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Transcranial magnetic stimulation for neuromodulation of the operculo-insular cortex in humans

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The insula is a cortical structure internally folded within the lateral sulcus, an anatomical border dividing the frontal, parietal and temporal lobes. Portions of these lobes that hide the insula are known as opercula (lids). Specifically, the part of the parietal lobe that forms the ceiling of the lateral sulcus operates as the secondary somatosensory cortex (S2). There is no clear functional distinction between the S2 neuronal population and the posterior insula, and thus both are jointly characterized as the operculo-insular cortex. The operculo-insular cortex is an integrative structure that detects the intensity of multimodal spinothalamic and, possibly, interoceptive inputs, painful or not. Functional magnetic resonance imaging studies based on cytoarchitectural maps and intracortical recordings suggest an integrated functional unit with subpopulations of neurons in posterior insula primarily processing nociceptive inputs. In turn, subpopulations of neurons in S2 preferentially discriminate the nature of non-nociceptive inputs (Mazzola *et al.* 2012). Importantly, the operculo-insular cortex seems to be an epileptic focus in specific types of seizure, and lesions in this region correlate with the occurrence of a distinct central, neuropathic pain syndrome (Garcia-Larrea & Mauguière, 2018). The functional characterization of the human operculo-insular cortex relies on electrophysiological recordings, intraoperative stimulation, assessment of pathological conditions and functional neuroimaging (Garcia-Larrea & Mauguière, 2018). Notwithstanding, the specific functional role of operculo-insular cortex neuronal populations in the processing of each submodality of somesthetic sensation remains elusive. Recently, transcranial magnetic stimulation (TMS) was proposed as a promising technique for neuromodulation and assessment of the operculo-insular cortex (Lenoir *et al.* 2018).

Repetitive TMS (rTMS) has been employed for modulation of cortical circuits based on phenomena like long-term potentiation (LTP) and depression (LTD) synaptic plasticity. The direction of the plastic effect depends on physiological and experimental conditions, such as the intrinsic ongoing activity in the underlying neuronal circuitry, stimulation frequency and the presence of a paired stimulus. It is important to note that rTMS after-effects are still unclear and present high variability across individuals (Suppa *et al.* 2016). In some cases, rTMS can relieve the symptoms in sensorimotor, emotional and cognitive-behavioral syndromes. Specifically, high-frequency rTMS (10–20 Hz) in the primary motor cortex (M1) may increase the motor-cortical excitability and promote analgesia in chronic pain patients. However, a significant number of subjects are refractory to such treatment. Some research groups have proposed alternative protocols for analgesia in non-responders to rTMS in M1. The elaboration of these protocols requires an understanding of cortical neurophysiology and the physical characteristics of TMS activation.

TMS can stimulate neuronal populations in the cortex, using an intense magnetic pulse generated by a coil positioned in contact with the scalp. A rapid change in the magnetic field intensity induces an electric field, which in turn depolarizes the neuronal membrane and triggers action potentials. The electric field depth, focality and magnitude depend on the coil design, stimulation intensity and brain morphology, among other factors (Deng *et al.* 2013). Regardless of the coil design, deeper penetrating electric fields result in larger, less-focally stimulated areas. Most importantly, the induced electric field has a maximum magnitude at the surface and critically declines with depth. Thus, rTMS of deep brain structures is followed by the stimulation of superficial structures in a broader area and with significantly higher intensity. Such a trade-off has a fundamental implication on the outcomes of the technique.

Recently, Lenoir *et al.* (2018) published a study in *The Journal of Physiology* in which they investigated the modulatory effect of continuous theta-burst stimulation (cTBS) over the operculo-insular cortex on somesthetic functions of healthy subjects. The presented results are of great relevance to expanding our knowledge of the operculo-insular cortex functional role, and to evaluating the therapeutic potential of cTBS as an alternative method for treatment of chronic pain syndromes. The cTBS is a variation of rTMS and is characterized by a sequence of pulse trains applied at defined, fixed intervals (Suppa *et al.* 2016). Lenoir *et al.* demonstrated that cTBS modulation of the operculo-insular cortex activity affects the perception threshold of heat pain in humans without any changes in the perception thresholds of cold, warm or vibrotactile stimuli. A secondary outcome was to determine whether changes in thermonociceptive sensations are related to neuromodulation of superficial or deep operculum regions. The authors suggested that the observed modulation in heat pain perception is probably due to the activation of deep neuronal populations in the operculum, specifically the right operculo-insular cortex. Also, the results suggest a possible lack of laterality of thermonociceptive neurons for heat pain in the right operculo-insular cortex. Accordingly, the increase in thermonociceptive threshold induced by deep cTBS manifested bilaterally in both hands. This modulatory effect was observed only 20 min after the application of the protocol and was specific to stimuli transduced by thermal nociceptor Aδ-fibres. Furthermore, a positive correlation was observed between the cTBS stimulation intensity and the increase in heat pain perception threshold. Finally, the authors reported seizure and partial seizure in two out of 18 healthy

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subjects during the deep cTBS protocol in the operculo-insular cortex.

The results observed by Lenoir *et al.* reinforce the crucial role of the operculo-insular cortex in the processing of thermonociceptive inputs (Mazzola *et al.* 2012). However, the physical characteristics of TMS stimulation may hinder the interpretation of the neurophysiological mechanisms induced by the deep cTBS protocol. The authors employed a flat figure-of-eight coil with intensity adjusted to 80% of the first dorsal interosseous resting motor threshold to control for the superficial stimulation. In turn, deep stimulation was achieved by a double-cone figure-of-eight coil at an intensity of 80% of the anterior tibialis resting motor threshold. The difference in electric field distributions induced by both coil designs possibly activated the operculum regions with substantially distinct intensities in each protocol. Therefore, the changes in heat pain perception could have been achieved by two possible mechanisms: first, greater activation of the superficial operculum regions due to a broader, superficial electric field profile induced by the double-cone compared to the flat figure-of-eight coil (Deng *et al.* 2013), and second, the actual activation of deeper regions, such as the insula. Indeed, due to the TMS-induced neuronal activation characteristics, it may be speculative to attribute the observed effects preferentially to either of these possibilities. Furthermore, the stimulation target estimated by the linear projection of the coil centre to a concentric surface within the brain might misinform physiological interpretations of TMS application over the operculo-insular cortex. The linear projection is a good approximation in very specific brain areas where the local anatomy has a relatively smooth curvature and is approximately tangential to the coil plane. However, such projection might not be accurate for the internally folded operculo-insular cortex morphology, and the area of the maximum induced electric field might not necessarily be directly below the coil, hindering estimations of potential contributions of neighbouring cortical structures. Computing the electric field in the anatomical brain scans would possibly provide a better estimate of the differences in stimulation distribution over the brain with the cTBS protocols using two coil models. Computing the electric field is not trivial and does not indicate the threshold for TMS neuronal activation. Nonetheless, determining the electric field may support further interpretations of the concurrent stimulation of neighbouring cortical regions by analysing the intensity at which they were exposed.

The adverse effects reported by Lenoir *et al.* after cTBS are of the utmost concern for future directions and the safety of the technique. This is the first study to assess cTBS modulation over the operculo-insular cortex, and therefore the first account of seizures using this protocol. Curiously, subjects manifested some clinical symptoms of seizure which are not primarily related to the opercular-insular cortex, such as euphoric thoughts (Garcia-Larrea & Mauguière, 2018). Most importantly, to our knowledge, the observed adverse responses have been reported before any clinical trials in chronic pain patients have taken place, in which a possible presence of catastrophism and/or depression might worsen the consequences of seizure. Consequently, the cost-benefit ratio for testing the new protocols for neuromodulation of operculo-insular cortex using rTMS seems unfavourable. Therefore, considering the balance between the potential analgesic effect and the risks, especially seizure, high-intensity deep stimulation with cTBS might not be beneficial for patients. The risk of seizure induction added to the lack of a clear dissociation between the activation of superficial and deep operculum regions discourages further use of this methodological approach.

In conclusion, the study by Lenoir *et al.* (2018) significantly contributes to elucidation of the effects of cTBS in the operculo-insular cortex associated with somesthetic functions. Employing a deep cTBS protocol over the operculo-insular cortex specifically increased the perception threshold for heat pain related to thermonociceptive activation of Aδ-fibres. Interestingly, this result corroborates the view that populations of neurons in this cortical structure may be related to the sensory-discriminative component of heat pain in humans (Mazzola *et al.* 2012). In addition, the study has shown that deep cTBS over the operculo-insular cortex presents possible adverse effects and does not allow clear discrimination between the functional roles of superficial and deep neuronal populations. Therefore, future endeavours should be cautious about using new rTMS protocols for stimulating this area. Achieving analgesic effects in cortical structures other than M1 is still challenging and needed, but new protocols must be thoroughly tested and firmly based on physical principles and neurophysiological mechanisms. Lastly, monitoring and reporting adverse effects is fundamental to avoiding potential risks for subjects and researchers.

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Additional information

Competing interests

The authors declare no conflict of interest.

Author contributions

Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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