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

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**Running title:** TMS neuromodulation of operculo-insular cortex

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**Keywords:** Transcranial magnetic stimulation, operculo-insular cortex, pain syndrome, seizure, theta burst stimulation, insula

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 named as operculum (lid). 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 correlated with the occurrence of a distinct central, neuropathic pain syndrome (Garcia-Larrea & Mauguière, 2018). The functional

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characterization of the human operculo-insular cortex relies on electrophysiological recordings, intraoperative stimulation, pathological conditions assessment, 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).

The 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 indefinite and present high variability across individuals (Suppa et al., 2016). In some cases, rTMS can relieve the symptoms in sensory-motor, 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 is refractory to such treatment. Some research groups proposed alternative protocols for analgesia in non-responder to rTMS in M1. The elaboration of these protocols requires the 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, brain morphology, among others (Deng *et al.*, 2013). Regardless of the coil design, deeper penetrating electric fields compromise on larger, less-focal stimulation areas. Most importantly, the induced electric field has a maximum magnitude in 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 trade-off has a fundamental implication on the outcomes of the technique.

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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 expand the knowledge of the operculo-insular cortex functional role, and to evaluate the feasibility of cTBS therapeutic potential as an alternative method for treatment in chronic pain syndromes. The cTBS is a variation of rTMS and is characterized by a sequence of pulse trains applied in 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 perception threshold of cold, warm or vibrotactile stimuli. A secondary outcome was to discriminate 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 likely 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 minutes after the application of the protocol and specific to stimuli transduced by thermal nociceptors A $\delta$ -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 healthy subjects during the deep cTBS protocol in the operculo-insular cortex.

The results observed by Lenoir et al. reinforce the crucial role of 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

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broader, superficial electric field profile induced by the double-cone compared to the flat figure-of-eight coil (Deng *et al.*, 2013). 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 any of these possibilities. Furthermore, the stimulation target estimated by the linear projection of the coil center to a concentric surface within the brain might mislead the physiological interpretations for the 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 potential contributions of neighbor cortical structures. Possibly, computing the electric field in the anatomical brain scans would provide a better estimate of the differences in stimulation distribution over the brain by the employed cTBS protocols with each coil model. Computing the electric field is not trivial and does not infer about the threshold for TMS neuronal activation. Nonetheless, the electric field may support further interpretations of the concur stimulation of neighbor cortical regions by analyzing the intensity at which they were exposed.

The adverse effects reported by Lenoir *et al.* after cTBS are of utmost concern to the future directions and safety of the technique. This was the first study to assess the cTBS modulation over the operculo-insular cortex, and therefore the first account of seizure with 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 were reported before any clinical trial in chronic pain patients, in which a possible presence of catastrophism and/or depression may worsen the consequences of seizure. Herein, the cost-benefit ratio for testing the new protocols for neuromodulation of operculo-insular cortex with rTMS seems unfavorable. Therefore, the balance between the potential analgesic effect and the risks, especially seizure, induced by high-intensity deep stimulation with cTBS might not be beneficial for patients. The risk of seizure induction added to the unclear dissociation between the activation of superficial and deep operculum regions discourage further use of the latter methodological approach.

In conclusion, the study by Lenoir et al. significantly contributed to elucidate the effects of cTBS in the operculo-insular cortex associated with somesthetic functions. The employed deep cTBS protocol over the operculo-insular cortex specifically increased the perception threshold for heat pain related to thermonociceptive activation of A $\delta$ -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, deep cTBS over the operculo-insular cortex presents possible adverse effects and hinders the discrimination between superficial and deep neuronal populations functional roles. Therefore, future endeavors should be cautious with new rTMS protocols for stimulating this area. Finding analgesic effects in cortical structures other than M1 is still challenging and needed but must be thoroughly tested with strong grounds on physical principles and neurophysiological mechanisms. Lastly, monitoring and reporting adverse effects are fundamental to avoid potential risks for subjects and researchers.

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