

The experience of pain plays a crucial role in our daily life. In normal conditions, painful sensations warn us of potential or actual threats, which can harm our tissues and compromise our bodily integrity. Thanks to this experience, we develop appropriate protection behaviours, and the aversive aspect of pain may condition the learning we can draw from pain.

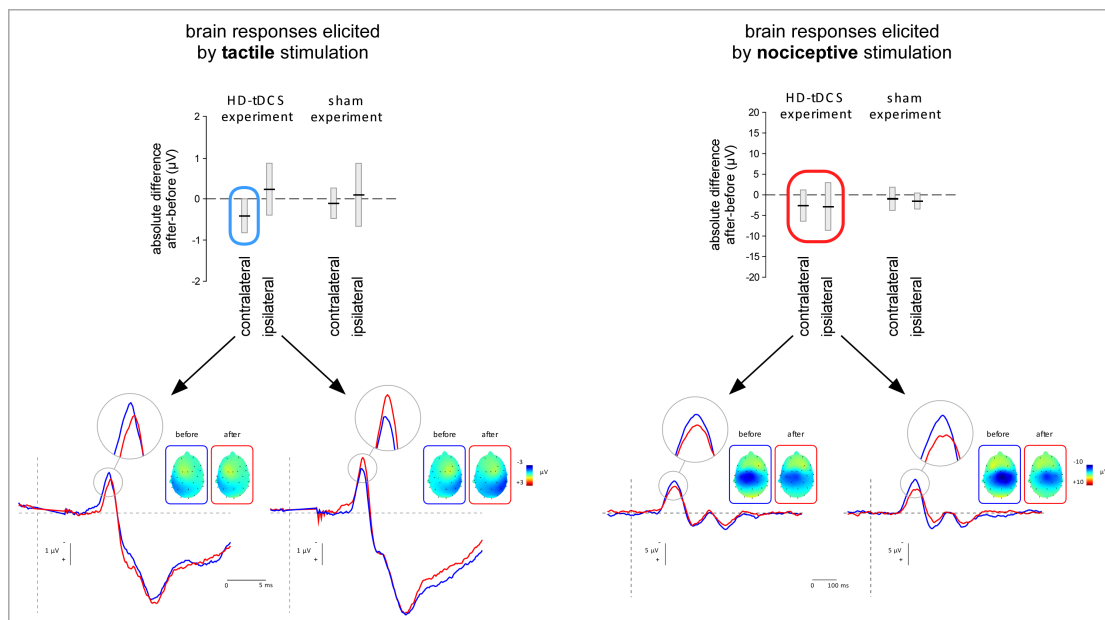
Pain is a complex experience resulting from the integration of several dimensions such as sensory, emotional, affective and contextual. Regarding the sensory aspect, pain may result from the activation of peripheral receptors called *nociceptors*, which are activated by different types of potentially harmful stimuli (thermal, mechanical or chemical). This nociceptive information is then interpreted at the central level and may lead – but not necessarily – to a conscious percept of pain. The term *nociception* refers to the neuronal encoding and processing of the activity resulting from the activation of these nociceptors. This has several implications. First, pain cannot be considered as a sensory modality per se, contrary to touch, vision or audition for which modality-specific receptors and primary cortices are identified. Secondly, the central processing and interpretation of a nociceptive stimulus highly depends on cognitive factors such as attention, emotion and past experiences and does not unequivocally lead to the perception of pain. Finally, it is possible to study the nociceptive system by the means of stimuli designed to selectively activate nociceptors and which do not elicit pain. This is why the conclusion of our work can refer to nociception or pain depending on the design of the study and the considered outcome.

To date, a specific cerebral activity responsible for the emergence of a transient painful experience has not been characterized. One of the aims of fundamental research in the field of pain is to better understand how the emergence of a painful experience is created by the central nervous system (CNS) and how this experience can be modulated.

It has been repeatedly observed that a set of brain regions, including the insular, the anterior and mid cingulate, and the secondary somatosensory cortices and, to a lesser extent, the primary somatosensory cortex, are activated when an individual is perceiving pain¹. This observation has led to the concept of a *cerebral pain signature* comprised of the global activation of these regions². Importantly, it has been shown that non-painful external stimuli – as salient as painful ones – elicit the same pattern of brain activity³. This observation refutes the existence of a pain-specific brain response, and suggests that the brain network activated by transient painful stimuli could reflect processes involved in the detection of stimuli which stand out from the environment, regardless of whether they are painful. If we assume that the same set of brain areas is activated by salient nociceptive and non-nociceptive stimuli, do these areas play a similar role in both cases? Related to this question, our project aims to characterize the specific and respective involvement of different brain regions such as the primary somatosensory (S1) and the insular cortices in nociceptive processing as compared to innocuous sensory processing. We developed a novel approach to address this question, combining functional neuroimaging techniques (such as electroencephalography [EEG] and functional magnetic resonance imaging [fMRI]) with non-invasive focal neuromodulation techniques (such as high-definition transcranial direct current stimulation [HD-tDCS] or transcranial magnetic stimulation

[TMS]). The general idea is to sample behavioural (perception, quality of sensation) and brain responses elicited by non-nociceptive and nociceptive somatosensory inputs before and after affecting the cortical excitability of a given brain structure. This approach is often called “lesion like paradigm”.

In a first study⁴, we investigated the role of S1 in the processing of different somatosensory stimulations. The role of S1 in touch is well established⁵. In contrast, its involvement in nociception remains debated⁶. We tested whether S1 is similarly involved in the processing of non-nociceptive (vibrotactile) and nociceptive (laser) somatosensory input in humans by comparing the after-effects of HD-tDCS of the hand representation of S1 on the perception and brain responses elicited by non-nociceptive and nociceptive somatosensory stimuli delivered to the ipsilateral and contralateral hand. We observed that modulating S1 significantly affected the responses to non-nociceptive somatosensory stimuli delivered to the contralateral hand. These results support the notion that S1 constitutes an obligatory relay for the cortical processing of non-nociceptive tactile input originating from the contralateral hemibody. Contrasting with this asymmetric effect of HD-tDCS on the responses to non-nociceptive somatosensory input, HD-tDCS over S1 led to a bilateral and symmetric reduction of the magnitude of the nociceptive evoked brain responses elicited by laser stimulation of the hand dorsum (see figure). Taken together, our results demonstrate, in humans, a differential involvement of S1 in touch and nociception.



Effect of HD-tDCS on early brain responses elicited by tactile and nociceptive stimulations delivered on the contralateral and ipsilateral hands relatively to the primary somatosensory cortex onto which HD-tDCS was applied. Note, after HD-tDCS, the asymmetric reduction of brain responses elicited by non-nociceptive stimulation of the contralateral hand and the symmetric reduction of brain responses elicited by nociceptive stimulation of the contralateral and ipsilateral hands.

In a second project, we tested whether affecting the excitability of the insular cortex would lead to a modification of the perception elicited by different types of somatosensory stimuli. In this study a specific repetitive TMS protocol referred to as continuous theta burst stimulation (cTBS) was used to affect the excitability of the insula. There are several reasons to believe that pain could be modulated by cTBS of the insular cortex. Studies have shown that the insular cortex is a main target of ascending spinothalamic input⁷, which convey nociceptive inputs. More precisely, the posterior part of the insular cortex appears to be preferentially involved in processing nociceptive input⁸. Moreover, lesions of the insula have been shown to affect thermal and pain perception⁹, and direct electrical stimulation of the posterior insula can elicit painful sensations in humans¹⁰. Based on previous results¹¹ showing the feasibility to deliver repetitive TMS over the insula using a TMS coil designed to target deep cortical structures, we applied neuronavigated cTBS over the right posterior operculo-insular cortex. We assessed thresholds and perception elicited by four different types of transient somatosensory stimuli (low and high temperature laser, cold and vibrotactile) before, immediately after, and 20 minutes after cTBS.

We observed that after cTBS over the right insula, the threshold to detect laser stimuli with reaction-times compatible with A δ -fiber first pain delivered to the left hand was significantly increased 20 minutes after cTBS. The intensity of perception of A δ -fiber first pain was significantly decreased. Thresholds and perceptions of the three other somatosensory stimuli were not significantly affected. Our results support an involvement of the operculo-insular cortex in the processing of painful thermal nociceptive inputs conveyed by the spinothalamic tract.

Our results provide further clarifications on the involvement of brain areas engaged in nociceptive processing. This could constitute the basis for future clinical investigations. A better understanding of the central organization of nociceptive processing may help to build neuromodulation approaches for pain relief in chronic pain patients for instance.

References:

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