephalographic study. Epilepsia 2004;45(9):1079-1090.

[5] Kreuzer PM, Schecklmann M, Lehner A, Wetter TC, Poeppl TB, Rupprecht R, de Ridder D, Landgrebe M, Langguth B. The ACDC pilot trial: targeting the anterior cingulate by double cone coil rTMS for the treatment of depression. Brain Stimul 2015;8(2):240-246.

[6] Oberman L, Edwards D, Eldaief M, Pascual-Leone A. Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. J Clin Neurophysiol 2011;28(1):67-74.

[7] Oberman LM, Pascual-Leone A. Report of Seizure Induced by Continuous Theta Burst Stimulation. Brain Stimul 2009;2(4):246-247.

[8] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120(12):2008-2039.

[9] Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijevic MR, Hallett M, Katayama Y, Lucking CH, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 1994;91(2):79-92.

[10] Wynford-Thomas R, Powell R. Navigating the Island of Reil: how to understand the insular cortex. Pract Neurol 2017;17(2):122-126.