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REVIEW

From the neuromatrix to the pain matrix (and back)

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Abstract Pain is a conscious experience, crucial for survival. To investigate the neural basis of pain perception in humans, a large number of investigators apply noxious stimuli to the body of volunteers while sampling brain activity using different functional neuroimaging techniques. These responses have been shown to originate from an extensive network of brain regions, which has been christened the Pain Matrix and is often considered to represent a unique cerebral signature for pain perception. As a consequence, the Pain Matrix is often used to understand the neural mechanisms of pain in health and disease. Because the interpretation of a great number of experimental studies relies on the assumption that the brain responses elicited by nociceptive stimuli reflect the activity of a cortical network that is at least partially specific for pain, it appears crucial to ascertain whether this notion is supported by unequivocal experimental evidence. Here, we will review the original concept of the "Neuromatrix" as it was initially proposed by Melzack and its subsequent transformation into a pain-specific matrix. Through a critical discussion of the evidence in favor and against this concept of pain specificity, we show that the fraction of the neuronal activity measured using currently available macroscopic functional neuroimaging techniques (e.g., EEG, MEG, fMRI, PET) in response to transient nociceptive stimulation is likely to be largely unspecific for nociception.

Keywords Nociception · Pain matrix · Saliency · Multimodal · fMRI · EEG

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Introduction

Nociception is defined as the afferent neural activity transmitting sensory information about noxious stimuli (Treede 2006). Although nociception is most often the cause of pain, it is not synonymous with pain, which is a conscious experience that can even occur in the absence of nociception. Similarly, the activation of nociceptors can trigger a reflexive motor withdrawal, or an autonomic response, without necessarily generating a conscious experience of pain. While it is now unanimously accepted that cortical activity is required for the generation of a painful experience (Treede et al. 1999), this has not always been the case. Indeed, besides Descartes' proposition that pain derives from nociceptive projections onto the pineal gland, which was considered as "*le siège de l'âme*" (Descartes 1649), the idea that the perception of pain originates from thalamic rather than cortical activity had been considered for a number of years (Head and Holmes 1911).

Investigating the cortical basis of perception in humans has been revolutionized by the introduction of non-invasive neuroimaging techniques that provide in vivo information about cortical function. Whereas electrophysiological techniques such as electroencephalography (EEG) measure voltage changes generated mainly by synchronized post-synaptic activity occurring in cortical pyramidal cells (Speckmann and Elger 1999), hemodynamic techniques

such as functional magnetic resonance imaging (fMRI) performed using the blood oxygen level–dependent (BOLD) contrast measure local changes in blood oxygenation resulting from neuronal activity and neurovascular coupling (Kwong et al. 1992).

During the past 30 years, researchers have extensively used these and other functional imaging techniques to investigate the neural basis of pain perception and shown that nociceptive stimuli commonly elicit activity within a very wide array of subcortical and cortical brain structures (Garcia-Larrea et al. 2003; Bushnell and Apkarian 2005). When interpreting the functional significance of these brain responses, initial reports have been extremely cautious (Carmon et al. 1976; Chapman et al. 1981a; Stowell 1984). For example, in his seminal paper introducing laser-evoked brain potentials (LEPs) as a technique to explore nociception in humans, Carmon et al. concluded that "it is possible that only the arousing and alerting effect of pain is responsible for the electroencephalographic phenomenon observed" (Carmon et al. 1976). Similarly, Chapman et al. stated, a few years later, that "amplitudes [of event-related potentials (ERPs) elicited by noxious stimuli] cannot be considered neurophysiological representations of pain sensations" (Chapman et al. 1981b). As the number of studies focusing on these brain responses increased exponentially, this carefulness has been somewhat lost. Indeed, at present, most investigators consider that because the stimulus elicits a sensation of pain, it is reasonable to assume that the elicited brain responses are at least partially pain specific (Talbot et al. 1991; Jones 1998a; Ingvar 1999; Ingvar and Hsieg 1999; Ploghaus et al. 1999; Avenanti et al. 2005; Brooks and Tracey 2005; Stern et al. 2006; Tracey and Mantyh 2007; Boly et al. 2008; Whyte 2008). Hence, structures such as the primary (S1) and secondary (S2) somatosensory cortices, the insula and the anterior cingulate cortex (ACC), which have been consistently shown to respond to nociceptive stimulation using either fMRI, positron emission tomography (PET), EEG or magnetoencephalography (MEG), are often considered to constitute a Pain Matrix, i.e., a network of cortical areas "mediating pain experience itself" (Ploghaus et al. 1999). Building further on the conception that these brain responses are pain specific, recent studies have proposed that this Pain Matrix may also be involved in experiencing, for example, empathy for pain (Singer et al. 2004; Godinho et al. 2006; Valeriani et al. 2008) or social rejection (Eisenberger et al. 2003). Most importantly, some investigators have proposed that the Pain Matrix could be used as a specific biomarker for drug development (Schweinhardt et al. 2006), as "objective evidence of pain perception" in minimally conscious patients (Boly et al. 2008) or even as an "objective measure of pain" that could constitute medico-legal evidence when seeking compensation (Miller 2009).

To support the idea that this measured pattern of brain activity is pain specific, investigators often put forward the following arguments: (1) that the perceived intensity of pain correlates strongly with the magnitude of the neural responses in the Pain Matrix (e.g., Derbyshire et al. 1997; Coghill et al. 1999; Tolle et al. 1999; Iannetti et al. 2005), (2) that factors modulating pain also modulate the magnitude of the neural responses in the Pain Matrix (Rainville et al. 1997; Hofbauer et al. 2001), (3) that epileptic seizures or direct electrical stimulation of various areas of the Pain Matrix through implanted electrodes can evoke painful sensations (Isnard et al. 2000; Ostrowsky et al. 2002). Therefore, the Pain Matrix would constitute a "representation" (Treede et al. 1999) or a "signature" (Tracey and Mantyh 2007) of pain in the brain and, thereby, a window to study the neural processes underlying pain function and dysfunction in humans (Apkarian et al. 2005).

Because the interpretation of a great number of studies relies on the notion that the brain responses elicited by nociceptive stimuli reflect the activity of a pain-specific cortical matrix, it appears crucial to ascertain whether this notion is supported by solid and unequivocal experimental evidence. Here, we will review the original concept of the "Neuromatrix" as it was initially proposed by Melzack (1989), and, through a critical discussion of the evidence in favor and against the concept of a Pain Matrix, we will provide evidence that the fraction of the neuronal activity measured using currently available functional neuroimaging techniques in response to a transient nociceptive stimulus is likely to largely reflect neural activities that are not nociceptive specific. Crucially, this notion by no means implies the lack of assemblies of neurons whose activity is uniquely related to the perception of pain, whereas it does imply that the contribution of pain-specific neural activities to the responses measured using current functional neuroimaging techniques may be negligible.

The "pain matrix": a concept that changed over time

It is difficult to provide a unique definition of the Pain Matrix. The term is derived from the Neuromatrix, a concept that was originally proposed by Ronald Melzack in 1989. However, the term "Pain Matrix" is currently used in a sense very different from its initial conception. As a matter of fact, the Neuromatrix was originally proposed *because* researchers had failed to identify spatially segregated cortical regions specifically devoted to the perception of pain. Most importantly, the function of the Neuromatrix was not restricted to the perception of pain, which was considered to be only one of its many possible perceptual outputs. Accordingly, the Neuromatrix was described as a widespread ensemble of neurons integrating various

sources of input, both nociceptive and non-nociceptive, in a Hebbian fashion. In other words, in its original definition, the Neuromatrix was certainly not pain specific: "the neuromatrix, distributed throughout many areas of the brain, comprises a widespread network of neurons that generates patterns, processes information that flows through it and ultimately produces the pattern that is felt as a whole body possessing a sense of self" (Melzack 2005).

It is only in later publications that the label "pain" was added to the term "Neuromatrix", leading to the current concept of a Pain Matrix (e.g., Talbot et al. 1991; Jones 1998a; Ingvar 1999; Ploghaus et al. 1999; Avenanti et al. 2005; Brooks and Tracey 2005; Boly et al. 2008; Whyte 2008). This relabeling introduced a fundamental deviation from the original concept, as it implied that the pattern of brain responses elicited by nociceptive stimuli reflects a specific "pain processing network" (Brooks and Tracey 2005), and that functional neuroimaging may be used to "delineate the functional anatomy of different aspects of pain" (Ingvar 1999).

Thus, at present, there seems to be a rather large consensus that the Pain Matrix is at least partially pain specific. However, this does not entail that all investigators agree on its definition. Indeed, some consider that it is the pattern of activation in the different structures of the Pain Matrix that constitutes, as an ensemble, the neural substrate for pain perception. In this view, the emergence of pain would not result from the activation of one or more specific brain areas but would emerge "from the flow and integration of information" among these areas (Tracey 2005). Therefore, this view is different from the original Neuromatrix concept only in the sense that the experience of pain is considered as the only possible output of the network. Others have deviated further from the original concept, by considering the Pain Matrix as an enumeration of different pain-specific structures of the brain (Albe-Fessard et al. 1985; Ingvar 1999). In such, the experience of pain is no longer an emergent property of the network. Instead, the different structures constituting the Pain Matrix are considered to have "specialized subfunctions" (Ingvar 1999) and, thereby, self-standingly encode different aspects of the pain experience. For example, sensory-discriminative aspects of pain perception are often thought to be independently and specifically represented in S1 and S2, constituting the so-called "lateral pain system" or "somatosensory node", while affective aspects of pain perception would be represented in medial brain structures such as the ACC, constituting the "medial pain system" or "affective node" (Albe-Fessard et al. 1985; Avenanti et al. 2005). Many recent studies have relied on this latest concept to interpret their data (e.g., Derbyshire et al. 1997; Schnitzler and Ploner 2000; Garcia-Larrea et al. 2002; Ploner et al. 2002; Gracely et al. 2004; Kakigi et al. 2004; Singer et al. 2004; Avenanti et al. 2005; Brooks and Tracey 2005; Moisset and Bouhassira 2007; Frot et al. 2008).

Evidence used to support the concept of a pain matrix

The ability to appreciate the different qualities of a painful percept elicited by a nociceptive stimulus is certainly sufficient to postulate the existence of "pain-specific" cortical activity. The evidence commonly used to support the concept that this "pain-specific" cortical activity is reflected in the Pain Matrix can be summarized as follows.

In *most* experimental conditions, the cortical structures constituting the Pain Matrix are activated by nociceptive stimuli or by stimuli that are perceived as painful (for a review, see Garcia-Larrea et al. 2003; Bushnell and Apkarian 2005). Indeed, whatever the method used to sample brain activity, applying a noxious stimulus is likely to elicit activity within S1, S2, the insula and the ACC.

In *most* experimental conditions, the magnitude of the Pain Matrix response correlates strongly with the intensity of pain perception (e.g., Derbyshire et al. 1997; Coghill et al. 1999; Tolle et al. 1999; Iannetti et al. 2005). This relationship has been studied extensively, mainly by recording the magnitude of the brain responses elicited by nociceptive stimuli of graded energies. The finding of a robust correlation between response magnitude and pain perception has been used to suggest that one of the main functions of the Pain Matrix is to encode pain intensity (Rainville 2002; Porro 2003).

Experimental factors that modulate selectively different aspects of the pain experience (e.g., pain intensity, pain unpleasantness) can also modulate selectively the activity within specific regions of the Pain Matrix. For example, a hypnotic suggestion of increased intensity of pain perception has been shown to increase selectively the response magnitude in S1 and S2, whereas a hypnotic suggestion of increased pain unpleasantness has been shown to increase selectively the response magnitude in the ACC (Rainville et al. 1997; Hofbauer et al. 2001). Despite the fact that these observations have not yet been replicated, they have been used as evidence that different regions of the Pain Matrix "process" different aspects of the pain experience; whereas S1 and S2 (part of the so-called lateral pain system) would encode the sensory-discriminative aspects of pain perception, the ACC (part of the so-called medial pain system) would encode the affective dimension of pain perception.

Finally, it has been shown that in epileptic patients implanted with intra-cerebral electrodes, stimulation of S2 or the insula can elicit painful sensations (Ostrowsky et al. 2002). Similarly, pain has been described as a manifestation of epileptic seizures occurring in the insula (reviewed in Charlesworth et al. 2009; see also Isnard et al. 2004).

Expectedly, the prospect of being able to measure non-invasively the neural activity underlying the different aspects of pain perception has generated a great amount of enthusiasm in the field of pain neuroscience, by opening the possibility of using functional neuroimaging to understand how pain is represented in the brain and how this representation may be modulated by specific experimental factors, as well as to develop pain-relieving strategies. However, as we will show in the following section, there is increasing evidence suggesting that the Pain Matrix identified using the currently available functional neuroimaging techniques is by no means specifically related to the perception of pain.

Evidence against the concept of a pain matrix

Anatomical and physiological properties of nociceptive-specific cortical neurons

Spatially segregated primary cortical areas devoted to the initial processing of thalamo-cortical sensory input have been identified in most sensory modalities (Kandel et al. 2000). In contrast, no cortical area devoted exclusively to the initial processing of thalamo-cortical nociceptive input (i.e., a primary nociceptive cortex) has ever been clearly identified.[1]

Mountcastle showed that neurons having similar receptive fields and response properties are arranged in vertical cortical columns that have been hypothesized to constitute an "elementary unit of organization" (Mountcastle 1957). This functional organization of cortical neurons has been shown clearly in the primary visual, auditory and somatosensory cortices (Mountcastle et al. 1957; Hubel and Wiesel 1968; Imig and Adrian 1977). In the primary somatosensory cortex, neurons within a given cortical column respond preferentially to a given submodality of somatosensation, such as light touch or deep pressure. In contrast, cortical columns responding preferentially to nociceptive stimuli have never been described. Indeed, somatosensory cortical columns containing neurons responding to nociceptive stimulation also contain neurons responding to non-nociceptive stimulation (Kenshalo et al. 2000).

Nevertheless, a large number of electrophysiological studies in non-human primates and other animals have identified nociceptive-specific neurons in different regions of the Pain Matrix, such as S1 and S2, the insula and the ACC (Whitsel et al. 1969; Robinson and Burton 1980; Kenshalo and Isensee 1983; Sikes and Vogt 1992; Yamamura et al. 1996; Kenshalo et al. 2000). However, a common finding across most of these studies is that nociceptive-specific neurons are sparsely distributed in space. Furthermore, it is important to highlight that nociceptive-specific neurons are often defined as such because they respond to high-intensity but not to low-intensity somatosensory stimuli. However, at least a fraction of these supposedly nociceptive-specific neurons may also respond to stimuli belonging to other sensory modalities, for example, to the occurrence of a threatening visual stimulus (Dong et al. 1994; Kenshalo and Douglass 1995; Hutchison et al. 1999). Taken together, such observations have led Patrick Wall to conclude that "it remains an act of faith to continue searching the brain and spinal cord for some still undiscovered nest of cells whose activity reliably triggers pain" (Wall 1995).

Nevertheless, recent studies have shown that some cortical regions are more densely populated by neurons responding preferentially to noxious stimuli. For example, Whitsel et al. (2009) described that unlike area 3b, area 3a of the primary somatosensory cortex of monkeys contains a large number of neurons that respond vigorously to nociceptive stimulation. However, the investigators also observed a "discrepancy between the time course of area 3a neuron activation and the human pain experience", thus questioning the involvement of these neurons in generating conscious painful percepts.

A large number of anatomical tracing studies have also attempted to define the cortical targets of nociceptive input (Craig et al. 1994; Craig 2003). In a very careful study using anterograde transneuronal viral tracing in monkeys, Dum et al. (2009) showed that spinothalamic nociceptive input reaches multiple cortical areas, in particular, the insular cortex, S2 and several subregions of the cingulate cortex, i.e., some of the key regions of the Pain Matrix. However, these findings cannot provide information as to whether these cortical targets are specifically involved in experiencing pain or whether they are also involved in the processing of salient, yet not necessarily nociceptive, sensory inputs. In fact, based on a meta-analysis of various fMRI studies, the authors concluded that a great part of these nociceptive projections, and particularly those targeting the cingulate cortex, could be mainly involved in action or the "evaluation of the consequence of action" and, hence, be largely unspecific for nociception.

In summary, notwithstanding the fact that several brain regions remain to be systematically studied using single-cell electrophysiology, especially in preparations where anesthesia is not a confound, the current lack of evidence

[1] Craig et al. (2000) proposed that the posterior insula may constitute a primary "thermosensory cortex". However, this claim is based mainly on the finding that the magnitude of the responses elicited in this area correlates linearly with the intensity of the noxious stimulus. As shown in the next section, the observation of such a correlation could be satisfactorily explained by the fact that stimuli of greater intensity are also more salient.

for nociceptive cortical columns, together with the small number and the sparse distribution of nociceptive-specific neurons in most of the cortical regions constituting the Pain Matrix, suggests that, at cortical level, nociception may not be represented as a distinct sensory modality or even as a distinct submodality of somatosensation (Andersson and Rydenhag 1985).

Disruption of the correlation between intensity of pain and magnitude of the pain matrix response

Functional neuroimaging studies using fMRI or PET have shown that the magnitude of the responses in the Pain Matrix can predict the amount of pain perceived by a human subject (Derbyshire et al. 1997; Porro et al. 1998; Coghill et al. 1999; Tolle et al. 1999; Bornhovd et al. 2002; Buchel et al. 2002). Similarly, electrophysiological studies using EEG and MEG have shown that the magnitude of nociceptive ERPs and event-related magnetic fields may correlate extremely well with the energy of the applied stimulus and, even better, with the perceived intensity of pain (Carmon et al. 1978; Beydoun et al. 1993; Arendt-Nielsen 1994; Plaghki et al. 1994; Garcia-Larrea et al. 1997; Timmermann et al. 2001; Mouraux et al. 2003; Ohara et al. 2004; Iannetti et al. 2005; Frot et al. 2007). For these reasons, it has been suggested that one of the main functions of the Pain Matrix is to encode the intensity of pain perception (e.g., Rainville 2002; Porro 2003).

However, recent studies using EEG have shown that, in a number of circumstances, the magnitude of the elicited brain responses can be clearly dissociated from both the intensity of the nociceptive stimulus and that of perceived pain (Chapman et al. 1981a; Dillmann et al. 2000; Mouraux et al. 2004; Mouraux and Plaghki 2007; Clark et al. 2008; Iannetti et al. 2008; Lee et al. 2009). For instance, Iannetti et al. (2008) delivered trains of three identical nociceptive laser pulses with a constant 1-s inter-stimulus interval, using four different stimulus energies. The magnitude of the nociceptive ERP elicited by the first stimulus of the train was strongly correlated with both the energy of the laser stimulus and the perceived pain intensity. In contrast, when considering the ERPs elicited by the second and third stimulus of the train, this correlation was markedly disrupted: although the first, the second and the third stimulus of the triplet elicited the same amount of pain, related to the energy of the laser stimulus, the magnitudes of the ERPs elicited by the second and the third stimulus were significantly decreased, and, most importantly, were no longer related to either the intensity of perceived pain or to the energy of the laser stimulus. Clark et al. (2008) obtained a similar result. By cueing nociceptive laser stimuli with preceding visual stimuli, they found that the delay between this visual cue and the nociceptive stimulus affected differently the intensity of perception and the magnitude of the elicited ERP. Whereas the intensity of perception was increased for longer delays, the magnitude of the ERP was unaffected by the delay duration. Instead, the magnitude of the ERP was increased when the duration of the delay was unpredictable, whereas the intensity of perception was not. Using an adaptive staircase algorithm, Lee et al. (2009) also showed that the magnitude of the elicited ERPs can be clearly dissociated from the intensity of perceived pain: when two nociceptive laser stimuli are presented at very short inter-stimulus intervals (e.g., 250 ms), the second stimulus elicits a distinct ERP even though it does not elicit a distinct percept. All these observations constitute strong evidence against the view that one of the main functions of the Pain Matrix is to encode the intensity of pain perceived.

The influence of the context on the pain matrix response

When a nociceptive stimulus is repeated at short and constant inter-stimulus interval, it elicits an ERP of smaller magnitude (e.g., Mouraux and Iannetti 2008). This effect of stimulus repetition is largely determined by the duration of the inter-stimulus interval: the shorter the interval, the more pronounced the response decrement (Bromm and Treede 1987; Raij et al. 2003; Truini et al. 2004; Truini et al. 2007). Previous studies have shown that the effect of stimulus repetition on the magnitude of nociceptive ERPs cannot be attributed to refractoriness of the afferent neural pathways or of the underlying cortical generators. Indeed, stimulus repetition affects the magnitude of nociceptive ERPs only if the inter-stimulus interval remains constant from trial-to-trial, but it does not if the inter-stimulus interval is varied randomly from trial-to-trial (Mouraux et al. 2004; Wang et al. in press). In other words, the effect of stimulus repetition appears to be strongly conditioned by the *context* within which the repetition occurs. The response reduction observed when the inter-stimulus interval is constant across trials could thus be the result of both bottom–up and top–down modulations, related to the fact that the repeated stimulus is both less novel and less unpredictable.

Importantly, a large number of studies have shown that also the magnitude of vertex potentials elicited by non-nociceptive somatosensory and even by non-somatosensory stimuli (e.g., auditory stimuli) is similarly modulated by stimulus repetition. Indeed, the amplitude of these vertex potentials is strongly reduced only when stimuli are repeated using a constant inter-stimulus interval, but not when stimuli are repeated using a varying inter-stimulus interval (Loveless et al. 1989; Budd and Michie 1994; Wang et al.

2008). This suggests that nociceptive ERPs and vertex potentials reflect similar brain processes, which are largely multimodal (i.e., independent of the activated sensory channel) and strongly dependent on the context in which the stimuli are presented.

The influence of the attentional context on the magnitude of the Pain Matrix response has been also investigated directly in experiments examining the effect of novelty (i.e., the difference in one or more physical dimensions in respect to previously occurring stimuli). In a series of elegant studies, Legrain et al. (2002, 2003, 2009b) have shown that when a long, regular and monotonous sequence of nociceptive laser stimuli are presented and a small number of novel stimuli (<20%) are randomly interspersed within this sequence, novel nociceptive stimuli elicit ERPs of increased magnitude, regardless of the physical property defining the novel stimulus from the standard stimulus (e.g., an increase in stimulus energy or a change in location). These findings suggest that the observed effect of novelty is not related to the processing of a particular physical feature of the stimulus, but to novelty per se.

Activation of the pain matrix by non-nociceptive sensory input

Several studies have highlighted that the EEG and fMRI responses elicited by nociceptive somatosensory stimuli are extremely similar to the EEG and fMRI responses elicited by non-nociceptive somatosensory stimuli (e.g., Kunde and Treede 1993; Lui et al. 2008). Furthermore, two recent studies have compared the brain responses elicited by nociceptive stimuli that were perceived as painful with the brain responses elicited by non-nociceptive somatosensory stimuli, as well as auditory and visual stimuli (Mouraux and Iannetti 2009; Iannetti et al. 2010). In both studies, the stimuli were presented within a random sequence, using a large and unpredictable inter-stimulus interval (5–10 s), in order to maximize their saliency content. In the study conducted using EEG (Mouraux and Iannetti 2009), a novel blind source separation technique (probabilistic independent component analysis, PICA; Beckmann and Smith 2004) was applied to decompose nociceptive, somatosensory, auditory and visual ERPs into a set of physiologically independent components. The results showed that ERPs elicited by nociceptive stimuli can be entirely explained by a combination of multimodal neural activity (i.e., neural activity that is elicited by any sensory stimulus, independently of its sensory modality) and somatosensory-specific, but not nociceptive-specific neural activity (i.e., neural activity that is elicited by both nociceptive and non-nociceptive somatosensory stimuli). Source analysis showed that the multimodal neural activity underlying nociceptive ERPs was optimally modeled by generators located in bilateral operculoinsular areas and in the ACC, thus suggesting that multimodal neural activity could explain a large part of the Pain Matrix. Importantly, although the blind source separation algorithm succeeded in identifying modality-specific neural activity contributing uniquely to non-nociceptive somatosensory, auditory and visual ERPs, not a single component contributed uniquely to the nociceptive ERP. In the study performed using fMRI (Iannetti et al. 2010), the hemodynamic responses elicited by the same types of stimuli were examined. A conjunction analysis showed that nociceptive, somatosensory, auditory and visual stimuli elicited spatially indistinguishable responses in the insula, in most of S2, as well as in the ACC. In addition to this multimodal activity, nociceptive and non-nociceptive somatosensory stimuli elicited an identical response in S1 and in a small region of S2. Strikingly, whereas auditory stimuli elicited a clear auditory-specific response in the primary auditory cortex and whereas visual stimuli elicited a clear visual-specific response in primary visual cortex, nociceptive stimuli did not appear to elicit any nociceptive-specific response.

These observations suggest that the Pain Matrix identified using currently available functional neuroimaging techniques that sample neural activity at population level (Speckmann and Elger 1999; Logothetis 2008) mainly reflects multimodal neural activity, i.e., the activity of neurons that respond to a range of stimuli, regardless of their sensory modality. However, the possibility that the activity of nociceptive-specific neurons does contribute to the responses recorded using these techniques but cannot be isolated from the activity of spatially intermixed, non-nociceptive-specific neurons cannot be ruled out. In any case, it is important to emphasize that in all regions of the Pain Matrix, the number of nociceptive-specific neurons is usually very small, especially when compared to the number of non-specific wide-dynamic range neurons (Dong et al. 1994; Kenshalo and Douglass 1995). Furthermore, single-cell studies have shown that at least some cortical neurons labeled as nociceptive-specific may also respond to stimuli belonging to another sensory modality, e.g., to a "menacing" visual stimulus (Dong et al. 1994; Kenshalo and Douglass 1995; Hutchison et al. 1999), thus suggesting that at least a fraction of these neurons are in fact multimodal and respond to potentially threatening sensory inputs, regardless of the sensory modality through which they are conveyed.

Interestingly, as mentioned in the Introduction, Melzack initially proposed that the experience of pain could emerge from the transient binding of a widespread network of neurons (Melzack 1989, 2005) and not from the activity of a spatially segregated cortical area containing nociceptive-specific neurons specifically and exclusively "encoding"

pain in the brain. Such a view would explain why both conventional macroscopic and microscopic neuroimaging approaches have repeatedly failed to isolate an unequivocal "neural representation" of pain in the brain.

Direct electrical stimulation of the pain matrix, ictal pain and lesion studies

In surgically implanted epileptic patients, the direct electrical stimulation of different areas of the Pain Matrix (e.g., S2 or the insula) can elicit painful sensations (Ostrowsky et al. 2002; Isnard et al. 2004). Although this observation is commonly interpreted as evidence that the stimulated region is specifically involved in generating conscious painful percepts, it is important to consider that in the study by Ostrowsky et al. (2002) painful sensations were elicited in only 17 out of 93 stimulation sites (18.2%) and in only 14 out of 43 patients (32.5%). Importantly, the areas whose stimulation elicited painful and non-painful somesthetic sensations were not spatially distinct, a finding that lead Ostrowsky et al. to conclude that "painful and non-painful somesthetic insular representations overlap". Furthermore, direct electrical stimulation of other parts of the Pain Matrix, such as the ACC, does not elicit painful sensations (Bancaud et al. 1976). Instead, it often produces a behavior characterized by arousal, motor activities and a diffuse "urge to move".

Similarly, although pain is a recognized manifestation of epileptic seizures (Young and Blume 1983; Isnard et al. 2004; Charlesworth et al. 2009), its occurrence is extremely uncommon (e.g., less than 3% in a series of 858 epileptic patients; Young and Blume 1983). Importantly, pain is virtually never the sole manifestation of a seizure (e.g., in a series of 8,939 patients with epilepsy, only 0.02% had seizures that were exclusively painful; Mauguiere and Courjon 1978). Instead, ictal pain is most often associated with the perception of non-painful paresthesias, thermal sensations, or a disturbance of somatognosia.

Although it has been observed that lesions of the operculo-insular region may increase pain thresholds (Greenspan and Winfield 1992; Greenspan et al. 1999), Starr et al. (2009) recently reported that two patients with extensive insular damage retained their ability to perceive and evaluate pain. In fact, both patients had significantly enhanced pain intensity ratings in response to suprathreshold noxious stimuli, leading the investigators to conclude that "a subjectively available experience of pain can be instantiated by brain mechanisms that do not require the insular cortex". Similarly, lesions of the ACC do not affect the ability to discriminate the sensory aspects of nociceptive stimuli, although these stimuli may no longer trigger marked avoidance behaviors (Foltz and White 1962, 1968; Hurt and Ballantine 1973; Corkin and Hebben 1981).

A multimodal network related to the detection of saliency?

The saliency of a given sensory stimulus is commonly defined as its ability to stand out relative to the background (Itti and Koch 2001). Therefore, the saliency of a stimulus is not defined by a particular physical dimension of the stimulus, but by how much the stimulus contrasts with its surrounding, along one or more physical dimensions (Itti and Koch 2001; Fecteau and Munoz 2006; Knudsen 2007; Yantis 2008). For example, a red poppy is salient when it stands isolated in a green grass field, but not when it is surrounded by hundreds of other red poppies. Stimulus saliency is also defined by how much the stimulus contrasts with past experiences (Naatanen and Picton 1987; Kayser et al. 2005; Naatanen et al. 2007). For example, the repeated ringing noise produced by a telephone will stand out more when it rings for the first time. It is generally recognized that the ability to detect, reorient attention and prioritize the cortical processing of salient sensory input is crucial for survival (Legrain et al. 2009a; Van Damme et al. 2010). Indeed, this ability allows individuals to adapt swiftly and efficiently their behavior to the changing environment. Because of their noxious nature, nociceptive stimuli have intrinsically high saliency content, and for this reason, this ability to detect and react to salient sensory input is often considered as one of the most important function of nociception.

Because the functional imaging responses to noxious stimuli do not appear to reflect nociceptive-specific neural activity, we suggest that they instead reflect, as originally proposed by Melzack for the Neuromatrix, the activity of a multimodal neural network. Furthermore, because the magnitude of the Pain Matrix response seems largely determined by factors that are known to modulate saliency (e.g., novelty and uncertainty), we propose that this multimodal network is mainly devoted to the detection and reaction to salient sensory input. This hypothesis agrees well with the results by Downar et al. (2000, 2003), showing that sudden changes in the sensory environment, independently of their sensory modality, elicit activity within a wide cortical network whose spatial distribution closely matches that of the Pain Matrix. Also, it agrees with the recent study by Seeley et al. (2007), who, using a task-free connectivity analysis of fMRI data, identified a "salience network" including several key regions of the Pain Matrix.

Viewing the Pain Matrix as a multimodal network related to the detection of salient sensory input would account for a number of experimental observations. First, it would account for the fact that nociceptive stimuli consistently elicit activity within this network of brain areas. Indeed, because of their homeostatic relevance, nociceptive

stimuli often have inherently high saliency content. Most importantly, this saliency hypothesis would account for the fact that in most (but not all) cases, the magnitude of the brain responses elicited by nociceptive stimuli correlates strongly with the intensity of the stimulus and/or with the intensity of pain perception. Indeed, when stimuli of graded energy are presented within the same attentional context, stimuli of greater energy are also unavoidably more salient (i.e., they are more contrasted relative to the surrounding environment).

Furthermore, this saliency hypothesis would also explain why watching a noxious stimulus delivered to another individual or watching a cue indicating the delivery of such a stimulus (in particular to someone we care about; Singer et al. 2004; Jackson et al. 2005), as well as watching a menacing stimulus such as a needle approaching the hand (Cheng et al. 2007), or even experiencing social rejection (Eisenberger et al. 2003) may elicit activity within the Pain Matrix. Indeed, although none of these stimuli activate nociceptors, they all have high saliency content.

Lastly, the saliency hypothesis could also contribute to explaining why concurrent innocuous somatosensory stimulation (e.g., continuous brushing of the skin surrounding the area where the noxious stimulus is applied) strongly reduces the magnitude of the responses elicited by nociceptive stimuli in the so-called Pain Matrix (Kakigi and Shibasaki 1992; Nahra and Plaghki 2003): undoubtedly, the additional innocuous somesthetic input reduces the contrast of the nociceptive stimulus relative to its surrounding and thus reduces its saliency content.

In the classical hierarchical view of sensory processing, multimodal cortical activity mainly reflects higher-order sensory and cognitive processes that occur after sensory information has undergone preliminary processing through modality-specific cortical structures (Mesulam 1998; Kaas and Collins 2001). However, another possibility is that at least part of the multimodal cortical responses is consequent to the convergence, already at subcortical level, of various sources of sensory information belonging to different sensory modalities (Andersson and Rydenhag 1985; Dum et al. 2009). Direct multimodal thalamo-cortical input could originate from unspecific laminar thalamic nuclei, probably part of the previously described "thalamic matrix", constituted by calbindin-positive cells that are present in all thalamic nuclei, and thus ignore the classical nuclear organization of the thalamus (Jones 1998b, 2002). The "thalamic matrix" projects diffusely to virtually all sensory and motor cortices and especially to the ACC. Thus, this parallel thalamic system could represent one of the neuroanatomical substrates for the multimodal cortical responses constituting the largest part of the Pain Matrix identified using functional neuroimaging techniques. Importantly, the activity of the "thalamic matrix" is not only driven by exogenous inputs, as it also receives widespread cortico-thalamic input and is tightly connected to the ascending reticular formation. These anatomical connections suggest a relationship to the orienting response that allows organisms to respond immediately to the occurrence of a change in its environment (Sokolov 1975), by triggering broad cortical activation following the detection of salient events, regardless of the sensory modality through which these events are conveyed.

Conclusion

We provide evidence suggesting that the brain responses to nociceptive stimuli measured using functional neuroimaging techniques that sample neural activity at population level (i.e., EEG, MEG, fMRI, PET) do not reflect nociceptive-specific brain activities, but, instead, brain activities equally involved in processing nociceptive and non-nociceptive salient sensory input. We hypothesize that at least part of these responses are involved in the detection of salient sensory events, regardless of whether these sensory events are conveyed by nociceptive pathways and also regardless of whether they are perceived as painful. Therefore, we suggest that the term "Pain Matrix" should be used with caution, because it misleadingly implies that the recorded responses are specific for pain.

Importantly, our hypothesis by no means implies the lack of assemblies of neurons whose activity is uniquely related to the perception of pain, or that the responses to nociceptive stimuli sampled by functional neuroimaging techniques do not reflect a crucial function for nociception. Instead, it suggests that these neuroimaging responses reflect a function that is crucial for *all* sensory systems: the ability to detect and react to salient (and possibly threatening) sensory input and thereby trigger swift and appropriate behavioral responses.

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