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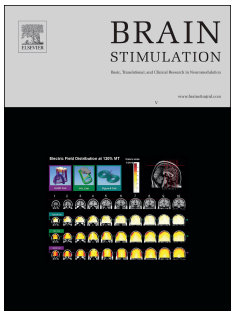

Reply to Letter to the Editor

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Reply to Letter to the Editor

We thank the Editor for giving us the opportunity to reply to the commentary of Hagiwara et al. on our recent report [6]. In their commentary, the authors argue that the clinical manifestations of the two seizures that we witnessed during deep continuous theta burst stimulation (cTBS) targeting the posterior operculo-insular cortex are suggestive of an involvement of the anterior insula rather than the posterior insula. In other words, the authors suggest that we might have missed our intended target.

We chose to qualify the observed manifestations as “operculo-insular seizures” because of their similarity with previous descriptions of seizures involving this area [4; 13]. We did not qualify these seizures as “ecstatic” – and, hence as possibly originating from the anterior insula – because the sensations reported by the participants and the manifestations of the two seizures did not closely correspond to the description of “ecstatic” seizures [3; 8], as witnessed by the neurologist present during the events and by the neurologists of the epileptology and emergency departments who took care of the participants after the seizure. The first participant produced a very sudden and short-lasting burst of laughter devoid of any emotional content. None of the subjective impressions usually described in ecstatic seizures were reported by the participant, such as a sense of physical well-being, a pleasant feeling, bliss, increased awareness and/or perception, clairvoyance, feeling of evidence, vividness and dilated time, mystic experience or anxiety [3; 8]. In the second case, the burst of laughter was also very short lasting, and the participant also did not report any of the subjective impressions associated with ecstatic seizure. Moreover, in this second participant, the loss of consciousness was almost immediate after the onset, which is not a typical presentation of ecstatic seizure [3].

Second, it is important to consider the fact that seizures induced by TMS can be elicited in an area distant from the stimulation site [9; 11], and this also applies to seizures induced by intracerebral stimulation [2]. Therefore, one should not assume that TMS-induced epileptic activity necessarily takes place at the site of stimulation. Furthermore, direct intracerebral electrical stimulation and non-invasive transcranial magnetic stimulation are not directly comparable methods of stimulation. Compared to the focal aspect of intracerebral electrical

stimulation, TMS activates a very extended volume of the brain. Most importantly, deep cTBS delivered using a double-cone coil with the aim of stimulating the insula will unavoidably also stimulate a large area of the more superficial cortex located between the coil and the insula. Furthermore, this more superficial cortex is exposed to a more intense and widespread electrical field than what is usually generated using a flat TMS coil. The relatively high intensity and frequency of the TMS pulses that we delivered could have facilitated the spreading of cortical excitability as suggested by Pascual-Leone et al. [7], which may play a role in the triggering of a seizure [12]. Moreover, the highly connected aspect of the opercula and the insula might have further facilitated the spread of the induced epileptic activity in the insula. Therefore, we cannot agree with the conclusion that the induced seizures "strongly suggest" that our deep cTBS procedure activated more the anterior part of the insula even if the ictal symptoms are not incompatible with an involvement of the anterior insula.

Third, it should be emphasized that, in our study, the coil was not "theoretically" positioned over the posterior part of the insular cortex but actually located over this region as controlled by means of a validated MRI-guided neuronavigation system and procedure including an online monitoring of the TMS coil position and orientation during the 20 seconds of cTBS and a verification of the co-registration after the cTBS protocol. The projection of the position of the center of the coil over the insular cortex are reported in Figure 2C of Lenoir et al. [5]. We partially agree with Hagiwara et al. that the parameters leading to the most efficient effects on non-motor areas are not known, and that the orientation of the TMS coil is likely to be one of the most critical factors [10].

Finally, the two TMS-induced seizures occurred in two participants of a study that was completed in a total of 17 participants. Following deep cTBS over the posterior operculo-insular cortex, all participants showed a significant perceptual decrease in sensitivity to thermonociceptive stimuli involving thinly-myelinated Aδ-fibres, while the perception of other types of somatosensory stimuli was not significantly changed. This consistent effect across all participants is in line with a previous study reporting a selective impairment of the ability to detect high-intensity thermonociceptive stimuli after direct stimulation of the posterior insula [1].

To conclude, the clinical manifestations of the two seizures that we reported did not closely correspond to the descriptions of "ecstatic seizures" and, hence, do not truly point towards a specific involvement of the anterior insula. Furthermore, the location at which TMS may trigger a seizure is not expected to necessarily correspond to the location targeted by TMS, especially in the case of deep TMS. For these different reasons, the main neuromodulatory effect on somatosensory perception that we observed consistently after deep rTMS of the operculo-insular cortex targeting the posterior part of the insula supports an involvement of this region in the processing of thermonociceptive input conveyed by thinly-myelinated Aδ fibers.

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