

Deep continuous theta burst stimulation of the operculo-insular cortex affects the perception of A δ -fiber first pain

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Aim of Investigation. There are several reasons to believe that pain could be modulated by continuous theta burst stimulation (cTBS) delivered over the insular cortex. First, studies have shown that the insular cortex is the main target of ascending spinothalamic input¹. Second, consistent early-latency brain responses elicited by painful stimuli have been recorded in the insular cortex using intracerebral EEG, especially in the posterior part of the operculo-insular cortex². Third, direct intracerebral electrical stimulation of the dorsal-posterior insular cortex can elicit painful sensations in humans³.

Methods. Based on previous results⁴ showing the feasibility to deliver transcranial magnetic stimulation to the insula using a double-cone coil designed to target deep cortical structures, we applied neuronavigated cTBS (300 pulses at 80% tibialis anterior rest motor threshold) over the right posterior operculo-insular cortex. In a first experiment, we delivered three different types of transient somatosensory stimuli to the contralateral hand: laser heat stimuli to assess the detection of A δ -fiber first pain and C-fiber second pain, cool stimuli to assess the detection threshold of A δ -fiber cold sensations, and vibrotactile stimuli to assess the detection threshold of A β -fiber mediated sensations. Participants were also asked to rate the intensity of suprathreshold stimuli. In a second experiment, we delivered either superficial cTBS (300 pulses at 80% first dorsal interosseous rest motor threshold) of the operculum using a flat figure-of-eight coil designed for superficial TMS or deep cTBS of the operculo-insular cortex using a double-cone coil, in two separate sessions. We compared detection thresholds and intensity of perception elicited by high intensity heat stimuli and vibrotactile stimuli delivered to the contralateral and ipsilateral hands. In both experiments, the assessment was performed before cTBS, immediately after cTBS, and 20 minutes after cTBS.

Results. Deep cTBS over the right operculo-insular cortex significantly increased the threshold to detect A δ -fiber first pain elicited by laser heat stimulation, both at the contralateral hand and at the ipsilateral hand. Deep cTBS had no effect on the detection of C-fiber second pain, the detection of cold stimuli, and the detection of vibrotactile stimuli. No effect was observed after superficial cTBS.

Conclusions. We show for the first time that affecting the excitability of the operculo-insular cortex leads to a bilateral reduction of the ability to detect heat sensations related to the

activation of A δ -fiber thermonociceptors. This observation supports an involvement of the operculo-insular cortex in the processing of painful thermal nociceptive inputs conveyed by the spinothalamic tract.

¹ Dum et al., J Neurosci (2009)

² zu Eulenburg et al., Neuroimage (2013)

³ Mazzola et al., 2009 et al., Brain (2010)

⁴ Ciampi de Andrade et al., Neurophysiol Clin (2012)