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One-sentence summary:

If a thermosensory and nociceptive cortex exists in the human brain, then the operculo-insular cortex is the best candidate.

The operculo-insular cortex is the only brain region where a direct electrical stimulation can produce a pain sensation. In this cortex, an optimal response can be recorded after a noxious stimulation. It is the most consistently activated region in functional imaging. It is selectively associated with painful symptoms in insular epileptic crises. Finally, a unique lesion in the operculo-insular cortices is enough to remove both thermosensory and nociceptive functions.

Abstract

In spite of systematic investigations, the existence of a specific cortex that could encode for the intensities of somatosensory stimuli, including within nociceptive ranges, is still a matter of debate. The present consensus is that pain is expressed in a distributed network made of thalamus, SII, insula, ACC, and, less consistently, SI. Here we argument that there must be an entrance to this network. The common denominator to every functional imaging study is that the subjects can distinguish between noxious and non-noxious stimuli, or between two different intensities of noxious stimuli. This is associated with a consistent activation of the insula-SII cortices while activations in other brain areas may be missing or sub-significant. In other words, the operculo-insular cortex activations are the most robust pain-related activations across studies, whatever the manipulation of the pain components, except the discriminative one. Intra-cerebral recordings also pointed out this piece of cortex as being able to encode for pain intensity. As a last physiological argument, stimulating directly the brain with small intensities standardized electrical shocks elicited pain sensations selectively if the electrode was in the operculo-insular cortex. Human models of disease confirmed that epileptic discharges in the insular cortex can produce ictal pain. Insular epilepsy (or propagation of discharges to the insular cortex) is the only focal epilepsy to be possibly associated with painful symptoms. Finally, unique and focal lesions of the posterior operculo-insular cortices were able to remove (or at least to impair) thermosensory and nociceptive functions. Thus, the operculo-insular area can be presented as the only area in the brain to respond to the features of a primary thermosensory and nociceptive cortex. This area is likely to be the starting point of the nociceptive-related networks. Future investigations are necessary to determine how this “pain symphony”

between these different brain areas is temporally orchestrated. Developments of new targets for functional neurosurgery could benefit of such localized and initiating processes, for instance focal neurostimulations.

Introduction

After more than fifty years of a sustained research dedicated to identify the brain areas that encode for pain in humans, here we propose an updated opinion on how the operculo-insular cortices could assume in the brain the function of encoding thermosensory and nociceptive information. The first observation is that searching to evoke a pain sensation by direct electrical stimulation of the human cortex has remained fruitless for several decades. Nevertheless, Penfield and colleagues have used extensively per-operative stimulations of the human cortical surface for functional mapping in a large sample of awake patients. They concluded that the degree of pain elicited by stimulating the human cortex 'is so slight as to cause one to wonder if the use of the term is not a misnomer' [1,2]. In the 80's, structures that were hypothesized to mediate such functions were those identified for lemniscal somato-sensory functions, namely, the lateral thalamus, the primary somatosensory cortex (SI), and, possibly, the secondary somatosensory cortex (SII). Only a few studies with surface electrodes or direct intra-cerebral recording demonstrated nociceptive responses in SI [3–8]. Functional imaging showed that during painful stimuli, thalamus and SI cortex were inconsistently activated across studies (approximately 50% of them) [9–11]. In the same time, the frequent activations that were found in the anterior cingulate cortex (ACC) [10–13] supported the view for almost one decade that ACC could be the major site of integration of pain sensation. This had been supported by a few confirmations of deep brain recording showing that ACC neurons may respond to noxious

events [16–18]. For the ensuing decade, the search of different modulations of the pain perception led to the concept of the 'pain matrix' that included several areas interacting together and making the modulations possible. Because no one could agree on what it is constituent of, and how it can/can't be manipulated [19], this keyword progressively disappeared. However, it may be useful to describe with a single word all the brain areas that are generally activated in various conditions of experimental pain without presuming a functional significance. In this paper, it is in that sense that we use this term.

Only recently, in retrospect, with the results of meta-analyses and reviews, it could be shown that the most consistently activated brain region across pain studies was not the ACC but the operculo-insular cortices [9,20,21]. This cortex was also found to be the main area in the brain to be still activated if pain components (except the discriminative one) were experimentally manipulated [22–26]. The operculo-insular cortex may thus appear as the common denominator to different experiments having as a constant, the ability to discriminate between one stimulus above pain threshold and one stimulus below the pain threshold or between two levels of pain intensities [9,27]. In addition, modulations of pain intensity perception were associated with a resulting change in operculo-insular activity [22–26]. However, because the accurate anatomy and functions of this cortex were not well circumscribed due to its position close to the complex vasculature of the sylvian fissure, functional imaging had been limited to conclude on the real meaning of the observed operculo-insular activations. For these reasons, the importance of this operculo-insular cortex in pain processes has probably been underestimated at the beginning of functional imaging. Several lines of evidence in humans further reinforce this interpretation:

Thanks to collaborations with departments of epilepsy neurosurgery, we have had the opportunity to collect many information on pain processes directly in the brain through brain electrodes and other neuroscientific approaches. This was in our group a unique opportunity to cross validate information obtained with different sources and different techniques. Using intracortical recordings to noxious laser stimuli but also by stimulating directly on these electrodes located in the operculo-insular cortex, it was possible either to record a clear nociceptive response [28–30] or to elicit a painful sensation [31] respectively. These data have been replicated by other groups for direct stimulation [29], and, more recently for direct recordings [32–34]. These last studies have argued that the activity evoked in the posterior insula was not at all specific to pain, but may be merely due to the salience aspect of any stimuli, and that observed responses overlap across stimulus modalities. However, very recent data based on correlational analysis approach, informed by an experimental design with graded stimulus intensities and matched stimulus salience, have illustrated the clear dissociation of systems involved in pain and sound processing [35]. The results showed that the operculo-insular cortex is critically linked to pain, and not to sound stimuli for instance. Taken together and from a very general (physiological) point of view, these data all concur, to present the operculo-insular cortices as a major structure for thermosensory, nociceptive and pain integration, including activity within the nociceptive range [9,19,20].

We propose that this cortex could represent the physiological entry in a complex neural network that has been described previously as the “pain matrix”, “pain signature”, “pain connectome” or even the “saliency network”. We consider that beyond strictly nociceptive processing, these activities also incorporate functions such as motor withdrawal

from pain, attention to pain, anticipation, memorization, habituation or other functions. Clinical data are convergent with this view since it has been recently argued from epilepsy patients, that a discharge born (or propagated) to the insular cortex was frequently associated with pain symptoms, and, conversely, that a discharge elsewhere in the brain did not [36–38]. Finally, lesion models demonstrated that unique and localized infarcts in the posterior operculo-insular cortex could associate not only an increase of thermosensory discrimination thresholds, but also an increase of nociceptive threshold, demonstrating that a lesion here could induce a loss of function, including the nociceptive one [39–41].

Arguments from physiology

Functional Imaging

Functional imaging was first applied to the study of pain in the early 90's, with the hope to identify and to localize the brain areas that were involved in pain processes. At that time, predictions were almost speculative because our knowledge in the field of cortical contributions to pain were rather scattered. The main candidates were SI, thalamus, and possibly Anterior Cingulate Cortex (ACC). These hypotheses were based on animal studies performed with direct recordings showing some nociceptive neurons in SI [3,42], but also in VPL nucleus of the thalamus [43], and in the area 24 of the ACC [44]. Based on these hypothesis, the two first PET studies revealed activations in SI [45], ACC [45,46], and thalamus [46], but also in two areas that were less expected, lenticular nucleus [46] and SII [45]. Then, a large number of functional imaging studies have investigated and described the so-called "pain matrix" or "pain signature" in the brain. These studies have almost all

been considered at the time of meta-analysis or reviews on pain [9,11,19,20]. First, it can be argued, that the anticipated candidates that should respond to pain were SI, ACC, and thalamus, and they were only inconsistently recruited in physiological pain conditions [9,21]. A second result in this overview of pain processes is that the most consistent responses across studies were located, bilaterally, in the operculo-insular cortices [9,20,21]. Since all these studies have in common that they compare two balanced conditions, one above and one below the pain threshold, it can be assumed from this first level of synthesis, that the operculo-insular cortices are decisive for the relative discrimination of two levels of pain (or sensory) intensities [9,19,25]. Then, functional imaging studies were designed not only with a descriptive purpose but also with the aim to determine the functional significance of the observed activations. To this aim, different contexts or different modulations were introduced in the experimental designs in addition to the thermal, laser or electrical noxious stimulations. Experiments have been successively conducted to dissociate the pain intensity coding component from other components such as attention [47–49], emotional, fear and anticipatory [50], memory [22,51], cognitive [52], motor [53] or autonomic [54,55] components. This is not an exhaustive list of what has been investigated. The particular point to all of these studies was that a consistent response, whatever the context or the modulation, was observed in the operculo-insular cortex. In extreme cases, for example, after removing the attentional factor associated with an intrusive stimulation (what could also be called the “saliency” of the stimulation), pain-related activations were restricted to these areas [47].

In modulations studies, a specific network [19,27] was generally recruited, according to the modulatory input that was used, but the activations of the operculo-insular

cortices were generally modified in parallel with the perceived changes in pain intensities [22–25]. These results suggest that the core activation in the brain, regardless of both the context and the modulations could be located in the operculo-insular cortices, bilaterally, with the physiological function of encoding how much it is painful and/or to distinguish between painful and non-painful stimuli [19,21,22]. As far as we can know, this view can accommodate all the results of previous studies and it has been further validated by experiments investigating specifically the relationship between brain activations and pain intensity [24]. At least three studies were consistent to point out the operculo-insular cortices as possibly encoding for pain intensity to heat [12] or cold [56] stimuli, in a linear fashion, or with a (non-linear) stimulus-response function [57]. Interestingly, in two of these studies, the areas with such a pattern of activation were restricted to the operculo-insular cortex [56,57]. From this core of activations in the areas receiving nociceptive inputs, it was proposed a multi-level processing of pain with interacting networks of relevant brain regions organized hierarchically [27]. More recent efforts have applied multivariate pattern analysis to decode hundreds of pain imaging datasets to identify which regions within these networks are specific to nociceptive-driven "physical" pain. Thalamus, posterior insula, anterior insula, SII, ACC, and the PAG are the brain regions described as the "pain signature" [21,58,59]. More recently, overlapping/interacting networks can be described dynamically with new imaging tools as a "pain connectome" [60].

To summarize the data obtained with functional imaging, the discriminative component of a physiological pain seems to involve primarily the operculo-insular cortices, this activity resisting to contexts or modulatory influences on pain perception. In experimental conditions, this cortex can be the only one to respond to noxious events [47],

but in no case, it means that the operculo-insular cortex is specialized or specific to nociceptive processes. Whatever the sophistication of experimental paradigms, the main limitation of functional imaging is to determine whether or not the observed activations are contingent or causal of the studied process, in other words, to determine the precise functions underlying the observed activations. The introduction of other techniques in our field of expertise has been a unique opportunity to precise what the observed activations could mean.

Brain recordings

Twenty years after the onset of the use of functional imaging in pain studies, interpretations of the results have received a powerful support from other techniques or observations that have been applied in humans. Series of data recorded with electrodes implanted throughout the brain have examined the issue of brain areas giving a synchronized electrical response to noxious laser stimulations [29,30,32–34,61–64]. Patients had these explorations as a part of their pre-surgical evaluation for medically refractory epilepsy with the aim to record epileptic discharges and propagations to monitor neurosurgical resection. Although several brain regions have been described as providing responses to noxious stimuli including in amygdala [61,62] or in primary motor cortex (M1) [8], these brain responses were not well synchronized or they were late or uncorrelated to the intensity of perceived pain. Previous studies using subdural grids identified nociceptive responses on the surface of the brain [63] around the parietal operculum. The main step to describe these responses was achieved as a nociceptive laser

evoked potential (LEPs) was described as a reliable response in the depth of the operculo-insular cortex after a noxious laser stimulation [29,64]. For the first time, it was also shown with intra-cranial LEPs that the operculo-insular response, consistently reported across pain studies, was actually made of two distinct responses in SII followed by a second one in the posterior insular cortices: stimulus response functions were found to be different since the SII cortex would almost encode for perception while the insular cortex would almost encode for more extreme pain intensities [30]. These data were recently complemented by similar recordings in the insular cortex of epileptic patients [32–34]. In their first experience, Liberati et al., (2016) [32] failed to distinguish thermal nociceptive field potentials from other multimodal activities but more refined investigations in gamma band oscillations succeeded in doing it [33]. Unfortunately, these activities that were robust for thermal intensity perception [34], could be dissociated from pain perception in case of repetition of thermonociceptive stimulation. Taken together and from a very general physiological point of view, these data all concur, to present the operculo-insular cortices as a major piece for thermosensory processes, including within nociceptive ranges, and for pain integration. One needs to emphasize that these studies are very challenging, based on small sample sizes (6, 9 and 6 patients respectively [32–34]), exploring discrete and limited brain areas because of the number of contacts and the incidence of electrode targeting. For instance, there was a major difference in brain sampling between Liberati's group and our group since they mostly sample the anterior insula while we mostly sample SII and the posterior subdivisions of insula. Given the physiology and the anatomy of the operculo-insular cortices, it is difficult to consider that these differences cannot have any impact on what is observed.

Such information that cannot be recorded with functional imaging because of the absence of clear border between SII and insula have been defined on the basis of the source localization across the sylvian fissure. These information together with the recently published details on the structural anatomy of the insula and SII areas [65,66], benefit to an accurate localization of the nociceptive responses in this area and to the dissociated activations of SII and insula. A major challenge for future investigations will be to obtain more precise spatial and temporal patterns of nociceptive responses within this operculo-insular areas.

Brain stimulations

Investigations of brain functions in the operculo-insular cortices would not have been complete if direct stimulation of the brain had not been performed. There have been many functions reported as being integrated within the insular cortex. Gustatory [67,68], autonomic [69,70], interoceptive [71,72], emotional [73,74], cognitive [75,76] or empathetic processes [77–80] have been shown to activate the insular cortices (see [38,81]). This is not, by far, an exhaustive list of insular functions. However, the thermo-sensory is one of the most represented function in the posterior subdivisions of this area, and stimulating this area may be associated with thermal and/or pain perception [37]. A strong evidence for a relatively specific participation of the operculo-insular cortex in pain processes is that, over more than 4000 calibrated stimulations delivered everywhere in the brain, only the 60 delivered here could induce a painful sensation [31]. Considering the 558 stimulations delivered in this area, up to 11% of them were able to induce pain sensation,

while we are not aware of any stimulation everywhere else in the brain that could consistently induce painful or even unpleasant sensations. If we take into account that stimulations were not designed to elicit pain, and that stimulation procedure was stopped as soon as a first somato-sensory sensation was reported by the patients, we can assume that this incidence of pain induced by stimulation is the minimal observation. Thus, this cortical area appears as a major site for the integration of physiological pain intensity and for pain discrimination.

Arguments from diseases

To investigate dysfunction in pathological states is far more difficult, mainly because lesion that cause disease is not necessarily the same from one patient to the other, but also because patients may have different individual strategies against pain. However, we can assess general trends in patients and common denominators to different kind of pain or common denominators to pathological and physiological pain. We would like to emphasize on 3 models of disease that corroborate the view that has been presented above.

Lesions

It is a common method in experimental neuroscience to confirm that a given function has been damaged after lesionning the site(s) where the function is supposed to be assumed. An impairment (or the absence) of the function after a selective lesion in animal models is generally the demonstration that the region exerts the studied function. Here we would like to emphasize on clinical situations that could be considered as human models of pertinent lesions. These are a few but demonstrative case-reports of unique and selective lesions involving the operculo-insular regions that simultaneously impaired thermal and

nociceptive functions [39–41,82,83]. Similar observations also exists after selective lesions of their afferences, particularly brainstem and thalamic inputs [27,84–91]. In the acute phase of their lesion (stroke), these patients have evidence of somato-sensory dysfunctions including within painful ranges, since their warm and cold perception threshold is generally increased as well as their pain threshold, what defines a loss of thermal and nociceptive functions [39].

Epilepsy

It is also a common method in neuroscience to consider that overactivity in a given area may drive to an increase of symptoms related to the afferent function. Until the insular epileptic syndrome has been revisited, it was a widely accepted assumption to relate pressure sensation or painful paresthesiae to parietal lobe epilepsy [92,93]. The recently re-discovered insular epileptic syndrome [37,94,95] clearly shows a high frequency of thermosensory and painful events during spontaneous epileptic discharge or discharge propagation to the insular/SII cortices. Thus, pain symptoms are rare in epilepsy but when present, these symptoms clearly oriented towards the insular/SII cortex, in agreement with the very early (but forgotten) reports of such functions in humans [1].

Neuropathic pain

After a lesion somewhere along the spinothalamic tract, patients may have an initial loss of thermal and nociceptive functions (see above). Then, they have various amount of recovery of these functions after a delay that is supposed to give rise to plastic phenomena. Unfortunately, approximately half of these patients have concomitant painful sensations arising during this phase of recovery. This is a disease called central neuropathic pain and it

has been demonstrated for example after lesion in lateral-inferior thalamus [96], but also in Wallenberg's syndrome [90,97], or after a lesion in the cortical and subcortical projections of this tract in the operculo-insular cortex [39]. This kind of plastic reorganizations leading to an impaired function is not specific to sensory and pain domains since visual hallucinations are commonly encountered in acquired blindness [98], tinnitus is frequently observed after partial or total deafness [99], olfactory hallucinations may occur after lesions of olfactory bundles [100], and therefore, it is quite conceivable that somato-sensory and/or painful sensations may occur after sensory-nociceptive deprivations. Such an original hypothesis on the onset of neuropathic pain as productive manifestations of a deafferented cortex may be argued by plastic changes that have been reported during allodynic pain, mainly in the operculo-insular cortices [87,88,101–105]. Even though these functional changes may show minor differences from one study to the other, they can concur to produce such a distortion between an innocuous input and a noxious perception, if one keeps in mind that an abnormal activity in this area may lead to a painful sensation.

Conclusions

Even though there have been many studies showing distinct activations in the brain in response to painful stimuli, recent findings obtained in physiological conditions but also in diseases argue in favor of a specific and major contribution of the insular and SII cortices to thermosensory and pain processes. After a lesion in this area (or on its afferents), plastic changes, that still are to be specified in functional imaging studies, may develop and drive

to some kind of “hallucinatory” experience of this thermosensory and pain cortex that we called neuropathic pain, including allodynic sensations.

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Figure captions

Figure 1:

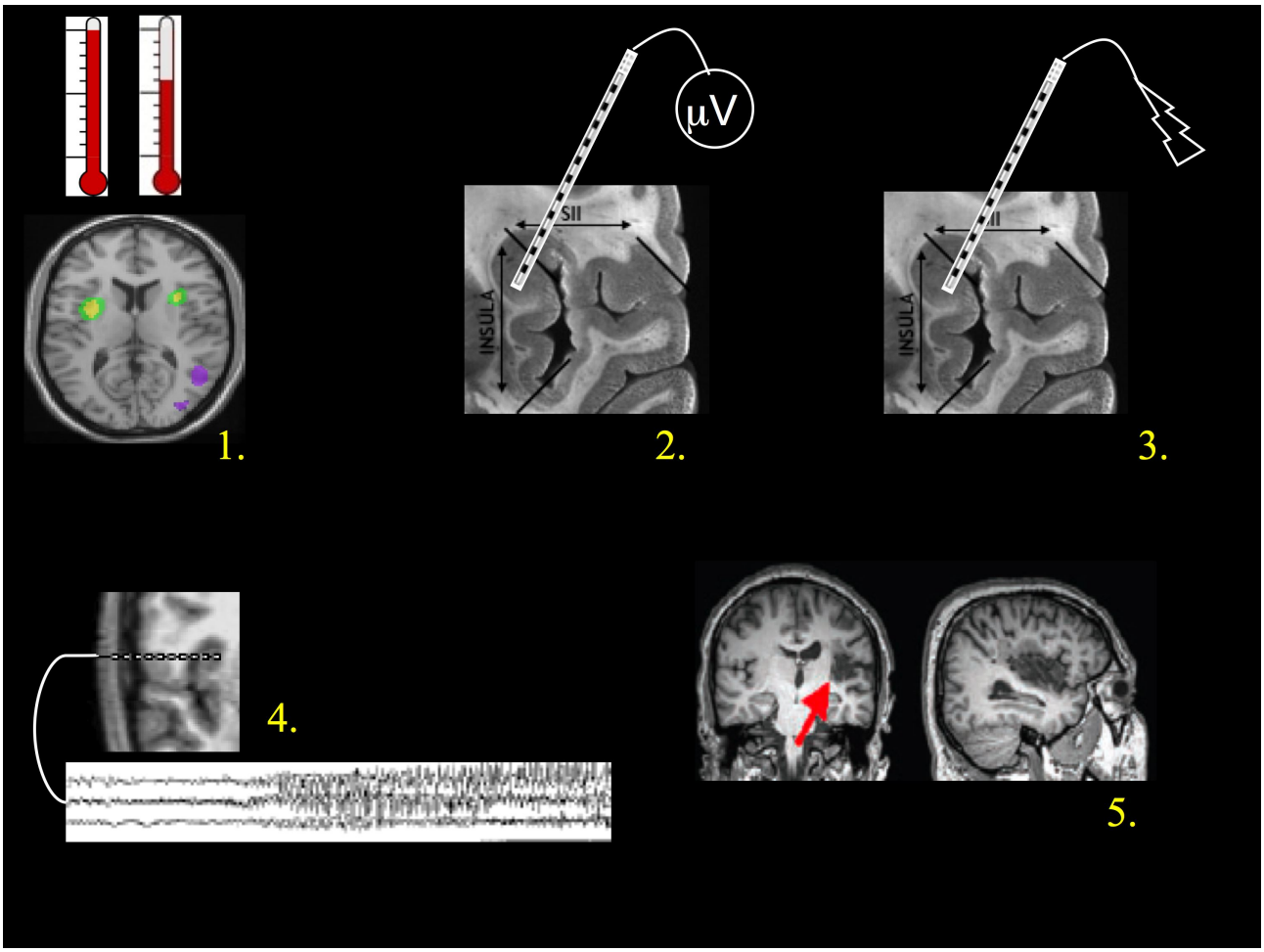
1. Superimposed onto a structural MRI, brain activations extracted from PET data by the comparison between two thermal stimulations (one painfully hot and the other warm) delivered on the right hand (neurological convention). In particular conditions for attentional load, the cortical activations may be restricted to the insular/SII cortices, bilaterally [47].

2. Direct recordings through intra-cerebral electrodes implanted in the insular and SII cortices, after a laser noxious stimulation of the hand (from [30]). This experiment allowed to reproducibly collect a Laser Evoked Potential (LEP) with two distinct responses, one in the insular and the other in the SII cortex.

3. Direct electrical stimulation of the brain never induced pain sensations except when electrodes were located in the insular/SII cortex. In that case, stimulation-induced painful events reached a frequency up to 11% [31].

4. In this disease, epileptic discharge or propagation arising from the operculo-insular cortices may be associated with a pain sensation. This is true either for spontaneous discharge or for pain elicited by a local electrical stimulation.

5. In this second disease, an isolated and unique lesion in the operculo-insular cortices was associated with a contralateral impairement of thermosensory and nociceptive function. In a various proportion of cases, patients with this kind of lesion or a lesion on its afferences may develop during recovery, abnormal or exagerated pain that are defined as neuropathic pain.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