# The Pain Matrix Reloaded.

# A Salience Detection System for the Body.

Valéry Legrain[1,2,*], Gian Domenico Iannetti[3], Léon Plaghki[2], André Mouraux[2].

[1] Department of Experimental-Clinical and Health Psychology, Ghent University, Belgium.

[2] Institute of Neuroscience (IoNS), Université catholique de Louvain, Belgium.

[3] Department of Neuroscience, Physiology & Pharmacology, University College London, United Kingdom.

* Corresponding author: Department of Experimental-Clinical and Health Psychology, Ghent University, Henri Dunantlaan 2, 9000 Ghent, Belgium Tel.: +32 9 264 91 43. Fax.: +32 9 264 64 89.

E-mail address: valery.legrain@ugent.be

**ABSTRACT** (word count: 247)

Neuroimaging and neurophysiological studies have shown that nociceptive stimuli elicit responses in an extensive cortical network including somatosensory, insular and cingulate areas, as well as frontal and parietal areas. This network, often referred to as the "*pain matrix*", is viewed as representing the activity by which the intensity and unpleasantness of the percept elicited by a nociceptive stimulus are represented. However, recent experiments have reported (i) that pain intensity can be dissociated from the magnitude of responses in the "*pain matrix*", (ii) that the responses in the "*pain matrix*" are strongly influenced by the context within which the nociceptive stimuli appears, and (iii) that non-nociceptive stimuli can elicit cortical responses with a spatial configuration similar to that of the "*pain matrix*". For these reasons, we propose an alternative view of the functional significance of this cortical network, in which it reflects a system involved in detecting, orienting attention towards, and reacting to the occurrence of salient sensory events. This cortical network might represent a basic mechanism through which significant events for the body's integrity are detected, regardless of the sensory channel through which these events are conveyed. This function would involve the construction of a multimodal cortical representation of the body and nearby space. Under the assumption that this network acts as a defensive system signaling potentially damaging threats for the body, emphasis is no longer on the quality of the sensation elicited by noxious stimuli but on the action prompted by the occurrence of potential threats.

**KEYWORDS**

Pain, Nociception, Salience, Attention, Multimodal, Peripersonal space

## TABLE OF CONTENTS

## 1. INTRODUCTION

Nociception, which is initiated by the activation of peripheral nociceptors, may be defined as the activity in the peripheral and central nervous system elicited by mechanical, thermal or chemical stimuli having the potential to inflict tissue damage (Sherrington, 1906). However, nociception is not synonymous with pain, which is experienced as a conscious percept. Indeed, nociception can trigger brain responses without necessarily causing the feeling of pain (Baumgärtner et al., 2006; Hofbauer et al., 2004; Lee et al., 2009). On the other hand, pain can occur in the absence of nociceptive input (Nikolajsen & Jensen, 2006).

In the last decades, a very large number of studies have aimed at better understanding how the cortex processes nociceptive stimuli and how the experience of pain may emerge from this processing. In humans, most of these studies have relied on non-invasive functional neuroimaging techniques to sample, directly (e.g., electroencephalography [EEG], magnetoencephalography [MEG]) or indirectly (e.g., positron emission tomography [PET], functional magnetic resonance imaging [fMRI]) the neural activity triggered by various kinds of nociceptive stimuli. These studies have shown that nociceptive stimuli elicit responses within a very wide array of subcortical and cortical brain structures (see Apkarian et al., 2005; Bushnell & Apkarian, 2006; García-Larrea et al., 2003; Ingvar, 1999; Peyron et al., 2000; Porro, 2003; Rainville, 2002; Tracey & Mantyh, 2007; Treede et al., 1999). Because responses in some of these structures appear to be observed consistently across studies, and seem to be correlated with the perceived intensity of pain, they have been hypothesized to be preferentially involved in experiencing pain. Hence, structures such as the primary (SI) and secondary (SII) somatosensory, the cingulate and the insular cortices are often referred to as belonging to the so-called “*pain*

*matrix*", i.e. a network of cortical areas through which pain is generated from nociception (Ingvar, 1999; Peyron et al., 2000; Porro, 2003; Rainville, 2002; Tracey & Manthy, 2007)[1]. To support the idea that this network is specifically involved in the perception of pain, investigators often put forward the following arguments: (i) that the perceived intensity of pain correlates strongly with the magnitude of the neural responses in the "*pain matrix*" (Bornhövd et al., 2002; Büchel et al., 2002; Coghill et al., 1999; Derbyshire et al., 1997; Iannetti et al., 2005; Tolle et al., 1999), and (ii) that factors modulating pain also modulate the magnitude of the neural responses in the "*pain matrix*" (Hofbauer et al., 2001; Rainville et al., 1997). Therefore, the activity of that network would constitute a "*representation*" (Treede et al., 1999) or a "*signature*" (Tracey & Mantyh, 2007) of pain in the brain, and, thereby, would provide a "*window*" to study the neural processes underlying pain function and dysfunction in humans (Apkarian et al., 2005). In other words, according to many authors, nociceptive input would generate a conscious percept of pain through the activity it elicits in the network constituting the "*pain matrix*", and, hence, measuring the activity within this network would constitute a direct and objective measure of the actual experience of pain (Borsook et al., 2010).

It is actually difficult to provide a unique and consensual definition of the "*pain matrix*". Some authors do not consider each area belonging to the "*pain matrix*" as specifically and individually involved in the perception of pain. Instead, they propose

[1] It should be emphasized that although SI, SII, the insula and the cingulate cortex are often considered to constitute the core of the so-called "*pain matrix*", several studies have shown that other brain structures can respond to nociceptive stimuli, such as the amygdala, the prefrontal and parietal cortices, various parts of the brainstem, as well as the cerebellum. These are often not explicitly included in the "*pain matrix*" either because they have not been consistently identified as responding to nociceptive input across different studies (Peyron et al., 2000), or because of the a priori assumption that they reflect brain processes that are unspecific for pain (Apkarian et al., 2005). For example, the amygdala is thought to be involved in assigning emotional valence to any type of stimulus (Tracey & Mantyh, 2007), whereas prefrontal and parietal cortices are thought to be involved in the direction of attention towards any type of stimulus (Peyron et al., 2000). Finally, the rostral part of the prefrontal cortex and the periaqueductal grey matter are thought to participate to descending nociceptive control mechanisms, and, hence, to modulate but not contribute directly the emergence of a painful percept (Tracey & Mantyh, 2007).

that the different areas form an ensemble of interplaying parts, and that it is the pattern of activation of this ensemble that contributes to the elaboration of the painful percept (e.g. Tracey & Mantyh, 2007). Other investigators consider the "*pain matrix*" as a collection of areas, each having specialized sub-functions, and, therefore, encoding a specific aspect of the pain experience (e.g. Ingvar, 1999; Porro, 2003; Rainville, 2002). Whatsoever, a great number of recent studies have relied on the notion that observing a pattern of brain activity similar to the so-called "*pain matrix*" can be considered as unequivocal and objective evidence that a given individual is experiencing pain, including in clinical pain states (Bushnell & Apkarian, 2006; Borsook et al., 2010; Ingvar, 1999).

Very recently, several studies have shown that this brain network cannot be reduced to a mere cortical "*representation*" of pain. Indeed, these studies have shown that the activity of the so-called "*pain matrix*" (i) can be clearly dissociated from the perception of pain intensity (Clark et al., 2008; Dillmann et al., 2000; Iannetti et al., 2008; Kulkarni et al., 2005; Lee et al., 2009; Mouraux et al., 2004; Mouraux & Plaghki, 2007; Seminowicz & Davis, 2007), (ii) is strongly influenced by factors independent of the intensity of the nociceptive stimulus (Hatem et al., 2007; Iannetti et al., 2008; Legrain et al., 2009a; Mouraux et al., 2004), and (iii) can be evoked by non-nociceptive and non-painful stimuli (Downar et al., 2000, 2003; Lui et al., 2008; Mouraux et al., 2010; Mouraux and Iannetti, 2009; Tanaka et al., 2008). Importantly, these experimental observations do not question the involvement of the cortical activity in the emergence of pain. Rather, they question the notion that the cortical activity involved in the generation of pain is necessarily and specifically reflected in the "*pain matrix*".

Here, we will review different studies that challenge the interpretation of the "*pain matrix*" as a specific cortical representation of pain, and propose a novel interpretation in which the activity of this cortical network would reflect a system involved in detecting, processing and reacting to the occurrence of salient sensory events regardless of the sensory channel through which these events are conveyed. Such a network could reflect some of the basic operations by which the brain detects stimuli that can represent a potential threat for the integrity of the body.

## 2. RELATIONSHIP BETWEEN MAGNITUDE OF RESPONSES IN THE "*PAIN MATRIX*" AND INTENSITY OF PAIN

The relationship between the perceived intensity of pain and the magnitude of the brain responses evoked by nociceptive stimuli has been studied extensively, mainly by comparing the magnitude of the brain responses elicited by nociceptive stimuli of graded intensity. Studies using PET (Coghill et al., 1999; Derbyshire et al., 1997; Tolle et al., 1999) and fMRI (Bornhövd et al., 2002; Büchel et al., 2002) have thereby shown that the magnitude of the hemodynamic responses in SI, SII, the insula and the anterior cingulate cortex can reliably predict the amount of pain perceived. Indeed, these studies have shown that the amplitude of the hemodynamic responses in these brain areas can correlate with the intensity of the nociceptive stimuli and also with the subjective rating of pain. In addition, experimental manipulations which modulate pain can also modulate the magnitude of the brain responses triggered by nociceptive stimuli (Bingel et al., 2007; Hofbauer et al., 2001; Rainville et al., 1997; Wager et al., 2004). For instance, distracting subjects' attention away from the nociceptive stimulus may result concomitantly in a decrease of pain rating and a decrease of the magnitude of the elicited brain responses (Bushnell et

al., 1999; Petrovic et al., 2000; Peyron et al., 1999; Valet et al., 2004; Seminowicz et al., 2004). In addition, the specific manipulation of some aspects of the pain experience (e.g. intensity vs. unpleasantness [Melzack & Casey, 1968]) has been shown to modulate the responses in specific sub-regions of the network, suggesting the existence of spatially-segregated sub-functions within the "*pain matrix*" (Rainville et al., 1997; Hofbauer et al., 2001). Despite these suggested sub-functions, each sub-region was postulated to produce a graded activity contributing to the intensity of the percept, related either to the sensori-discriminative or to the affective aspect of this percept (Rainville, 2002). Similarly, EEG and MEG studies have shown that the magnitude of event-related potentials (ERPs) (Figure 1) and event-related magnetic fields (ERFs) elicited by nociceptive stimuli, and originating from operculo-insular, post-central and cingulate areas, i.e. from brain regions belonging to the "*pain matrix*" (see García-Larrea et al., 2003), may correlate with the physical intensity of the stimuli, and, even more, with the perceived intensity of pain (Arendt-Nielsen, 1994; Beydoun et al., 1993; Carmon et al., 1978; Frot et al., 2007; García-Larrea et al., 1997; Iannetti et al., 2005; Ohara et al., 2004; Plaghki et al., 1994; Timmermann et al., 2001). For these reasons, the evaluation of pain intensity has been suggested to constitute one of the main functions reflected by the "*pain matrix*".

However, recent studies have shown that, in a number of circumstances, the magnitude of the responses in that network may be dissociated from the subjective intensity of pain as well as from the physical intensity of the nociceptive stimulus (Clark et al., 2008; Dillmann et al., 2000; Iannetti et al., 2008; Mouraux et al., 2004; Mouraux & Plaghki, 2007). For instance, Iannetti et al. (2008) delivered trains of three identical nociceptive laser pulses with a constant 1-second inter-stimulus interval, using four different stimulus intensities. Following the first stimulus of the train, the

magnitude of the elicited ERPs was strongly related to the perceived intensity of pain, and both were related to the actual intensity of the nociceptive stimulus. In contrast, following the second and third stimuli, the relationship between the magnitude of ERPs and the magnitude of perceived pain intensity was markedly disrupted. Indeed, stimulus repetition decreased significantly the magnitude of nociceptive ERPs, but did not affect the perception of pain intensity (Figure 2). Additionally, Lee et al. (2009) showed with pairs of nociceptive stimuli that when the time interval within a pair of nociceptive stimuli is very short, the second stimulus elicits a distinct and reproducible brain response, even though it does not elicit a distinct percept. Conversely, when a nociceptive stimulus is applied such as to activate simultaneously nociceptive Aδ- and C-fibers, the afferent inputs carried by these two distinct types of nociceptive fibers produce two separate sensations – a pinprick sensation related to Aδ-fibers followed by a diffuse warmth sensation related to C-fibers – but elicits only one single ERP response related to Aδ-fibers (see Plaghki et Mouraux, 2005)[2].

Other examples of dissociation between the magnitude of the brain responses to nociceptive stimuli and the intensity of pain have been reported. In an EEG study, Mouraux & Plaghki (2007) delivered nociceptive stimuli either alone or shortly after

[2] High-energy thermal stimuli applied to the skin activate concomitantly thin myelinated Aδ-fibers and unmyelinated C-fibers (Bromm & Treede, 1984). However, because of their different conduction velocities, the Aδ-fiber afferent volley reaches the cortex well before the C-fiber afferent volley. Consequently, two sensations are often reported by the subjects: a sharp pinprick sensation evoked by the first-arriving Aδ-fiber, followed by a more diffuse and long lasting warmth sensation evoked by the later-arriving C-fiber volley (see for a review Plaghki & Mouraux, 2003). Paradoxically, the latency of the ERPs elicited by the concomitant activation of Aδ- and C-nociceptors is only compatible with the conduction velocity of the Aδ-fibers, i.e., although the C-fiber volley elicits a clear percept, it does not appear to elicit any measurable ERP. Only when the concomitant activation of Aδ-fibers is avoided, the C-fiber volley is able to elicit ERPs (Bromm et al., 1983; Bragard et al., 1996; Magerl et al., 1999). Source-analysis studies have shown that the ERPs related to the selective activation of C-fibers reflect activity originating from the same cortical sources as the ERPs related to the activation of Aδ-fibers (Opsommer et al., 2001; Cruccu et al., 2003). The explanation to this apparent suppression of C-fiber brain responses by preceding Aδ-fiber input remains a matter of debate (Arendt-Nielsen, 1990; Bromm & Treede, 1987; García-Larrea, 2004; Mouraux & Iannetti, 2008).

an innocuous somatosensory stimulus. The intensity of perception induced by the nociceptive stimuli was not different between the two conditions. In contrast, the nociceptive stimuli presented after a tactile stimulus elicited ERPs of reduced magnitude relatively to the ERPs elicited by single nociceptive stimuli. Similarly, an fMRI study also suggested that repetition of nociceptive stimuli may lead to dissociation between the habituation of the blood oxygen level dependent (BOLD) signal in brain areas activated by nociceptive stimuli and the persistence of pain (Becerra et al., 1999).

Using a different approach, Clark et al. (2008) presented nociceptive laser stimuli cued by a visual signal preceding the nociceptive stimulus with a variable time delay. Duration of the delay could be predicted or not predicted by the participants. They observed that the perceived intensity of pain and the magnitude of the elicited ERPs were affected differently by the delay separating the visual cue and the nociceptive stimulus. Longer-duration delays led to an increased intensity of perception. In contrast, the magnitude of ERPs did not depend on the duration of the delay, but on whether or not this delay was predictable, being larger when the delay was unpredictable.

It is also noteworthy to mention other experiments having shown that the attentional or emotional context may strongly modulate the hemodynamic or electrophysiological activity evoked by nociceptive stimuli without necessarily modifying the experience of pain (Dillman et al., 2000; Kulkarni et al., 2005; Seminowicz and Davis, 2007). For example, Kulkarni et al. (2005) engaged participants in tasks involving the evaluation of specific features of nociceptive stimulation (e.g. evaluation of spatial location or unpleasantness) and showed that these tasks significantly modulated the elicited brain responses without affecting the

perception of pain. Recently, Tiede et al. (2010) showed that sleep deprivation attenuates the magnitude of ERPs evoked by nociceptive stimuli but tends to amplify the perception of pain. In this study, sleep deprivation suppressed the modulator effect of attention on pain ratings, but did not suppress its effect on ERP amplitude.

Finally, other authors reported that nociceptive stimuli may elicit activity in the "*pain matrix*" in reduced or altered states of consciousness. For example, Bastuji et al. (2008) delivered short series of nociceptive stimuli to healthy sleeping subjects, using an intensity that was clearly perceived and qualified as painful when awake. When asleep, 70% of the stimuli did not produce any arousal reaction, and only 11% of the stimuli triggered an electromyographic response. In contrast, nociceptive stimuli elicited reproducible ERPs, albeit of reduced magnitude, both during stage 2 and paradoxical sleep. Similarly, activation in SI, SII, the insula and the anterior cingulate cortex by high-intensity electrical stimuli has been reported in patients in a minimally conscious state (Boly et al., 2008), and even, albeit residually, in patients in a vegetative state (Kassubek et al., 2003), although these patients did not display any strict behavioral evidence suggesting a conscious experience of pain. Indeed, in minimally conscious state patients, the electrical stimulus sometimes triggered responses such as flexion withdrawal and stereotyped posturing (Boly et al., 2008) that do not require integration of the nociceptive input at cortical level (Schnakers & Zasler, 2007). Furthermore, in humans exposed to a high-dose propofol sedation producing loss of consciousness, the brain responses to nociceptive stimuli are suppressed in the anterior cingulate cortex but maintained in SII and in the insula (Hofbauer et al., 2004). Likewise, in monkeys anesthetized using alphaxalone-alphadolone, nociceptive stimuli still elicit intracortical ERPs in the operculo-insular cortex (Baumgärtner et al., 2006). These different examples all show that the neural

activity recorded in the so-called "*pain matrix*" cannot be considered as a direct correlate of the conscious perception of a somatosensory stimulus as painful.

## 3. THE EFFECT OF NOVELTY AND ORIENTING OF ATTENTION

Studies examining the effect of stimulus repetition on the magnitude of nociceptive-evoked brain responses have shown that when nociceptive stimuli are repeated at a short and regular inter-stimulus interval, they elicit brain responses of reduced magnitude as compared to the responses elicited by nociceptive stimuli that are presented for the first time (Iannetti et al., 2008). The effect of repetition on nociceptive-evoked brain responses is largely determined by the duration of the inter-stimulus interval: the shorter the interval, the more pronounced the decrement of response magnitude (Bromm & Treede, 1987; Raij et al., 2003; Truini et al., 2004, 2007). A number of investigators have proposed that this repetition suppression results from refractoriness (Raij et al., 2003; Truini et al., 2007). Accordingly, repetition suppression would result from the fact that the neural receivers of the repeated stimulus enter a transient state of refractoriness following their prior activation. However, other studies have shown that the effect of stimulus repetition is strongly conditioned by the context within which the repetition occurs (Mouraux et al., 2004; Wang et al., 2010). Indeed, the effect of stimulus repetition is found only when pairs of nociceptive stimuli are presented using an interval that is constant from trial to trial, thus making the time of occurrence of the repeated stimuli predictable (Wang et al., 2010). In contrast, when the inter-stimulus interval varies randomly from trial to trial and, consequently, when the time of occurrence of the repeated stimulus is irregular and unpredictable, the magnitude of nociceptive ERPs is unaffected by stimulus repetition, even at very short time intervals (e.g., 250 ms) (Mouraux et al.,

2004). This indicates that refractoriness cannot be held responsible for the repetition suppression of ERPs and most importantly, that contextual information is a crucial determinant of the magnitude of the brain responses elicited by a nociceptive stimulus.

The influence of contextual information on the magnitude of the brain responses elicited by nociceptive stimuli was also investigated directly in experiments examining the effect of novelty (Legrain et al., 2002, 2009a). These experiments used long, regular and monotonous series of nociceptive stimuli during which a small number of infrequent novel stimuli (< 20%) were randomly interspersed. The novel stimulus differed from the regular standard stimulus by one or more physical features. Results showed that novel nociceptive stimuli elicit ERPs of greater magnitude than standard stimuli. This enhancement of the ERPs elicited by novel nociceptive stimuli was observed whatever the physical feature making the novel stimuli different from the standard stimuli. Indeed, increased ERP magnitudes have been observed for novelty characterized by a change in the spatial location of the nociceptive stimulus (Legrain et al., 2003b, 2009a) as well as a change in its intensity (Legrain et al., 2002, 2003a, 2005). Spatial novelty included changes from one hand to the other hand (Legrain et al., 2003b) and from one specific location to another location on the same hand (Legrain et al., 2009a). Taken together, these findings indicate that the effect of novelty on the magnitude of the ERPs elicited by nociceptive stimuli is not related to the processing of a particular deviant physical feature *per se*, but instead is related to the detection of novelty independently of the physical feature differentiating the novel stimulus from the standard stimuli. The effect of novelty was also observed when stimuli are not relevant for the subject's current task (Hatem et al., 2007), or when the subject's attention is focused away from the nociceptive stimuli, e.g. when

the focus of attention is selectively directed towards a different body location (Legrain et al., 2002) or towards stimuli belonging to a different sensory modality (Legrain et al., 2005, 2009a). Thus, the effect of novelty on the magnitude of nociceptive ERPs is not driven directly by the subject's explicit expectations or by his intention to direct attention towards the nociceptive stimulus. Instead, it is driven by the ability of the novel nociceptive stimulus to involuntarily capture attention from its current focus (Legrain et al., 2009b). In agreement with this view, Legrain et al. (2009a) showed in a recent experiment that the occurrence of a novel nociceptive stimulus can impair the performance of the behavioral responses to a shortly-following visual stimulus and alter the brain responses elicited by that visual stimulus (Figure 3). In this experiment, nociceptive laser stimuli and visual stimuli were delivered in pairs. The laser stimuli were delivered regularly on a specific region of the left hand dorsum (standard nociceptive stimuli). Occasionally (i.e. in 17% of the trials) novel laser stimuli were delivered to a different part of the same hand. Standard and novel nociceptive stimuli were of the same intensity. Participants were instructed to respond only to visual stimuli and were thus not attending the nociceptive stimuli. Novel nociceptive stimuli elicited ERPs of greater amplitude than standard nociceptive stimuli. In turn, the magnitude of ERPs elicited by the visual stimulus was reduced when the preceding nociceptive stimulus was novel. Furthermore, the latency of the motor responses to visual stimuli was delayed. This suggests that the sensorimotor processing of visual stimuli was disrupted due to an involuntary shift of attention towards the nociceptive input (Eccleston & Crombez, 1999). The relationship between stimulus novelty, attention and magnitude of nociceptive ERPs was further confirmed by experiments showing that fully engaging attention on a very demanding visual task reduces the effect of novelty on the magnitude of ERPs

evoked by nociceptive stimuli (Legrain et al., 2005). Conversely, the effect of novelty on the magnitude of ERPs is increased when the novel stimulus is also relevant for the task (Legrain et al., 2002).

Taken together, the different studies having examined the effect of novelty (Legrain et al., 2002; 2003a, 2003b, 2005, 2009a) support the view that nociceptive ERPs reflect mainly mechanisms by which the cortical processing of a particular nociceptive stimulus receives attentional priority, and that the activity of these mechanisms is largely determined by contextual information independently of the intensity of the nociceptive stimulus. Therefore, the brain activity observed in response to nociceptive stimuli appears to be at least partially related to mechanisms underlying the stimulus-driven orientation of attention towards the nociceptive stimulus (Legrain et al., 2009b).

The effects of stimulus novelty on the ERPs elicited by nociceptive stimuli resemble closely the effects observed on the ERPs elicited by stimuli belonging to other sensory modalities (Escera et al., 2000; Friedman et al., 2001). Furthermore, the effect of novelty appears to involve all of the components of nociceptive ERPs (Iannetti et al., 2008; Legrain et al., 2009a), originating from operculo-insular and cingulate areas (see García-Larrea et al., 2003). In accordance with these observations, fMRI studies have identified a network of different cortical regions involved in the detection of change in a stream of sensory input, independently of the sensory modality within which the change occurs (Downar et al., 2000, 2003). In these experiments, subjects were passively confronted to a continuous flow of stimuli belonging to different sensory modalities (visual, auditory, tactile and nociceptive). Occasionally, a change occurred in one modality. Authors demonstrated that several brain areas, including the cingulate and insular cortices, responded specifically to the

occurrence of a change in the stream of sensory stimulation, regardless of the sensory modality within which the change occurred.

## 4. ACTIVATION OF THE "*PAIN MATRIX*" BY NON-NOCICEPTIVE INPUTS

Because brain structures such as the operculo-insular and cingulate cortices respond to novelty independently of the sensory modality carrying the novel information, the activation of these brain areas by nociceptive stimuli, as classically described in pain neuroimaging studies, could mainly reflect brain processes that are not directly related to the emergence of pain and that can be engaged by sensory inputs that do not originate from the activation of nociceptors. In support of this view, two recent studies using EEG and fMRI respectively, demonstrated that nociceptive, tactile, auditory and visual stimuli can elicit spatially indistinguishable responses in the insula, the anterior cingulate cortex and the largest part of SII (Figure 4), thus indicating that the bulk of the brain responses to nociceptive stimuli reflects multimodal neural activity (i.e. activity that can be triggered by any kind of stimulus independently of sensory modality) (Mouraux & Iannetti, 2009; Mouraux et al., 2010). Furthermore, the only fraction of the brain responses elicited by nociceptive stimuli that was not explained by multimodal neural activity, located in SI and a small portion of SII, could be explained by somatosensory-specific activity that was not nociceptive-specific (i.e. activity that can be triggered by both nociceptive and tactile somatosensory stimuli). Interestingly, in both studies, the magnitude of the multimodal responses correlated significantly with the subjects' self-evaluation of how much the eliciting stimuli were able to capture their attention. Using fMRI, another group of investigators compared the pattern of brain responses triggered by nociceptive vs. tactile somatosensory stimuli (Liu et al., 2008), and showed strikingly

more similarities than differences. In fact, the reported differences could be largely explained by differences in response magnitude, as the spatial distribution and temporal dynamics of the elicited brain responses were almost identical between tactile and nociceptive stimuli (see also Tanaka et al., 2008). Therefore, even if we admit the existence of nociceptive-specific neurons contributing to the brain responses sampled using neuroimaging and neurophysiological techniques – and this hypothesis is certainly not rejected – this contribution cannot be isolated from that of multimodal neurons.

In fact, it is well known that the different brain areas constituting the "*pain matrix*", such as SII, the insula and the anterior cingulate cortex, can be activated by various kinds of sensory stimuli and cognitive settings (Ackermann & Riecker, 2004; Augustine, 1996; Bamiou et al., 2003; Botvinick et al., 2004; Bush et al., 2000; Corbetta & Shulman, 2002; Macaluso & Driver, 2005; Uddin & Menon, 2009). Considering the very low proportion of nociceptive-specific neurons in these brain areas (Dong et al., 1989, 1994; Kenshalo et al., 2000; Koyama et al., 1998; Robinson & Burton, 1980; Sikes & Vogt, 1992), as already stated by Wall in 1995, it would be "*an act of faith to continue searching the brain [...] for some still-undiscovered nest of cells whose activity reliably triggers pain*". Actually, this is probably the reason why the original concept of a "*neuromatrix*" was introduced by Melzack in 1989. Indeed, Melzack's "*neuromatrix*" was defined as a widespread ensemble of neurons whose activity results in the feeling of the "*body-self*", i.e. the feeling of "*a whole body possessing a sense of self*" (Melzack, 2001). This network integrates different sources of input in order to produce output patterns labelled "*neurosignatures*". Crucially, pain is considered as representing only one of many possible perceptual outputs, i.e. only one of many "*neurosignatures*" that can be generated by the

"*neuromatrix*". Therefore, the activity of the "*pain matrix*" would not unequivocally represent the emergence of pain in the brain. In turn, similar if not identical patterns of activity (at least at the mesoscopic level of fMRI or scalp EEG), could be generated independently of nociceptive input, and could give rise to a similar feeling of imminent threat for the body (Melzack, 2001). In accordance with this view, Crombez et al. (1998a) observed that, exactly as it was shown for painful stimuli (Crombez et al., 1994), occasional innocuous electrocutaneous stimuli are able to disrupt the performance of participants in an auditory discrimination task, but only when these innocuous stimuli were believed to be potentially very painful. Then, it is reasonable to suggest that in these studies a similar feeling of threat for the body was triggered by innocuous somatosensory stimuli independently of the actual experience of pain.

## 5. A SALIENCE DETECTION SYSTEM

There is thus converging evidence to consider that the bulk of the brain responses to nociceptive stimuli that have been commonly identified using fMRI and EEG reflects a system involved in the extraction and the processing of particular sensory information from the sensory environment independently of sensory modality. The activity of the this network appears to be determined by parameters that are not always related directly to the intensity of the stimulus, and that could be characterized by the concept of salience (Iannetti et al., 2008; Legrain et al., 2009a, 2009b). The salience of a given stimulus is defined as its ability to stand out relative to neighboring stimuli (Yantis, 2008). This concept refers to the physical distinctiveness or conspicuity of a stimulus, a relative property that depends on its relationship to the other surrounding stimuli in the scene (Fecteau & Munoz, 2006). Therefore, the salience of a stimulus is determined by how much it contrasts, along

one or more physical dimensions, from its surrounding (Itti & Koch, 2001; Knudsen, 2007; Yantis, 2008). Salience is also determined according to the past context and memories (Näätänen & Picton, 1987; Näätänen et al., 2007). In this case, novel events are salient because they are completely new or because they deviate from the expectations built from recent past experiences.

Prioritizing the processing of salient events in the sensory environment is an important function to guarantee coherent and adaptive behavior: it contributes to select in the stream of incoming sensory inputs the inputs that are likely to signal changes in the environment, and thereby which of these inputs request priority processing (Egeth & Yantis, 1997; Knudsen, 2007). Indeed, because sudden changes in the sensory environment often signal the occurrence of an unknown event, these changes must be promptly and reliably evaluated, in order to decide whether or not they request a modification of behavior, such as, for example, to fight against or to flee from a potential danger.

Different neural mechanisms have been proposed to be involved in the detection of salience. Some of these mechanisms may involve the detection of local contrasts along various physical dimensions (Itti & Koch, 2001; Kayser et al., 2005). Other mechanisms may involve the detection of transient variations in the flow of afferent energy (Näätänen & Picton, 1987), or the detection of a mismatch between the afferent sensory input and a memory template of recent past events (Näätänen et al., 2007). By reacting to the sensory inputs that are the most salient, all these mechanisms provide a weighted and enhanced neural representation of these stimuli (Desimone & Duncan, 1995), thereby biasing perceptive analysis (Serences & Yantis, 2006) and the execution of motor responses (Castiello, 1999; Cisek & Kalaska, 2010). Indeed, salience detectors represent neural mechanism by which

selective attention is captured and oriented towards the most salient stimuli in order to prioritize their processing over background stimuli, to improve their perception and to prompt appropriate action (Corbetta & Schulman, 2002; Desimone & Duncan, 1995; Egeth & Yantis, 1997; Schröger, 1996)[3].

The finding that stimulus novelty enhances the magnitude of nociceptive ERPs (Legrain et al., 2002, 2003a, 2003b, 2005, 2009a) and disrupts consecutively ongoing task performance (Legrain et al., 2009a, 2010) supports strongly the view that these brain responses reflect, at least partially, mechanisms by which the processing of salient sensory input is enhanced and receives more attention as compared to less salient sensory input. In fact, differences in stimulus salience could account for most of the previously-reported experimental modulations of the brain responses elicited by nociceptive stimuli observed in electrophysiological and functional neuroimaging studies. Indeed, the experiments reviewed in the previous section have all shown that factors that contribute to increase stimulus salience also enhance the magnitude of the brain responses elicited by nociceptive stimuli. Furthermore, it could explain why innocuous sensory stimuli, provided that they are salient, may elicit a pattern of brain activity virtually identical to the pattern elicited by nociceptive stimuli (Mouraux & Iannetti, 2009; Mouraux et al., submitted). Factors contributing to the salience of the stimulus include stimulus novelty (Iannetti et al.,

[3] Competition model of selective attention consider attention as a competition between sensory inputs to gain access to conscious perception. Competition is determined by the relative strengths of the neuronal responses to the stimuli. The strengths of these signals are thought to be biased, i.e. modulated, by two main mechanisms (Desimone & Duncan, 1995; Egeth & Yantis, 1997; Knudsen, 2007; Yantis, 2008). The first mechanism, described in the present section, allows attention being captured by the stimulus itself based on its physical properties which define how much the stimulus contrasts relative to other stimuli (bottom-up selection). The second mechanisms orient and focus attention to the stimuli that are useful for current cognitive activities. This kind of attentional selection is controlled by expectations and decision processes (top-down selection). Decisions are made in working memory which holds active the features of the attended target stimulus in order to identify it (Desimone & Duncan, 1995; Knudsen, 2007). Based on the distinction between bottom-up selection and top-down selection, it is accepted that salience refers to the physical properties of the stimulus that captures attention (bottom-up), whereas relevance refers to the characteristics of the stimulus that make it pertinent for cognitive goals (top-down). Therefore, salience cannot be considered as a synonym of relevance (Fecteau & Munoz, 2006).

2008; Legrain et al., 2009a), sharpness of stimulus onset (Iannetti et al., 2006), stimulus deviance (Legrain et al., 2003a), and stimulus intensity.

The well-known relationship usually observed between the magnitude of the brain responses evoked by nociceptive stimuli and stimulus intensity or perceived intensity could also be related to the fact that when nociceptive stimuli are presented using graded intensities, stimuli that are more intense are obviously also more salient. An intense stimulus is the one that produces the largest response, and also the one that is more contrasted relative to the surrounding and preceding sensory input. Interestingly, it has been observed that when the amount of background somatosensory noise is increased, for instance by brushing continuously the skin, nociceptive stimuli is made more difficult to detect (Nahra & Plaghki, 2003) and elicit ERPs of reduced magnitude (Kakigi & Watanabe, 1996). This observation indicates that the magnitude of the elicited brain responses does not depend only on the absolute intensity of the nociceptive stimulus, but also on the contrast between its intensity and the intensity of the surrounding input, and, hence, its salience. Similarly, novelty enhances the magnitude of nociceptive ERPs when the novel nociceptive stimuli consist of high-intensity stimuli intermixed with frequent low-intensity stimuli, but not when the novel nociceptive stimuli consist of low-intensity stimuli intermixed with frequent high-intensity stimuli (Legrain et al., 2003a).

The proposed notion according to which the brain responses to nociceptive stimuli reflect mainly neural activity involved in the detection of saliency does not imply that these brain responses are not important for nociception and pain. Indeed, it is well known that attention is determinant for how a stimulus is perceived as painful (see Van Damme et al., 2010). In addition, novelty enhances responses in brain regions responding to affective stimuli like the amygdala (Weierich et al., 2010)

and attention contributes to modify the emotional valence of a stimulus (Fenske & Raymond, 2006). Also, it is generally agreed that the purpose of pain is not merely to induce and to associate the feeling of unpleasantness to a somatosensory sensation, but it also to warn the body about potential physical threats. This functional role of pain is completely taken into account by our alternative interpretation because it outlines the *final cause* of salience detection in terms of attentional selection for perception and for action. Indeed, a salience detection system would reflect mechanisms by which the brain detect and orient attention to any event in the sensory environment that may have a significant impact on the organism, such as an event signaling a potential threat for the individual's integrity. In that perspective, it is important to highlight that information about potential threats is by no means uniquely conveyed by the nociceptive system. For instance, viewing a potentially damaging threat will be recognized by any individual as highly significant whatever the target of the threat (Constantini et al., 2008; Singer et al., 2004). Therefore, the present interpretation of the salience detection system suggests that its activity underlies a crucial function for all sensory systems, including the nociceptive system, providing the ability to detect and to orient selectively attention to significant sensory events, in particular those that could represent a potential threat.

One could argue that, as compared to other sensory modalities, the nociceptive system could be more predominantly involved in the detection of salience. In fact, because of their high threshold (at least when not sensitized), peripheral nociceptors may be viewed as cutaneous receptors which react selectively to high-intensity somatosensory stimuli (Belmonte & Viana, 2008). Furthermore, in the nociceptive system, the ability to promote the processing of salient somatosensory inputs could already be implemented at the level of the spinal cord,

through the mechanism of a spino-bulbo-spinal loop called *diffuse noxious inhibitory control* (DNIC) (Le Bars et al., 1979). Indeed, studies have shown that if a nociceptive stimulus is applied at a specific body location, it enhances the responses of wide dynamic range (WDR) neurons at the segmental level of the dorsal horn receiving inputs from that body location and concurrently inhibits the responses of WDR neurons originating from all other body locations. It has been proposed that DNIC could constitute a mean by which the spinal transmission of somatosensory signals is modulated in order to enhance the contrast of potentially dangerous somatosensory inputs relative to the "*basic somesthesic activity*" (Le Bars, 2002). In that perspective, nociceptors enhance the ability of the individual to detect potential threats to the body's integrity. However, there is no reason to consider that the cortical processing of the *inherently highly salient content* of nociceptive input should involve different mechanisms or structures than those involved in the cortical processing of the salience content of non-nociceptive input.

## 6. A SALIENCE DETECTION SYSTEM FOR THE BODY

In the previous section, we have provided an alternative interpretation of the functional significance of the cortical network described in pain studies by proposing that it mainly reflects a multimodal network involved in the detection of salience. However, its contribution to the experience pain was not dismissed as salience detection would constitute a fundamental mechanism by which the brain detects events that are significant for the integrity of the body in order to prompt appropriate action. In that perspective, we can suggest the possibility that the detection of salience could be used as a mechanism to assist attentional systems in localizing the

stimuli that are the most susceptible to signal an important change, such as a threat, occurring in the proximal space surrounding the body.

Electrophysiological studies have identified neurons in the frontal and parietal areas of non-human primates that respond specifically to multimodal threats occurring in the space proximal to the body and that participate to defensive behaviors (Cooke et al., 2003; Cooke & Graziano, 2002). Frontal and posterior parietal areas are also frequently reported as contributing to the brain responses triggered by nociceptive stimuli (Ingvar, 1999; Peyron et al., 2000; Porro, 2003; Treede et al., 1999). The role of these cortical areas in cognitive functions, particularly in attention, is well recognized: they are involved in selectively biasing the cortical processing of incoming sensory inputs according to their salience and their relevance (Corbetta & Shulman, 2002; Yantis, 2008). Frontal and posterior parietal areas are also involved in coordinating perception and action. More specifically, specific parieto-frontal networks have been shown to map sensory information according to specific representation frames for the purpose of particular actions (e.g., retinal space for saccades, peripersonal space for grasping, extrapersonal space for reaching) (Rizzolatti et al., 1997; Colby & Goldberg, 1999; Gottlieb, 2007). For example, neurons in the anterior intraparietal (AIP) area respond to local visuospatial dimensions of the stimuli such as shape and orientation (Sakata et al., 1995; Shikata et al. 1996), and are intimately connected to neurons in the premotor F5 area which execute hand movements (Rizzolatti et al., 1988). In other words, this AIP-F5 cortical network appears to construct an internal representation of the space surrounding the hand that is relevant for grasping objects. Regarding threats, responding adequately to events that threaten the body's integrity constitutes an action whose achievement requires close interaction with systems that are able to localize threatening

information in the proximal space of the body. In monkeys, such an interaction between perceptual processing and motor output was suggested between the ventral parts of intraparietal (VIP) and premotor (F4) areas. Direct stimulation of neurons within these areas has been shown to produce defensive behaviors, such as eye blinks or arm withdrawals (Cooke et al., 2003; Cooke & Graziano, 2004), similar to the behaviors observed when threats are directly applied on the surface of the body (Cooke & Graziano, 2003). In addition, these neurons also respond to visual objects when they are approaching the body but not when they move away from the body (Graziano et al., 1997). Indeed, neurons in premotor and parietal areas have multimodal receptive fields: they can be activated by somatosensory stimuli as well as by visual stimuli appearing in the proximity of their somatosensory receptive field (Duhamel et al., 1998; Graziano & Gross, 1998). This implies that the visual receptive field of these multimodal neurons is circumscribed to the space surrounding the tactile receptive field. One important property of such neurons with multimodal receptive fields is that their visual receptive fields remain anchored to the part of the body they code regardless of the position of the stimulus on the retina and regardless of the position of the body part in external space (Avillac et al., 2005; Colby et al., 1993; Duhamel et al., 1998; Fogassi et al., 1996; Graziano et al., 1994, 1997). As a consequence, even when the gaze is shifted, these neurons continue to respond to visual objects presented close to the tactile receptive fields to which they are anchored. In turns, the visual receptive fields will move with movements of the body part to which they are anchored. The activity of such neurons is likely to contribute to the construction of a multimodal map of the body extended to the nearby space (Graziano & Gross, 1994) in order to guide defensive action against threats (Cooke et al., 2003; Cooke & Graziano, 2003; 2004; Graziano et al., 1997). Note that similar

multimodal threat-detection neurons were found in area 7b close to SII (Dong et al., 1994).

In humans, the existence of a mental representation of the space around the body was already suggested (e.g. the "*body schema"* of Head & Homes [1911]). More recently, the existence of different frames of reference for spatial perception have been more precisely investigated by cognitive psychology and neuropsychology studies (Driver & Spence, 1998; Làdavas, 2002; Landis, 2000). The frame that maps multimodal events in the space surrounding the body is conceptualized by the notion of peripersonal space, i.e. a representation of the body and environment within grasp. Such a frame of reference was evidenced by studies having shown a close relationship between visual, proprioceptive and tactile processing (e.g. Kennet et al., 2001; Làdavas et al., 1998; Lloyd et al., 2003; Pavani et al., 2000; Shore et al., 2005; Spence et al., 2001). Regarding pain, cross-modal influences were reported from behavioral studies on spatial attention suggesting a multimodal integration between pain and vision (Honoré et al., 1995; Van Damme et al., 2007; Van Ryckeghem et al., 2010). Compatible with the view according to which nociceptive inputs are also integrated in a multimodal representation of the body extended to the surrounding space, a recent study demonstrated that the magnitude of the ERPs evoked by nociceptive stimuli are modulated by the act of viewing the stimulated hand (Longo et al., 2009). In addition, viewing a noxious stimulus applied to the hand has been shown to activate the mid-cingulate cortex and parietal areas extending from the superior parietal gyrus to the parietal operculum, even in the absence of concomitant nociceptive input (Lloyd et al., 2006). This visually-induced *noxious* illusion was obtained by applying the noxious stimulus to a fake rubber hand experienced by the subject as belonging to his own body. Interestingly, cortical responses faded when

the illusion was disrupted, thus showing that the effect appeared only when the noxious stimulus was perceived as occurring close to the body. Therefore, at least some components of the system previously referred to as the "*pain matrix*" may be hypothesized to reflect a brain network devoted to processing sensory information that is the most susceptible to signal potential danger in the proximal space and to prompt appropriate actions. Therefore, we hypothesize that the salience detection system represents mechanisms by which attentional systems are informed about changes in the representations of the body. Obviously, the somatosensory system is particularly involved in such a function because it encodes the portion of space delimiting the boundaries of the body, and, therefore, mainly conveys input generated by external objects that have an immediate impact on the surface of the body, i.e. the somatic space (Müller & Giabbiconi, 2008). However, there is no reason to exclude the involvement of auditory and visual systems as they may also convey sensory information originating from the peripersonal space (Kennet et al., 2001; Làdavas, 1998; Lloyd et al., 2003; Pavani et al., 2000; Spence et al., 2001).

In fact, our proposal shares some similarities with the hypothesis proposed by Le Bars (2002), in which WDR spinal neurons are considered to participate to a general representation of the state of the body. Accordingly, the role of DNIC would be to inform the brain when the basic state of the body is modified by changing the weight of the sensory inputs that are transmitted to the cortex. Here, we propose that similar mechanisms may exist at the cortical level, which would be involved in the detection of important changes in the peripersonal representation of the body. In that perspective, what has been previously labeled as the "*pain matrix*" would no longer constitute a sensory-specific cortical network, but, instead, it would constitute an

action-specific cortical network (Dum et al., 2009) representing the activity by which the individual is able to identify and responds adequately to an immediate threat.

## 7. TOWARS A NEUROPSYCHOLOGY OF THREAT DETECTION

Our hypothesis relative to the existence of a body-centered salience detection system is supported by several neuropsychological observations. For instance, Berthier et al. (1988) reported cases of pain asymbolia consecutive to operculo-insular lesions. Although the patients were able to recognize nociceptive stimuli as *painful*, the stimuli did not elicit a feeling of unpleasantness, nor did they elicit withdrawal motor reactions or emotional facial expressions. Moreover, in accordance with our proposal, the patients also failed to react to viewing approaching objects such as threatening gestures against their body. Interestingly, some patients expressed also neglect-like behaviors to visual, auditory and tactile stimuli. Liu et al. (2010) described two neglect patients presenting a nociceptive extinction in the absence of sensory loss. These patients were able to correctly report the occurrence of a nociceptive stimulus applied to the hand contralateral to the side of the lesion, when it was delivered alone, but not when it was delivered concurrently to a nociceptive stimulus applied on the ipsilesional hand. Liu et al. (2010) described other neglect patients in whom detection of the stimulation applied the contralesional hand was transferred to the ipsilesional hand. These results show that in neglect syndromes, nociceptive inputs can lose their *attentional weight*, similarly to what has been extensively described in the other sensory modalities (Brozzoli et al., 2006). Similarly, it has been reported that patients suffering from complex regional pain syndrome (CRPS) tend to neglect their affected limb (Galer & Jensen, 1999; Moseley, 2004; Lewis et al., 2007). Although the data remain controversial, neglect-

like symptoms in CRPS could also affect the perception of visual stimuli (Sumitani et al., 2007). Most interestingly, Moseley et al. (2009) have shown that neglect-like behaviors in CRPS are not tied to the side of affected limb, but to the space where the affected limb normally resides. Indeed, the authors demonstrated that during concurrent tactile stimulation of both the affected and the unaffected limb, when the limbs were in a normal posture, the perception of stimuli applied to the affected limb was biased in favor of the perception of stimuli applied to the unaffected limb. In contrast, when the limbs were crossed, the pattern of perception was reversed: the perception of stimuli applied to the unaffected limb was biased in favor of the perception of stimuli applied to the affected limb. These observations show clearly that the deficits observed in CRPS patients are based on a spatial representation of the body that is independent of the somatotopic localization of the symptoms.

These neuropsychological investigations provide further support to our hypothesis. In turn, our hypothesis could incite a reinterpretation of some aspects of the pathophysiology of chronic pain syndromes. Indeed, our hypothesis suggests that the weight that is given to somatic sensory input is dependent on different attentional mechanisms that could be more or less selectively altered in certain chronic pain syndromes. An impairment of these mechanisms could contribute to bias or amplify the perception of somatic or nociceptive input (Pincus & Morley, 2001). For example, some chronic pain syndromes, such as fibromyalgia, are thought to be characterized by a kind of *over-responsiveness* to sensory stimuli, especially those conveying pain and body-related information (Crombez et al., 2005). Our proposal prompts to interpret this *over-responsiveness* as resulting from a modification of the attentional sensitivity to stimuli entering the peripersonal space. In the previous sections, we

have focused exclusively on the attentional mechanisms that allow the detection and the selection of sensory information based on the physical properties defining its salience (bottom-up filter). However, the selection of sensory information is also determined by its relevance relatively to cognitive goals (top-down bias) (Corbetta & Schulman, 2002; Knudsen, 2007; Yantis, 2008) (see footnote 3). This top-down attentional selection is thought to be under the control of working memory, because working memory transiently stores and rehearses information that is relevant for the achievement of cognitive and behavioral activities, i.e. current goals (Desimone & Duncan, 1995; Knudsen, 2007). Decision about which information is relevant and, therefore about which information is transiently maintained in working memory to guide attention, is driven by ongoing cognitive goals but also by motivation and personally traits such as catastrophizing, i.e. a tendency to consider any experience of pain as awful and unbearable (Legrain et al., 2009b). in accordance with this view, when performing a visual task, subjects with strong catastrophizing traits are more disrupted by the occurrence of novel electrocutaneous stimuli (Crombez et al., 1998b), suggesting that, in these subjects, bodily sensations have acquired a stronger attentional weight, facilitating selection and perception of body-related information. Conversely, it was recently shown that controlling the content of working memory with pain-unrelated information can inhibit the ability of nociceptive stimuli to capture attention (Legrain et al., 2010). Interestingly, the magnitude of the responses to nociceptive stimuli in cingulate, insular, prefrontal and posterior parietal cortices has been shown to be related to catastrophizing in healthy volunteers (Seminowicz & Davis, 2006), as well in fibromyalgia patients (Gracely et al., 2004). It is likely that these observations result from increased attention to nociceptive stimuli. Therefore, it reasonable to hypothesize that these effects are due to the fact that these patients

are unable to keep body-associated information out of working memory, making them *over-attentive* to threat sensations.

## 8. CONCLUSION

In summary, we propose that the activity of the cortical areas classically observed in response to nociceptive stimuli constitutes a network involved in detecting salient sensory events in order to prioritize their access to attentional and executive functions. Through biasing operations, the main function of the proposed salience detection system would be thus to facilitate the processing of behaviorally significant (e.g., potentially threatening) sensory input and to select the appropriate response, regardless of whether this input is conveyed through nociceptive pathways. This view does not imply that the cortical processing underlying the salience detection system does not contribute to the experience of pain. On the contrary, it highlights the fact that such a system subtends one of the most important functions of the nociceptive system, namely the ability to detect salient changes and, possibly, to integrate them into a peripersonal representation of our body. In order words, the salience detection system would represent a network by which we react to a wasp when viewing the wasp approaching the hand, but even before being stung by it.

## ACKNOWLEDGMENTS

Authors would like to thank Michael Andres, Julie Duqué, Samar Hatem, Gaëlle Meert (Université catholique de Louvain, Belgium), Geert Crombez, Gilles Pourtois (Ghent University, Belgium), and Alexandre Zénon (The Salk Institute for Biological

Studies, California) for their insightful comments. G.D. Iannetti is University Research Fellow of The Royal Society, and acknowledges the support of BBSRC.

## REFERENCES

[1] Ackermann, H., Riecker, A., 2004. The contribution of the insula to motor aspects of speech production: A review and a hypothesis. Brain Lang. 89, 320-328.

[2] Apkarian, A.V., Bushnell, M.C., Treede, R.D., Zubieta, J.K., 2005. Human brain mechanisms of pain perception and regulation in health and disease. Eur. J. Pain 9, 463-484.

[3] Arendt-Nielsen, L., 1990. Second pain event related potentials to argon laser stimuli: recording and quantification. J. Neurol. Neurosurg. Psychiat. 53, 405-410.

[4] Arendt-Nielsen, L., 1994. Characteristics, detection, and modulation of laser-evoked vertex potentials. Acta Anaesthesiol. Scand. Suppl. 101, 7-44.

[5] Arendt-Nielsen, L., Chen, A.C.N., 2003. Lasers and other thermal stimulators for activation of skin nociceptors in humans. Neurophysiol. Clin. 33, 259-268.

[6] Augustine, J.R., 1996. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res. Brain Res. Rev. 22, 229-244.

[7] Avillac, M., Denève, S., Olivier, E., Pouget, A., Duhamel, J.R., 2005. Reference frames for representing visual and tactile locations in parietal cortex. Nat. Neurosci. 8, 941-949.

[8] Bamiou, D.E., Musiek, F.E., Luxon, L.M., 2003. The insula (Island of Reil) and its role in auditory processing. Literature review. Brain Res. Brain Res. Rev. 42, 143-154.

[9] Bastuji, H., Perchet, C., Legrain, V., Montes, C., García-Larrea, L., 2008. Laser evoked responses to painful stimulation persist during sleep and predict subsequent arousals. Pain 137, 589-599.

[10] Baumgärtner, U., Tiede, W., Treede, R.D., Craig, A.D., 2006. Laser-evoked potentials are graded and somatotopically organized anteroposteriorly in the operculoinsular cortex of anesthetized monkeys. J. Neurophysiol. 96, 2802-2808.

[11] Becerra, L.R., Breiter, H.C., Stojanovic, M., Fishman, S., Edwards, A., Comite, A.R., Gonzalez, R.G., Borsook, D., 1999. Human brain activation under controlled thermal stimulation and habituation to noxious heat: an fMRI study. Magn. Reson. Med. 41, 1044-1057.

[12] Belmonte, C., Vianna, F., 2008. Molecular and cellular limits to somatosensory specificity. Molecular Pain 4, 14.

[13] Berthier, M., Starkstein, S., Leiguarda, R., 1988. Asymbolia for pain: a sensory-limbic disconnection syndrome. Ann. Neurol. 24, 41-49.

[14] Beydoun, A., Morrow, T.J., Shen, J.F., Casey, K.L., 1993. Variability of laser-evoked potentials: attention, arousal and lateralized differences. Electroencephalogr. Clin. Neurophsyiol. 88, 173-181.

[15] Bingel, U., Schoell, E., Herken, W., Büchel, C., May, A., 2007. Habituation to painful stimulation involves the antinociceptive system. Pain 131, 21-30.

[16] Boly, M., Faymonville, M.E., Schnakers, C., Peigneux, P., Lambermont, B., Phillips, C., Lancellotti, P., Luxen, A., Lamy, M., Moonen, G., Maquet, P., Laureys, S., 2008. Perception of pain in the minimally conscious state with PET activation: an observational study. Lancet Neurol. 7, 1013-1020.

[17] Bornhövd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C., Büchel, C., 2002. Painful stimuli evoke different stimulus-response functions in the amygdala,

prefrontal, insula and somatosensory cortex: a single-trial fMRI study. Brain 125, 1326-1336.

[18] Borsook, D., Sava, S., Becerra, L., 2010. The pain imaging revolution: advancing pain into the 21st century. Neuroscientist 16, 171-185.

[19] Botvinick, M.M., Cohen, J.D., Carter, C.S., 2004. Conflict monitoring and anterior cingulate cortex: an update. Trends Cogn. Sci. 8, 539-546.

[20] Bragard, D., Chen, A.C.N., Plaghki, L., 1996. Direct isolation of ultra-late (C-fiber) evoked brain potential by $CO_2$ laser stimulation of tiny cutaneous surface areas in man. Neurosci. Lett. 209, 81-84.

[21] Bromm, B., Neitzel, H., Tecklenburg, A., Treede, R.D., 1983. Evoked cerebral potential correlates of C-fiber activity in man. Neurosci. Lett. 43, 109-114.

[22] Bromm, B., Treede, R.D., 1984. Nerve fibre discharges, cerebral potentials and sensations induced by CO2 laser stimulation. Hum. Neurobiol. 3, 33-40.

[23] Bromm, B., Treede, R.D., 1987. Human cerebral potentials evoked by $CO_2$ laser stimuli causing pain. Exp. Brain Res. 67, 153-162.

[24] Brozzoli, C., Demattè, M.L., Pavani, F., Frassinetti, F., Farnè, A., 2006. Neglect and extinction: within and between sensory modalities. Restor. Neurol. Neurosci. 24, 217-232.

[25] Büchel, C., Bornhövd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C., 2002. Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance imaging study. J. Neurosci. 22, 970-976.

[26] Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn. Sci. 4, 215–222.

[27] Bushnell, M.C., Duncan, G.H., Hofbauer, R.K., Ha, B., Chen, J.I., Carrier, B., 1999. Pain perception: is there a role for primary somatosensory cortex? Proc. Natl. Acad. Sci. U.S.A. 96, 7705-7709.

[28] Bushnell, M.C., Apkarian, A.V., 2006. Representation of pain in the brain. In: Wall and Melzack's Textbook of Pain (5th ed.), pp. 107-124. Eds S.B. McMahon, M. Koltzenburg. Churchill Livingstone: Philadelphia.

[29] Carmon, A., Dotan, Y., Sarne, Y., 1978. Correlation of subjective pain experience with cerebral evoked responses to noxious thermal stimulations. Exp. Brain Res. 33, 445-453.

[30] Castiello, U., 1999. Mechanisms of selection for the control of hand action. Trends Cogn. Sci. 3, 264-270.

[31] Cisek, P., Kalaska, J.F., 2010. Neural mechanisms for interacting with a world full of action choices. Annu. Rev. Neurosci. 33, 269-298.

[32] Clark, J.A., Brown, C.A., Jones, A.K.P., El-Deredy, W., 2008. Dissociating nociceptive modulation by the duration of pain anticipation from unpredictability in the timing of pain. Clin. Neurophysiol. 119, 2870-2878.

[33] Coghill, R.C., Sang, C.N., Maisog, J.M., Iadarola, M.J., 1999. Pain intensity processing within the human brain: a bilateral, distributed mechanism. J. Neurophysiol. 82:1934-1943.

[34] Colby, C. L., Duhamel, J.R., Goldberg, M. E., 1993. Ventral intraparietal area of the macaque: anatomic location and visual response properties. J. Neurophysiol. 69, 902–914.

[35] Colby, C.L., Goldberg, M.E., 1999. Space and attention in parietal cortex. Annu. Rev. Neurosci. 22, 319-349.

[36] Cooke, D.F., Graziano, M.S.A., 2003. Defensive movements evoked by air puff in monkeys. J. Neurophysiol. 90, 3317-3329.

[37] Cooke, D.F., Taylor, C.S.R., Moore, T., Graziano,M.S.A., 2003. Complex movements evoked by microstimulation of the ventral intraparietal area. Proc. Natl. Acad. Sci. U.S.A. 100, 6163-6168.

[38] Cooke, D.F., Graziano, M.S.A., 2004. Sensorimotor integration in the precentral gyrus: polysensory neurons and defensive movements. J. Neurophysiol. 91, 1648-1660.

[39] Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201-215.

[40] Costantini, M., Galati, G., Romani, G.L., Aglioti, S.M., 2008. Empathic neural reactivity to noxious stimuli delivered to body parts and non-corporeal objects. Eur. J. Neurosci. 28, 1222-1230.

[41] Crombez, G., Baeyens, F., Eelen, P., 1994. Sensory and temporal information about impending pain: the influence of predictability on pain. Behav. Res. Ther. 32, 611-622.

[42] Crombez, G., Eccleston, C., Baeyens, F., Eelen, P., 1998a. Attentional disruption is enhanced by the threat of pain. Behav. Res. Ther. 36, 195-204.

[43] Crombez, G., Eccleston, C., Baeyens, F., & Eelen, P., 1998b. When somatic information threatens, catastrophic thinking enhances attention interference. Pain 75, 187-198.

[44] Crombez, G., Van Damme, S., & Eccleston, C., 2005. Hypervigilance to pain: An experimental and clinical analysis. Pain 116, 4-7.

[45] Cruccu, G., Pennisi, E., Truini, A., Iannetti, G.D., Romaniello, A., Le Pera, D., De Armas, L., Leandri, M., Manfredi, M., Valeriani, M., 2003. Unmyelinated

trigeminal pathways as assessed by laser stimuli in humans. Brain 126, 2246-2256.

[46] Derbyshire, S.W., Jones, A.K., Gyulai, F., Clark, S., Townsend, D., Firestone, L.L., 1997. Pain processing during three levels of noxious stimulation produces differential patterns of central activity. Pain 73:431-445.

[47] Desimone, R., Duncan, J., 1995. Neural mechanisms of selective visual attention. Annu. Rev. Neurosci. 18, 193-222.

[48] Dillmann, J., Miltner, W.H., Weiss, T., 2000. The influence of semantic priming on event-related potentials to painful laser-heat stimuli in humans. Neurosci. Lett. 284, 53-56.

[49] Dong, W.K., Salonen, L.D., Kawakami, Y., Shiwaku, T., Kaukoranta, E.M., Martin, R.F., 1989. Nociceptive responses of trigeminal neurons in SII-7b cortex of awake monkeys. Brain Res. 484, 314--324.

[50] Dong, W.K., Chudler, E.H., Sugiyama, K., Roberts, V.J., Hayashi, T., 1994. Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. J. Neurophysiol. 72, 542-564.

[51] Downar, J., Crawley, A.P., Mikulis, D.J., Davis, K.D., 2000. A multimodal cortical network for the detection of changes in the sensory environment. Nat. Neurosci. 3, 277-283.

[52] Downar, J., Mikulis, D.J., Davis, K.D., 2003. Neural correlates of the prolonged salience of painful stimulation. Neuroimage 20, 1540-1551.

[53] Driver, J., Spence, C., 1998. Cross-modal link in spatial attention. Phil. Trans. R. Soc. Lond. B. 353, 1319-1331.

[54] Duhamel, J. R., Colby, C. L., Goldberg, M. E., 1998. Ventral intraparietal area of the macaque: Congruent visual and somatic response properties. J. Neurophysiol. 79, 126–136.

[55] Dum, R.P., Levinthal, D.J., Strick, P.L., 2009. The Spinothalamic system targets motor and sensory areas in the cerebral cortex of monkeys. J. Neurosci. 29, 14223-14235.

[56] Eccleston, C., Crombez, G., 1999. Pain demands attention: a cognitive-affectivemodel on the interruptive function of pain. Psychol. Bull. 125, 356-366.

[57] Egeth, H.E., Yantis, S., 1997. Visual attention: control, representation, and time course. Annu. Rev. Psychol. 48, 269-297.

[58] Escera, C., Alho, K., Schröger, E., Winkler, I., 2000. Involuntary attention and distractibility as evaluated with event-related brain potentials. Audiol. Neurootol. 5, 151-166.

[59] Fecteau, J.H., Munoz, D.P., 2006. Salience, relevance, and firing: a priority map for target selection. Trends Cogn. Sci. 10, 382-390.

[60] Fenske, M.J., Raymond, J.E., 2006. Affective influences of selective attention. Curr. Dir. Psychol. Sci. 15, 312-316.

[61] Fogassi, L., Gallese, V., Fadiga, L., Luppino, G., Matelli, M., & Rizzolatti, G., 1996. Coding of peripersonal space in inferior premotor cortex, area F4. J. Neurophysiol. 76, 141–157.

[62] Friedman, D., Cycowicz, Y.M., Gaeta, H., 2001. The novelty P3: An event-related brain potential, ERP. sign of the brain’s evaluation of novelty. Neurosci. Biobehav. Rev. 25, 355-373.

[63] Frot, M., Magnin, M., Mauguière, F., García-Larrea, L., 2007. Human SII and posterior insula differently encode thermal laser stimuli. Cereb. Cortex 17, 610-620.

[64] Galer, B.S., Jensen, M., 1999. Neglect-like symptoms in complex regional pain syndrome: results of a self-administered survey. J. Pain Symptom. Manage. 18, 213-217.

[65] García-Larrea, L., 2004. Somatosensory volleys and cortical evoked potentials: 'First come, first served'? Pain 112, 5-7.

[66] García-Larrea, L., Peyron, R., Laurent, B., Mauguière, F., 1997. Association and dissociation between laser-evoked potentials and pain perception. NeuroReport 8, 3785-3789.

[67] García-Larrea, L., Frot, M., Valeriani, M., 2003. Brain generators of laser-evoked potentials: from dipoles to functional significance. Neurophysiol. Clin. 33, 279-292.

[68] Gottlieb, J., 2007. From thought to action: the parietal cortex as a bridge between perception, action, and cognition. Neuron 53, 9-15.

[69] Gracely, R.H., Geisser, M.E., Giesecke, T., Grant, M.A.B., Petzke, F., Williams, D.A., Clauw, D.J., 2004. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain 127, 835-843.

[70] Graziano, M.S.A., Gross, C.G., 1994. The representation of extrapersonal space: a possible role for bimodal, visual-tactile neurons. In: The Cognitive Neurosciences, pp. 1021-1034. Ed M. Gazzaniga. The MIT Press: Cambridge.

[71] Graziano, M. S. A., Yap, G. S., & Gross, C. G., 1994. Coding of visual space by premotor neurons. Science 266, 1054–1057.

[72] Graziano, M.S.A., Hu, X.T., Gross, C.G., 1997. Visuospatial properties of ventral premotor cortex. J. Neurophysiol. 77, 2268-2292.

[73] Graziano, M.S.A., Gross, C.G., 1998. Spatial maps for the control of movement. Curr. Opin. Neurobiol. 8, 195-201.

[74] Hatem, S.M., Plaghki, L., Mouraux, A., 2007. How response inhibition modulates nociceptive and non-nociceptive somatosensory brain-evoked potentials. Clin. Neurophysiol. 118, 1503-1516.

[75] Hofbauer, R.K., Fiset, P., Plourde, G., Backman, S.B., Bushnell, M.C., 2004. Dose-dependent effects of propofol on the central processing of thermal pain. Anesthesiology 100, 386-394.

[76] Hofbauer, R.K., Rainville, P., Duncan., G.H., Bushnell, M.C., 2001. Cortical representation of sensory dimension of pain. J. Neurophysiol. 86, 402-411.

[77] Honoré, J., Hénon, H., Naveteur, J0, 1995. Influence of eye orientation on pain as a function of anxiety. Pain 63: 213-218.

[78] Iannetti, G.D., Zambreanu, L., Cruccu, G., Tracey, I., 2005. Operculoinsular cortex encodes pain intensity at the earliest stages of cortical processing as indicated by amplitude of laser-evoked potentials in humans. Neuroscience 131, 199-208.

[79] Iannetti, G.D., Zambreanu, L., Tracey, I., 2006. Similar nociceptive afferents mediate psychophysical and electrophysiological responses to heat stimulation of glabrous and hairy skin in humans. J. Physiol. 577, 235-248.

[80] Iannetti, G.D., Hughes, N.P., Lee, M.C., Mouraux, A., 2008. Determinants of laser-evoked EEG responses: pain perception or stimulus saliency? J. Neurophysiol. 100, 815-828.

[81] Ingvar, M., 1999. Pain and functional imaging. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 354,1347-1358.

[82] Itti, L., Koch, C., 2001. Computational modelling of visual attention. Nat. Rev. Neurosci. 2, 194-203.

[83] Kakigi, R., and Watanabe, S., 1996. Pain relief by various kinds of interference stimulation applied to the peripheral skin in humans: pain-related brain potentials following CO2 laser stimulation. J. Peripher. Nerv. Syst. 1, 189–198.

[84] Kakigi, R., Inui, K., Tamura, Y., 2005. Electrophysiological studies on human pain perception. Clin. Neurophysiol. 116, 743-763.

[85] Kassubek, J., Juengling, F.D., Els, T., Spreer, J., Herpers, M., Krause, T., Moser, E., Lücking, C.H., 2003. Activation of a residual cortical network during painful stimulation in long-term postanoxic vegetative state: a $^{15}O$-$H_2O$ PET study. J. Neurol. Sci. 212, 85-91.

[86] Kayser, C., Petkov, C.I., Lippert, M., Logothetis, K., 2005. Mechanisms for allocating auditory attention: an auditory salience map. Curr. Biol. 15, 1943-1947.

[87] Kennet, S., Eimer, M., Spence, C., Driver, J., 2001. Tactile-visual links in exogenous spatial attention under different postures: convergent evidence from psychophysics and ERPs. J. Cogn. Neurosci. 13, 462-478.

[88] Kenshalo, D.R., Iwata, K., Sholas, M., Thomas, D.A., 2000. Response properties and organization of nociceptive neurons in area 1 of mony primary somatosensory cortex. J. Neurophysiol. 84, 719-729.

[89] Knudsen, E.I., 2007. Fundamental components of attention. Ann. Rev. Neurosci. 30, 57-78.

[90] Koyama, T., Tanaka, Y.Z., Mikami, A., 1998. Nociceptive neurons in the macaque anterior cingulate activate during anticipation of pain. NeuroReport 9, 2663-2667.

[91] Kulkarni, D., Bentley, D.E., Elliott, R., Youell, P., Watson, A., Derbyshire, S.W.G., Frackowiak, R.S.J., Friston, K.J., Jones, A.K.P., 2005. Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. Eur. J. Neurosci. 21, 3133-3142.

[92] Làdavas, E., di Pellegrino, G., Farnè, A., Zeloni, G., 1998. Neuropsychological evidence of an integrated visuatactile representation of peripersonal space in humans. J. Cogn. Neurosci. 10, 581-589.

[93] Làdavas, E., 2002. Functional and dynamic properties of visual peripersonal space. Trends Cogn. Sci. 6, 17-22.

[94] Landis, T., 2000. Disruption of space perception due to cortical lesions. Spat. Vis. 13, 179-191.

[95] Le Bars, D., 2002. The whole body receptive field of dorsal horn multireceptive neurones. Brain Res. Rev. 40, 29-44.

[96] Le Bars, D., Dickenson, A.H., Besson J.M., 1979. Diffuse noxious inhibitory controls, DNIC.: I. Effects on dorsal horn convergent neurones in the rat, Pain 6, 283–304.

[97] Lee, M.C., Mouraux, A., Iannetti, G.D., 2009. Characterizing the cortical activity through which pain emerges from nociception. J. Neurosci. 29, 7909-7916.

[98] Legrain, V., Guérit, J.M., Bruyer, R., Plaghki, L., 2002. Attentional modulation of the nociceptive processing into the human brain: selective spatial attention, probability of stimulus occurrence, and target detection effects on laser evoked potentials. Pain 99, 21-39.

[99] Legrain, V., Bruyer, R., Guérit, J.M., Plaghki, L., 2003a. Nociceptive processing in the human brain of infrequent task-relevant and task-irrelevant noxious stimuli. A study with ERPs elicited by CO2 laser radiant heat stimuli. Pain 103, 237-248.

[100] Legrain, V., Guérit, J.M., Bruyer, R., Plaghki, L., 2003b. Electrophysiological correlates of attentional orientation in humans to strong intensity deviant nociceptive stimuli, inside and outside the focus of spatial attention. Neurosci. Lett. 339, 107-110.

[101] Legrain, V., Bruyer, R., Guérit, J.M., Plaghki, L., 2005. Involuntary orientation of attention to unattended deviant nociceptive stimuli is modulated by concomitant visual task difficulty. Evidence from laser evoked potentials. Clin. Neurophysiol. 116, 2165-2174

[102] Legrain, V., Perchet, C., García-Larrea, L., 2009a. Involuntary orienting of attention to pain. Neural and behavioral signatures. J. Neurophysiol. 102, 2423-2434.

[103] Legrain, V., Van Damme, S., Eccleston, C., Davis, K.D., Seminowicz, D.A., Crombez, G., 2009b. A neurocognitive model of attention to pain: Behavioral and neuroimaging evidence. Pain 144, 230-232.

[104] Legrain, V., Crombez, C., Verhoeven, K., Mouraux, A., 2010. The role of working memory in the attentional control of pain. Pain, in press.

[105] Lewis, J.S., Kersten, P., McCabe, C.S., McPherson, K.M., Blake, D.R., 2007. Body perception disturbance: a contribution to pain in complex regional pain syndrome (CRPS). Pain 133, 111-119.

[106] Liu, C.C., Veldhuijzen, D.S., Ohara, S., Winberry, J., Greenspan, J.D., Lenz, F.A., (2010). Spatial attention to thermal pain stimuli in subjects with visual spatial

hemi-neglect: extinction, mislocalization and misidentification of stimulus modality. Pain, in press.

[107] Lloyd, D.M., Shore, D.I., Spence, C., Calvert, G.A., 2003. Multisensory representation of the limb position in human premotor cortex. Nat. Neurosci. 6, 17-18.

[108] Lloyd, D., Morrison, I., Roberts, N., 2006. Role for human posterior parietal cortex in visual processing of aversive objects in peripersonal space. J. Neurophysiol. 95, 205-214.

[109] Longo, M.R., Betti, V., Aglioti, S.M., Haggard, P., 2009. Visually induced analgesia: seeing the body reduces pain. J. Neurosci. 29, 12125-12130.

[110] Lui, F., Duzzi, D., Corradini, M., Serafini, M., Baraldi, P., Porro, C.A., 2008. Touch or pain? Spatio-temporal patterns of cortical fMRI activity following brief mechanical stimuli. Pain 138:362-374.

[111] Macaluso, E., Driver, J., 2005. Multisensory spatial integrations: a window onto functional integration in the human brain. Trends Neurosci. 28, 264-271.

[112] Magerl, W., Ali, Z., Ellrich, J., Meyer, R.A., Treede, R.D., 1999. C- and Aδ-fiber components of heat-evoked cerebral potentials in healthy human subjects. Pain 82, 127-137.

[113] Melzack, R., 1989. Phantom limbs, the self and the brain. Can. Psychol. 30, 1-16.

[114] Melzack, R., 2001. Pain and the neuromatrix in the brain. J. Dent. Educ. 65, 1378-1382.

[115] Melzack, R., Casey, K.L., 1968. Sensory, motivational and central control determinants of pain: a new conceptual model, pp. 423-443. In: The Skin Senses. Ed D.R. Kenshalo. Thomas: Springfield.

[116] Moseley, G.L., 2004. Why do people with complex regional pain syndrome take longer to recognize their affected hand? Neurology 62, 2182-2186.

[117] Moseley, G.L., Gallace, A., Spence, C., 2009. Space-based, but not arm-based, shift in tactile processing in complex regional pain syndrome and its relationship to cooling of the affected limb. Brain 132, 3142-3151.

[118] Mouraux, A., Guérit, J.M., Plaghki, L., 2004. Refractoriness cannot explain why C-fiber laser-evoked potentials are recorded only if concomitant Aδ-fiber activation is avoided. Pain 112, 16-26.

[119] Mouraux, A., Plaghki, L., 2007. Cortical interactions and integration of nociceptive and non-nociceptive somatosensory inputs in humans. Neuroscience 150, 72-81.

[120] Mouraux, A., Iannetti, G.D., 2008. A review of the evidence against the “first come first served” hypothesis. Comment on Truini et al. [Pain 2007;131:43–7]. Pain 136, 219-221.

[121] Mouraux, A., Iannetti, G.D., 2009. Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. J. Neurophysiol. 101, 3258-3269.

[122] Mouraux, A., Diukova, A., Lee, M.C., Wise, R.G., Iannetti, G.D., 2010. A multisensory investigation of the functional significance of the “pain matrix”. NeuroImage, in press.

[123] Müller, M.M., Giabbiconi, C.M., 2008. Attention in sense of touch. In: Human haptic perception. Basics and applications, pp. 199-206. Ed M. Grunwald. Birkhäuser Verlag: Basel.

[124] Näätänen, R., Picton, T., 1987. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 24, 375-425.

[125] Näätänen, R., Paavilainen, P., Rinne, T., Alho, K., 2007. The mismatch negativity (MMN) in basic research of central auditory processing: A review. Clin. Neurophysiol. 118, 2544-2590.

[126] Nahra, H., Plaghki, L., 2003. Modulation of perception and neurophysiological correlates of brief CO2 laser stimuli in humans using concurrent large fiber stimulation. Somatosens. Mot. Res. 20, 139-147.

[127] Nikolajsen, L., Jensen, T.S., 2006. Phantom limb. In Textbook of pain (5th Edition), pp. 961-971. Eds S.B. McMahon, M. Koltzenburg. Churchill Livingstone: Edinburgh.

[128] Ohara, S., Crone, N.E., Weiss, N., Treede, R.D., Lenz, F.A., 2004. Amplitudes of laser evoked potential recorded from primary somatosensory, parasylvian and medial frontal cortex are graded with stimulus intensity. Pain 110, 318-328.

[129] Pavani, F., Spence, C., Driver, J., 2000. Visual capture of touch: out-of-the-body experiences with rubber gloves. Psychol. Sci. 11, 353-359.

[130] Petrovic, P., Peterson, K.M., Ghatan, P.H., Stone-Elander S., Ingvar M., 2000. Pain-related cerebral activation is altered by a distracting cognitive task. Pain 85, 19-30.

[131] Peyron, R., García-Larrea, L., Grégoire, M.C., Costes, N., Convers, P., Lavenne, F., Mauguière, F., Michel, D., Laurent, B., 1999. Haemodynamic brain responses to acute pain in humans. Sensory and attentional networks. Brain 122, 1765-1779.

[132] Peyron, R., Laurent, B., García-Larrea, L., 2000. Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol. Clin. 30, 263-288.

[133] Pincus, T., Morley, S., 2001. Cognitive-processing bias in chronic pain: a review and integration. Psychol. Bull. 127, 599-617.

[134] Plaghki, L., Delisle, D., Godfraind, J.M., 1994. Heterotopic nociceptive conditioning stimuli and mental task modulate differently the perception and physiological correlates of short CO2 laser stimuli. Pain 57, 181-192.

[135] Plaghki, L., Mouraux, A., 2003. How do we selectively activate skin nociceptors with high power infrared laser? Physiology and biophysics of laser stimulation. Neurophysiol. Clin. 33, 269-277.

[136] Plaghki, L., Mouraux, A., 2005. EEG and laser stimulation as tools for pain research. Curr. Opin. Investig. Drugs 6, 58-64.

[137] Porro, C.A., 2003. Functional imaging and pain: behavior, perception, and modulation. Neuroscientist 9, 354-369.

[138] Raij, T.T., Vartiainen, N.V., Jousmäki, V., Hari, R., 2003. Effects of interstimulus interval on cortical responses to painful laser stimuli. J. Clin. Neurophysiol. 20, 73-79.

[139] Rainville, P., 2002. Brain mechanisms of pain affect and pain modulation. Curr. Opin. Neurobiol. 12, 195-204.

[140] Rainville, P., Duncan, G.H., Price, D.D., Carrier, B., Bushnell, M.C., 1997. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277, 968-971.

[141] Rizzolatti, G., Camarda, R., Fogassi, L., Gentilucci, M., Luppino, G., Matelli, M., 1988. Functional organization of inferior area 6 in the macaque monkey: II. Area F5 and the control of distal movements. Exp. Brain Res. 71, 491-507.

[142] Rizzolatti, G., Fogassi, L., Gallese, V., 1997. Parietal cortex: from sight to action. Curr. Opin. Neurobiol. 7, 562-567.

[143] Robinson, C.J., Burton, H., 1989. Somatic submodality distribution within the second somatosensory (SII), 7b, retrosinsular, postauditory, and granular insular cortical areas of M. fascicularis. J. Comp. Neurol. 192, 93-108.

[144] Sakata, H., Taira, M., Murata, A., Mine, S., 1995. Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. Cereb. Cortex 5, 429–438.

[145] Schröger E., 1996. A neural mechanism for involuntary attention shifts to changes in auditory stimulation. J. Cogn. Neurosci. 8, 527-539.

[146] Schnakers, C., Zasler, N.D., 2007. Pain assessment and management in disorders of consciousness. Curr. Opin. Neurol. 20, 620-626.

[147] Seminowiz, D.A., Mikulis, D.J., Davis, K.D., 2004. Cognitive modulation of pain-related brain responses depends on behavioral strategy. Pain 112, 48-58.

[148] Seminowicz, D.A., Davis., K.D., 2006. Cortical responses to pain in healthy individuals depends on pain catastrophizing. Pain 120, 297-306.

[149] Seminowicz, D.A., Davis, K.D., 2007. Interactions of pain intensity and cognitive load: The brain stays on task. Cereb. Cortex 17, 1412-1422.

[150] Serences, J.T., Yantis, S., 2006. Selective visual attention and perceptual coherence. Trends Cogn. Sci. 10, 38-45.

[151] Sherrington, C., 1906. The Integrative Action of the Nervous System. Oxford University Press: Oxford.

[152] Shikata, E., Tanaka, Y., Nakamura, H., Taira, M., Sakata, H., 1996. Selectivity of the parietal visual neurons in 3D orientation of surface of stereoscopic stimuli. Neuroreport 7, 2389–2394.

[153] Shore, D.I., Gray, K., Spry, E., Spence, C., 2005. Spatial modulation of tactile temporal-order judgements. Perception 34, 1251-1262.

[154] Sikes, R.W., Vogt, B.A., 1992. Nociceptive neurons in area 24 of rabbit cingulate cortex. J. Neurophysiol. 68, 1720-1732.

[155] Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D., 1994. Empathy for pain involves the affective but not sensory components of pain. Science 303, 1157-1162.

[156] Spence, C., Kingstone, A., Shore, D.I., Gazzaniga, M.S., 2001. Representation of visuotactile space in the split brain. Psychol. Sci. 12, 90-93.

[157] Sumitani, M., Shibata, M., Iwakura, T., Matsuda, Y., Sakaue, G., Inoue, T., Mashimo, T., Miyauchi, S., 2007. Pathologic pain distorts visuospatial perception. Neurology 68, 152-154.

[158] Tanaka, E., Inui, K., Kida, Y., Miyazaki, T., Takeshima, Y., Kakigi, R., 2008. A transition from unimodal to multimodal activations in four sensory modalities in humans: an electrophysiological study. BMC Neuroscience 9, 116.

[159] Tiede, W., Magerl, W., Baumgärtner, U., Durrer, B., Ehlert, U., Treede, R.D., 2010. Sleep restriction attenuates amplitudes and attentional modulation of pain-related evoked potentials, but augments pain ratings in healthy volunteers. Pain 148, 36-42.

[160] Timmermann, L., Ploner, M., Haucke, K., Schmitz, F., Baltissen, R., Schnitzler, A., 2001. Differential coding of pain intensity in the human primary and secondary somatosensory cortex. J. Neurophysiol. 86, 1499-1503.

[161] Tolle, T.R., Kaufmann, T., Siessmeier, T., Lautenbacher, S., Berthele, A., Munz, F., Zieglgansberger, W., Willoch, F., Schwaiger, M., Conrad, B., Bartenstein, P., 1999. Region-specific encoding of sensory and affective components of pain in the human brain: a positron emission tomography correlation analysis. Ann. Neurol. 45, 40-47.

[162] Tracey, I., Mantyh, P.W., 2007. The cerebral signature for pain perception and its modulation. Neuron 55, 377-391.

[163] Treede, R.D., Kenshalo, D.R., Gracely, R.H., Jones, A.K., 1999. The cortical representation of pain. Pain 79, 105-111.

[164] Truini, A., Rossi, P., Galeotti, F., Romaniello, A., Virtuoso, M., De Lena, C., Leandri, M., Cruccu, G., 2004. Excitability of the Adelta nociceptive pathways as assessed by the recovery cycle of laser evoked potentials in humans. Exp. Brain Res. 155, 120-123.

[165] Truini, A., Galeotti, F., Cruccu, G., García-Larrea, L., 2007. Inhibition of cortical responses to Adelta inputs by a preceding C-related response: testing the "first come, first served" hypothesis of cortical laser evoked potentials. Pain 131, 341-347.

[166] Uddin, L.Q., Menon, V., 2009. The anterior insula in autism: under-connected and under-examined. Neurosci. Biobehav. Rev. 33, 1198-1203.

[167] Valet, M., Sprenger, T., Boecker, H., Willoch, F., Rummeny, E., Conrad, B., Erhard, P., Tolle, T.R., 2004. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain. An fMRI analysis. Pain 109, 399-408.

[168] Van Damme, S., Crombez, G., Lorenz, J., 2007. Pain draws visual attention to its location: experimental evidence for a threat-related bias. J. Pain 8, 976-982.

[169] Van Damme, S., Legrain V., Vogt, J., Crombez, G., 2010. Keeping pain in mind: a motivational account of attention to pain. Neurosci. Biobehav. Rev. 34, 204-213.

[170] Van Ryckeghem, D.M.L., Van Damme, S., Crombez, G., Eccleston, C., Verhoeven, K., Legrain, V., 2010. The role of spatial attention in attentional control over pain: an experimental investigation. Submitted.

[171] Wager, T.D., Rilling, J.K., Smith, E.E., Sokolik, A., Casey, K.L., Davidson, R.J., Kosslyn, S.M., Rose, R.M., Cohen, J.D., 2004. Placebo-induced changes in FMRI in the anticipation and experience of pain. Science 303, 1162–1167.

[172] Wall, P.D., 1995. Independent mechanisms converge on pain. Nat. Medicine 1, 740-741.

[173] Wang, A.L., Mouraux, A., Liang, M., Iannetti, G.D., 2010. Stimulus novelty, and not neural refractoriness, explains the repetition suppression of laser-evoked potentials. J. Neurophysiol., in press.

[174] Weierich, M.R., Wright, C.I., Negreira, A., Dickerson, B.C., Feldman Barrett, L., 2010. Novelty as a dimension in the affective brain. NeuroImage 49, 2871-2878.

[175] Yantis, S., 2008. The neural basis of selective attention. Cortical sources and targets of attentional modulation. Curr. Dir. Psychol. Sci. 17, 86-90.

## FIGURE CAPTIONS

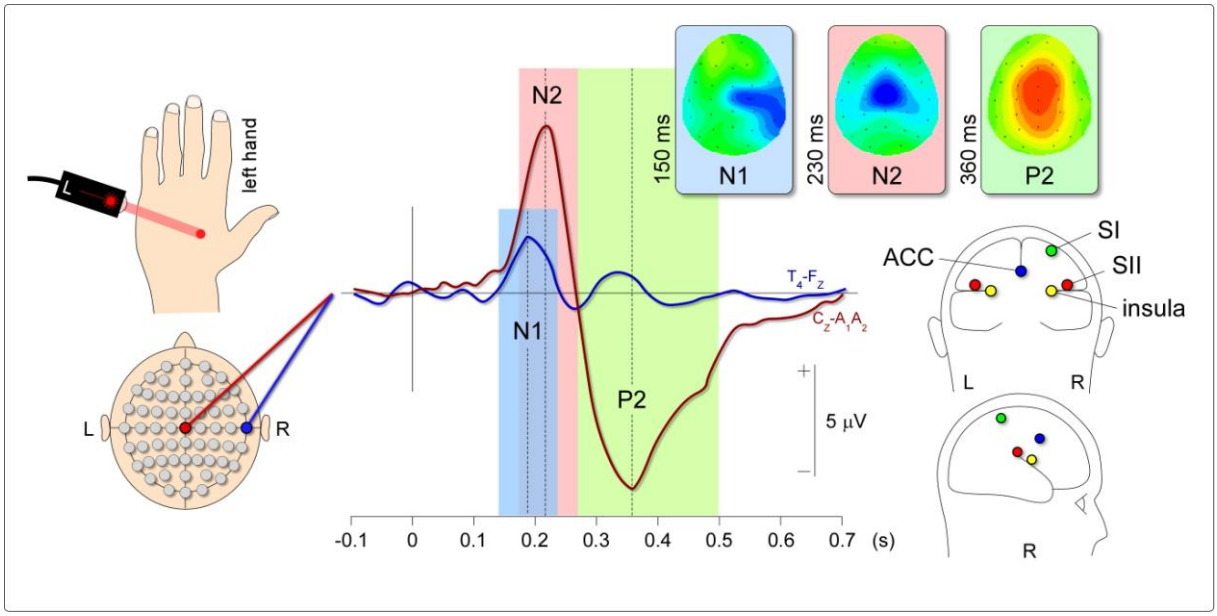


**Figure 1. Nociceptive laser-evoked brain potentials.**

Nociceptive event-related potentials (ERPs) correspond to time-locked electroencephalographic (EEG) responses elicited by the phasic activation of peripheral skin nociceptors. Most often, nociceptive ERPs are obtained by applying brief pulses of radiant heat to the skin using an infrared laser (Arendt-Nielsen & Chen, 2003). Laser pulses allow activating selectively the heat-sensitive Aδ- and C-fiber nociceptive free nerve endings located in the superficial layers of the skin, without concomitantly activating low-threshold mechano-receptors (Plaghki & Mouraux, 2003). The high energy density of laser stimulator allows producing very steep profiles of skin heating, and thereby activates skin nociceptors in a highly-synchronized fashion making it possible to record phasic, time-locked events such as reaction times and ERPs. Nociceptive ERPs reflect the sequential activation of an extensive cortical network, which is mainly expressed on the scalp by the occurrence of three successive waves: N1, N2 and P2 (Plaghki & Mouraux, 2005). The figure illustrates nociceptive ERPs recorded at the scalp vertex electrode (red waveform) and at the contralateral temporoparietal electrode (blue waveform) and evoked by

brief nociceptive laser heat stimuli directed to the left hand dorsum. The three successive ERP components are shown in their respective time windows outlined by colored boxes: N1 (blue box), N2 (pink box), and P2 (green box). The time t=0 corresponds to the onset of the laser stimulus. The upper right part of the figure represents the scalp distribution maps (top view) of nociceptive ERP magnitude at the latency of the N1, N2 and P2 waves respectively. The lower right part of the figure illustrates the localization of the different sources contributing to ERPs obtained from dipole modeling studies and confirmed by direct subdural or deep intracortical recordings (see García-Larrea et al., 2003). Most of these studies have located sources in the secondary somatosensory (SII) and insular cortex bilaterally, as well in the anterior cingulate cortex (ACC). A smaller number of studies, most of them relying on MEG, have located an additional source in the contralateral primary somatosensory cortex (SI) (Kakigi et al., 2005).

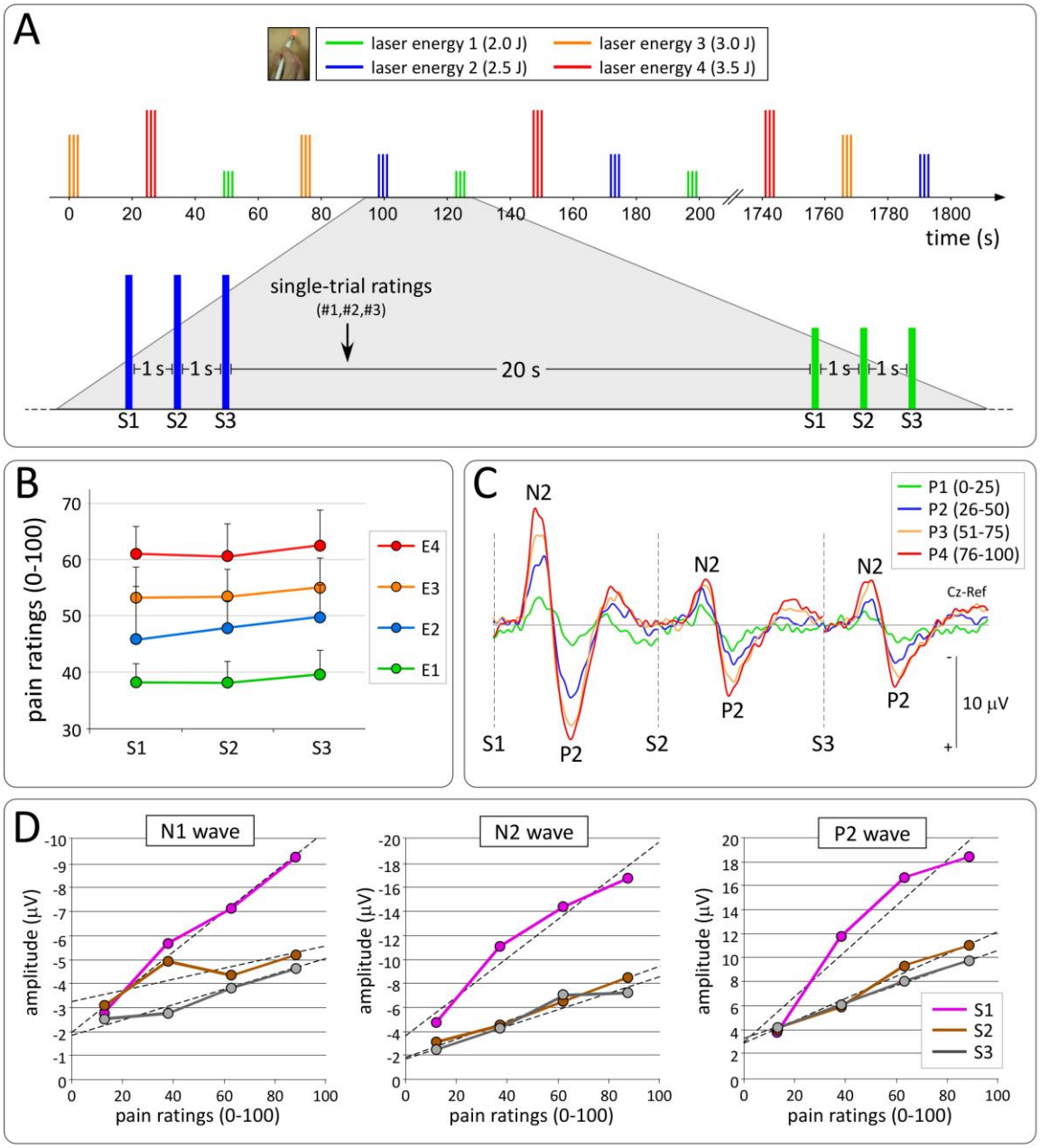


**Figure 2. Dissociation between the magnitude of nociceptive ERPs and the intensity of pain by stimulus repetition.**

A. Experimental design. Laser pulses were delivered in trains of three identical stimuli (S1, S2 and S3) using a constant interstimulus time interval of 1 s. After each train, participants were asked to rate the intensity of the painful percept elicited by each of the three stimuli of the train. Across trials, four different energy intensities

were used (E1 to E4). B. Pain ratings according to the energy of the laser pulses (E1 to E4) and the position of the stimulus in the train (S1 to S3). While the intensity of perception was graded with the physical energy of the laser pulses, the repetition of the stimulus did not affect the intensity of perception. C. Group-level average event-related potentials elicited by the laser stimuli according their position in the trains (S1 to S3 from left to right), and according to the intensity of perception (P1 to P4). EEG epochs were classified in four categories according to the participants' pain ratings, from the lowest ratings (P1) to the largest ones (P4). The magnitude of the ERPs evoked by the second and third stimuli of the train was markedly reduced, as compared to the magnitude of ERPs evoked by the first stimulus of the train. In addition, while the magnitude of ERPs evoked by the first stimulus of the train was strongly related to the subjective intensity of perception, the magnitude of ERPs evoked by the second and third stimuli was less related to perception. D. Relationship between pain rating and magnitude of the N1, N2 and P2 components of nociceptive ERPs according to stimulus order. The magnitude of ERP components evoked by the first stimulus (in purple) was significantly and positively correlated to the subjective intensity of perception. The correlation between ERP magnitude and pain rating disappeared when stimuli were repeated a second and a third time, showing that stimulus repetition disrupted the relationship between perception and ERP magnitude. Adapted from Iannetti et al. (2008).

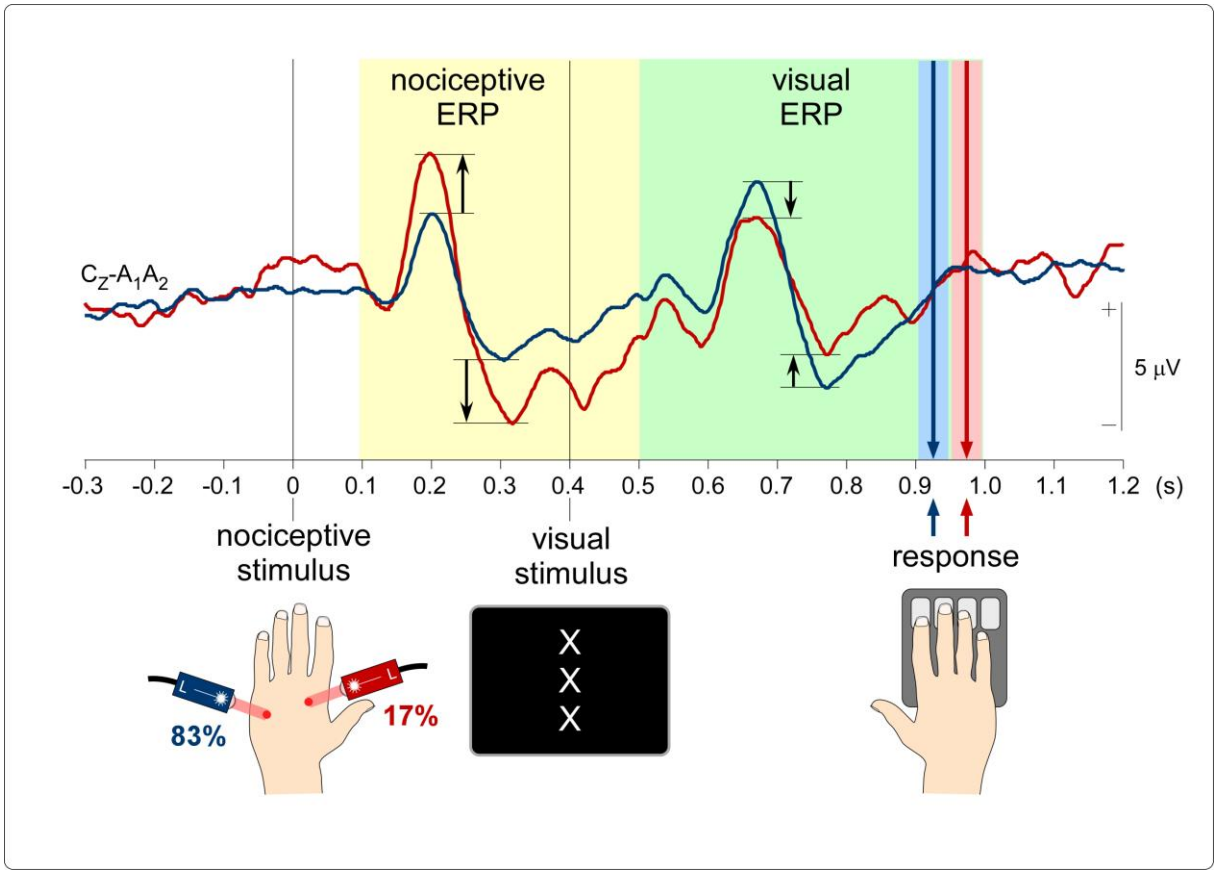


**Figure 3. Effects of stimulus novelty on nociceptive ERPs and attention.**

In this experiment, nociceptive laser stimuli and visual stimuli were delivered in pairs. The laser stimuli were regularly delivered on a specific area of the left hand dorsum. Occasionally (17% of the trials), the location of the laser stimuli was shifted to another area of the same hand. Nociceptive stimuli were followed 400 milliseconds later by a visual stimulus. The participants were instructed to report as quick as possible the number of displayed symbols on each visual stimulus (choice reaction-time task), while ignoring the nociceptive stimuli. The figure contrasts the results obtained in trials where the laser stimulus was applied to the standard area (in blue) to those obtained in trials where the laser stimulus was applied to the novel location (in red). As compared to standard trials, novel nociceptive stimuli elicited ERPs of larger magnitude (orange box). In contrast, the occurrence of novel nociceptive stimuli led to a decreased magnitude of ERPs evoked by the subsequent visual

stimuli (green box) and delayed the behavioral responses to those visual targets (illustrated by the difference between the red and the blue arrows respectively). These observations indicate that novel nociceptive stimuli distracted the subjects from their ongoing task by disrupting the cortical processing of visual targets. Adapted from Legrain et al. (2009).

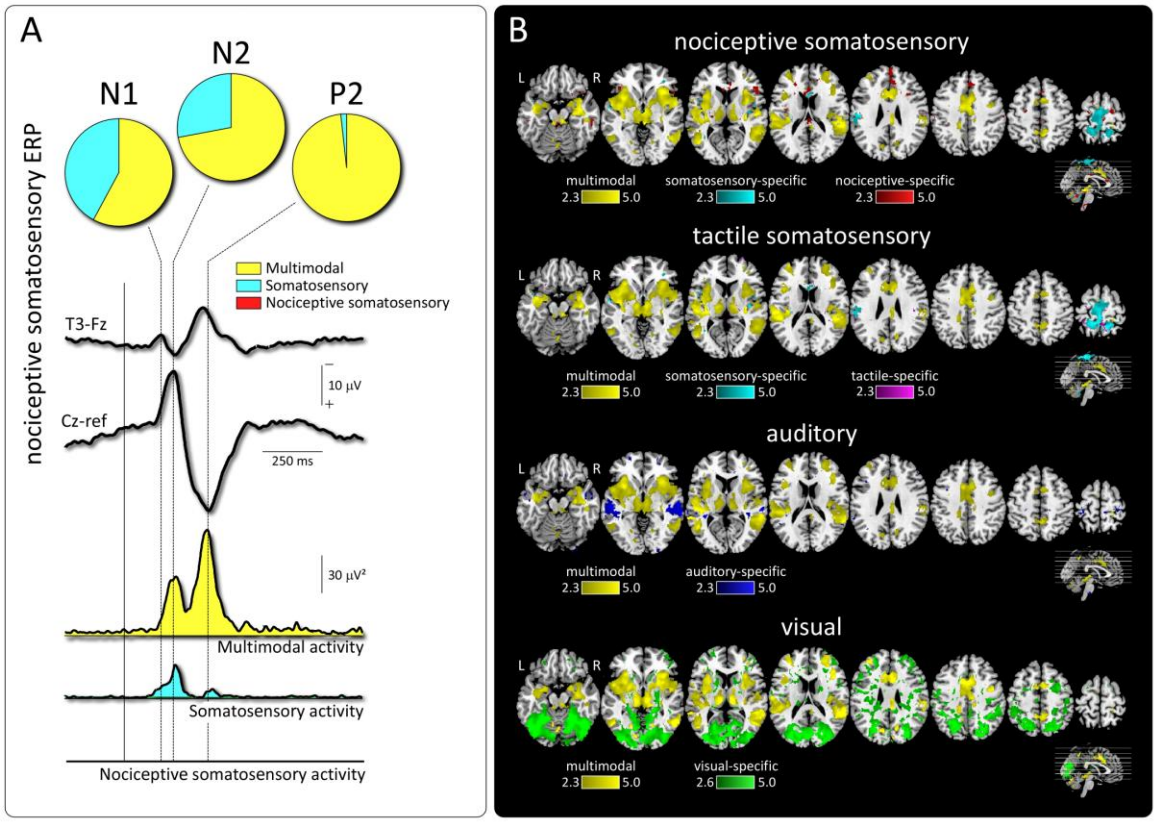


**Figure 4. The multimodal activation of the "*pain matrix*".**

A. EEG study. Multimodal and modality-specific contributions to ERPs elicited by a random sequence of nociceptive, tactile, visual and auditory stimuli were separated using a Probalistic Independent Component Analysis. The analysis showed that the greater part of nociceptive ERPs can be explained by multimodal activities (i.e. activities elicited by all stimuli) (in yellow). The time course of multimodal activities, expressed as global field power, shows that these activities contributed to the greater

part of the N1 and N2 waves and to the almost entire P2 wave of nociceptive ERPs. The remaining fraction of nociceptive ERPs that was not explained by multimodal activities could be explained by somatosensory-specific but not nociceptive-specific activities (i.e. elicited by both tactile and nociceptive stimuli) (in blue). The time course of somatosensory-specific activities, expressed as global field power, shows that these activities contributed mainly to the N1 and N2 waves. No contribution to laser-evoked potentials of nociceptive-specific activities (i.e. elicited uniquely by nociceptive stimuli) (in red) was found. Adapted from Mouraux & Iannetti (2009). B. fMRI study. A conjunction analyses of the BOLD signal observed in the same experimental design yielded similar results. Multimodal activities (voxels shown in yellow) were found in parietal operculum, insula, posterior parietal cortex, anterior cingulate cortex. These voxels represent the largest part of the BOLD response to nociceptive stimulation. The fraction of the BOLD response to nociceptive stimulation that was not explained by multimodal activities was again largely explained by somatosensory-specific activities located in the contralateral post-central gyrus (SI) (voxels shown in light blue). Voxels responding uniquely to nociceptive stimuli (in red) were extremely sparse. Adapted from Mouraux et al. (2010).