Pain Myths and the Genesis of Central Pain

Despite clear advancements in our understanding of the genesis of central pain (CP) [1,2], four notions continue to stand out in the neuropathic pain literature that—we will argue—must be thoroughly revised, if not discarded. We will refer to them as Pain Myths.

Myth 1: Pain Matrix

In light of the supposed failures of cortectomies or thalamotomies to relieve phantom percepts and pain, Melzack [3] proposed that the anatomical substrate of the physical self is a network of neurons that extends throughout widespread areas of the brain (Neuromatrix). The repeated cyclical processing and synthesis of nerve impulses in the neuromatrix imparts a characteristic pattern (neurosignature) produced by the pattern of synaptic connections in the entire neuromatrix. Neuromodules of the matrix are dedicated to process specialized sensory events, which impress subsignatures on the larger one. This active neuromatrix, when deprived of modulating inputs, produces an abnormal signature pattern that subserves the different qualities of, e.g., neuropathic pain. Ever since 1991, many investigators concluded that the neurosignature of pain is dependent on a core neuromodule of four cortical areas: primary somatosensory cortex (SI), secondary somatosensory cortex (SII), insula and anterior cingulate cortex (ACC), the so-called pain matrix (e.g., [4]).

A review of imaging studies concluded that "acute physiological pain and neuropathic pain have distinct although overlapping brain activation patterns, but there is no unique "pain matrix" or "allodynia network"" [5]. Importantly, conclusive evidence [6] has emerged that this so-called pain matrix is actually a multimodal network related to the detection of and reaction to salient sensory inputs, regardless of whether these sensory events are conveyed by nociceptive pathways or are perceived as painful: "the neural activity recorded in the so-called 'pain matrix' cannot be considered as a direct correlate of the conscious perception of a somatosensory stimulus as painful" [7], but rather reflects non nociceptive-specific cognitive processes. The neuromatrix construct as a possible substrate for the maintenance of neuropathic pain (NP) collapses on the simple observation that focal parietal brain lesions can abolish NP, often permanently, i.e., NP is sustained by a focal parietal brain generator. Focal lesions abolishing CP of both brain and cord origin are reviewed in Canavero and Bonicalzi’s study [1] (pp. 238–240). Lesions abolishing phantom percepts, including pain [8–13], are reviewed elsewhere [14]. Other less detailed cases are on record [15,16]. Similar disappearances are also found for other peripheral NPs (PNPs). Canavero et al. [17] reported on a temporary abolition of trigeminal anesthesia dolorosa following a minor parietal sensory cortex iatrogenic cerebrovascular accident. Benbow et al. [18] reported on a 50-year-old female patient suffering diabetic PNP. She experienced sudden left hemiparesis and hemianesthesia, the latter resolving within 48 hours and the former within 3 months. Pain in the left foot resolved completely (Visual Analog Scale 0) after recovery of hemisensory loss, whereas the right foot pain was scored at VAS 5.5. A computerized tomography scan, previously reported normal, showed a right anterior thalamic, a right pontine and a right parieto-occipital cortical lesions.

Thus, a lesion along the parieto (SI)-thalamic axis can stop NP, be it central or (likely) peripheral.

This focal generator has—of course—brain-wide repercussions, altering the resting state networks of the brain along the connectome [1,19,20]: these can be viewed as "ripple effects" of the primary focal event.

Myth 2: Insula and Ventromedial Posterior Thalamic Nucleus (VMpo)

According to Dr. Craig and other researchers, a cold-signaling interoceptive, Aδ spinothalamic tract (STT) path from spinal lamina I (LI) to the VMpo to thermosensory (cold-recipient) dorsal mid/posterior insula (which then modulates brainstem thermoregulatory stations) normally inhibits a medial heat-pinch-cold (HPC) nociceptive STT path (from multimodal cells receiving input from C fibers) passing from LI through the mediadorsal ventral thalamic nucleus en route to ACC. In CP patients, a lesion of the cold path disinhibits the medial path, with cold allodynia and deep burning pain being selectively felt in the ACC, with activation of homeostatic behaviors. Cold allodynia would be due to impairment of thermal sensibility [21]. According to Craig [22], the anterior insula “instantiates all subjective feelings from the body and feelings of emotion.” According to Harris [23], pain is the bodily response to a discrepancy: CP would thus be due to an amplification of the thalamic/posterior insular response to pain due to discrepant sensory input. Kim [24] concluded that “disconnection between the thalamus and SI area and subsequent reorganization process seem to be
Commentary

responsible for the CPSP in patients with DIPS (dominant impairment of primitive sensation).” Garcia-Larrea et al. [25] emphasize how “The importance of thermal sensation deficits in central pain is the basis for the hypothesis that lesions of spinothalamic pathways, including their cortical projections, are necessary (although not sufficient) for central pain development . . . In the cortex, this necessary condition appears to be present only in lesions of the posterior operculo-insular cortex, which puts patients with such lesions at higher risk of developing a painful syndrome . . . Insular pain networks . . . might form . . . a third somatosensory area.” In fact, cases of central post-stroke pain (CPSP) following insular injury are on record [1]. Bowsher [26] too suggested that “it would be worthwhile . . . looking to the (insular) cortex for the explanation/seat of spontaneous pain following stroke.” The emphasis on insula also stems from the clinical observation that painful sensations from direct cortical stimulation are elicited in roughly 10% of all SI and insula stimulations (both in the same amount), whereas SI stimulation never gave rise to pain reports [27]; see also [1]. Thus, according to these authors, the posterior granular part of the insula contralateral to a painful stimulus and the anterior part of SI bilaterally are specific for pain processing [28].

According to the late thalamologist Edward G. Jones [29]:

Craig et al. . . . proposed and . . . reiterated that thalamic terminations of axons arising from lamina I cells throughout the spinal and medullary dorsal horns are restricted to a very small focal area outside the confines of VPL and VPM and characterized by strong immunoreactivity for 28 kDa calbindin. This new nucleus, they christened the posterior portion of the VM and gave it the acronym VMpo. Moreover they claim that VMpo relays these inputs to cingulated and insular cortex . . . rather than to primary somatosensory cortex . . . The construction, however, does not stand up to critical examination . . . The VMpo is like one of those religious apparitions that appear to few but become believed in by many. The VMpo is not an independent thalamic nucleus and not a specific relay nucleus in the ascending pain system (p738) . . . This is a dogma that rests upon the faith of conviction rather than upon documented evidence (p752) . . . a posterior region (“VMpo”), whose localization not only bears no relationship to the nuclear anatomy of the thalamus but also seems to change with each new publication . . . Moreover, to deny the pain pathways any role in the conscious awareness of pain as a uniquely unpleasant sensation and to see them instead as part of some visceral “homeostatic” system concerned in some ill-defined way with the internal well-being of the body (Craig 2003 (flies) in the face of all evidence to the contrary,

Certainly, poststroke CP has arisen from purely ventrocaudal (Vc)-restricted lesions, outside the supposed location of VMpo (see references in [1]): lesions of Vc are sufficient to impair cold and tactile sensibility. Moreover, thermal qualities are not found in many CP patients.

Although frequently observed in pain imaging, insular activation is not necessary for the conscious experience of pain, as clearly shown in a functional magnetic resonance imaging (fMRI) study of two stroke patients [30]; both could rate the pain normally despite absent bilateral fMR insular activation. The authors conclude that “the subjective awareness of noxious stimuli involves multiple, distinct patterns of brain activity where insular cortex is not a prerequisite.” Mouraux et al.’s [31] fMR results showed that the largest part of the blood-oxygen-level dependent signal both in the anterior and posterior insula following noxious stimuli reflects multimodal neural activities, rejecting the view that the insula is the primary thermosensory cortex or is primarily involved in somatosensation and nociception. As mentioned above, painful sensations are elicited in only a minority of subjects following direct insular stimulation: for instance, out of a group of 61 patients submitted to 276 electrical stimulations in the insular cortex, only two instances of subjective pain were reported [32]. In another large series of 4,160 cortical stimulations using intracerebral electrodes, pain responses were found only in 1.4% and concentrated in the medial part of the parietal operculum and neighboring posterior insula [33]. Clearly, were the insula the primary pain area, ALL patients should display painful sensations upon stimulation. Both insula and SI do not have the same degree of fine somatotopographical representation found in SI [34]. In a series of human stimulation studies of SI, insula, and SI, the authors concluded that insular somatotopy is blurred compared with SI and that insular pain somatotopy is likely to be even fuzzier than reported here [27]. Receptive fields (RFs) were large and often bilateral. The skin surface involved by painful sensations varied from 0.5% to 50% of total skin surface, differing considerably between subjects but also for a single subject from one stimulation to another. CP is a somatotopographically projected syndrome, and only SI can account for the clinical findings [2]. Most importantly, insula has no efferents to thalamus and thus cannot be involved in any anomalous direct loop with it, as occurs in CP [1,2] (Figure 1).

Actually, it is the supposedly necessary role of the insulas for interoceptive awareness and more generally for creating the “sentient self” or all of “human awareness” that is unwarranted. A stroke patient with virtual complete destruction of both insulas, both ACC, medial prefrontal cortex (mPFC), and medial temporal lobes, but intact SI bilaterally, and intact interoception, has been reported, showing that the insula and ACC are not necessary for interoceptive awareness and that both the pathway involving visceral afferents projecting to the insula (and ACC) and another involving skin afferents projecting to SI (and SII) work independently [35]. This patient supports the view that interoception involves “afferent information that arises from anywhere and every where within the body,” including through the skin, via pathways that are usually considered exteroceptive. In this same patient, self-awareness remained fundamentally intact, including basic self-recognition, sense of self-agency, self-concept, and intact higher order metacognitive abilities [36].
Figure 1  Genesis of central pain. An anomalous reverberant loop is established between the sensory thalamus (in gray) and primary sensory cortex (SI). STT = spinothalamic tract; SRT = spinoreticular tract; ML = medial lemniscus; RTN = reticular thalamic nucleus, (from [1], with permission).
Myth 3: Entrenched Neuroplasticity

It is a widely accepted view that neuropathic pain owes both its onset and chronicity to aberrant “neuroplastic” changes both at neuronal and glial levels. As chronic pain is so often “entrenched,” the major and extensive peripheral and central somatosensory changes, including gross structural nerve damage sustained over many years (e.g., tumoral or bony compression), are envisioned as irreversible. Under this rubric, several alterations are generally discussed: central sensitization, sprouting, somatotopographical (map) rearrangements, neuronal degeneration, and gliopathy (discussed in 1). Recently, several papers apparently found evidence of gray matter volumetric changes on MRI scans, which have been considered key to the genesis of chronic pain.

This theoretical construct is easy to refute. There are many reports of mostly sudden disappearance of CP after treatment of the triggering lesion (generally removal of the tumor), so called reversible CP (reviewed in [1], pp. 314–316). Similarly, cases of years-long peripheral neuropathic pains, including trigeminal neuralgia and carpal tunnel syndrome pain, resolve immediately after pain relieving surgery [37]. As for phantom limb pain (PLP), several reports are on record. Aydin et al. [38] reported on a woman with postamputation phantom leg pain begun at age 5 and lasting 60 years. About 1 year before admission, paraparesis appeared and PLP gradually decreased and disappeared. A meningioma at L1-2 compressing the cauda equina was removed en bloc. Full sensory function and sphincter control recovered about 3 months later, but her PLP began to resurface and was clearly felt 10 months later. No neuroma was observed. Brihaye [39] also observed a painless phantom extinguishing itself in parallel with the aggravation of cervical radiculopathy because of herniated disk; it reappeared slowly within 6 months of surgery. Iida et al. [40] reported on a man with left arm, right distal leg, and three right fingers amputations at age 49. Within a month, PLP arose (arm and leg), which gradually receded after 6 months replaced by numbness. At 65, he was operated for cervical spondylotic myelopathy at C4-7 with fusion. The morning immediately after surgery, left arm PLP was again present and reached previous intensity and extension within 24 hours. No neuroma was observed. The other two locations did not show any reactivation. PLP disappeared within 15 days, and the previous state was reinstalled. When phantom pain is alleviated by plexus anesthesia, the amount of cortical reorganization is also reduced. Brief anesthesia of a finger results in the expansion of the remaining fingers’ SI representation, and this is reversed on removal of the block [41]. So-called long-term micro-circuital plasticity drives neurons to disconnect from some neurons and connect with others within hours; spike timing-dependent plasticity can lead to rapid redistribution of synaptic efficacy (metaplasticity). Thus, the discussed neuroplastic/degenerative changes, whether rapidly reversible (e.g., RF expansion) or not (e.g., cell loss), would be inconsiderential. Importantly, immediate and delayed-onset CP are clinically identical: in the former, processes involving slowly developing, continually progressive neuronal changes cannot be essential for the generation of pain; likewise, loss of sensory input produces an immediate and simultaneous change in neuronal activity at multiple centenal nervous system (CNS) levels—for instance, human thalamic neurons develop novel RFs within minutes (5–15) of lidocaine block [42]. Such changes are observed also in cases without pain. According to Tasker’s group [43], the role of somatotopic reorganization in the genesis of CP—but also PNP—is entirely speculative. Unlike animal models, there appears to be different patterns and degrees of somatotopic reorganization in the human, all (or none) of which may be associated with a pain syndrome. They conclude: “Although in some cases changes in somatotopic representation were observed, these changes were not consistent in all the groups and therefore unlikely to be the common cause of pain in these patients.” Unlike many primate models of SI plasticity, humans display a relative preservation of the cortical sensory homunculus. Ojemann and Silbergeld [44] found that “adult human sensory cortex retains its somatotopy even after two decades without conscious perception of that body part,” after major peripheral denervation—unlike primary motor area (MI), whose volume decreases and N-acetyl aspartate levels increase following SCI [45]. Woolsey et al. [46] also found maintenance of cortical sensory maps. Experience with extradural cortical stimulation in CP [1] confirms that sensory maps (the “homunculus”) are stable. Thus, in humans, deprived but reactivated neurons do not take on new and appropriate functions, but carry out their original roles long after they have had time to adopt new ones. In a study of 12 thoracic SCI patients, nine reported phantom sensations and two referred phantom sensations (CP was not assessed). In these two, fMRI showed a relation between SI activation and the perception of referred phantom sensations. The authors concluded that, instead of somatotopic cortical reorganization, cortical plasticity may be the expression of coactivation of nonadjacent representations even distant between them, supported by somatotopic subcortical remapping projected to the cortex [47]. Turner et al. [48] examined with fMRI a group of SCI patients vs healthy controls. Unlike amputation, no evidence of expansion of the hand representation into nearby cortical areas was found, with hand sensory representation undergoing a much smaller posterior shift of hand motor representation. A magnetoencephalography study of eight patients said to suffer CP [49] found the SI digit1-to-digit5 distance significantly decreased in the hemisphere contralateral to the painful hand. First, the authors’ description of the patients (all developing pain following herpes) does not fit CP; second, the decrease was not correlated with long-term average pain; lastly, there was no change in one patient. Wrigley et al. [50] studied 10 complete SCI (T1-10) CCP patients vs 10 complete nonpainful SCI (T3-10) patients (but one patient had allodynia) and 21 healthy controls in a 3T MRI protocol of sensory stimulation blocks with plastic brush at two strokes/s. The overall pattern of brain activation and the pattern of SI activation was similar in all three groups and the sensory homunculus confirmed. In patients, a medial shift of the thumb and little
finger occurred (i.e., the hand region shifted toward lower trunk/leg area of SI). In those with CP, the medial shift of the little finger (but not of the thumb and lip representations) representation was statistically different from the other two groups and correlated positively with pain intensity. The authors do not explain what might be the relevance of this single little finger shift in the face of no change in thumb and lip in patients with leg pains. Human evidence disproves the role of somatotopic rearrangement (e.g., [51,52]) and referred sensations/mislocalization do not appear to be a direct perceptual correlate of cortical reorganization [53]. Phantom sensations can be evoked even in normal persons without deafferentation [54] and pain itself in chronic pain patients can lead to representational reorganization (references in [53]). Vetrugno et al. [55] described a man who had his left arm amputated 19 years before diagnosis of rapid eye movement sleep behavior disorder (no sleep atonia and acting out of dreams) and suffered PLP ever since. However, starting at age 53 and for 5 years, PLP disappeared with full subjective recovery of the amputated limb including motor awareness. This case also speaks against changes in sensory maps as a viable mechanism of PLP but suggests maintenance of somatosensorimotor representation in cortex.

As further contrary evidence, Tasker and Dostrovsky [56] concluded that, if sprouting occurs, it is of very limited extent and probably limited to a subpopulation of primary afferents and/or axons of CNS neurons, playing no role in RF expansion. Denervation supersensitivity is present in both pain and nonpain cases, and transneuronal degeneration with neuronal loss is incompatible with concurrently extant central sensitization. For instance, in nontraumatic cervical anterior spinal artery syndrome, in which practically complete interruption of the STT at the spinal level is observed, STT fibers cannot be involved in any kind of transmission from the periphery, and thus maintain sensitization (discussed in 1). Studies have not confirmed loss of inhibitory gamma-aminobutyric-acid (GABA) interneurons or receptors after nerve injury [57]. Notably, “There is no satisfactory explanation for the observed relative decrease in thalamic rCBF in neuropathic pain patients . . . The reversal of this decrease . . . following various types of analgesic procedures suggest that this decrease results from functional impairment rather than degenerative processes” [5]; full discussion in [1]. An analysis of the literature shows that structural (gray matter volume) differences between brains of individuals with chronic pain and healthy controls are more likely related to comorbidities of chronic pain, e.g., fatigue and emotional and cognitive impairments [58]. Finally, there is no direct evidence that central glia have a role in the pathophysiology of chronic pain in man and glia activation is found after neural injury with or without pain. Microglia activation occurs in the early postinjury phase, is transient, and may occur in the absence of axonal degeneration and cell death, whereas the astrocyte response occurs later, after axonal degeneration [59]: “Glia are involved in all types of brain pathology. . . . Astrocytes . . . may represent an integral component of the computational power of the brain. The fundamental question of whether neuroglia is involved in cognition and information processing remains . . . open” [60].

Myth 4: Pain as an Emotion

The great French surgeon René Leriche wrote [61]:

The pain-malady . . . has no well-marked anatomical basis, and no organic lesion to explain it can be made out. The disease and its manifestation are concentrated in the nervous system. Apparently localized, it affects practically the whole individual . . . In the suffering patient, the pain is like a storm . . . (the patient) powerless to understand, distressed in the face of this abyss into which you cannot descend . . . Our conception of pain of the mechanism of pain is a sort of sketch-plan . . . according to it, the whole process is concerned only with receptors, conductors, and centers, through the medium of which the pain phenomenon develops like a well-regulated film . . . adhering . . . to a lifeless or stereotyped conception . . . the pain-malady . . . has no receptors, no specific apparatus.

This (unacknowledged) line of thinking has been re-elaborated on the basis of neuroimaging evidence. Thus, neuroimaging studies “strongly support the case for dysfunctional pain processing, especially in affect regulating regions, and . . . these patterns of brain activity strongly reflect patients being in true discomfort and distress” [62]. Apkarian et al. [63], noting how the prefrontal cortex was the area most frequently activated in neuroimaging studies of chronic pain (81% of studies), concluded that chronic pain may entail decreased sensory processing and enhanced emotional/cognitive processing (hyperactive prefrontal cortex). Again, Apkarian [64] emphasized how, although distinct chronic pains may have unique associated brain activity, reorganize the brain in unique ways, and also impact modulation of information processing in specific ways, nonetheless “cortical reorganization seems to impinge mainly on circuitry involved in emotional learning and memory,” and May [65] concluded that chronic pain shows strong activation and reduced gray matter density of the prefrontal cortex. Bilateral cingulotomy/capsulotomy result in decreased pain tolerance and hyperphasic-type responses to acute painful stimuli following frontal surgery (e.g., [66,67]). In schizophrenia, affective psychosis and psychopathic personalities (but not in controls), painful paresthesias (pathologic), and a high percentage of thermal (hot > cold) paresthesias have been elicited by compression ischemia, pointing to abnormal paresthetic response in psychoses [68]. Prefrontal activity may lead to an increased salience of pain at the cost of other cognitive and emotional behavioral abilities, with pain constantly interfering with attention to other tasks.

Unlike other chronic pains [69], results of frontal surgery (lobotomy, topectomy, cingulotomy/cingulotomy, and leucotomy) are generally disappointing for CP (see [1], pp. 323–5). In rare cases in which it was deemed effective, the pain was simply less distressing and bothersome (pain
indifference), the patient less anxious or depressed by pain; spontaneous complaints about pain are diminished and a patient’s ability to appreciate the meaning of the pain may be disrupted. According to Turnbull [70], “bilateral cingulotomy alone is ineffective when pain is caused by a major organic disease” (p. 962), including CP. According to Freeman and Watts [71], “the frontal lobes are important structures, not so much for the experiencing of pain as for the evaluating of the sensation, the estimation of its significance in terms of the self and of the future.” The mid-cingulate cortex, where cutaneous nociceptive neurons are most abundant, was also included in such lesions. Studies show task-specific electrocorticography synchrony between SI, the parasylvian (PS) cortex and ACC. SI is functionally connected with PS during anticipation of the stimulus, whereas SI and PS are functionally connected with ACC during the response to the stimulus [72,73]. However, “it is not clear . . . how these structures are related to each other and to pain perception” [73]. A functional connectivity fMRI study of tonic pain in healthy subjects found that, using SI as a seed region, synchronized activity was observed in bilateral sensorimotor cortex (SI/MI), mPFC/mid-cingulate cortex (midCC), posterior insula/SII, and occipital cortex, but not in ACC (seed ACC also did not show a correlation with SI/SII). Using the left SI as a seed, bilateral SII, insula/operculum, left SI, and lateral prefrontal cortex (PFC) were correlated, but again not ACC. Instead, using the right anterior insula, bilateral anterior insula/operculum, ACC, midCC, striatum, thalamus, cerebellum, and brainstem were all correlated [74]. Opioids, whose receptors are particularly dense in the prefrontal cortex, are scarcely effective on CP [1]. Thus, the cingulum does not appear to be a vital link in tonic pain processing.

In sum:

1. there is no neuropathic pain matrix responsible for CP; 2. the insula likely participates in self-monitoring [75] and saliency detection [31] explaining its activation in imaging studies. It plays no key role in the genesis of CP; 3. neuroplasticity as currently envisioned is something intrinsic to the nervous system, independent of injury; and 4. the role of the prefrontal cortex may go beyond the unpleasantness, but may relate to control, namely cognitive and attentional processing of painful stimuli, and memory of past events. Loss of the frontal lobe-mediated expectancy mechanism disrupts placebo analgesia and clinical analgesia [76]. CP is not driven by emotion-labeled brain areas.

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