Pain matrices and neuropathic pain matrices: A review

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A R T I C L E   I N   P R E S S

A B S T R A C T

The pain matrix is conceptualised here as a fluid system composed of several interacting networks. A nociceptive matrix receiving spinothalamic projections (mainly posterior operculoinsular areas) ensures the bodily specificity of pain and is the only one whose destruction entails selective pain deficits. Transition from cortical nociception to conscious pain relies on a second-order network, including posterior parietal, prefrontal and anterior insular areas. Second-order regions are not nociceptive-specific; focal stimulation does not evoke pain, and focal destruction does not produce analgesia, but their joint activation is necessary for conscious perception, attentional modulation and control of vegetative reactions. The ensuing pain experience can still be modified as a function of beliefs, emotions and expectations through activity of third-order areas, including the orbitofrontal and perigenual/limbic networks. The pain we remember results from continuous interaction of these subsystems, and substantial changes in the pain experience can be achieved by acting on each of them. Neuropathic pain (NP) is associated with changes in each of these levels of integration. The most robust abnormality in NP is a functional depression of thalamic activity, reversible with therapeutic manoeuvres and associated with rhythmic neural bursting. Neuropathic allodynia has been associated with enhancement of ipsilateral over contralateral insular activation and lack of reactivity in orbitofrontal/perigenual areas. Although lack of response of perigenual cortices may be an epiphenomenon of chronic pain, the enhancement of ipsilateral activity may reflect disinhibition of ipsilateral spinothalamic pathways due to depression of their contralateral counterpart. This in turn may bias perceptual networks and contribute to the subjective painful experience.

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1. Introduction

Concepts are tools: they wear out by ensuring their function. —Claude Bernard

1.1. Trials and tribulations of the pain matrix

The concept of pain matrix defines a group of brain structures jointly activated by painful stimuli. It owes much to the notion of neuromatrix, developed by Ronald Melzack, who proposed that the anatomical substratum of the physical self is a network of neurons extending throughout widespread areas of the brain (a neuromatrix) and generating characteristic patterns of neural impulses that distinguish each bodily sensation. In Melzack’s words, “the neuromatrix for the physical self . . . generates the neurosignature pattern for pain” [180].

The pain matrix (PM) notion represented a conceptual advance over many prevailing concepts, which viewed pain-related emotional and cognitive phenomena as reactions to, rather than components of, pain [eg, [100]]. As early as 1968, Melzack and Casey [181] suggested that the pain experience reflected interacting sensory, affective and cognitive dimensions which could influence each other. This view, of which the PM was an expansion, implied that there was no such thing as a “brain pain centre”: pain was considered multidimensional and produced by distributed neural patterns, usually triggered by sensory inputs but potentially generated independently of them.

These theoretical notions were rapidly endorsed by functional imaging studies. Using positron-emission tomography, 2 seminal papers in 1991 reported that noxious stimuli activated a distributed pattern of brain structures consistent with the notion of a pain matrix [125,241]. A bulk of consistent data rapidly accumulated showing not only distributed activity to noxious inputs, but also linear and nonlinear correlations among the energy of the stimulus, the subjective perception, and PM responses [eg, [28,48,61]]. It became also clear that most of the activated areas were not specific for pain: PM regions such as the anterior cingulate cortex, the anterior insula,
and the prefrontal and posterior parietal areas showed enhanced activity in a wide range of non-pain experiments, especially in emotionally or cognitively laden contexts, whereas the sensory encoding of noxious intensity was reflected by very tiny brain activations [205,213,228], reviews [206,10].

Among the contrasting conceptual positions that have emerged since, some authors posit that functional imaging data may contain a genuine and objective signature of the painful experience (eg, [254]) which, for a number of investigators, may imply that functional imaging could be used to derive an individual pain phenotype [29,44,168], and comment in [7]. Pushing this logic further, activation of PM subsets (essentially the anterior insulae and cingulate) has sometimes been equated with physical pain, leading to questionable conclusions such as that “social rejection hurts physically” (eg, [68,169]). In contradistinction, other investigators have assailed the very concept of a specific pain-related network, claiming that most, if not all, the regions present in the PM represent a nonspecific salience-detection system for the body, activated by relevant events “regardless of the sensory channel through which these events are conveyed” [117,115]; review [145]. In between, the idea that the pain matrix cannot be unequivocally defined, the role of different regions being dependent on the context in which the stimuli are delivered, has been put forward by a few investigators (eg, [206,207,245]).

Because spinothalamic projections inform brain networks about the bodily nature of the input, the healthy brain recognises at once whether a menacing signal arrives through a somatosensory channel. Information on the somatic origin is likely to be transferred to PM regions secondarily ignited, hence giving to perceptive networks a stable reference to the own body. In this review, the neural substrate of the pain experience is conceptualised at different levels of progressively higher-order cortical networks, from cortical nociception to the conscious experience we call pain—itself subject to reappraisal by internal states, feelings and beliefs prior to stabilisation into memory stores.

1.2. First-order processing: a nociceptive cortical matrix

The primate spinothalamic system originates chiefly from neurons in spinal laminae I, V, and VII, whose axons terminate in multiple nuclei of the posterior thalamus, essentially the ventral posterior, centrolateral, mediodorsal and posterior group nuclei [8,9,179,219]. Using trans-synaptic viral transport, main spinothalamic cortical targets in primates were defined in the posterior insula (~40%), medial parietal operculum (~30%) and mid-cingulate cortex (~24%) [65]. These receiving regions are the source of the earliest responses to noxious stimuli recorded in the human brain [74,75,153,154,193] and contain a nociceptive matrix specific for spinothalamic projections. The posterior insula and inner operculum are the only regions in the human brain where stimulation triggers acute pain [177,178], where focal lesions entail selective pain deficits [21,93,86], and where cortical injury gives rise to neuropathic pain [21] (review in [80]). Lenz and associates (1995) [150] reported “full pain experiences” when stimulating thalamic regions projecting to the posterior insula and operculum, and intense pain was specifically reported during surgical dissection of the operculoinsular area [197]. Focal epileptic activity in the posterior insula can trigger painful seizures by igniting other PM areas in less than 100 ms; in a recent report, purely painful seizures were stopped by millimetric thermocoagulation of the posterior insular focus, and the patient has remained free from pain seizures for more than 2 years [118].

However, although this nociceptive matrix appears as a necessary entry to generate physiological pain experiences, it cannot provide the countless nuances that characterise human pain and is unable to sustain consciousness; indeed, activation of the nociceptive matrix persists during sleep, coma and vegetative state [18,27,127]. The transition from cortical nociception to conscious pain and its multiple attentional-cognitive modulations requires the recruitment of a second set of cortical networks.

1.3. From nociception to pain: a second-order perceptual matrix

The classical PM encompasses activity in many areas distinct from the nociceptive network described above, the most consistent being the mid and anterior insulae; the anterior cingulate, prefrontal and posterior parietal areas; and, with less consistency, the striatum, supplementary motor area, hippocampus, cerebellum, and temporoparietal junction. These second-order areas share a number of features: (1) none of them is a direct target of the spinothalamic system; (2) direct stimulation does not evoke pain; (3) selective destruction does not induce analgesia; (4) they are also activated in contexts not involving pain; and (5) their contribution to the PM, from nil to predominant, depends on the context in which noxious stimuli are applied.

The mid and anterior insulae participate almost constantly with the PM. Their activation may reflect a posterior-to-anterior information flux within the insula [76,214], supporting the transformation of sensory events into vegetative reactions and associated internal feelings [39,49,260]. The cognitive section of the anterior cingulate (BA 24–32) is also activated consistently by painful stimuli [252], and together with prefrontal and posterior parietal areas, it is thought to sustain attentional and evaluative processes of anticipation, learning and cognitive control. The contributions of these areas to the PM vary enormously with contextual factors (eg, [34,205,233]; review [10]), and their activation can be dissociated from actual stimuli intensity (eg, [28,210]). Activity in this second-order contextual matrix can influence the nociceptive areas via top-down projections; attending actively to noxious stimuli enhances activity in sensory and orienting areas receiving spinothalamic system afferents, such as the posterior insula and mid-cingulate, whereas distraction tends to suppress such activities [14,83,167,192,193,250], review [263,264]. Such top-down influences modify perception by changing the sensory gain at the source, that is, in cortical receiving areas (eg, [82]), thalamus [251], and even at the brainstem [246] and spinal cord [239,267]. Further, vegetative peripheral reactions driven by anterior insular networks generate new ascending information through splachnic and vagus nerves, spinothalamic tract and dorsal column systems, thus providing new input to cortical and subcortical nociceptive targets [243,268]. Of note, hypnotic suggestions of hypo- or hyperalgesia appear to influence either nociceptive, second-order or both matrices, depending on the instructions given to the subject (eg, [71,108,217]) consistent with its action through top-down influences. A dissociation between preserved activity in posterior insula but abated response in second-order parietal and temporal cortices has also been described under hypnosis [2].

Regions of this second-order matrix are activated in many contexts other than physical pain. For instance, the anterior insulae and anterior cingulate pertain to a salience network responding to behaviourally-relevant stimuli, which they integrate into perceptual decision making [265]. These 2 regions are jointly activated not only in response to painful stimuli, but also when subjects are confronted with unpleasant situations such as observing expressions of disgust [260], feeling guilt [236], experiencing social and moral suffering [67,133], or seeing or imagining other people in pain [120,140,237]. This has led to considerable controversy as to whether subjects confronted with such unpleasant situations do physically feel pain (eg, [67,133]). Obviously, this is not the case, at least in physiological conditions1; neither the midanterior insula

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1 Transformation of visual or auditory sensations into somatic experiences has been described as a rare condition such as vision-touch synaesthesia [23], which is seen as an “abnormal form of empathy” [73].
nor the rostral ACC pertain to the nociceptive matrix and therefore cannot support by themselves the corporeal specificity that characterises somatic pain, as shown in both stimulation and lesion studies [93,177,178]. Their activation in response to unpleasant stimuli simply reflects their belonging to a broad system for salience detection which (1) generates internal state modifications and (2) alters the individual responsiveness to specific stimuli. In this vein, responses in both anterior insula and ACC can be triggered by pleasant stimuli to the same degree as unpleasant ones (eg, [101,104,272]), and direct stimulation of the ventral (disgranular and agranular) insula in monkeys was able to elicit not only disgusting but also socially affiliative behaviours [39].

Activity in the second-order pain matrix is also crucial to ensure the conscious perception of the stimulus because sensory inputs become conscious only if they create distributed brain activation [56,58]. Activity constrained to unimodal areas does not produce conscious perception (eg, [11,59]), which emerges only when sensory responses are associated with activation in parietal-temporal and prefrontal cortices, ie, areas integrating the second-order pain matrix. Functional connectivity within the frontoparietal network appears to be crucial for declarative consciousness [141], and abundant evidence shows that the contribution of these regions separates undetected vs detected stimulus changes [20,199]; masked vs unmasked words [57,102]; extinguished vs seen visual objects [220]; and missed vs reported stimuli during attentional blinks [234,59]. The functional coupling between stimulus-specific areas and parietofrontal networks is considered an essential signature of the access of sensory information to consciousness [58,59,95,102,157], making it available to high-level processes, including perceptual categorization, long-term memorization, evaluation, and intentional action.

To sum up, although the nociceptive matrix provides the sensory specificity of the pain experience, the joint activity of the nociceptive and second-order matrices is essential to ensure (1) the modulation of vegetative reactions and internal feelings via anterior insular networks; (2) the attentional modulation of sensory gain by top-down and bottom-up transactions; and (3) the access of nociceptive information to declarative consciousness.

1.4. From immediate perception to pain memories: third-order networks

Impressive changes in the pain experience can occur without changes in the matrices described above. For instance, the enhancement of subjective pain during the observation of other people’s suffering [55,90,161] in the absence of significant changes in thalamus, insula, operculum, or mid-anterior cingulate, and is associated instead with activity in high-level polymodal regions outside the classical PM, such as the perigenual cingulate, the orbitofrontal cortex, the temporal pole, and the anterolateral prefrontal areas [90,91]. Similarly, the pain-relieving effects derived outside the classical PM, such as the perigenual cingulate, the associated instead with activity in high-level polymodal regions [20,199]; masked vs unmasked words [57,102]; extinguished vs seen visual objects [220]; and missed vs reported stimuli during attentional blinks [234,59]. The functional coupling between stimulus-specific areas and parietofrontal networks is considered an essential signature of the access of sensory information to consciousness [58,59,95,102,157], making it available to high-level processes, including perceptual categorization, long-term memorization, evaluation, and intentional action.

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1.5. The pain experience: an intersection of matrices

The great merit of the PM concept was to underscore that pain experiences result from coordinated activity in a number of brain regions, that is, the absence of any single pain centre. Although some investigators consider the PM as a genuine biomarker of the pain experience (a direct measure of the actual pain), others claim that the PM simply reflects a nonspecific system of salience detection. The viewpoint proposed here, which elaborates and expands existing notions (eg, [160,245]), is that the final experience of pain (ie, the pain we shall remember) results from the confluence of 3 orders of brain processing that have progressive complexity, in networks that we may tentatively label as nociceptive, perceptive-attentional and reappraisal-emotional matrices (Fig. 1). Regions receiving spinopthalamic input ensure the somatic-specific (corporal) quality of the sensation; they trigger activity in parietal, frontal and anterior insular circuits, supporting conscious perception, vegetative reactions and their modulation by attention and vigilance. The immediate perception issued from these activities can itself be modulated by higher-order networks driven by emotional contexts and internal states. This reappraisal determines a privately generated assessment of instant percepts, tuning them up or down as a function of affective states and previous memories and building what will represent the subjective experience available to long-term memory buffers. Dissociation of such different processing levels is useful for conceptualisation purposes, but in real life their activity is interdependent and extremely fluid [49]; hence, the perception of pain appears as an active process, continuously reconstructing itself by integration of sensory inputs with ongoing memories and internal representations [94,160,189].
2. Is there a “neuropathic pain matrix”?

Constructing a model is making a bet.
—Anonymous

Previous literature has discussed brain activation differences between experimental and neuropathic pain (NP) abundantly, but systematic investigations in large samples of patients with NP remain an exception. Functional imaging in NP cannot be examined with the same confidence as the experimental studies of physiological pain reviewed above. Some features observed in NP are reproducible across studies, whereas others remain controversial; some particularities have been described in single case reports but not reproduced in larger series. In some cases, similar results have been interpreted in different ways. The set of brain structures activated during neuropathic hyperalgesia and allodynia grossly corresponds to those of the pain matrix, but a number of features have been described that are highly characteristic of the neuropathic state. The most reproducible patterns associated with NP are: (1) tonic hypoactivity of the thalamus contralateral to the painful region; (2) deficit in responsiveness of the ventromedial (and often dorsolateral and anterolateral) prefrontal cortices during neuropathic allodynia; and (3) change in the operculoinsular interhemispheric balance, with increased incidence of responses ipsilateral to pain.

2.1. Thalamic hypoactivity in ongoing NP

A deficit in thalamic metabolism contralateral to the side of NP was first described by Laterre et al. [143] in a patient with post-stroke central pain. Shortly afterward, Di Piero and colleagues [62] reported decrease in thalamic blood flow contralateral to the side of pain in 5 cancer patients with plexus invasion, the abnormality being reversible after successful cordotomy. Since then, the observation of functional thalamic depression contralateral to NP (hypoperfusion/hypometabolism) has been replicated by at least 10 different teams using different pathological models and functional techniques and is now one of the most robust and consistent observations in patients with NP [35,54,62,85,105,106,110,113,119,135,196,203,242], although a few exceptions exist [88,111,232]. The locus of functional depression within the thalami (reported in about half of the cases) tends to involve predominantly its posterior sections, consistent with the loci of arrival of ascending somatosensory afferents [35,62,105,106,113,110,143]. Although the robustness of thalamic hypoactivity in NP is widely acknowledged, its functional significance remains a matter of debate. Four questions incompletely solved are (1) its specificity regarding NP; (2) the role of sensory deafferentation; (3) the causal or consecutive nature of the dysfunction; and (4) the possible mechanisms leading to decreased local metabolism.

2.2. Specificity of thalamic hypoactivity

If not totally specific, thalamic hypoperfusion/hypometabolism is at least highly characteristic of ongoing neuropathic pain and has not been described as a feature of mechanical, inflammatory or mixed pains, which instead entail enhanced PM activity (eg, [176,256]). Although experimental tonic pain induced by capsaicin can mimic some NP features, it fails to reproduce the characteristic thalamic hypoactivity and enhances the thalamic perfusion [114,270]. Migraine with visual auras may include hypoperfusion in the occipital lobes [128,273]; review [16], but in the rare cases in which a migraine attack could be scanned on line, hypoperfusion either spared the thalamus [273] or was bilateral despite unilateral attack [128]. Bilateral thalamic hypoactivity was described in early single-photon emission computed tomographic (SPECT) studies of central sensitisation syndromes, such as chronic fatigue syndrome and fibromyalgia [138,187], but this has not been reproduced in more recent reports, which either did not find significant thalamic changes (eg [97,249,266,277]) or reported thalamic hyperperfusion (eg [63]).

2.3. Thalamic hypoactivity and sensory deafferentation

Neuropathic pain occurs within areas of hypaesthesia, and therefore thalamic hypoactivity might be the result of sensory deafferentation. However, although deafferentation induces electrophysiological and metabolic changes in denervated thalami [87,151–154,191,218], it cannot fully explain the changes observed in patients with NP. The fact that thalamic hypoperfusion was rapidly reversible with analgesic manoeuvres that left untouched, or increased, deafferentation, such as cordotomy [62], motor cortex stimulation [84,203] and propofol or lidocaine infusion [35,38,110] indicates that the state of afferent information is not the decisive element maintaining thalamic hypoactivity. In 1 case with bilateral thalamic deafferentation, the thalamus contralateral to pain, albeit the less deafferented, showed the more severe hypoperfusion [85]. The contribution of deafferentation should not be neglected, however, because some thalamic asymmetry may persist even when differences in pain intensity are removed [135].
and thalamic hypoactivity may be lacking in peripheral lesions, inducing limited and indirect (functional) deafferentation [88,111,232]. Current evidence suggests, therefore, that sensory deafferentation of the thalamus may represent an important primum movens triggering functional thalamic hypoactivity, which eventually becomes autonomous and participates in the pathophysiology of NP.

2.4. Is thalamic hypoactivity causal or consequential?

Longer duration of pain is more likely to be associated with thalamic hypoperfusion (eg. [79]) suggesting either that thalamic dysfunction is a consequence of pain or that patients who develop thalamic hypoactivity are more likely to develop long-lasting pain. In their seminal observations, Di Piero et al. [62] and ladarola et al. [113] considered the possibility that thalamic hypoactivity could reflect compensatory mechanisms of functional reorganisation after functional damage, hence being a consequence of the pain state. However, in patients submitted to analgesic procedures, thalamic flow can increase significantly while pain still remains [66,84,203], which is contradictory to the notion of its being an epiphenomenon of the pain itself. Also, thalamic flow increase during analgesia may be disproportionate and uncorrelated with pain relief [135], or it may precede clinical improvement by hours or days [78,84,248], suggesting that thalamic hypoactivity can hardly be interpreted as a compensatory epiphenomenon of the pain itself and should be viewed as a functional concomitant of NP, reverted by analgesic procedures.

2.5. Which mechanisms underlie thalamic hypoactivity?

The association of a “positive” symptom like pain with neural hypoactivity is a paradox. This paradox is not exclusive to NP and has been reported in other instances of positive symptoms such as epilepsy and movement disorders, in which the affected regions show decreased flow and metabolism relative to the surrounding and contralateral tissues [43,244,257,109,139,223]. Spikes of neuronal bursting and electroencephalographic slowing are found in hypometabolic epileptogenic regions [1,182] as well as in the thalamus of patients with neuropathic pain [96,106,107,147,149,151,183,222,226,275] and in animals models of deafferentation [5,162,247], [258,259]. Rather than reflecting neuronal hyperactivity [132,222,247], it was soon acknowledged that thalamic bursts in cases of NP fulfilled the criteria of low-threshold calcium spikes (LTS) [121,122,148,259], reflecting a state of thalamic cell inhibition by hyperpolarisation [148,158,240]. Combined positron emission technology scans and intrathalamic recordings in central poststroke pain have demonstrated a direct link between hypometabolism and thalamic bursting [105,106], hence thalamic LTS bursting is a good candidate to provide the neurophysiological basis for NP thalamic hypoactivity in functional imaging. Although thalamic deactivation can be dissociated from deafferentation (see above), deafferentation may be its primum movens and probably is a condition necessary but not sufficient for rhythmic bursting to occur. Models of neural network deafferentation in epilepsy suggest that the arrival of sparse inputs during refractory periods and the sprouting of remaining afferents may favour the development of abnormal spikes [69]. The possible relevance of these epilepsy models regarding rhythmic bursting in the thalamus of patients with NP remains, however, highly uncertain.

The relationship between thalamic bursting and NP pathophysiology remains a point of strong controversy. A number of authors have suggested that abnormal thalamic bursts are intimately related to the genesis of central pain [106,121,147], and enhanced thalamocortical coherence in low-frequency EEG rhythms was interpreted as LTS-related resonant thalamocortical interactions [36,121,159,171,227]. The occasional observations that small lesions interrupting the thalamocortical connections may terminate instantly central poststroke pain [238,276] were in line with this hypothesis. In sharp contradistinction, investigators that had participated in the original discovery of thalamic LTS bursts reported them to be equally prevalent in patients with and without pain, suggesting that their presence was not necessarily related to the occurrence of NP [215]. In patients with Parkinson disease, LTS prevail in motor rather than in somatosensory thalamic regions [170], whereas the reverse is true in patients with phantom limb pain [152], suggesting that the spatial distribution of bursting within the thalamus might be, by virtue of different cortical projections, the crucial element determining whether the associated clinical expression will be pain related or not. In this vein, microstimulation in areas of increased bursting within the ventrocaudal thalamus is more likely to produce pain than microstimulation in other areas of the ventral posterior lateral nucleus of the thalamus [52,152].

In summary, the functional thalamic depression in NP appears to reflect mechanisms that, once triggered by anatomical deafferentation, favour the transition to neuropathic pain. Resting thalamic hypoactivity may represent the metabolic counterpart of abnormal thalamic bursting observed in these patients. However, before considering this phenomenon as a putative marker of neuropathic pain, direct comparison of thalamic activity in series of patients with similar lesions but presenting with NP or not appears to be mandatory. Longitudinal studies are also needed to determine whether or not patients with thalamic functional findings at NP onset are more likely to develop uncontrolled NP. Should this be the case, assessment of thalamic blood flow might become a means of estimating the likelihood of developing NP after a potentially pain-inducing neural lesion.

2.6. Provoked pain: allodynia and hyperalgesia

Provoked pain permits easier access to haemodynamic imaging than ongoing pain, so studies of stimulus-evoked NP largely outnumber those assessing its continuous component. Provoked NP can be contrasted with surrogate models of allodynia or hyperalgesia which generate experimentally controlled abnormal pain sensations. These models, based mostly on capsaicin injections, share with NP the induction of anomalous peripheral and central sensitisation but lack the somatosensory deafferentation which is a key feature of NP.

2.7. Experimental hyperalgesia and allodynia

When compared with either a resting state or nonpainful stimuli, experimental allodynia is consistently associated with activation in the posterior operculoinsular region, the anterior insulae, the mid and anterior cingulate, and the posterior parietal and prefrontal cortices (Table 1). Responses in third-order regions linked to emotional appraisal are more variable: activation of perigenual and orbitofrontal cortices was reported in a majority of experimental studies [114,136,144,164,166,163,172,186,261,270,278] but was absent in others [15,174,116,235]. Activation of these areas may reflect methodological issues, such as the acquisition methods (positron emission technology [PET] or functional magnetic resonance imaging [fMRI]) or the presence or absence of ongoing pain, but it also appears to be contingent to the degree of unpleasantness attained during the experiment: Lorenz and coworkers [164,163] used capsaicin to compare physiological pain with alldynic pain of matched intensity but much higher unpleasantness scores. The latter yielded significant blood-flow enhancement in perigenual, orbitofrontal and ventral striatal regions not activated
Table 1: Regional activation changes during experimental allodynia and hyperalgesia in 21 group studies published between 1998 and 2012.

<table>
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<th>Author year</th>
<th>Method</th>
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<th>MCC -ACC</th>
<th>pgACC/OFC</th>
<th>DLPPC/ALPPC</th>
<th>PPC</th>
<th>Basal ganglia</th>
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<th>Other</th>
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<td>Iadarola et al. (1997)</td>
<td>Capsaicin</td>
<td>13</td>
<td>Brush &amp; thermal</td>
<td>Punctate</td>
<td>Rest &amp; innocuous brush</td>
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<td>Tables 3-4; Figs. 3 and 4</td>
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<td>Baron et al. (1999)</td>
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<td>Witting et al. (2001)</td>
<td>Capsaicin</td>
<td>8</td>
<td>PET</td>
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<td>Heat</td>
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<td>Heat</td>
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<td>Heat</td>
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<td>Punctate</td>
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<td>Table 1 Fig 2</td>
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</table>

* rCBF increase;  † rCBF decrease, no change found or reported; mix, both rCBF increase and rCBF decrease within a single region.

** Note: Responses to different types of allodynia (eg, thermal or brush) within a single article are split into 2 separate lines. Laterality of effects (con, contralateral; ipsi, ipsilateral; bil, bilateral) is indicated only for thalamus, S1, basal ganglia, and opercular-insular regions.

The last column indicates the original articles' tables and figures. Data were obtained from.

* Activation bilateral vs rest; ipsilateral vs innocuous brush.

** Activation present vs innocuous brush, absent vs rest.

*** Results from this study may be biased by use of a placebo.
by normal thermal pain (see Fig. 5 in [164]. These authors underscored that midfrontal activity moved from the caudal cingulate (BA24) during normal pain toward perigenual cingulate areas during heat allodynia ([164]). Maihofner and Handwerker [172] also showed that activity in the medial PFC correlated with enhanced unpleasantness in thermal vs mechanical allodynia, and other authors have speculated that midfrontal and perigenual activation in pain studies may be associated with higher pain ratings (see, eg, [136], p. 290). The specific activations in ventromedial PFC during highly unpleasant allodynia have been considered to reflect

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**Fig. 2.** Graphical summary of reported incidence in regional brain activation during experimental and neuropathic allodynia and hyperalgesia. Data from 39 reports published between 1991 and 2012 (see Tables 1 and 2). The lower panels summarise the most significant differences between experimental and neuropathic allodynia. Arrows indicate significant differences in reported frequency. Activation of the ipsilateral opercular and insular cortices, relative to their contralateral counterparts, was more frequently reported during neuropathic than experimental allodynia (lower right panel). On the contrary, activation of perigenual, orbitofrontal and lateral prefrontal cortices was significantly more prevalent during experimental allodynia (lower right).

**Fig. 3.** Enhanced activation of ipsilateral operculo-insular areas during neuropathic allodynia, peripheral (top) or central (bottom). In each case, the upper row depicts regions activated during innocuous brush to the healthy side (control), and the lower row depicts the effect of brushing identically the allodynic side, where stimuli become painful. Control stimuli activate primarily the contralateral operculum and insula, whereas allodynic stimuli activate predominantly the ipsilateral regions. (Reproduced from Witting xxx and Peyron.xxx See text for details.).
recruitment of associative limbic loops [164,163], possibly enhanced by anticipation phenomena (eg. [213]).

Enhanced perigenual or orbitofrontal activity associated with intense offensiveness of the stimulus can also, and simultaneously, set up powerful mechanisms aimed at controlling pain. Indeed, ventromedial frontal areas have been considered crucial for the control of unpleasantness [155,194], and during experimental allodynia, their activity is most often accompanied by midbrain activation in regions consistent with the periaqueductal grey matter (PAG) [114,136,144,164,163,278], while such brainstem contribution was absent in cases with no ventromedial activation [174,235,270]. The PAG is one of the major sites involved in descending, opioid-mediated inhibition of pain [17,25,60,221]. Functional connectivity between the orbitofrontal cortex, the perigenual cingulate and the PAG has been demonstrated in humans (eg. [209,250]), and activity enhancement in both regions is typically associated with successful analgesia by opioid administration [72]; distraction [250]; neurostimulation [209,210,269]; and placebo [202]. Thus, the exquisite enhancement of midfrontal, perigenual and upper brainstem regions during experimental allodynia may reflect not only an internal state of high unpleasantness but also the triggering of descending controls aimed at interrupting, or at least downregulating, an abnormally enhanced nociceptive inflow (review in [81]). The negative correlation observed between brainstem activity and pain scores during hyperalgesia due to opioid withdrawal also supports a pain-inhibitory role of upper brainstem activation [255]. Notwithstanding the above, brainstem activity has also been occasionally considered as an index of descending facilitatory processes (eg. [116,144,278]), thereby reflecting mechanisms that maintain central sensitisation rather than controlling it [195].

2.8. Neuropathic hyperalgesia and allodynia

Grouped analysis of neuropathic hyperalgesia and allodynia is hindered by drawbacks that have been well summarised by Kupers and Kehlet [134]. These include the heterogeneity in pain location (different zones stimulated across patients introduce confounding effects); the use of the homologous contralateral body as control, which may itself be subject to abnormal sensitivity [42]; and the study of patients who differ in the causes, durations, and levels of spontaneous pain. We tried to circumvent some of these difficulties by stressing the consistency of findings across studies, rather than the quantitative importance of the findings. Because the crucial variable was consistency, we may have underestimated important changes that only a few studies were able to tag. Although there is large overlap among networks activated during experimental and neuropathic allodynia (eg. [142]), the latter is associated with characteristic quantitative and qualitative changes. Quantitatively, the blood-flow response is out of proportion to the actual intensity of the stimulus: the magnitude of response to subtle rubbing of the skin may become virtually identical with that observed in response to normal painful stimuli [211]. In addition, responses during neuropathic allodynia exhibit qualitative changes, in particular: (1) the transformation of thalamic resting hypoactivity into hyperactivity, with possible changes in activated nuclei; (2) the displacement of operculoinsular equilibrium toward hypoactivity into hyperactivity, with possible changes in activated nuclei; (2) the displacement of operculoinsular equilibrium toward hypoactivity into hyperactivity, with possible changes in activated nuclei; and (3) the lack of reactiveness in ventromedial PFC.

2.9. Transformation of thalamic hypoactivity into hyperactivity

Cesaro et al. [46] first drove attention to the association of hyperpathia and thalamic hyperactivity in 2 patients with central NP (Fig. 4, [46]). At the group level, thalamic hyperactivity to mechanothermal allodynia was demonstrated by Peyron et al. [204] in 9 patients with Wallenberg syndrome, and it has been confirmed since in a number of studies (eg. [40,41,89,137]). It has been speculated that NP hypoactivity in the thalamus at rest may mask an underlying hyper-responsiveness to external stimulation due to loss of resting intrathalamic inhibition [41,44,45]. Thalamic hypoactivity in ongoing NP has been associated with abnormal thalamic bursting (see above) which, in the context of epilepsy, has been suggested, paradoxically, to favour the development of hyper-reactivity to external inputs [69]. More recent data indicate that thalamic hyper-responsiveness in patients with central pain may concern medial, rather than lateral, thalamic subregions [42,211].

2.10. Changes in interhemispheric activation balance

In experimental pain studies, haemodynamic activation of the contralateral operculoinsular cortex is more frequently reported than that of its ipsilateral counterpart, while this is reversed in neuropathic allodynia, in which ipsilateral activation of the operculoinsular cortex predominates. As a result, the ipsilateral/contra-lateral incidence ratio passes from 50% (experimental) to 111% (neuropathic allodynia) in the operculum, and from 80% (experimental) to 160% (neuropathic) in the insula (P < 0.001; Fig. 2). Such paradoxical lateralisation towards the hemisphere ipsilateral to
Table 2
Regional activation changes during neuropathic allodynia in 18 studies published since 1991. Responses to different types of allodynia (eg, thermal and brush) within a same article are listed separately.

<table>
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<th>Operc (inc S2)</th>
<th>Insula</th>
<th>MCC-ACC</th>
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Case reports

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† = rCBF increase; † = rCBF decrease; – = no change found or reported; Mix = both rCBF increase and decrease within a same region. Laterality of effects (con = contralateral; ipsi = ipsilateral; bil = bilateral) is indicated only for thalamus, S1, basal ganglia and opercular-insular regions. The last column indicates the original articles from which the tables and figures data were obtained.

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- Bilateral vs rest; ipsilateral vs innocuous brush.
- Present vs innocuous brush, absent vs rest.
- ** Results from this study may be biased by use of a placebo.
alldynia has been described in patients with cortical damage [207,208] but also in the absence of direct cortical lesions, as in peripheral neuropathy or spinal injury [64,201,271] (Fig. 3). In other cases, both posterior insulae were activated, but only the ipsilateral side remained significant after contrasting alldynic vs nonpainful control stimuli (eg, [229]). In accordance with these data, the activation likelihood estimate (ALE) meta-analysis of Lanz et al. [142] showed the insula activated bilaterally in experimental hyperalgesia but ipsilaterally in patients with NP (Table 3 in [142]).

Disinhibition of ipsilateral thermoalgesic pathways appears as a likely candidate to support the enhancement of ipsilateral activity in NP, and this ipsilateral overreaction may be mechanistically related to painful symptoms. It has been estimated that about 17% of primate spinothalamic axons project to the ipsilateral thalamus [89,47], and clinical data indicates that ipsilateral transmission, normally suppressed when both spinothalamic pathways are intact, may become functional after a unilateral lesion [30,188,190]. Based on detailed psychophysical testing, Casey et al. [42] suggested that bilateral effects of unilateral spinothalamic lesions and uncrossed painful symptoms have been described in patients with neuropathic pain resulting from unilateral lesions [129,37]. Central pain ipsilateral to a brain lesion may mirror the site of previous contralateral pain [129], and poststroke alldynia can be abolished by a new lesion involving Ol areas in the other hemisphere [50,103]. In physiological conditions, Ol activity contralateral to the stimulus is thought to inhibit tonically its ipsilateral counterpart [30,188,129], such inhibition being overcome only at intensely noxious levels (eg, [114,174,270]). Therefore, significant ipsilateral Ol responses may be physiologically encoded as a signal specifically associated to very strong noxious input. Disinhibition of ipsilateral responses following a neuropathic lesion might also be (erroneously) interpreted by perceptive networks as a signal that the magnitude of the stimulus was abnormally high. Under this perspective, overactivation of the ipsilateral Ol region would contribute directly to a perceptive bias sustaining the subjectively enhanced sensation.

2.11. Deficit in ventromedial prefrontal activation

A second source of imbalance in neuropathic allodynia concerns the activity in ventromedial PFC. Activation enhancement in sensory regions has been similarly reported in experimental or neuropathic allodynia (Fig. 2), but a conspicuous feature of neuropathic allodynia is the lack of activation of ventromedial (perigenual and orbitofrontal) PFC. Grouped analysis of 39 published reports shows that the incidence of ventromedial frontal activation was significantly lower in neuropathic than in experimental allodynia (17% vs 58%, P < 0.01), whereas the mid and caudal cingulate sections (MCC–ACC, Brodmann areas 24–32) were equally activated in both instances (67% vs 71%, ns) (Fig. 2). The response shortfall of ventromedial PFC in neuropathic allodynia has been reproduced by many independent groups and in various pain models, including central poststroke pain [204,206–208]; syringomyelia [64]; peripheral neuropathy [173,201,229]; trigeminal or postherpetic neuralgia [19,89]; and complex regional pain syndrome ([175]).

Dampened perigenual responses were also incidentally reported during ongoing NP [110]. Some reports underscored the large variability in perigenual activation, which could be present in individual patients yet absent in group analysis, and suggested that high preactivation levels due to background pain might prevent further increases in neuropathic alldynia [271]. Such a ceiling effect, however, appears to be unlikely because, in healthy subjects, significant ongoing pain due to capsaicin injection did not prevent ventromedial activation during alldynia [136,172,270]. Further, ventromedial frontal activity in NP could even decrease during alldynic pain (eg, [137,204]) or be anticorrelated with pain intensity [89].

As part of a corticolimbic circuitry, the perigenual and orbitofrontal cortices have important roles in the integration of cognitive and emotionally relevant information [70,126]. They are crucial to cope adaptively with physiological challenges [77] and to support production and regulation of affective states [155,212]. This region is also the source of descending connections which, in animal models, trigger opioid-mediated inhibition of pain signals via the periadquedal grey [4,17,221]. In accordance with this, enhanced functional connectivity between perigenual and PAG regions correlates with pain relief [209,210,250], and all kind of analgesic procedures in humans trigger perigenual and orbitofrontal activity, hence compensating their functional depression (eg, [53,110,250,269]; review in [81]) (Fig. 4). In the same vein, decreased ventromedial activation in somatof orm pain disorder has been interpreted as a diminished top-down inhibition of ascending pain pathways [98].

Chronic stressors entail morphological changes in ventromedial PFC: prolonged immobilization simplifies the branching and shortens the apical dendrites of rat ACC neurons, a damage reversible following a stress-free period [216]. Such structural changes lead to functional depression and may result from release of glucocorticoids and excitatory amino acids via PFC glutamate neurotransmission (review, [184]). As a chronic stressor, NP can also trigger the above cascades and lead to reduced responsiveness of the ventromedial PFC as a consequence rather than a cause of chronic NP. This is consistent with the fact that similar ventromedial depression has been reported in patients with non-neuropathic pain [6,123,124]. In turn, weakening of ventromedial PFC function may decrease descending pain-inhibitory signals, with relative unleashing of ascending noxious input and therefore continuing and increased pain. As a maladaptive consequence of persistent pain, lack of ventromedial responsiveness would not only change the subjective appraisal of the pain experience but would also limit the system’s capacities to react adaptively to ascending pain signals.

2.12. Other features of neuropathic alldynia

Table 1 and 2 and Fig. 2 also show a drastic decrease in the reporting of lateral prefrontal cortex activation in neuropathic hyperalgesia and alldynia as compared with experimental studies (50% vs 90%). Lateral PFC can exert active control on pain perception through top-down influences on sensory cortices and, via the thalamus and the cingulate, on midbrain structures [166,250]. Data from experimental models in rodents have not yielded univocal results: although ventromedial PFC stimulation is quite consistently antinociceptive [4,99], that of lateral PFC has been occasionally found to enhance nociceptive responses (shorten the latency of tail flick and enhance activity of rostroventral “on” cells) [112]. Given the enormous volume of prefrontal cortex in humans, it is likely that multiple interacting networks with different contributions to pain processing are simultaneously active during experimental and neuropathic alldynia, precluding any firm discussion at this point.

2.13. Conclusions

Data reviewed in this article allow the drawing of some tentative mechanistic conclusions concerning the relationship between brain activity and normal and abnormal pain sensations. Concerning neuropathic pain, studies with larger sample sizes are badly needed, as is adequate control of a number of crucial variables, including fluctuations of spontaneous pain, magnitude of sensory deafferentation, changes in brain morphology, and baseline blood
flow or blood-oxygen-level dependence signals at rest. Yet, although largely incomplete, existing data also show that functional imaging is now able to go beyond the phenomenological description of a physiological photograph and propose testable hypotheses that will, or will not come, in the subsequent years. Above all, data from dozens of laboratories in the world underscore that pain, normal or abnormal, is an emergent property of the brain, lending substance to the nociception-perception-suffering model [160]. As stated by Loeser [160], “It is suffering, not pain, that brings patients into doctors’ offices. Suffering is an suffering model [160].” Only the study of integrated brain function will underscore that pain, normal or abnormal, is an emergent property of the human brain and is dependent upon consciousness.” Only the study of integrated brain function will eventually lead to its correct understanding and proper management.

**Conflict of interest statement**

None of the authors have conflicts of interest with respect to this work.

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**References**


Further reading


