

# **Do nociception and pain affect the perception of peripersonal space?**

**Studies in healthy volunteers and patients  
with complex regional pain syndrome**

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**Studies in healthy volunteers and patients with complex regional pain syndrome**

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de l'éducation

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*Für meine Eltern*

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## Abstract

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This thesis has been articulated around the question whether nociceptive stimuli and pain can impact the perception of the visual space around the body. This was investigated in healthy volunteers by experimentally applying brief nociceptive stimuli, and in patients suffering from chronic pain in one limb. In healthy participants, we showed that nociceptive stimuli can actually facilitate the processing of visual stimuli. Crucially, such crossmodal facilitation is more efficient when visual stimuli occur in close proximity to the hand on which the nociceptive stimuli are applied. We furthermore showed that patients suffering from upper-limb complex regional pain syndrome paid less attention to visual stimuli occurring in the immediate vicinity of their affected limb. This suggests that the way we perceive and represent our near visual surrounding is influenced by somatic, e.g. nociceptive, sensations and that pain is processed according to a representation of the body that is not limited to its physical boundaries.

## Résumé

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L'objectif de cette thèse était de déterminer si les stimuli nociceptifs et la douleur peuvent influencer la perception de l'espace visuel entourant le corps. Cette question a été étudiée en appliquant de brefs stimuli nociceptifs sur les mains de participants sains, ainsi qu'à l'aide de patients souffrant de douleur chronique d'un membre supérieur. Chez les participants sains, nous avons montré que des stimuli nociceptifs peuvent faciliter le traitement de stimuli visuels. Cette facilitation crossmodale est d'autant plus importante que les stimuli visuels sont présentés à proximité de la main sur laquelle les stimuli nociceptifs sont appliqués. En outre, nous avons montré que les patients souffrant du syndrome douloureux régional complexe d'un membre supérieur portent moins d'attention aux stimuli qui entourent directement le membre affecté. Cela suggère que la manière dont nous percevons et nous représentons notre environnement proche est influencée par des sensations somatiques (nociceptives) et que la douleur est traitée selon une représentation du corps qui ne se limite pas à ses frontières physiques.

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Brussels, April 2017

Lieve

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## Acknowledgments

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## **General introduction**

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## General introduction

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Our body constitutes the mean by which we interact with the external world. Consequently, this raises the question to which extent the state of our body and the way we perceive it influences how we perceive and process sensory inputs, not only those emerging from the body itself, but also those occurring outside the body. How a change in the structure of the body can affect the perception of external space, has for instance been demonstrated in patients who underwent upper-limb amputation, with distortions of the visuospatial perception of the space directly surrounding the body (Makin, Wilf, Schwartz, & Zohary, 2010) and changes in the boundaries between individual near and far space (Canzoneri, Marzolla, Amoresano, Verni, & Serino, 2013). Such interactions between body perception and the processing of sensory inputs can also be considered in the context of pain. For instance, Torta et al. (2017) showed that intense and prolonged nociceptive stimulation can change the cortical responses to visual stimuli. Furthermore, patients suffering from complex regional pain syndrome (CRPS), a unilateral chronic pain disorder, are described, besides their primarily sensory, trophic, autonomic and motor symptoms, as being affected by cognitive perceptual difficulties (see Legrain, Bultitude, De Paepe, & Rossetti, 2012 for a review), similar to those observed in hemispatial neglect, a cognitive disorder consecutive to brain lesions characterized by an inability to orient to, explore and report sensory events from the side of space contralateral to the damaged hemisphere. These observations may be explained within the framework of a recent theory that emphasizes the functional aspects of pain, and more specifically of nociception, i.e. the somatosensory modality devoted to the coding, the transmission and the processing of potentially noxious information, by defining it as a warning signal (Legrain & Torta, 2015). Nociception would thus allow detecting, localizing and reacting to stimuli potentially threatening the physical integrity of the body. According to this cognitive theoretical framework, nociceptive inputs would be processed in a multisensory system that prioritizes stimuli that are meaningful for the integrity of the body and which integrates these nociceptive inputs with other sensory information into a multisensory representation of the body and its proximal space (called peripersonal representation). Such a cognitive approach of nociception has led, amongst others, to investigations of the effects of cognition on pain perception, with studies suggesting that the experience of pain can be influenced through attention manipulations (e.g. Honoré, Hénon, & Naveteur, 1995; Van Ryckeghem et al., 2011; Van Ryckeghem, Crombez, Eccleston, Legrain, & Van Damme, 2013), such as distraction for example (see Eccleston & Crombez, 1999; Morley, 2011). Other research has focused, for instance, on how the posture (i.e. proprioception) and the vision of body parts on which nociceptive stimuli were applied can modulate the level of painfulness evoked by the nociceptive stimuli (e.g. Beck, Ladavas, & Haggard, 2016; Gallace, Torta, Moseley, & Iannetti, 2011; Longo, Betti, Aglioti, & Haggard, 2009; Longo, Iannetti, Mancini, Driver, & Haggard, 2012; Mancini, Longo, Kammers, & Haggard, 2011; Torta,

Legrain, & Mouraux, 2015). These studies have in common that they investigated how the manipulation of sensory information other than nociception can impact pain perception and nociceptive processing. However, what is, surprisingly not well represented in the literature, are studies investigating whether, and how, nociceptive sensations can impact the perception of sensory inputs occurring outside the body space, both in experimentally induced nociception and clinical (chronic) pain conditions. This lack in the literature contrasts with the high ecological validity of such an influence of nociception on visual processing in many everyday situations. For instance, when being stung on the hand while weeding the flower-beds to prepare the garden for the summer, one would probably orient towards the hand that got hurt and its direct surrounding to identify which of the multiple insects or plants in the flower-bed caused the sting and to eliminate the threat, as well as to check for other possible threats in the surrounding, to prevent the hand from further damage. In the same manner, when getting burned by a splash of oil while preparing dinner on different hotplates, one would probably direct his attention to the position of the burned hand in order to identify which pan caused the splash of oil and to turn the hotplate down. This question is also of particular interest when considering, for instance, that acting on distorted visuospatial perception, on its part, has been proposed in preliminary studies as an effective mean to alleviate pain and associated symptoms in chronic pain (for review see Torta, Legrain, Rossetti, & Mouraux, 2016). In this perspective, understanding the exact mechanisms by which rehabilitation of visuospatial abilities also influences sensorimotor symptoms in pain syndromes firstly requires clarifying how a distorted perception of external space can be induced by nociception and pain.

The aim of this dissertation was to clarify to which extent the perception of multisensory external space is dependent on nociceptive and pain-related body sensations, by investigating whether and under which conditions the occurrence of nociceptive stimuli on the body as well as the presence of chronic pain states affects the spatial perception of visual stimuli occurring outside the body.

This general introduction will be followed by several theoretical chapters. In a first chapter I will specify the concepts of pain and nociception and the difference that can be made between the two. I will quickly review some studies focused on the understanding of the neural mechanisms underlying the unpleasant experience of pain, before concentrating on studies emphasizing the functional aspects of pain and nociception. Particular emphasis will be put on the conceptualization of cortical nociceptive processing as part of a saliency detection system.

The second theoretical chapter will describe more in detail one specific process that has been hypothesized to be part of the cortical processing of nociceptive information: spatial perception. The different frames of reference for the spatial coding of sensory inputs will be presented, with a more focused review of the literature relating visual-tactile interactions in the space near the body.



The third theoretical chapter will focus more thoroughly on the existing literature concerning the different frames of reference involved in the spatial processing of nociceptive stimuli and the particular interest of the space directly surrounding the body, i.e. the peripersonal space.

The fourth theoretical chapter is aimed at introducing perceptual difficulties as part of the symptomatology of a unilateral chronic pain disorder that I specifically studied within the theoretical framework of my dissertation: complex regional pain syndrome (CRPS). CRPS patients seem to be affected by cognitive difficulties in mentally representing, perceiving and using the affected limb, as well as distortions in representing and perceiving the space external to the affected limb.

In the fifth and last chapter of this theoretical section I will specify the aims and objectives that have been formulated based on the aforementioned theoretical background. The temporal order judgment (TOJ) task will furthermore be presented, since this paradigm was used throughout the experiments performed in the context of this dissertation. The advantages of our modified paradigm as compared to the classical approach will be highlighted.

The theoretical section will be followed by the experimental parts of this dissertation. A first part, comprising four studies, will describe under which conditions nociceptive stimuli can impact the perception of visual stimuli, when the nociceptive stimuli are experimentally applied in healthy participants. In a second part I will report the results we obtained by studying peripersonal space perception in a population of patients suffering from CRPS.

In a general discussion the main findings and the theoretical implications of the presented experiments will be discussed, as well as their limitations and challenges for future research. Finally, I will finish by some concluding remarks.

## **1. Pain and nociception**

Everybody experiences pain in life. In spite of its inherently unpleasant character, pain is usually adaptive, since its biological functionality is to protect the organism from potential damage. Sometimes, however, pain can become maladaptive, thus losing its physiological protective effects, as in the case of chronic pain. Since alleviating pain is a major healthcare issue, it constitutes a very active field of research, both in its fundamental and clinical aspects. Nonetheless, there are still many aspects of pain experience that are still incompletely understood and its conceptualization has proven to be difficult.

Pain is currently defined as « an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage » (IASP, 1994, p. 210). In normal situations, pain results from the activation of sensory receptors, called nociceptors, which are present on the skin surface or the viscera. These nociceptors are characterized by a high activation threshold, that is, they are usually activated by high intensity potentially noxious stimuli (Belmonte & Viana, 2008). Noxious stimuli are stimuli that are harmful for the body tissue and are thus defined as representing a potential or real threat for the integrity of the body. Nociception can thus be defined as the neural processes specifically devoted to the coding, the transmission and the processing of information about potentially noxious stimuli (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2013).

The nociceptive system operates at different levels of the nervous system. The peripheral level is characterized by the nociceptors, which are free nerve endings associated to A $\delta$  and/or C fibers. A $\delta$  fibers are thinly myelinated and are projecting information later resulting in the so called first pain sensation, that is pricking, brief and localized. C fibers are unmyelinated and have a slower conduction velocity than A $\delta$  fibers. Their activation is resulting in the secondary pain sensations, which are described as burning, more diffuse and prolonged (Le Bars & Plaghki, 2009). Most of the nociceptors are polymodal, since they can be activated by thermal, mechanical and chemical stimuli. These nociceptive fibers are then projecting the nociceptive message to the spinal cord. After being integrated by neurons at the spinal level, the nociceptive information is then further projected to the subcortical and cortical levels via the anterolateral system through the spinothalamic, the spinoreticular and the spinotectal tracts.

It is important to note that the activation of the nociceptive system and the corresponding cortical activity does however not always result in an experience of pain (e.g. Hofbauer, Fiset, Plourde, Backman, & Bushnell, 2004; Lee, Mouraux, & Iannetti, 2009). Furthermore, one can also experience pain in the absence of nociceptive input, as, for instance, demonstrated in phantom limb pain after amputation (Nikolajsen & Jensen, 2006).

Pain and nociception should thus be dissociated and cannot be used as synonyms, with pain as a subjective and conscious experience being, in normal conditions, a possible response of afferent activity in the nociceptive system.

An important part of pain research has been devoted to the investigation of the cortical correlates underlying pain perception, that is, to defining a specific system transforming nociceptive information into the experience of pain at the cortical level. By using various non-invasive functional brain imaging techniques in humans, such as electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), studies showed that nociceptive stimuli can elicit responses in several subcortical and cortical brain structures (for a review see e.g. Bushnell & Apkarian, 2006; Tracey & Mantyh, 2007). Since some of these structures, i.e. the primary (SI) and secondary (SII) somatosensory, the cingulate and the insular cortices, have been observed recurrently to respond to nociceptive stimuli across studies and because these responses seem to be correlated with the perceived intensity of pain, they have been hypothesized to be preferentially involved in experiencing pain. Consequently, these structures have been hypothesized to constitute the core structure of a so-called “pain-matrix”, a network of cortical areas through which conscious pain perception would emerge from nociceptive processes (e.g. Peyron, Laurent, & García-Larrea, 2000; Rainville, 2002; Tracey & Mantyh, 2007), which would in a way constitute the “cerebral signature of pain” (Tracey & Mantyh, 2007). Measuring the activity of this network of cortical structures has furthermore been proposed as a direct, objective and quantifiable measure of pain experience (e.g. Borsook, Sava, & Becerra, 2010).

However, there are also several studies that challenge the interpretation of this “pain matrix” as a specific cortical correlate of pain perception (for a review see Legrain, Iannetti, Plaghki, & Mouraux, 2011). Indeed, these studies showed that the subjective perception of pain intensity can be dissociated from the magnitude of the brain responses in the “pain matrix” evoked by nociceptive stimuli (e.g. Clark, Brown, Jones, & El-Deredy, 2008; Iannetti, Hughes, Lee, & Mouraux, 2008; Mouraux & Plaghki, 2007). For instance, it has been demonstrated that the repetition of a nociceptive stimulus can significantly decrease the magnitude of the triggered brain response, while not affecting the perception of pain intensity (Iannetti et al., 2008). It seems thus that the cortical responses of this so-called “pain matrix” network cannot be considered as a direct correlate of the conscious perception of pain. Furthermore, the neural activity recorded in the “pain matrix” can be modulated by factors other than the intensity of the nociceptive stimulus, such as the context (e.g. evaluation of spatial location vs. unpleasantness, Kulkarni et al., 2005; after sleep deprivation, Tiede et al., 2010) in which this stimulus appears, its novelty (e.g. Legrain, Guérit, Bruyer, & Plaghki, 2002; Legrain, Perchet, & Garcia-Larrea, 2009), as well as the attention allocated to it (e.g. Legrain, Bruyer, Guérit, & Plaghki, 2005; Legrain, Crombez, Plaghki, & Mouraux, 2013). The activity in these neural structures would thus be less related to perceived pain than to cognitive processes susceptible to be influenced by the

context in which a nociceptive stimulus occurs. Finally, it has been repeatedly demonstrated that some of the cortical structures of the “pain matrix” can also be activated by non-nociceptive, non-painful and, importantly, even non-somatosensory stimuli, such as tactile, auditory and visual stimuli, with brain responses that are spatially indistinguishable from those elicited by nociceptive stimuli (e.g. Liberati et al., 2016; Lui et al., 2008; Mouraux, Diukova, Lee, Wise, & Iannetti, 2011; Mouraux & Iannetti, 2009). Therefore, these brain areas would rather reflect multimodal neural activity, triggered irrespective of the modality of the sensory stimulus.

As a consequence of the aforementioned results, it has been proposed that the activity of this so-called “pain matrix” would rather reflect a network for the detection of salient sensory events, which would be non-specific for nociceptive perception and not always related to stimulus intensity (Legrain et al., 2011). According to Yantis (2008), salience is defined as the ability of a given stimulus to stand out relative to other stimuli, and would thus depend on the distinctiveness and the contrast, along one or multiple physical dimensions, with its surrounding (Itti & Koch, 2001; Yantis, 2008), as well as on past context and memories (Näätänen, Paavilainen, Rinne, & Alho, 2007). The cortical network that has been shown to be activated in the context of nociceptive stimulation could thus be considered as a saliency detection system, subserving the processing of behaviorally relevant sensory information and preparing of the appropriate response. An important function of this system would be to signal any sensory event that may have an impact on the organism, including those related to the presence of threat in the proximity of the body. In this sense, such an interpretation does not dismiss the importance of nociceptive and painful stimuli, since pain can be considered as the archetype of physical threat. Importantly, such a system would be multimodal, taking into account the fact that not only nociceptive inputs can be relevant for the integrity of the body. Simply put, « the saliency 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 » (Legrain et al., 2011, p. 121).

Such cognitive theoretical framework allows emphasizing the functional role of the nociceptive system, by defining it as a warning signal, prompting the detection, localization and reaction to stimuli that could be a threat to the physical integrity of the body (Legrain & Torta, 2015). This definition highlights three important processes that are (non-specifically) involved in the cortical processing of nociceptive stimuli: (1) *selective attention*, prioritizing the processing of the most relevant or salient stimuli, (2) *spatial perception*, localizing adequately these relevant or salient stimuli on the body and in external space, and (3) *action selection*, preparing the most appropriate motor response in reaction to these stimuli. The second process, i.e. spatial perception, is of primary importance in this PhD thesis, since it emphasizes that nociceptive stimuli are integrated in multisensory spatial representations, allowing reciprocal interactions between nociceptive stimuli and stimuli from other sensory modalities.

## **2.     *Reference frames for spatial perception***

Even if space is most of the time perceived as a unitary representation, sensory information can be spatially processed according to different frames of reference, which seem to rely on distinct brain and cognitive mechanisms (Colby, 1998; Colby & Duhamel, 1996; Gross & Graziano, 1995; Previc, 1998; Vallar & Maravita, 2009). These multiple representations would be constructed in order to act on the world around us, with the aim to guide specific actions, as those that allow us to manipulate or avoid an object (Colby, 1998; Colby & Duhamel, 1996; Fogassi et al., 1992). This implies that a same object could be differently represented as a function of the actions that can be performed on it (Colby & Duhamel, 1996). The spatial position of sensory information can thus be differently coded according to the frame of reference, i.e. the coordinate system, that is used.

The neural correlates of space representations in the brain can be considered as a network of multiple interconnected structures that work in parallel, but particularly the parietal cortex seems to be indispensable to construct these spatial coordinate systems (Colby & Goldberg, 1999; Vallar & Maravita, 2009). Indeed, lesions in the parietal lobe can induce important deficits of spatial perception and action, with hemispatial neglect being one of the most striking examples. Hemispatial neglect occurs most of the time after right hemisphere damage and is characterized by a deficit in consciously responding to, orienting toward and exploring stimulations from the contralesional side of space (the left side in the case of right hemisphere damage) which cannot be primarily attributed to peripheral sensory or motor loss. Patients often show less explorative behaviors towards the contralesional space and deficits in the mental representation of this space (Bisiach & Luzzatti, 1978; Driver & Vuilleumier, 2001; Heilman & Valenstein, 1979; Vallar, 1998). Hemispatial neglect has mainly been explained by an exaggeration in orienting attention towards the ipsilesional side (Kinsbourne, 1993), a deficit in directing attention towards the left contralesional side (see Heilman & Valenstein, 1979) or by impairments in representing the contralesional space and body (Bisiach & Luzzatti, 1978) (for a review, see Kerkhoff, 2001). An often associated deficit of hemispatial neglect, which has frequently been considered as a milder form of it, is the phenomenon of extinction. Extinction is characterized by an incapacity to detect a contralesional stimulation if it is presented simultaneously with an ipsilesional stimulus, whereas being usually capable to detect the contralesional stimulus when presented alone (Jacobs, Brozzoli, Hady-Bouziane, Meunier, & Farne, 2011; Vallar, 1998). Since various clinical symptoms, depending on the differently affected spatial reference frames and sensory modalities, can be observed in hemispatial neglect and extinction patients, neuropsychological investigations in these patients contributed notably to the view that the brain uses distinct spatial frames of reference for spatial perception (see e.g. Caramazza & Hillis, 1990; Colby, 1998; di Pellegrino, Làdavas, & Farné, 1997; Guariglia & Antonucci, 1992; Halligan, Fink, Marshall, & Vallar, 2003; Halligan & Marshall, 1991; Landis, 2000; Smania & Aglioti, 1995). Accordingly, while outlining the different possible reference frames for the coding

of sensory information, I will regularly highlight studies that have been performed with patients suffering from hemispatial neglect and/or extinction to illustrate possible dissociations between these reference frames.

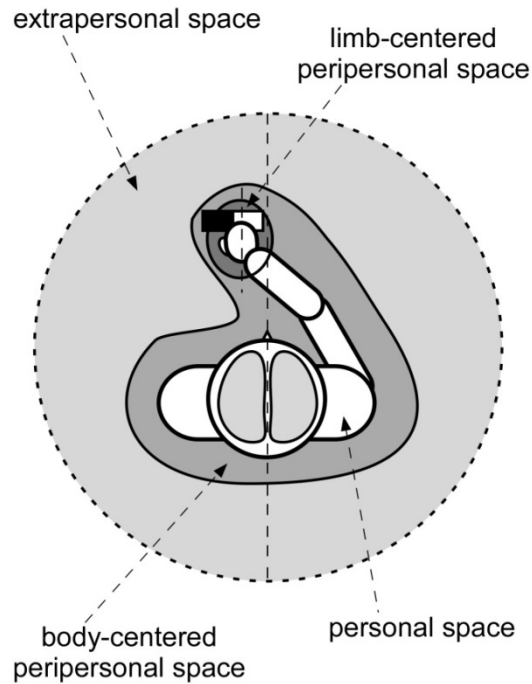
### **2.1. Egocentric vs. allocentric**

A first traditional distinction classifies spatial reference frames in two broad classes: egocentric and allocentric representations. In an egocentric or viewer-centered reference frame, locations are represented relative to the perspective of the perceiver (Klatzky, 1998), that is, the location of an object is defined relative to the perceiver's body or body parts. Egocentric reference frames can thus be eye-centered, head-centered, trunk-centered, arm-centered, and so forth (Colby, 1998; Vallar & Maravita, 2009). In an allocentric or object-centered frame of reference, locations are represented independently of the position of the perceiver, that is, the location of objects is defined relative to the location of other objects, or part of an object relative to other parts of this object.

### **2.2. Anatomical vs. spatiotopic**

Sensory inputs are initially processed in anatomically constrained reference frames which are anchored to the part of the body in which their sensory receptive fields (RFs) are located, corresponding to representations of the stimulus in primary sensory cortices, specific for each sensory modality. Such anatomical representations are, for instance, retinotopic for vision or somatotopic for somatosensation (i.e. touch and nociception). However such anatomically-based information is also integrated with signals about the position of body and body parts (i.e. eye position, proprioception), giving rise to more space-based reference frames (Galati, Pelle, Berthoz, & Committeri, 2010; Vallar & Maravita, 2009).

More specifically for somatosensation, the personal reference frame, representing the space occupied by the body, can either be somatotopic (i.e. anatomical representations which derive from projections of spatially organized somatosensory RFs to specific groups of cortical neurons) or non-somatotopic (i.e. egocentric spatiotopic representations that interact with proprioception, using external space as coordinate system) (see also Fig. 1).



**Fig. 1.** Different frames of reference for the coding of the spatial position of somatic and non-somatic inputs. The personal reference frame codes the space of the body and can be dissociated in a somatotopic personal reference frame, based on anatomical projections of somatosensory receptive fields to specific segregated groups of neurons in the cortex (e.g. Penfield's homunculus), and a spatiotopic reference frame, integrating proprioceptive information to locate somatic stimuli according to the relative position of the limb in space. A spatiotopic reference frame allows, for instance, taking into account that, when the eyes are closed, the right hand crossing the body midline is touched by the object in the left side of space, despite the fact that the tactile input is projected into the left hemisphere. The extrapersonal reference frame codes extra-somatic information in far out-of-reach space and is used to perceive and explore the environment by eye movements. Objects in that space can only be reached by displacement of the whole body. In between, the peripersonal reference frame is used to integrate the body space and external space to code spatial locations of both somatic (tactile and nociceptive) stimuli and non-somatic (visual and auditory) stimuli occurring close to the body. The peripersonal reference frame can be centered on the body as a whole, using the trunk or the head as main coordinate axes. It is used to code the proximal space in which objects can be reached by upper-limb movements. It can also be centered on each body part individually, coding the space immediately surrounding each limb where objects can have a direct impact or be directly grasped (in the case of the peri-hand space). According to a peri-limb reference frame, near visual space is anchored to one limb and moves with it, independently of the position of the limb according to the trunk reference and of the gaze according to the head reference. From Legrain and Torta (2015).

Evidence that these two reference frames can be dissociated comes from studies using the crossed hands procedure during somatosensory stimulation applied on the hands. When the hands are in an uncrossed posture, i.e. the left hand in the left side of space and the right hand in the right side of space (with regard to the body midline), both somatotopic and spatiotopic reference frames coincide and cannot be dissociated. A touch on the left hand, for instance, would thus in any case attract spatial attention to the left side of space, independently of the reference frame used to guide spatial attention. When the hands are however crossed over the body midline, i.e. the left hand is now in the right side of space and vice-versa, a somatotopic reference frame would guide spatial attention to the left side of space, since a left tactile stimulus, even with the left hand laying in the right side of space, still activates the right hemisphere. A spatiotopic reference however, taking the relative (proprioceptively perceived) position of the hands into account, would guide spatial attention to the right side of space. Using the crossed hands procedure in healthy participants, it has for instance been shown that when judging the temporal order of tactile stimuli, one applied on each hand, performance is impaired when the hands are crossed over the body midline, as compared to an uncrossed hand posture (e.g. Shore, Spry, & Spence, 2002; Yamamoto & Kitazawa, 2001). It has been suggested that these observations reveal a competition between a somatotopic reference frame and a spatiotopic reference frame. This competition has been hypothesized to be due to a remapping of the perception of the tactile stimulus according to external coordinates (e.g. Azanon & Soto-Faraco, 2008; Azanon, Stenner, Cardini, & Haggard, 2015; Heed, Buchholz, Engel, & Roder, 2015; Shore, Spry, & Spence, 2002). Further evidence that these reference frames can be dissociated comes from studies that used the crossed hands procedure in patients suffering from tactile extinction. While the patients in the study of Smania and Aglioti (1995) were unable to correctly detect tactile stimuli applied on their left hand when hands were in an uncrossed posture, their performance improved when the hands were crossed over their body midline.

### **2.3. Peripersonal vs. extrapersonal**

The representation of the space outside the body can be dissociated into peripersonal and extrapersonal frames of reference, traditionally differentiated into near and far external space, respectively (Vallar & Maravita, 2009). The peripersonal frame of reference codes the space directly surrounding the body and can be defined as a coordinate system that integrates the space of the body and the space near the body. It allows interactions between somatic and non-somatic (e.g. visual) stimuli that occur close to the body and their integration into a global multisensory representation of space (Cardinali, Brozzoli, & Farne, 2009; Holmes & Spence, 2004; Rizzolatti, Fadiga, Fogassi, & Gallese, 1997; Rizzolatti, Matelli, & Pavesi, 1983; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981a, 1981b). The peripersonal reference frame can thus be considered as a coherent multisensory representation of the body space extended into external space and seems therefore to be particularly important for optimizing interactions with proximal objects



(Cardinali et al., 2009; Rizzolatti et al., 1997), or defense behaviors against a potential danger (Graziano & Cooke, 2006; Graziano, Gross, Taylor, & Moore, 2004). Probably with reference to the actions that can be performed and the motor effector that is used (Vallar & Maravita, 2009), the peripersonal frame of reference can either be centered on the body as a whole (i.e. body-centered), using the main axes of the body as coordinate reference (i.e. the trunk and also the head for vision), or centered on each specific body part (i.e. limb-centered) (Brozzoli, Ehrsson, & Farne, 2014; Serino et al., 2015), using the body part itself as a coordinate. The extrapersonal reference frame codes the position of sensory inputs (i.e. vision, audition and olfaction) in the far out-of-reach space, where objects can only be explored by movements of the eyes or displacement of the whole body, as well as by using a tool.

Evidence for the existence of different reference frames for the perception of the space outside the body comes, for instance, from neuropsychological studies that have shown possible double dissociations between hemispatial neglect in near vs. far space. Halligan and Marshall (1991), for example, reported a patient with right hemisphere lesions who presented with severe visuospatial neglect when bisecting lines presented close to the body, but not when lines were presented far away, whereas hemispatial neglect patients in the study of Cowey, Small, and Ellis (1994) were mainly characterized by visuospatial distortions in far space.

In accordance with the research questions considered in the present dissertation, the theoretical parts that follow will further focus on the importance of the peripersonal reference frame for somatosensory perception and the mechanisms underlying visual-tactile interactions, which have been commonly used as the source for conceptualizing investigations on nociceptive-visual interactions.

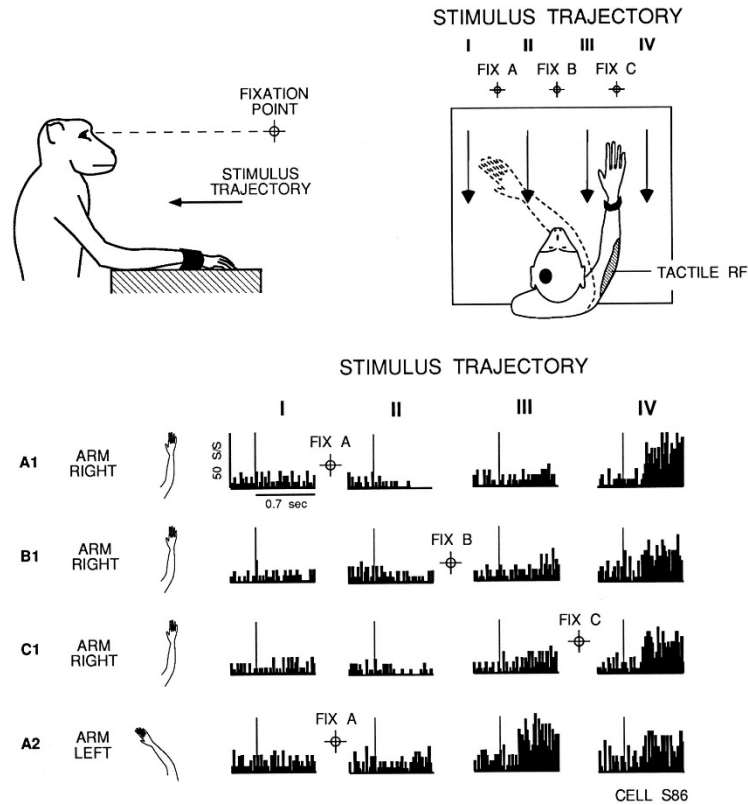
## **2.4. Visual-tactile interactions in peripersonal space**

The existence of a peripersonal representation, extending the physical boundaries of the body slightly into external space, has been extensively studied in the recent years. This is not surprising, since such a coordinate system that takes into account and integrates somatosensory input, informing us about physical contact between our body and external events, and visual input, informing us about external events that may have an impending impact on the body, is considered to be of primary importance to be able to interact with our environment, as well as to react efficiently to physically threatening events (Brozzoli et al., 2014). Much of this research has focused on investigating visual-tactile interactions and crossmodal visual-tactile perception, as well as the conditions under which they might occur, since a peripersonal reference frame for spatial processing of sensory events supposes that somatosensory stimuli and stimuli from other sensory modalities (e.g. vision) interact closely.

In the present section I will present evidence from animal and human studies that suggest the construction of multiple body-part-centered representations of space, based on the integration of visual, somatosensory and proprioceptive information.

#### 2.4.1. *Evidence from bimodal neurons in non-human primates*

In non-human primates, such multisensory representations of the body extended into external space, characterized by visual-tactile interactions, are thought to be based on the existence of interconnected multimodal areas in the brain, which would subserve the monitoring of the location and movements of objects occurring near the body (i.e. in peripersonal space) and the control of defensive responses (di Pellegrino & Làdavas, 2015; Graziano et al., 2004; Làdavas, 2002; Maravita, Spence, & Driver, 2003). These areas contain multimodal neurons, that is, neurons able to respond to sensory inputs from different sensory modalities. For instance, several authors (Graziano, Hu, & Gross, 1997; Graziano, Yap, & Gross, 1994; Rizzolatti et al., 1981a, 1981b) discovered neurons in the ventral premotor cortex (PMv) responding to tactile stimuli applied on a given body part, with tactile receptive fields (RF) that are located on the face, shoulder, arm or upper torso, but also to visual stimuli. Importantly, for some of these PMv neurons, the visual RFs are limited to the portion of external space immediately adjacent to the associated tactile RFs. Moreover, the RFs of these neurons do not move with eye movement (Fogassi et al., 1992; Gentilucci, Scandolara, Pigarev, & Rizzolatti, 1983; Graziano et al., 1997; Graziano et al., 1994), but with movements of the body part (e.g. the arm or the head) to which they are anchored (Graziano et al., 1997; Graziano et al., 1994) (see Fig. 2). As far as visuospatial perception is concerned, the function of such PMv bimodal neurons would thus be to remap the location of visual inputs from a retinotopic to a spatiotopic frame of reference, but, crucially, by using body parts as coordinate references. It could thus be hypothesized that such bimodal neurons may underlie a limb-centered peripersonal representation of space (see Fig. 1).



**Fig. 2.** Visual responses of a typical bimodal neuron situated in the ventral premotor cortex (PMv) of the monkey, with a tactile receptive field (RF) on the arm (shaded) and an associated visual RF extending in the immediately adjacent external space. The upper part of the graph depicts the experimental set-up. Depending on the trial, the monkey fixated one of three fixation points (FIX A, FIX B or FIX C), a visual stimulus approached along one of four possible trajectories (I-IV), and the arm was placed in one of two positions. The lower part depicts the histograms of the visual responses of the bimodal neuron, as a function of eye position (A-C), visual stimulus position (I-IV) and arm position (to the right: row A1, B1, C1; to the left: row A2). The vertical line on the histograms represents the stimulus onset. Neuron activity was the highest when the visual stimulus was the closest to the position of the tactile RF, i.e. for the rightmost visual stimulus position (IV) when the arm was placed to the right (A1, B1, C1) and for visual stimulus position III when the arm was placed to the left (A2), independently of the eye position. From Graziano et al. (1997).

Similar bimodal neurons have been found in the ventral intraparietal sulcus (VIP), mostly responding to tactile stimulation on the face and visual stimulation near the face (Duhamel, Colby, & Goldberg, 1998). However, some of these neurons have also visual RFs that are anchored to the retina, that is, which move with eye-movements and some other neurons that seem to be intermediate, moving in the same direction as the eyes move but not to the same extent (Avillac, Deneve, Olivier, Pouget, & Duhamel, 2005; Duhamel, Bremmer, BenHamed, & Graf, 1997). This suggests that several neurons in the VIP encode the location of visual inputs in different frames of reference that can be head-centered, eye-centered or intermediate between the two (Avillac et al., 2005).

Multimodal neurons with tactile and visual RFs have also been described in the parietal area 7b (e.g. Graziano & Gross, 1995; Leinonen, Hyvärinen, Nyman, & Linnankoski, 1979; Leinonen & Nyman, 1979). The tactile RFs can be located on the arm, face, or torso, but can also cover more than one body part and sometimes the entire body. The visual RFs match roughly these tactile RFs, but as for neurons in the VIP, in some neurons these visual RFs move, at least partially, with eye-movements (Graziano & Gross, 1995). It could be hypothesized that such neurons in parietal area 7b with tactile and corresponding visual RFs that cover the entire body may play a part in a body-centered peripersonal representation of space (see also Serino et al., 2015).

In humans, direct evidence for neuronal integration at the single-cell level for inputs of different sensory modalities has still to be provided. Whether the same principles of visual-tactile interactions and integration as demonstrated in non-human primates also apply in humans has mainly been investigated in brain-damaged patients and healthy participants.

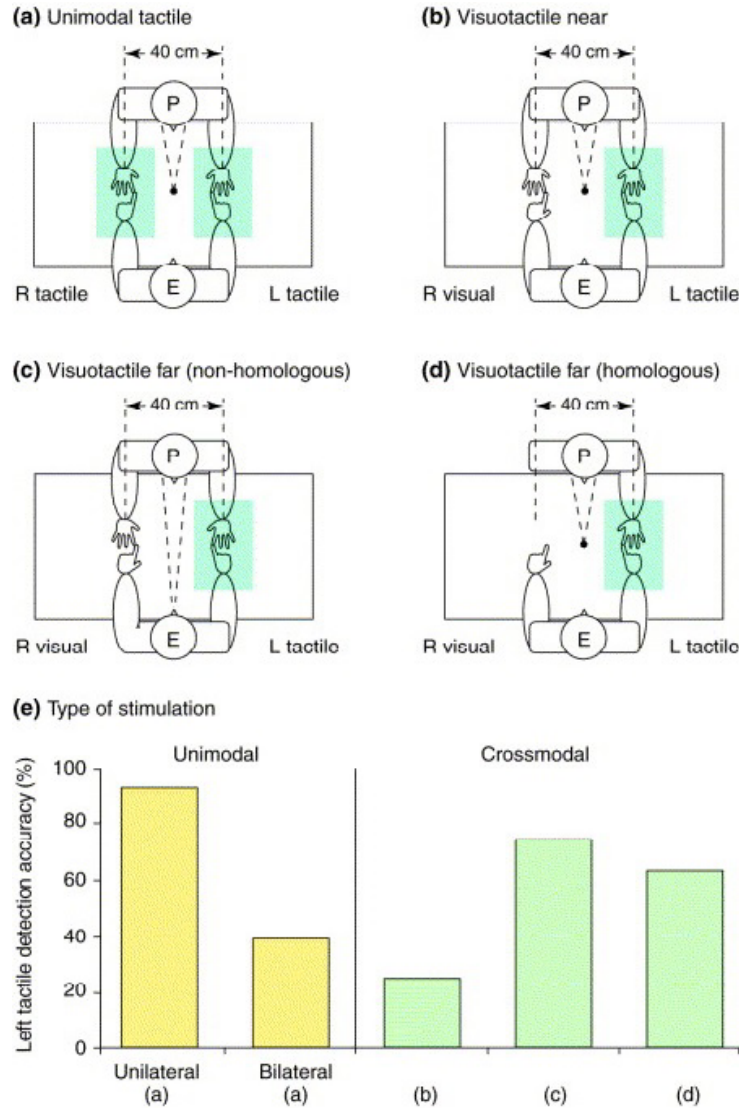
#### 2.4.2. *Evidence from crossmodal spatial extinction in brain-damaged humans*

In humans, evidence for selective (peripersonal) representation of the space near the body and its parts has been particularly supported by neuropsychological studies in patients suffering from left contralesional tactile extinction consecutive to right hemisphere damage.

It has repeatedly been shown (e.g. di Pellegrino et al., 1997; Làdavas, di Pellegrino, Farnè, & Zoloni, 1998) that a visual stimulus occurring close to the right ipsilesional hand of a patient suffering from left tactile extinction inhibits the processing of a tactile stimulus applied on the left hand, in the same manner as does a right tactile stimulus. Crucially, this effect of the visual stimulus on tactile perception is much weaker when the visual stimulus is presented far from the right ipsilesional hand (see Fig. 3). These results suggest that a visual stimulus presented near a body-part (i.e. in its peripersonal space) can activate the corresponding somatosensory representation of this specific body part. In the case of extinction, this induces a competition between the simultaneous

activation of the somatosensory representation of the ipsilesional hand by an ipsilesional near visual stimulus and the activation of the somatosensory representation of the contralesional hand by a contralesional tactile stimulus, to the detriment of the representation of the contralesional hand (Làdavas, 2002). On the contrary, it has also been shown that a visual stimulus presented near the contralesional hand can improve the detection of a tactile stimulus applied on this hand (Làdavas et al., 1998). In the same manner as for the crossmodal effects of vision on tactile extinction, the perception of a visual stimulus presented close to the left hand can be extinguished by a tactile stimulus applied on the right hand in patients suffering from left visual extinction (Mattingley, Driver, Beschin, & Robertson, 1997). Furthermore, it has also been suggested that crossmodal visual-tactile extinction arises in hand-centered rather than in trunk or retinal-centered coordinates. di Pellegrino et al. (1997), for instance, showed that in patients suffering from left tactile extinction, the perception of a left tactile stimulus is extinguished by a visual stimulus presented next to the right hand (see above), but much less by the exact same visual stimulus when the right hand is placed behind the participant's back, although, in both cases, the visual stimulus is presented in the same visual field location and thus at the same distance from the participant's trunk (see Fig. 3). This has also been shown by Farné, Demattè, and Làdavas (2005), who demonstrated that extinction of tactile stimuli delivered to the left hand was stronger when visual stimuli were presented close to the homologous right hand, as compared to visual stimuli presented close to the non-homologous right cheek. Moreover, when patients with left tactile extinction are asked to cross their hands over their body midline, a visual stimulus presented close to the right hand (but in left space), still inhibits the tactile stimulus applied to the left hand (placed in right space), which has been interpreted by the authors as a spatiotopic, hand-centered, reference frame for visual-tactile integration (di Pellegrino et al., 1997).

## Do nociception and pain affect the perception of peripersonal space?



**Fig. 3.** Experimental set-up in studies of patients with left tactile extinction. The patient's (P) hands are placed on a table and are shielded from vision (green rectangle). (a) In the unimodal tactile condition, tactile stimuli are applied on the hands. (b) In the near visuotactile condition, a visual stimulus is presented near the right hand and a tactile stimulus is applied on the left hand. (c) In the non-homologous far visuotactile condition, a visual stimulus is presented above the right hand, at eye-level and a tactile stimulus is applied on the left hand. (d) In the homologous far visuotactile condition, a visual stimulus is presented in the previous location of the right hand that is no longer placed on the table and a tactile stimulus is applied on the left hand. (e) Mean percentage of left tactile stimulus detection accuracy in each experimental condition. From Làdavas (2002).

Models of crossmodal competition (i.e. extinction) and facilitation between somatosensation (i.e. touch and nociception) and vision in the healthy brain have meanwhile also been developed (Jacobs et al., 2011; Filbrich, Blandiaux, Farnè, & Legrain, in preparation)<sup>1</sup>, and may also potentially give insights into the cognitive mechanism on which multisensory representations of space rely.

#### 2.4.3. *Evidence from exogenous crossmodal cueing paradigms in healthy humans*

In healthy participants, visual-tactile interaction has often been studied with exogenous<sup>2</sup> crossmodal attention paradigms. In such paradigms, a stimulus of one sensory modality is used to attract attention to its location in a non-informative way (i.e. the cue), and the effect of attention on the processing and the perception of a stimulus of another modality is measured. More specifically, the conditions under which such cueing effects take place are evaluated (e.g. whether the target is presented adjacent to the cue's location or not).

For instance, a task that has regularly been used is the crossmodal distractor congruency task (see Kennett, Spence, & Driver, 2002; Maravita et al., 2003; Pavani, Spence, & Driver, 2000; Spence, McDonald, & Driver, 2004; Spence, Pavani, & Driver, 2004), in which participants usually make speeded elevation discrimination responses to vibrotactile targets applied on the thumb (in the lower position) or the index finger (in the upper position), on one of the hands, while simultaneously ignoring a visual distractor randomly presented from either the same or the different hand and from the same or different elevation. It has been shown that incongruent visual distractors, i.e. presented in the opposite elevation than the vibrotactile target stimulus, delay the tactile judgments and induce more errors as compared to congruent visual distractors. Importantly, such a crossmodal congruency effect is more pronounced when both the vibrotactile target and the visual distractor are presented on the same hand, suggesting space-specific visual-tactile interactions, modulated by the proximity between visual and tactile stimuli (Maravita et al., 2003; Spence, Pavani, et al., 2004).

The aforementioned studies demonstrated that visual-tactile interactions are space-specific, i.e. that crossmodal influence is maximal when both stimuli are spatially congruent, that is, presented close to each other. However, in these studies, effects of spatial congruence on crossmodal visual-tactile influence could be due to bimodal stimulation of the same hemisphere or to the spatial alignment of tactile and visual stimuli in external space. The former case implies that irrespective of the position of the tactile and visual

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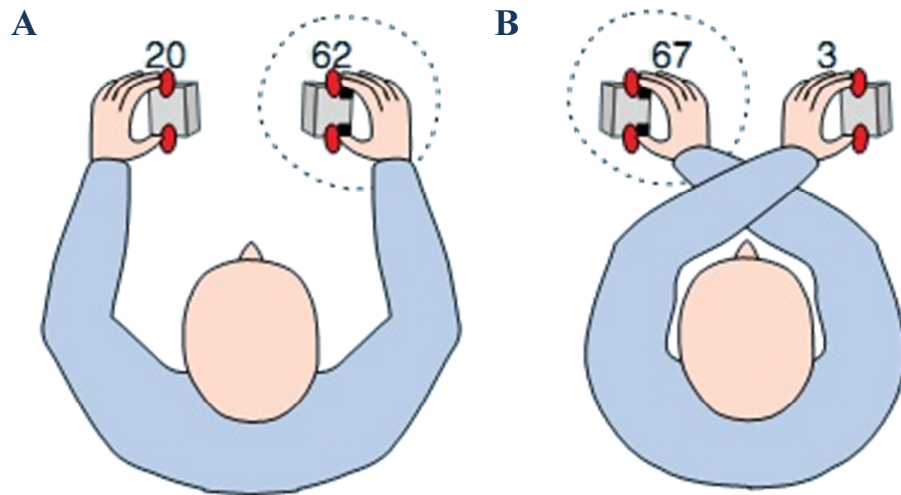
<sup>1</sup> Filbrich, L., Blandiaux, S., Farnè, A., & Legrain, V. (in preparation). Unimodal and crossmodal perceptual extinction of nociceptive stimuli in healthy volunteers.

<sup>2</sup> In the present dissertation I will especially review studies that used exogenous, i.e. stimulus-driven, cueing paradigms, to minimize confounding effects in their interpretation that could be due to decisional and/or motivational factors usually observed in endogenous attention orientation.

stimuli in external space, a tactile stimulus applied to the left hand, for instance, always interacts with visual stimuli presented in the left visual hemifield because both modalities activate the same hemisphere. The latter case implies that a tactile stimulus applied on the left arm can either interact with visual stimuli in the left visual hemifield or visual stimuli in the right visual hemifield, depending on the current position of the hand with regard to the retina. This suggests that, for instance, information regarding current posture is taken into account to update the mapping between spatial representations for different sensory modalities that initially use different coordinate systems (e.g. Macaluso, Frith, & Driver, 2002; Macaluso & Maravita, 2010). These two accounts of the spatial nature of spatially specific visual-tactile crossmodal interactions have been disentangled by manipulating the alignment of tactile and visual reference frames, either by changing hand posture or gaze posture of the participants without moving their head (Macaluso & Maravita, 2010). Several behavioral (Kennett et al., 2002; Pavani et al., 2000; Spence, Pavani, et al., 2004) (see Fig. 4), electrophysiological (Kennett, Eimer, Spence, & Driver, 2001) and neuroimaging studies (Macaluso et al., 2002) demonstrated that crossmodal visual-tactile influence is dependent on the co-occurrence of both stimuli in external space rather than on their hemispheric correspondence. These studies show that visual-tactile interactions due to bimodal spatially congruent stimulation arise independently of gaze or arm posture and that the representation of the space around the body is characterized by an integration of tactile, visual and proprioceptive information.

It is however important to note that albeit such crossmodal interaction between tactile and near visual stimuli may be an indicator for an integrated multisensory representation of the body and space nearby, the involvement of multisensory neurons similar to those observed by single-cell recordings in non-human primates has yet to be demonstrated directly. Nonetheless, there are several neuroimaging and electrophysiological studies which shed some light on the neural correlates and functional mechanisms of visual-tactile interactions, and which will be highlighted in the following paragraph.





**Fig. 4.** Example of a crossmodal distractor congruency task measuring the impact of visual distractors on tactile performance. Participants make speeded elevation discrimination responses to vibrotactile stimuli either presented in an upper or a lower position, while ignoring visual stimuli presented from the same (congruent) or different (incongruent) elevation on the same or opposite hand. Vibrotactile stimulators and visual distractor lights are embedded in two foam cubes, one held in each hand. In this example, crossmodal congruence effects for vibrotactile targets presented on the right hand are shown. The crossmodal congruence effect is defined as the difference in reaction time between incongruent vs. congruent trials and its magnitude is indicated above the hands in the illustration. This effect follows the right hand in space when the hands are displaced. If the cube is held by the right hand in an uncrossed posture, visual distractors on the right cube interfere more strongly (A). When the hands are however crossed, and the right hand now holds the left cube, visual distractors on the left cube interfere more (B). From Maravita *et al.* (2003).

#### 2.4.4. Neuroimaging evidence for crossmodal visual-tactile interactions and peripersonal space representation in humans

In line with the findings of multimodal neurons in non-human primates that respond to both somatosensory and non-somatosensory stimuli, multisensory interactions between different modalities that have been demonstrated in humans are thought to rely on multimodal areas in fronto-parietal brain structures. Crossmodal effects would thus reflect

interactions within such multimodal structures, where inputs from different sensory modalities converge. In other words, crossmodal interactions and multisensory representations of near space would rely on feed-forward convergence from different sensory-specific areas initially activated by sensory inputs of different modalities (e.g. tactile inputs activating somatosensory regions in the post-central gyrus and visual inputs activating the visual occipital cortex) to multimodal associative frontal, parietal and temporal cortices (Macaluso & Maravita, 2010). Such possible neural correlates for visual-tactile interactions are corroborated by findings of multimodal activations in brain regions in humans that are homologous to multimodal areas discovered in monkeys, such as the PMv, the posterior parietal lobe and the intraparietal sulcus (IPS), the human equivalent of macaque area VIP (e.g. Bremmer et al., 2001; Gentile, Petkova, & Ehrsson, 2011; Sereno & Huang, 2006). In addition, recent neuroimaging studies in healthy participants showed increased blood-flow activity in the IPS (Makin, Holmes, & Zohary, 2007) or selective blood-oxygen-level dependent (BOLD) signal adaptation in the IPS, PMv, and inferior parietal lobe (Brozzoli, Gentile, Petkova, & Ehrsson, 2011) induced by visual stimuli presented near the hand as compared to other spatial locations, indicating spatially specific multisensory representations of near body space. However, it has also been shown that visual-tactile interactions can affect activity in brain areas that have traditionally been considered as unimodal and sensory-specific, probably through back-projections from multimodal associative areas to those areas (Macaluso et al., 2002; Macaluso & Maravita, 2010). For instance, it has been demonstrated that a touch applied on one hand can boost the responses in the occipital cortex to visual stimuli presented near the stimulated hand, as compared to visual stimuli in other positions, even when the touch is uninformative as to the location of the visual stimulus (Macaluso, Frith, & Driver, 2000; Macaluso et al., 2002). Furthermore, magnitudes of early event-related potential (ERP) components elicited by visual stimuli presented close to a hand on which a tactile stimulus is applied are enhanced (e.g. Kennett, Eimer, et al., 2001).

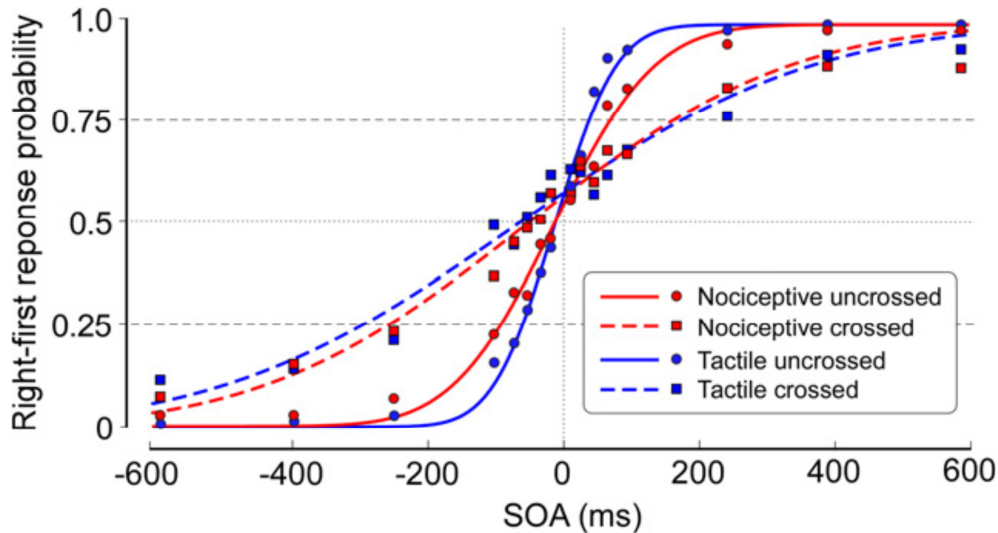
### 3. ***Frames of reference involved in the spatial processing of nociceptive stimuli***

The functional role of the nociceptive system is to warn the brain about possible body damage and to adapt behavior to possibly damaging stimuli in order to protect the integrity of the body. To this aim, the brain needs to locate which body part is potentially being harmed, an ability that partly depends on spatially organized projections of the somatosensory RFs to specific spatially segregated groups of neurons in the cortex (Kenshalo & Isensee, 1983). Such a coordinate system, based on anatomical representations of the body surface, is however not sufficient. Responding adequately to a potentially damaging stimulus requires also to perceive the posture of the limbs (*where is the threatened limb?*) and to locate, for instance visually, the cause of the potential damage in external space (*where is the threatening stimulus?*) (Legrain et al., 2011). It is therefore necessary to coordinate the representation and perception of the space of the body and its surrounding external space, an ability that is thought to rely on the construction of a coherent multisensory representation of the body space and its surrounding space, that is, a peripersonal reference frame.

The importance of such a multisensory coordinate system for defending the body integrity has already been considered in the context of the multimodal coding of the space near the body. Indeed, it has been shown that defensive motor reactions can be elicited in the monkey when the bimodal neurons in the PMv and VIP are activated with direct electrical stimulation (Cooke & Graziano, 2004; Cooke, Taylor, Moore, & Graziano, 2003). The defensive motor reactions were similar to those evoked by direct application of unpleasant somatosensory stimuli on the monkeys' skin (Cooke & Graziano, 2004). Such multimodal neurons could thus also be involved in coding threat information (Graziano & Cooke, 2006). However, such bimodal neurons have mainly been observed for the coding of both innocuous tactile and visual stimuli, and there is, up to now, only one study that demonstrated the existence of such bimodal neurons in parietal area 7b that specifically code both thermo-nociceptive and visual inputs that approach the body part on which the nociceptive stimulus is applied (Dong, Chudler, Sugiyama, Roberts, & Hayashi, 1994). Likewise, research on the spatial perception of somatosensory inputs in humans has almost exclusively focused on the tactile modality, resulting in an approximate clear picture of tactile localization, whereas studies considering different reference frames for the spatial localization of nociceptive stimuli have been relatively scarce in comparison.

Most studies on the spatial perception of nociceptive stimuli in humans focused on the somatotopic organization of its neural correlates (e.g. Baumgartner et al., 2010; Bingel et al., 2004; Kenshalo & Isensee, 1983; Mancini, Haggard, Iannetti, Longo, & Sereno, 2012), demonstrating a relatively precise ability to localize the position of a nociceptive stimulus on the body. The ability to localize nociceptive stimuli according to more space-based coordinate systems, taking into account proprioception and non-somatic stimuli

occurring outside the body, has only recently become the topic of some studies. For instance, Sambo et al. (2013) and De Paepe, Crombez, and Legrain (2015) showed that judgments about the spatial perception of nociceptive stimuli depend on the relative position of the stimulated limbs. In both studies a TOJ task was used (see part 5.1 of this general introduction), and participants judged which of two nociceptive stimuli, one applied on either hand, was perceived as being presented first. The task was performed with the hands either in a normal, uncrossed posture or with the hands crossed over the body midline. As explained before, the crossed posture is known to reveal a competition between somatotopic and spatiotopic reference frames for tactile perception, indexed by a deterioration of performance when the hands are placed in a crossed posture (see Heed & Azañón, 2014). Similarly, TOJs on nociceptive stimuli were also affected by the crossed posture (see Fig. 5), suggesting that space-based reference frames are used to code nociceptive stimuli (De Paepe et al., 2015; Sambo et al., 2013). Other studies have shown that nociception can interact with vision or proprioception. For instance, it has been demonstrated that vision of a nociceptively stimulated body part can decrease its perceived level of painfulness (Longo et al., 2009; Longo et al., 2012; Mancini et al., 2011; Valentini, Koch, & Aglioti, 2015) (however, see also Beck et al., 2016; Torta et al., 2015 for contrasting results) and change the cortical processing of the nociceptive stimulus (Longo et al., 2009; Mancini, Longo, Canzoneri, Vallar, & Haggard, 2013; Torta et al., 2015; Valentini et al., 2015). Furthermore, changes in posture of the body part on which nociceptive stimuli are applied have also been observed to modify the cortical processing and perceived intensity of nociceptive stimuli (Gallace et al., 2011; Torta et al., 2013; however, see also Valentini et al., 2015).



**Fig. 5.** Data from temporal order judgments (TOJs) on pairs of tactile (blue curves) or nociceptive (red curves) stimuli, when the hands were uncrossed (solid lines) and crossed (dashed lines), fitted with cumulative Gaussian functions. The x-axis indicates the different time intervals (stimulus onset asynchronies, SOAs) between the two stimuli of a pair. Negative SOAs indicate that the stimulus on the left hand was applied first. The y-axis indicates the proportion of trials in which the stimulus on the right hand was perceived as being applied first. The steepness of the curves indexes the mean performance of the participants, with steeper curves indicating better performance. The curves are in general less steep when the hands are crossed, indicating a reduced ability in correctly reporting temporal order, for both tactile and nociceptive stimuli. From Sambo et al. (2013).

Even more compelling evidence for a non-somatopic reference frame for the localization of nociceptive stimuli was provided by De Paepe, Crombez, Spence, and Legrain (2014) and De Paepe et al. (2015) who showed, also using TOJ tasks, that nociceptive perception was systematically impacted by the presence of a visual stimulus shortly preceding nociceptive stimuli in the same side of space. This visual cue indeed facilitated the perception of the nociceptive stimulus applied on the ipsilateral hand (by biasing temporal order judgments to its advantage), to the detriment of the nociceptive stimulus applied on the opposite hand. Importantly, this effect of the visual cue on the perception of the nociceptive stimulus was more pronounced when the visual cue was presented close to the participant's hand, as compared to conditions in which the cue was presented farther away. Moreover, the effect of this close proximity between visual and nociceptive stimuli was independent of the relative posture of the stimulated hands (De Paepe et al., 2015). Indeed, when the participants crossed their hands over their body

midline, the perception of the nociceptive stimuli applied to the left hand (but now located in right space) was facilitated by right-sided visual stimuli. The reverse was shown for nociceptive stimuli applied to the right hand. In a series of unpublished studies<sup>3</sup>, they demonstrated furthermore that the influence of the visual stimuli on nociceptive judgments was most efficient when the stimulated hand was positioned in proximity to the visual stimuli, independently of their distance to the body considered as a whole (i.e. from the trunk). Finally, De Paepe, Crombez, and Legrain (2016) showed that reaction times to nociceptive stimuli were differently influenced by the vision of a visual stimulus approaching the to-be-stimulated hand (that is, a stimulus possibly contacting the body) as compared to a receding visual stimulus (that is, a stimulus that will not contact the body). Since De Paepe and colleagues elegantly demonstrated that nociceptive spatial processing is multimodal, spatiotopic and depends on the proximity to surrounding visual stimuli, it seems reasonable to assume that nociceptive stimuli can be integrated in multisensory representations of the body and its surrounding space, and thus be spatially processed according to peripersonal reference frames.

Such peripersonal reference frames for the processing of nociceptive stimuli imply that nociceptive stimuli interact with non-somatic stimuli external to the body, as for example visual stimuli. Whereas the aforementioned studies indicate that nociceptive perception can be influenced by visual stimuli that may have an impending impact on the body, little is known about the effects that potentially harmful nociceptive stimuli can exert on the perception of the visual space just outside the body.

So far, to the best of our knowledge, this question has only been explicitly examined by two studies (Favril, Mouraux, Sambo, & Legrain, 2014; Van Damme, Crombez, & Lorenz, 2007) which were aimed to investigate how nociceptive stimuli can attract attention to the space surrounding the stimulated limb in order to prioritize the visual perception of stimuli occurring close to that limb. Van Damme et al. (2007) showed that reaction times to visual stimuli were speeded-up when a spatially congruent painful stimulus preceded the occurrence of the visual stimulus as compared to a spatially incongruent painful stimulus. However, in this study, transcutaneous electrical current was used to induce the painful stimulation, which is known for not being specific in activating nociceptive pathways, since it also activates fibers responsible for tactile sensation. The attentional effects observed in this study were thus not related to the nociceptive specificity and the painfulness of the somatosensory stimuli, but rather to tactile input<sup>4</sup>. By using intra-epidermal electrical stimulation (IES) delivered at low intensities, a technique that has been shown to be more selective in activating nociceptive A $\delta$  fibers (Inui, Tran, Hoshiyama, &

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<sup>3</sup> De Paepe, A.L., Crombez, G., Legrain, V. (submitted). Remapping nociceptive stimuli into a peripersonal reference frame is spatially locked to the stimulated limb.

<sup>4</sup> Attentional capture induced by these painful stimuli was triggered by the fastest and first somatosensory inputs that reached the cortex, that is, the inputs conveyed by non-nociceptive A $\beta$  fibers which are characterized by a faster velocity conduction than the slow conducting finely myelinated nociceptive A $\delta$  and unmyelinated nociceptive C fibers (Kandel et al., 2013).

Kagiki, 2002; Inui, Tsuji, & Kakigi, 2006; Mouraux, Iannetti, & Plaghki, 2010), Favril et al. (2014) obtained similar results. However, since an endogenous cueing paradigm was used in this study, it was difficult to disentangle whether the effects on visual processing were driven by the motivation of the participants to allocate attention to one side of space, or by the capture of attention triggered by the nociceptive stimulus itself to its own location. In a third study, using a different paradigm, Filippopoulos, Grafenstein, Straube, and Eggert (2015) showed that continuous experimental pain did not induce any preferential orientation to one side of space as measured by saccade latencies to visual stimuli presented rather far from the body. However, as for Van Damme et al. (2007), these results can be questioned with regard to the specificity of the stimulation in activating the nociceptive system, since electrical stimulation was used. To date, there is thus no clear empirical evidence that nociception can influence the processing of visual stimuli.

Specifying the mechanisms that may underlie such possible crossmodal effects of nociception on vision is not only important in the theoretical framework of peripersonal space perception, but is also of high clinical relevance, since it has been suggested that some specific chronic pain conditions can impact patients' abilities to represent and perceive space (see e.g. Legrain et al., 2012; Reinersmann, Maier, Schwenkreis, & Lenz, 2013) and that targeting such spatial difficulties has been suggested as a potentially useful method to treat chronic pain (see Torta et al., 2016).

#### **4. Complex regional pain syndrome**

One chronic pain disorder in which cognitive difficulties in perceiving and representing body and space are more and more often described as being part of its symptomatology is the complex regional pain syndrome (CRPS).

CRPS is a chronic pain condition affecting one limb, usually initiated by minor or moderate tissue trauma, as a contusion, tendinitis or a surgical intervention in an extremity of the body, and is characterized by continuous pain disproportionate to the triggering event. A distinction has traditionally been made between CRPS type I (no associated nervous system lesions) and type II (associated nervous system lesions), but which has not been without criticism (for a review see e.g. Marinus et al., 2011). Unilateral pain is accompanied by other sensory (hyperalgesia, allodynia), autonomic (temperature and skin color changes, edema, sweating), trophic (changes in hair/nail growth) and motor (weakness, tremor, dystonia) symptoms that can vary in time (e.g. Harden et al., 2010). CRPS is difficult to treat, since the pathophysiology is complex and still not well understood. It can involve different mechanisms at different stages (at an individual time frame) of the disorder, such as neurogenic inflammation, vasomotor dysfunction as well as structural and functional changes at the cortical level (Juottonen et al., 2002; Krause, Forderreuther, & Straube, 2006; Maihofner et al., 2007; Maihofner, Handwerker, Neundorfer, & Birklein, 2003, 2004; Pleger et al., 2014; Pleger et al., 2006; Pleger et al., 2005; Pleger et al., 2004). Probably as a consequence of these cortical changes, unilateral cognitive symptoms have also been described, affecting patients' abilities to represent, use and perceive their affected limb (see e.g. Legrain et al., 2012; Legrain & Torta, 2015; Reinersmann et al., 2013 for a review).

Especially disrupted mental representations of the affected limb have been increasingly recognized as being part of the symptomatology in an important subset of CRPS patients over the last few years (Reinersmann et al., 2013)<sup>5</sup>. Patients regularly report feelings of disownership over the affected limb (Forderreuther, Sailer, & Straube, 2004; Galer, Butler, & Jensen, 1995; Galer & Jensen, 1999; Lewis, Kersten, McCabe, McPherson, & Blake, 2007), as well as distortions in representing its size, shape (Lewis et al., 2007; Moseley, 2005; Peltz, Seifert, Lanz, Muller, & Maihofner, 2011) and position (Lewis et al., 2010). Furthermore, altered laterality recognition of the affected limb has been repeatedly demonstrated (Moseley, 2004; Reid et al., 2016; Reinersmann et al., 2010; Schwoebel, Friedman, Duda, & Coslett, 2001). At the motor level, patients are often described to struggle in order to voluntarily move their limb, with movements that are difficult to initiate (hypokinesia) and slower (bradykinesia) than normal (Galer et al., 1995; Galer & Jensen, 1999; Lewis et al., 2007). Because there are similarities between the

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<sup>5</sup> One has however to note that there is no clear definition for the concept of body representation, as it encompasses different notions which are often used in different manners and sometimes with opposite meanings by different authors (Berlucchi & Aglioti, 2010), which makes systematic comparisons between studies difficult.

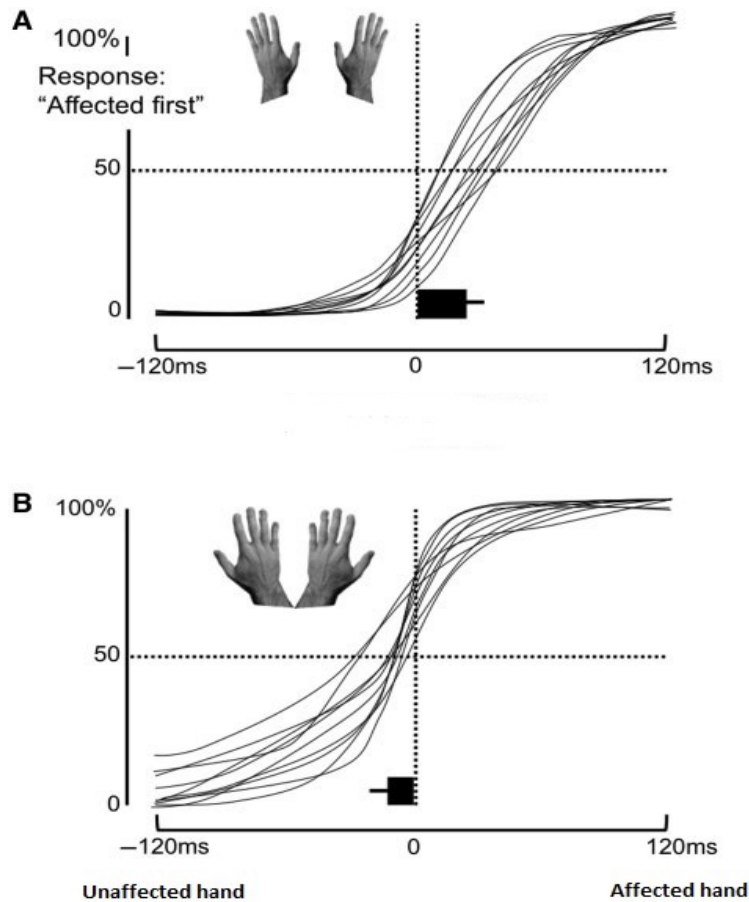


aforementioned symptoms and those reported in hemispatial neglect after right hemispheric damage, the cognitive symptoms observed in CRPS have often been considered as “neglect-like” symptoms (Galer et al., 1995; Galer & Jensen, 1999; however, see Legrain et al., 2012; Punt, Cooper, Hey, & Johnson, 2013 for discussion). Despite the fact that hemispatial neglect can affect different sensory modalities, as well as representational (e.g. Bisiach & Luzzatti, 1978; Salvato, Sedda, & Bottini, 2014) and motor processing (e.g. Coulthard, Parton, & Husain, 2006; Husain, Mattingley, Rorden, Kennard, & Driver, 2000), the presence of hemispatial neglect after brain damage is classically characterized by tests investigating perceptual abilities in the visuospatial domain, that is, the patients’ abilities to perceive and locate stimuli in extra-body space (Brozzoli, Demattè, Pavani, Frassinetti, & Farne, 2006; Hach & Schutz-Bosbach, 2014; Jacobs, Brozzoli, & Farne, 2012). However, when used in CRPS patients, these neuropsychological tests classically used to investigate disrupted visuospatial perception were generally not able to highlight the presence of neglect symptoms (Christophe et al., 2016; Forderreuther et al., 2004; Kolb, Lang, Seifert, & Maihofner, 2012; Reid et al., 2016; Reinersmann et al., 2012), with some individual differences (e.g. Jacquin-Courtois, Christophe, Chabanat, Reilly, & Rossetti, In Press). Some perceptual difficulties in CRPS have nevertheless been reported for the tactile modality, such as decreased tactile acuity of the affected limb (Lewis & Schweinhardt, 2012; Peltz et al., 2011), and referred sensations between stimulated body parts (Maihofner, Neundorfer, Birklein, & Handwerker, 2006; McCabe, Haigh, Halligan, & Blake, 2003), but it is difficult to disentangle the cortical from the peripheral origins of these unilateral tactile perceptual symptoms. For these reasons, the “neglect-like” nature of the cognitive symptomatology in CRPS has often been questioned (see Punt et al., 2013). One could however argue that cognitive testing instruments classically used to diagnose hemispatial neglect after hemispheric damage are not sensitive enough to clearly characterize spatial perception deficits in CRPS (Legrain et al., 2012; Legrain & Torta, 2015). This idea is corroborated by the fact that Moseley, Gallace, and Spence (2009) and Moseley, Gallace, and Iannetti (2012), by using a TOJ task, succeeded to demonstrate that some tactile perceptual deficits observed in CRPS can obviously be attributed to neuro-cognitive deficits affecting spatial perception. Moseley et al. (2009) applied pairs of tactile stimuli, one stimulus on either hand, in rapid temporal succession and patients judged which of the two stimuli was presented first. They showed that CRPS patients’ perceptual judgments were biased to the detriment of the stimulation on the affected hand. However, this was only observed when the patients’ hands were in a normal, i.e. uncrossed posture. When patients were asked to cross their hands over their body midline, perceptual judgements were biased to the detriment of the unaffected hand, as if the patients’ performance did not rely on the actual stimulation of the affected hand, but rather on the side of space in which the affected hand normally resides (i.e. on space-based reference frames) (see Fig. 6). These results clearly show that CRPS can be characterized by somatosensory perceptual difficulties that cannot be attributed to altered peripheral coding or spinal transmission of somatosensory inputs, but rather to deficits in their cognitive processing. Furthermore, they also suggest that the presence of pain can change the perception of other somatic sensations

Do nociception and pain affect the perception of peripersonal space?

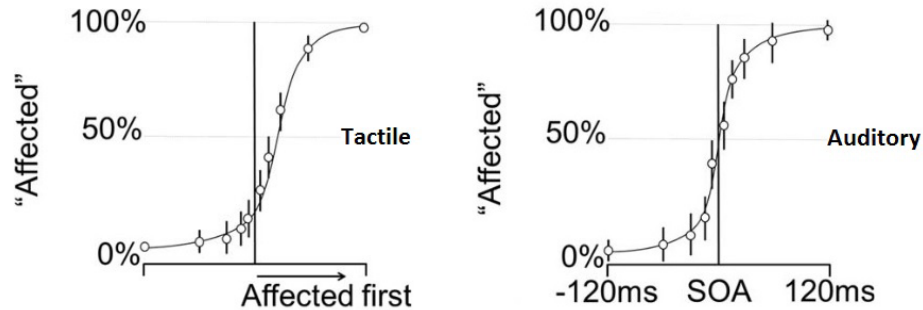
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according to a personal reference frame that interacts with proprioception, i.e. the relative position of the limbs in space.



**Fig. 6.** Fitted curves from the mean data of tactile temporal order judgments (TOJs) for each CRPS patient in Moseley et al. (2009). The x-axis indicates the different stimulus onset asynchronies (SOAs) between the two stimuli of a pair. Negative SOAs indicate that the stimulus on the unaffected hand was applied first. The y-axis indicates the proportion of trials in which the stimulus on the affected hand was perceived as being applied first. (A) Uncrossed hand posture: the curves are shifted to right (positive values), indicating that tactile stimuli on the affected hand have to be applied before tactile stimuli on the unaffected hand to have the chance to be perceived as occurring simultaneously. (B) Crossed hand posture: the curves are shifted to the left (negative values), indicating that tactile stimuli on the unaffected hand have to be applied before tactile stimuli on the affected hand to have the chance to be perceived as occurring simultaneously. From Moseley et al. (2009).

On the other hand, the question whether perceptual difficulties in CRPS can also extend to non-somatic stimuli occurring in the space outside the body is still debated. For instance, in a recent study, Reid et al. (2016) showed, with the same TOJ task than in the aforementioned studies in the tactile modality, that spatial perception of auditory stimuli, i.e. stimuli occurring outside the body space, was not impaired (see Fig. 7). Auditory stimuli were delivered using speakers placed close to the patients' hands. The authors concluded that cognitive difficulties in CRPS would be limited to the representation of body-related information and the perception of body space, and would not extend to the perception of external space. However, it could be argued that the auditory modality is not the ideal modality to test lateralized perceptual difficulties in external space, since audition, conversely to touch and vision, is not primarily spatially coded. Indeed, because both ears are stimulated (especially with external speakers), sound localization is extracted from interaural intensity or time differences (Pickles, 2012). In a previous study, Filippopoulos et al. (2015) came to the same conclusion than Reid et al. (2016), by showing that there is no difference between CRPS patients and control participants when measuring saccade latencies in a visuospatial attention cueing paradigm. Since the visual stimuli were always presented at far distance with regard to the participant's body (i.e. in far extrapersonal space), the study of Filippopoulos et al. (2015) can however not exclude the possibility that other reference frames could be affected in CRPS, such as a representation of the space near the body. These results are in sharp contrast with studies that were able to demonstrate perceptual difficulties for external space when CRPS patients judged the position of far visual stimuli with regard to their own body midline, with judgments that were moreover made to the advantage of the side of space of the affected hand (Sumitani, Rossetti, et al., 2007; Sumitani, Shibata, et al., 2007). However, these latter findings have not always been corroborated by more recent studies using the same task, which either obtained results that differed as to the direction of the bias (Reinersmann et al., 2012), or didn't obtain any biases at all (Christophe et al., 2016).



**Fig. 7.** Fitted curves from the mean data across patients from temporal order judgments (TOJs) on pairs of tactile (left panel) or auditory (right panel) stimuli, in Reid et al. (2016). The x-axis indicates the different stimulus onset asynchronies (SOAs) between the two stimuli of a pair. Negative SOAs indicate that the stimulus on the unaffected hand/side of space was presented first. The y-axis indicates the percentage of trials in which the stimulus on the affected hand/side of space was perceived as being presented first. In the tactile TOJ, the curve is shifted to right (positive values), indicating that tactile stimuli on the affected hand have to be applied before tactile stimuli on the unaffected hand to have the chance to be perceived as occurring simultaneously. In the auditory TOJ, the curve is not significantly shifted, indicating the absence of any significant bias to any of the hands. From Reid et al. (2016).

To date, it is thus still unclear if and to which extent the presence of chronic pain could also have an impact on how patients perceive their visuospatial environment. However, the fact that some clinical trials successfully alleviated CRPS pain and other related symptoms by using cognitive rehabilitation techniques based on the manipulation of visual perception (Bultitude & Rafal, 2010; Christophe et al., 2016; McCabe, Haigh, Ring, et al., 2003; Sumitani, Rossetti, et al., 2007), speaks strongly in favor of the hypothesis that the perception of (multisensory) external space is in some way part of the complex symptomatology of CRPS. For instance, it has been shown in several patients that acting on visuospatial perception, by visual displacement with prismatic goggles combined with sensorimotor coordination, can, besides the effects on visuospatial perception, reduce pain as well as autonomic and motor symptoms (Bultitude & Rafal, 2010; Christophe et al., 2016; Jacquin-Courtois et al., In Press; Sumitani, Rossetti, et al., 2007). However, results are still preliminary and have to be confirmed. Furthermore, the exact mechanisms through which such manipulations of visuospatial perception may act on pain have still to be elucidated, which in turn also requires knowledge about the exact nature of visuospatial deficits in CRPS patients (Torta et al., 2016).

## **5.     *Aims and hypotheses***

A peripersonal frame of reference supporting efficient reactions to defend the physical integrity of the body would be important in that sense that it would not only allow to localize potentially noxious stimuli on the body surface by taking into account the position of the body and the stimulus in external space, but also to monitor the space just outside the body for the presence of potentially threatening events even before they contact the body.

The previous chapters indicate that nociceptive stimuli are highly likely to be integrated in such reference frames, by showing that nociceptive processing is space-based and can be influenced by external visual sensory inputs that occur in the proximity of the limb on which a nociceptive stimulus is applied. Studies in CRPS patients might corroborate this hypothesis, since there are reasons to believe that the representation and perception of external space might be in some way distorted by the presence of chronic pain, especially if stimuli are processed according to frames of reference based on interactions with the body.

A peripersonal frame of reference for the processing of nociceptive inputs however also logically implies that nociception, on its part, should be able to determine how external, visual inputs are perceived. The general aim of this dissertation is to investigate whether, and under which conditions, nociception and pain can impact peripersonal space perception, i.e. the external visual space close to the body.

We used two approaches to investigate this question: a first approach consisted in studying, in healthy participants, whether brief nociceptive stimulation can influence the spatial perception of visual stimuli. In a series of experiments we hypothesized more precisely that such influence can actually be observed, that it would depend on the proximity in external space between the visual stimuli and the body limb on which nociceptive stimuli are applied, and that it would be independent of a reference that uses the trunk as a coordinate to separate the left and right sides of space. The second approach consisted in studying the abilities of CRPS patients in perceiving stimuli occurring in external space, while hypothesizing specific deficits in the perception of stimuli presented in peripersonal space.

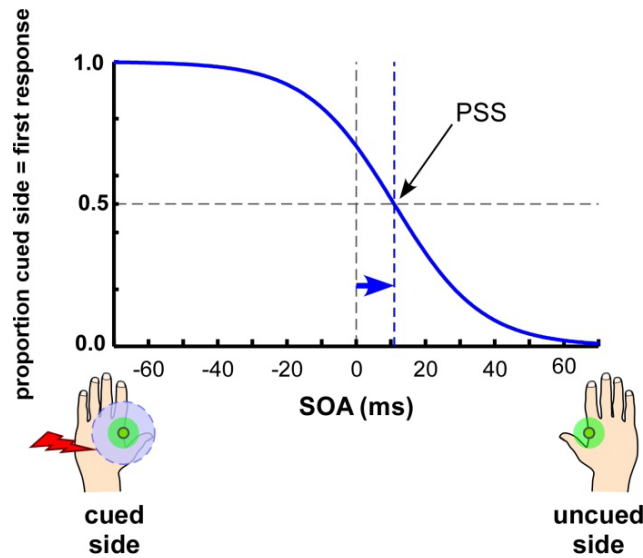
These hypotheses in healthy participants and CRPS patients were all tested with an adapted TOJ task.

### **5.1.     The temporal order judgment task**

In TOJ tasks, pairs of stimuli are presented with various time intervals (SOAs, for stimulus onset asynchronies) between them, and participants have to judge which of the two stimuli they perceive as having been presented first. As compared to classic detection

and reaction tasks, TOJ tasks offer the advantage to be unspeeded and can thus highlight the effects of experimental manipulations on changes in the perceptual processing of a target stimulus without the confound of faster response selection and/or execution (Spence, McDonald, et al., 2004; Zampini et al., 2007). TOJs have been used in the past to study spatial reference frames involved in somatosensory, and more specifically, nociceptive perception (De Paepe et al., 2015; De Paepe et al., 2014; Moseley et al., 2009; Sambo et al., 2013). Furthermore, they have also been regularly used as an effective mean to study crossmodal spatial interactions between different sensory modalities (e.g. De Paepe et al., 2015; De Paepe et al., 2014; Shore, Spence, & Klein, 2001), since they allow characterizing biases in spatial attention which are indexed by a shift of TOJs to the advantage of one of the two stimuli. Attentional biases observed during TOJ are interpreted in light of the theory of prior entry (Titchener, 1908), according to which the perception of attended stimuli is speeded up as compared to unattended ones. As a consequence, an unattended stimulus has then to be presented before the attended stimulus to be perceived as occurring simultaneously. The SOA at which the two stimuli are perceived as simultaneous has been defined as the point of subjective simultaneity (PSS) (for a review see Spence & Parise, 2010). When studying spatial attention, shifts in the PSS are used to highlight changes or abnormalities in the perceptual sensory processing of target stimuli, due to attentional manipulations such as attending to a particular location, for instance, induced by spatial cueing, or due to the presence of disorders affecting attentional abilities, as in hemispatial neglect for instance (e.g. Rorden, Mattingley, Karnath, & Driver, 1997).

In the TOJ tasks used in the context of my thesis, we mainly used pairs of visual stimuli, and experiments were adapted to investigate the potential effects of unilateral nociceptive cues (in healthy participants) or of the presence of a painful limb (in CRPS patients) on the processing of these visual stimuli. Such an influence has been characterized by biases in spatial attention, as indexed by shifts in the PSS to the advantage of one of the two visual stimuli (see Fig. 8).



**Fig. 8.** In temporal order judgment (TOJ) tasks, pairs of stimuli are presented with various time intervals (SOA for stimulus onset asynchronies) between them. Participants judge which of the two stimuli had been presented first. TOJ is based on the idea that paying attention to a stimulus accelerates its perception. Therefore, a competing unattended stimulus has to precede the attended one in order to get the chance to be perceived as occurring simultaneously. The SOA at which the two stimuli are equally likely to be judged as being presented first has been defined as the point of subjective simultaneity (PSS). In other words, the PSS is defined as the amount of time one stimulus has to precede or follow the other in order for the two stimuli to be perceived as occurring simultaneously. In the case of spatial attention, shifts in the PSS are used to highlight changes in the perceptual sensory processing of the target (here, lateralized visual) stimuli due to attentional manipulations such as attending to a particular location, for instance, induced by spatial cueing (here, with a nociceptive stimulus randomly applied on one of the hands). In the figure, the x-axis represents different SOAs between the two visual stimuli: negative values indicate that the visual stimulus occurring in the cued side of space was presented first, while positive values indicate that the visual stimulus occurring in the uncued side of space was presented first. The y-axis represents the proportion of trials in which the participants perceived the visual stimulus presented in the cued side of space as occurring first. The PSS is obtained by deriving the point with (x, 0.5) as coordinate, that is, the x value of SOA at which the two visual stimuli have equal chances to be perceived as first presented. In this example the PSS is shifted towards the visual stimuli in the uncued side of space, at a SOA of ~11 ms. This means that, because the nociceptive stimulus captured attention at the opposite side of space, the visual stimulus in the uncued side of space has to be presented ~11 ms before the visual stimulus in the cued side of space, in order to have the chance to be perceived as occurring first.



Besides providing information about attention biases, another measure that can be obtained with TOJ tasks is an index of performance sensitivity, as for example used to demonstrate the crossed hands effect revealing space-based reference frames for somatosensory perception (see Heed & Azañon, 2014; Sambo et al., 2013).

Throughout the experiments with healthy participants, attention was manipulated exogenously. The location of the nociceptive cue was thus uninformative as to the location of the first visual stimulus of the pair, suggesting that, in case of attentional biases, attention would be attracted automatically by the nociceptive stimuli to their location, thus minimizing the effects of voluntary control or decision of the participants. To avoid furthermore effects of other task-unrelated decision and/or response biases that have been observed in TOJ tasks (e.g. Frey, 1990; Jaskowski, 1993; Scharlau, 2004; Spence, Shore, & Klein, 2001) and which could be mistaken for genuine perceptual biases induced by attentional manipulation, we also used a second response modality during all the performed TOJ tasks. Indeed, in half of the experimental blocks, participants judged which of the two stimuli they perceived second. This procedure, as well as other possible strategies, such as using orthogonal response modalities, have been shown to minimize potentially confounding effects of response bias (for a recent review, see Filbrich, Torta, Vanderclausen, Azanon, & Legrain, 2016).

Finally, the specificity of the TOJ tasks used in the context of this dissertation was that we adapted them based on an adaptive procedure (the *adaptive PSI method*, see Kontsevich & Tyler, 1999). In most of the existing TOJ studies the method of constant stimuli is used (Spence & Parise, 2010). With this method a sample of SOAs is chosen a priori, and the SOAs are repeated several times during the experiment. The disadvantage of the method of constant stimuli is that testing can be time-consuming and tedious as many trials have to be presented for each SOA to reliably derive the parameters of interest (Kingdom & Prins, 2010). By adopting a Bayesian framework, the *adaptive PSI method* that we used is aimed at adjusting the experimental procedure and the presented SOAs according to the performance of the participant on all previous trials. Thanks to this specific method, the tested SOAs are adapted to each participant's own performance and the parameters of interest can be estimated without probing extensively all the possible SOAs, and thus with a lower number of trials as in the classic approach. This allows reducing experiment duration and minimizing confounding effects related to, for instance, fatigue or habituation.

## **5.2. Outline experimental parts**

The first part of the experimental section describes the experiments that were conducted in healthy volunteers to investigate under which conditions nociceptive stimuli can influence the perception of visual stimuli.

In **Study 1**, we firstly investigated whether, and in which time-window, a nociceptive stimulus can actually attract attention to its location, in order to facilitate the processing of visual stimuli occurring in the same side of space as the limb on which the nociceptive stimulus is applied. This was investigated with a TOJ task, in which participants judged which of two visual stimuli, one presented next to either hand in either side of space, had been perceived first. Each pair of visual stimuli was preceded (by 200, 400 or 600 ms) by a nociceptive stimulus applied either unilaterally on one single hand, or bilaterally, on both hands simultaneously. We hypothesized that visual TOJs would be influenced by unilateral nociceptive stimuli, to the advantage of the visual stimulus presented in the same side of space as the lateralized nociceptive stimulus, but not by bilateral nociceptive stimuli.

In **Study 2**, we further investigated in two experiments whether nociceptive stimuli primarily impact the perception of visual stimuli presented close to the body as compared to visual stimuli that are presented farther away, and whether such an effect would be due to the proximity of the visual stimuli to the body as a whole, or rather to their proximity to the stimulated body part. In two TOJ tasks, participants judged which of two lateralized visual stimuli had been presented first. Pairs of visual stimuli were either presented in near or in far space with regard to the body and were shortly preceded by nociceptive stimuli, either applied unilaterally or bilaterally. In a first experiment, the participants' hands were always placed next to the visual stimuli in near space, while in the second experiment they could also be placed next to the visual stimuli in far space, allowing the comparison of hand positions that were either congruent or incongruent with regard to the position of the visual stimuli. We expected that only the presence of unilateral nociceptive stimuli would bias temporal order perception of visual stimuli, prioritizing the visual stimulus presented in the same side of space as the stimulated hand, and that this effect would only be significant when visual stimuli were presented in near space as compared to when they were presented farther away. Furthermore, for the second experiment, we expected that such effects would be due to the spatial congruency between the nociceptive and the visual stimuli, independently of the relative distance of both the nociceptive stimuli and the visual stimuli locations from the body considered as a whole.

In **Study 3** we investigated whether the influence that a nociceptive stimulus can exert on the perception of a visual stimulus depends on the relative spatial congruence between the location of the nociceptive stimulus (i.e. of the stimulated limb) and that of the visual stimulus in external space, independently of their exact position according to their respective sensory receptive space (i.e. the skin for the nociceptive stimulus and the retina for the visual stimulus). Participants performed TOJs on pairs of visual stimuli, one centrally positioned in front of the participant and one presented more laterally. Nociceptive stimuli could occasionally be applied on one hand placed close to the central visual stimulus. The central visual stimuli were therefore always the ones spatially congruent with the nociceptive stimuli. Gaze shift was changed between blocks, so that the central visual

stimuli appeared as left-sided stimuli when participants' gaze was shift toward the right side of space, and as right-sided stimuli when gaze was shift to the left side. We hypothesized that if nociception influences vision based on their spatial correspondence in external space, the nociceptive stimuli would bias visual TOJs always in favor of the visual stimuli presented close to the stimulated hand, i.e. the centrally positioned visual stimuli, independently of the gaze direction, that is, of the side of space the stimuli are seen in.

In **Study 4** we further wanted to corroborate our hypothesis that the crossmodal influence of nociception on the perception of visual stimuli is dependent on the proximity of the visual stimuli to the stimulated hand rather than on the occurrence of both stimuli in the same hemispace as defined by the midsagittal plane of the body, by avoiding the classic left vs. right dimension usually used in TOJ tasks. Participants placed their hands in front of them on their body anteroposterior axis, one hand at a proximal, the other one at a distal location. They performed a TOJ task on pairs of visual stimuli, one delivered close to either the proximal or the distal hand. Visual stimuli were preceded by nociceptive stimuli applied either on both hands simultaneously or on one hand unilaterally. Using such a setting, nociceptive stimuli were still applied to the left vs. right parts of the body, but judgments about visual stimuli were independent of such a spatial organization. We expected that only in conditions in which nociceptive stimuli were applied unilaterally, participants' judgments would be biased in favor of the visual stimuli the closest to the stimulated hand, irrespective of their distance from the trunk.

The second part of the experimental section describes the experiments conducted in CRPS patients. This part was aimed to demonstrate that lateralized chronic pain can also entail, besides deficits in perceiving somatosensory stimuli applied on the body, an impaired perception of visual stimuli presented in peripersonal space. In **Study 5**, upper-limb CRPS patients performed TOJ tasks with tactile (i.e. body) or visual (i.e. extra-body) stimuli. In the visual TOJ tasks, pairs of stimuli were presented, one stimulus in either side of space, i.e. in the side of space of the affected hand and that of the unaffected hand. Visual stimuli were presented either near or far from the participants' body, with the hands placed either close to the nearest visual stimuli or close to their body. In the tactile TOJ tasks, pairs of stimuli were applied, one stimulus on either hand. Tactile tasks were performed with the hands in an either uncrossed or crossed posture. For the tactile task, we expected to replicate previous findings, showing that CRPS patients judge temporal order to the disadvantage of stimuli applied on the affected hand in the uncrossed hand posture and to the disadvantage of stimuli applied on the unaffected hand in the crossed hand posture. In the visual task we hypothesized to find biases to the disadvantage of the visual stimuli presented in the same side of space as the affected hand, but only when these stimuli were presented close to the hands.

Do nociception and pain affect the perception of peripersonal space?

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**Part 1**  
**Do nociceptive stimuli influence visual stimuli**  
**perception?**

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Do nociception and pain affect the perception of peripersonal space?

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**Study 1**

***Orienting attention in visual space by nociceptive stimuli: investigation with a temporal order judgment task based on the adaptive PSI method<sup>1</sup>***

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**Abstract**

Despite their high relevance for defending the integrity of the body, crossmodal links between nociception, the neural system specifically coding potentially painful information, and vision are still poorly studied, especially the effects of nociception on visual perception. This study investigated if, and in which time-window, a nociceptive stimulus can attract attention to its location on the body, independently of voluntary control, in order to facilitate the processing of visual stimuli occurring in the same side of space as the limb on which the visual stimulus was applied. In a temporal order judgment task based on an adaptive procedure, participants judged which of two visual stimuli, one presented next to either hand in either side of space, had been perceived first. Each pair of visual stimuli was preceded (by 200, 400 or 600 ms) by a nociceptive stimulus applied either unilaterally on one single hand, or bilaterally, on both hands simultaneously. Results show that, as compared to the bilateral condition, participants' judgments were biased to the advantage of the visual stimuli that occurred in the same side of space as the hand on which a unilateral, nociceptive stimulus was applied. This effect was present in a time-window ranging from 200 to 600 ms, but importantly, biases increased with decreasing time interval. These results suggest that nociceptive stimuli can affect the perceptual processing of spatially congruent visual inputs.

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<sup>1</sup> Based on: Filbrich, L., Alamia, A., Burns, S., & Legrain, V. (2017). Orienting attention in visual space by nociceptive stimuli: investigation with a temporal order judgment task based on the adaptive PSI method. *Exp Brain Res, in Press*.

Do nociception and pain affect the perception of peripersonal space?

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## Study 1

# ***Orienting attention in visual space by nociceptive stimuli: investigation with a temporal order judgment task based on the adaptive PSI method***

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## **1. Introduction**

Pain is an unpleasant sensation usually evoked by the activation of nociceptors. Nociceptors are sensory receptors characterized by a high activation threshold, that is, by the ability to respond to high intensity and potentially harmful stimuli. The functional role of the nociceptive system is to warn the brain about possible body damage and to adapt behavior to possibly damaging stimuli in order to protect the integrity of the body. To this aim, the brain needs to locate which part of the body is potentially being harmed, an ability that depends partly on spatially organized projections of the receptor fields to specific spatially segregated groups of neurons in the cortex (Kenshalo & Isensee, 1983). This mapping mechanisms, based on an anatomical representation of the body surface, is however not sufficient. Indeed, responding adequately to a potential threat requires also to perceive the posture of the body (*where is the threatened limb?*) and to locate, for instance visually, the cause of the damage in external space (*where is the threatening stimulus?*) (Legrain et al., 2011). In other words, by integrating the relative position of the body limbs in external space, and by coordinating the representation of the body space with that of external space, the brain should be able, based on the perception of the location of a nociceptive and potentially painful stimulus, to orient attention selectively to the location of the external, e.g. visual, stimuli in order to prioritize their processing (Legrain & Torta, 2015). Surprisingly, up to now, most of the research studying crossmodal attention between nociceptive/painful and external (auditory or visual) stimuli investigated the reverse link, i.e., how auditory or visual stimuli can attract attention to a particular spatial location and impact the processing and the perception of the intensity of a nociceptive/painful stimulus<sup>1</sup> applied to the limb adjacent to this spatial location (e.g. Bushnell, Duncan, Dubner, Jones, & Maixner, 1985; Dowman, 2004; Van Damme & Legrain, 2012; Van Ryckeghem et al., 2011). Most of these studies used cueing paradigms in which participants had to react to and/or to rate the intensity of a nociceptive/painful stimulus preceded by a visual stimulus at a congruent versus incongruent spatial position. For instance, De Paepe et al. (2014) and De Paepe et al. (2015), using temporal order judgements (TOJ) tasks (see below), have shown that the perception of a nociceptive stimulus applied on one limb was facilitated

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<sup>1</sup> The term “nociceptive” is used to describe stimuli that selectively activate nociceptors, while the term “painful” is used to describe stimuli that are explicitly perceived as pain by the participant, regardless of the selectivity of the eliciting stimuli.

when it was preceded shortly by a visual stimulus presented in the proximity of the stimulated limb.

It is certainly interesting to understand how the reaction to a nociceptive stimulus and the pain elicited by such a stimulus can be modulated by the visual perception of an external object that might have an impending impact on the body. However, it seems even more ecologically relevant to understand how the perception of a nociceptive stimulus on the body can attract attention to the space surrounding the affected limb in order to prioritize the visual perception of stimuli occurring around that limb. To our knowledge, this question was only investigated in two studies. Van Damme et al. (2007) instructed their participants to react as fast as possible to visual stimuli presented at two possible locations, corresponding to each side of space, at the proximity of the wrist of each hand. They show that reactions to these visual stimuli were speeded-up when a painful stimulus preceded the occurrence of the visual stimulus by 200 ms, while being applied on the wrist of the hand spatially congruent with the visual stimulus, as compared to a painful stimulus applied to the opposite hand. However, these authors used transcutaneous electrical current induced by bipolar electrodes as painful stimuli, a stimulation that is known to activate all underlying somatosensory fibers, including large-diameter myelinated A $\beta$  nerve fibers responsible for tactile sensation. Therefore, attentional capture produced by these painful stimuli was triggered by the fastest and first somatosensory inputs that reached the cortex, that is, the inputs conveyed by non-nociceptive A $\beta$  fibers which are characterized by a faster velocity conduction than the slow conducting finely myelinated nociceptive A $\delta$  and unmyelinated nociceptive C fibers (Kandel et al., 2013). In other words, the attentional effects observed in the study of Van Damme et al. (2007) were not related to the nociceptive specificity and the painfulness of the somatosensory stimuli. Using a slightly modified paradigm, Favril et al. (2014) obtained similar results, but with intra-epidermal electrical stimulation delivered at low intensities, a technique that has been shown to be more selective in activating nociceptive A $\delta$  fibers (Inui et al., 2002; Inui et al., 2006; Mouraux et al., 2010). However, since in that study, the position of the visual target was highly predictable for the participants, it is difficult to disentangle whether the effects on visual processing were driven by the motivation of the participants to allocate attention to one side of space, or by the capture of attention triggered by the nociceptive stimulus itself to its own location.

The first objective of the present study was to show how a somatosensory stimulus applied to a particular body limb and specifically coded and transmitted by the nociceptive system, can attract attention to its location, independently of voluntarily control, in order to facilitate the processing of visual stimuli occurring in the same side of space as the limb on which the nociceptive stimulus is applied.

To this aim, we used a TOJ task during which participants were instructed to discriminate the temporal order of two stimuli presented in rapid temporal succession. As compared to classic detection and reaction tasks, TOJ tasks offer the advantage to be

unspedded and can thus highlight the effects of experimental manipulations on changes in the perceptual processing of a target stimulus without the confound of faster response selection and/or execution (Spence, McDonald, et al., 2004; Zampini et al., 2007). These tasks are regularly used to study crossmodal links in spatial attention between different sensory modalities (see for example De Paepe et al., 2015; De Paepe et al., 2014; Spence et al., 2001). Attentional effects observed during TOJ are interpreted in light of the theory of prior entry (Titchener, 1908), according to which the perception of attended stimuli is speeded up as compared to unattended ones. As a consequence, an unattended stimulus has then to be presented before the attended stimulus to be perceived as occurring simultaneously. The stimulus onset asynchrony (SOA) at which the two stimuli are perceived as simultaneous has been defined as the point of subjective simultaneity (PSS) (for a review see Spence & Parise, 2010). In prior-entry related TOJ tasks, shifts in the PSS are used to highlight changes in the perceptual sensory processing of target stimuli due to attentional manipulations such as attending to a particular location induced by spatial cueing. In the present study, we asked the participants to perform a TOJ on pairs of lateralized visual stimuli, one stimulus presented close to either hand, while measuring the effects on the PSS induced by a nociceptive stimulus applied on one of the hands shortly before the pair of visual stimuli. We predicted a shift of the PSS values to the advantage of the visual stimuli presented close to the stimulated hand, indexing that their processing was facilitated by the nociceptive stimulus applied to the congruent spatial location.

The second aim of our study was to implement a TOJ task based on an adaptive procedure to vary the different SOA's between the two stimuli on which the temporal order judgments are made and to finally derive the PSS. Indeed, in most of the existing TOJ studies the method of constant stimuli is used (see Spence & Parise, 2010). With this method a sample of SOAs is chosen a priori, and the SOAs are repeated several times during the experiment. The disadvantage of the method of constant stimuli is that testing can be time-consuming and tedious as many trials have to be presented for each SOA to reliably derive the parameters of interest (Kingdom & Prins, 2010). As a consequence, the number of tested experimental conditions has often to be reduced. The modification of the TOJ task used in the present study is based on the adaptive PSI method (Kontsevich & Tyler, 1999). This specific method adapts the experimental procedure and the presented SOA's according to the performance of the participant to all the previous trials. Specifically, the algorithm adopts a Bayesian framework, with the ultimate goal to estimate the posterior probability of the parameters of interest without probing extensively all the SOA's. The core idea is to minimize the expected entropy of the posterior distribution trial by trial, such that the response of the participant at each trial provides the most information about the distribution of the parameters. Notably, the distributions are shaped during the experiment considering all the previous trials, thus exploiting an adaptive approach (Kingdom & Prins, 2010). The advantage of using the PSI method is that it allows to estimate the distributions of the parameters (e.g. the PSS) with a lower number of trials, which accelerates the testing procedure, thus reducing confounding effects usually

associated with long tasks, such as task independent attention shifts and fatigue. Furthermore, the tested SOA's are adapted to each participants own performance, which is of great interest for avoiding floor or ceiling effects when for example comparing the performance of two distinct types of participant populations. Indeed, TOJ tasks are regularly used to test perceptual capacities in clinical populations in which sensory processing might be disturbed, as for example in chronic pain (see e.g. Moseley, Gallace, & Iannetti, 2012; Moseley et al., 2009; Reid et al., 2016) or right-hemisphere damaged patients (see e.g. Eramudugolla, Irvine, & Mattingley, 2007; Roberts, Lau, Chechlacz, & Humphreys, 2012; Sinnett, Juncadella, Rafal, Azanon, & Soto-Faraco, 2007). However, in these clinical studies, selection of presented SOA levels seems often based on studies assessing the performance of healthy subjects and rarely on the patients' own performances (for exceptions see Robertson, Mattingley, Rorden, & Driver, 1998; Rorden et al., 1997). Using procedures specifically adapted to individual performances seems to be more indicated when the aim is to highlight potentially subtle differences between experimental conditions or between specific participant populations. Besides the more theoretical aim of demonstrating crossmodal influence of nociception on visual perception with a TOJ task, the present study served thus also to assess an adaptive method aimed to increase the efficiency of the testing procedure.

The final aim of the present study was to test the time window during which a somatosensory stimulus specifically conveyed by the nociceptive system can efficiently capture attention and positively impact the processing of another stimulus presented in its spatial surrounding. One issue in cueing paradigms is that involuntary stimulus-driven capture of attention is short-living, and, that there is, therefore, a critical time window during which the cueing stimulus can efficiently impact the processing of the forthcoming target stimulus (Posner & Cohen, 1984). While this aspect was already investigated for the other sensory modalities (e.g. Spence, McDonald, et al., 2004), the optimal time window for a nociceptive cue is completely unknown. Such a critical time window is partly dependent on the velocity of the sensory transmission. Since the conduction velocity of A $\delta$  fibers is relatively slow as compared to A $\beta$  fibers (Campbell & LaMotte, 1983), nociceptive-induced attentional effects cannot be directly predicted from studies having used non-nociceptive somatosensory stimuli as cues, but are expected at a longer latency. For instance, Kennett, Eimer, et al. (2001) found strong crossmodal attentional effects when a tactile cue preceded the visual target by 160 ms, and less efficient, but still significant effects by 310 ms. On the other hand, since no cortical response is expected from nociceptive IES before 100-150 ms (Inui et al., 2003; Mouraux et al., 2013; Mouraux, Marot, & Legrain, 2014), no attentional effect is therefore expected in such a time window. Here, we tested three time intervals: 200, 400 and 600 ms between the onset of the nociceptive cue and that of the first visual stimulus of the pair.

## **2. Methods**

### **2.1. Participants**

Sixteen participants volunteered to take part in the experiment. One participant was not able to finish the experiment because of an uncontrolled startle response to the electrocutaneous stimuli. The mean age of the remaining 15 participants (10 women) was 23.4 years (SD = 4.99, range: 18-35 years). Participants had normal or corrected-to-normal vision and did not report any neurological, psychiatric, cardiac or chronic pain problems, regular use of psychotropic drugs, or any traumatic injury of the upper limbs within the 6 months preceding the experiment. They reported having slept at least 6 hours before the experiment and not having used any analgesic drugs (e.g. NSAIDs and paracetamol) within the 12 hours preceding the experiment. All but one of the participants were right-handed according to the Flinders Handedness Survey (Flanders) (Nicholls, Thomas, Loetscher, & Grimshaw, 2013). The experimental procedure was approved by the local ethic committee in agreement with the latest version of the Declaration of Helsinki, and all participants signed a consent form prior to the experimental session. Participants received financial compensation.

### **2.2. Stimuli and apparatus**

Nociceptive stimuli were delivered at the hand dorsum by means of intra-epidermal electrical stimulation (IES) (DS7 Stimulator, Digitimer Ltd, UK) using stainless steel concentric bipolar electrodes (Nihon Kohden, Japan; Inui et al., 2006), which consisted of a needle cathode (length: 0.1 mm, Ø: 0.2 mm) surrounded by a cylindrical anode (Ø: 1.4 mm). By pressing gently against the participant's skin, the electrode was inserted in the epidermis of each hand dorsum in the sensory territory of the superficial branch of radial nerve. To selectively activate skin nociceptors, the intensity of the electrical stimulation was individually adjusted to twice the absolute detection threshold with a maximum of 0.5 mA as restriction criteria (Mouraux et al., 2010). For each of the participants' hands, the detection threshold to a single 0.5 ms square-wave pulse was determined using a staircase procedure (Churyukanov, Plaghki, Legrain, & Mouraux, 2012). If necessary, intensity values were adapted to guarantee that stimulus intensities were perceived as equivalent for both hands, by slightly increasing or decreasing the intensity of one of the two stimuli (see Favril et al., 2014 for details). During the experiment, stimuli consisted of trains of three consecutive pulses separated by a 5 ms interpulse interval (Mouraux et al., 2013; Mouraux et al., 2014). The participants described the IES sensation as pricking but not necessarily unpleasant. Using such a procedure, IES was shown to selectively activate A $\delta$  nociceptors without co-activation of A $\beta$  mechanoreceptors (Mouraux et al., 2013; Mouraux et al., 2010).

Visual stimuli were presented by means of two white light emitting diodes (LED) with a 17 lm luminous flux, a 6.40 cd luminous intensity, and a 120° visual angle

(GM5BW97330A, Sharp Corporation, Japan). They were perceived as brief flashes. To ensure the visibility of the LEDs, participants were asked to report the position of the flashing LED (i.e. the left or the right one). A third yellow LED (min. 0.7 cd luminous intensity at 20mA, 120° viewing angle) was used as fixation point during the task (Multicomp, Farnell element14, UK).

### **2.3. Procedure**

Participants were sitting in a dimly-illuminated testing room with their arms positioned on a table and their palms down. Their heads were stabilized with a chin-rest placed approximately 10 cm from the trunk, in order to minimize head movement. The two white LEDs were fixed on the table, approximately 40 cm away from the trunk and with a distance of 40 cm between them. Each participant's hand was placed next to one of the two LEDs, with a maximum distance of 1 cm between the LED and the metacarpophalangeal joint of the index finger. The yellow fixation LED was placed equidistantly from the two white LEDs at a distance of 65cm in front of the body midline.

A trial started with the illumination of the fixation point. After 500 ms, the nociceptive stimulus was applied either unilaterally, on the left or the right hand, or bilaterally, i.e. on both hands simultaneously. The nociceptive stimulus was followed by a pair of visual stimuli of 5 ms duration each, one stimulus presented next to either hand (i.e. the left LED next to the left hand and the right LED next to the right hand). Depending on the block, the time interval between the onset of the nociceptive stimulus and that of the first visual stimulus of the pair was either 200, 400 or 600 ms. During a pre-testing session in which we tested a 150 ms interval, some of the participants perceived the first visual stimulus clearly before the nociceptive cue, an effect that can very likely be accounted for by the slow velocity of the nociceptive input transmission. Twenty possible time intervals (SOAs for stimulus onset asynchronies) were used between the two visual stimuli of the pair:  $\pm 200, \pm 145, \pm 90, \pm 75, \pm 60, \pm 45, \pm 30, \pm 15, \pm 10, \pm 5$  ms (negative values indicate that the left LED was illuminated first). The participants were instructed to keep their gaze on the fixation point during the whole trial. In half of the blocks participants had to respond verbally which of the two visual stimuli they perceived as occurring first (by answering 'left' or 'right'), while they had to respond which stimuli was perceived as second in the other half of the blocks. These two response modalities were used to dissociate a genuine perceptual spatial bias from a response/decisional bias (for a discussion see Filbrich et al., 2016; Scharlau, 2004; Shore et al., 2001; Spence & Parise, 2010). The participant's response was encoded by the experimenter. No specific instruction was given regarding response speed. As soon as the response was encoded, illumination of the fixation point was switched off and the next trial started 2000 ms later. No feedback regarding the accuracy of participant's responses was given.

The experiment was composed of six blocks resulting from the combination of the time interval (200 vs. 400 vs. 600 ms) and the response modality ('which is first' vs. 'which

is second'). The order of the blocks was pseudo-randomized for the different time intervals. The two blocks of the same time interval were performed consecutively, and the order of the different response modalities was randomized. Each block consisted of 3 series of 20 trials, one for each cueing condition: unilateral left vs. unilateral right vs. bilateral nociceptive stimuli. The trials of the 3 series were randomly and equiprobably intermixed. Within each of the series, the presented SOAs were determined online for each trial according to the adaptive PSI procedure (Kontsevich & Tyler, 1999), i.e. based on participants' performance on all previous trials within one cue condition (implemented through the Palamedes Toolbox, Prins & Kingdom, 2009).

After each block, levels of perceived intensity of the nociceptive stimuli were assessed (on a scale from 0 to 10, with 0 = no sensation and 10 = very intense sensation) to ensure that IES were still perceived and that their intensities were rated as equivalent for both hands. If these criteria were not met, the intensities were adapted by increasing or reducing slightly the intensity of the stimuli, with 0.5 mA as a limit (see Favril et al., 2014 for details). If the limit was reached, the electrodes were displaced and the threshold measurements were restarted. A rest period between the blocks was possible when requested. Duration of the whole experiment was approximately 60 min.

#### **2.4. Measures**

For each participant and each condition, data were fitted with a logistic function, i.e.  $f(x) = 1 / (1 + \exp(-\beta(x - \alpha)))$ , to derive the two measures of interest: the point of subjective simultaneity (PSS) and the slope. More in detail, we estimated these measures as the  $\alpha$  (i.e. threshold) and  $\beta$  (i.e. slope) of the logistic function, respectively. In our study, the  $\alpha$  corresponds to the SOA at which the two visual stimuli are perceived as occurring first equally often (i.e. the 0.5 criterion on the ordinate). Accordingly, this measure corresponds to the PSS, which is defined as the amount of time one stimulus has to precede or follow the other in order for the two stimuli to be perceived as occurring simultaneously (Spence et al., 2001). The  $\beta$  parameter describes the noisiness of the participant's performance, i.e. the precision or the variability of the participant's responses during the experiment (Kingdom & Prins, 2010). The  $\beta$ , i.e. slope, has often been used to derive the just noticeable difference (JND) reported in TOJ studies. In order to estimate the logistic function we used the PSI method (Kontsevich & Tyler, 1999), in which the psychometric curve and its parameters are estimated at each trial. Specifically, the method updates at each trial the joint distribution of the threshold and the slope (initialized as a uniform distribution in a range of prior values which were chosen based on pilot experiments), and proposes an SOA for the subsequent trial such that the expected entropy of the posterior distribution would be minimized. The advantage of this approach relies on the fact that not all the SOAs have to be tested extensively in order to estimate the values of the measures for each participant, thus reducing the total number of trials.

The average of the PSS values for left sided cues and the values for right sided cues (multiplied by -1 for the PSS for right sided cues) was calculated to derive a unilateral cue condition for each participant and each experimental condition. Accordingly, for the unilateral cue condition, we plotted the proportion of trials in which the visual stimulus presented in the cued side of space was reported as appearing first as a function of SOA. For the bilateral cue condition, we plotted the proportion of trials in which the left visual stimulus was reported as appearing first as a function of SOA.

## **2.5. Data analysis**

Before statistical analyses, data from the two response modalities ('which is first' and 'which is second') were merged to reduce potential response biases. To compare the mean scores of the maximal intensity of the nociceptive stimuli between both hands, a paired-samples t-test was used. Self-reported mean intensities between the two hands were compared using a Wilcoxon signed-rank test. To characterize the existence of potential perceptual biases in TOJs in the different experimental conditions, each PSS value was compared to 0 using simple t-tests. The effects of these conditions on PSS and slope were tested using an analysis of variance (ANOVA) for repeated measures with *cue condition* (unilateral vs. bilateral) and *time interval* (200 vs. 400 vs. 600 ms) as within-participant factors. Greenhouse-Geisser corrections of degrees of freedom and contrast analyses were used when necessary. Effect sizes were measured using Cohen's d (t-tests) or partial Eta squared (ANOVA). Significance level was set at  $p \leq 0.05$ .

## **3. Results**

### **3.1. Intensity of nociceptive stimuli**

The mean score of the maximal intensity of the nociceptive stimuli was  $0.35 \pm 0.09$  mA for the left hand and  $0.34 \pm 0.09$  mA for the right hand (no significant difference:  $t(14)=0.33$ ,  $p=0.75$ ). These values are in the range of intensities that have been shown to selectively activate nociceptors (Mouraux et al., 2013; Mouraux et al., 2010; Mouraux et al., 2014). The self-reported mean intensities were  $4.47 \pm 2.11$  and  $4.43 \pm 1.93$  for the left hand and the right hand respectively, the difference was not significant ( $Z = -0.34$ ,  $p=0.73$ ).

### **3.2. PSS**

The fitted psychometric curves and mean PSS data for each condition are illustrated in Fig. 1. Simple t-tests revealed that PSS values were significantly different from zero for the unilateral cue condition for the 200 ms ( $t(14)=6.99$ ,  $p < 0.001$ ,  $d=1.80$ ), the 400 ms ( $t(14)=4.87$ ,  $p < 0.001$ ,  $d=1.25$ ), as well as the 600 ms ( $t(14)=3.82$ ,  $p=0.002$ ,  $d=0.99$ ) time interval between the nociceptive and the visual stimuli. As for the bilateral cue



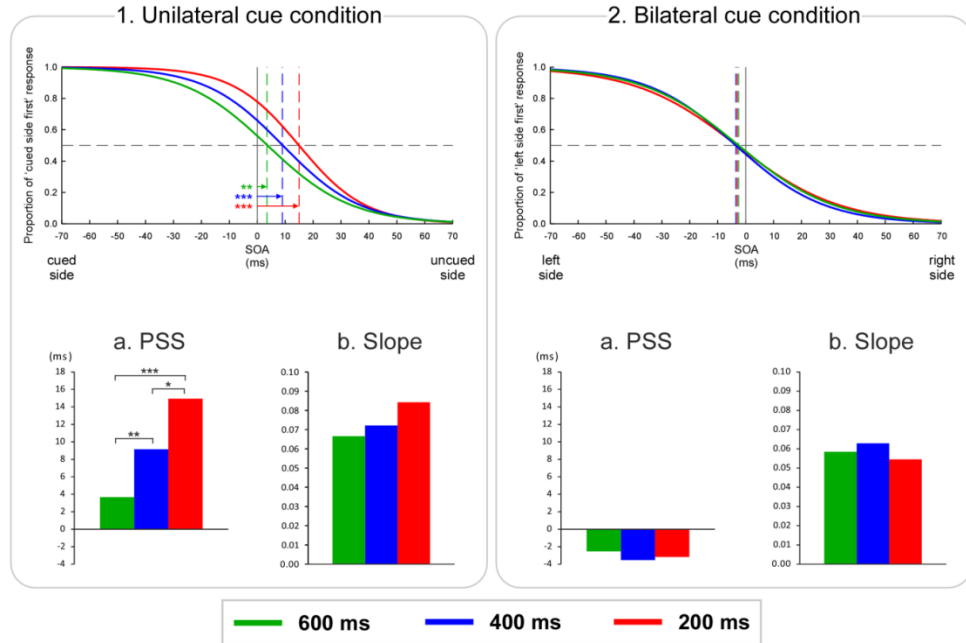
condition, PSS values for none of the three time intervals were significantly different from zero (all  $t(14) \leq -1.84$ ,  $p \geq 0.09$ ). The PSS seems thus biased by the occurrence of a unilateral nociceptive stimulation.

The repeated measures ANOVA revealed significant main effects for the factors *cue condition* ( $F(1,14)=25.80$ ,  $p<0.001$ ,  $\eta^2p=0.65$ ) and *time interval* ( $F(2,28)=7.21$ ,  $p=0.003$ ,  $\eta^2p=0.34$ ). The interaction between these two factors did also reach significance ( $F(2,28)=7.22$ ,  $p=0.003$ ,  $\eta^2=0.34$ ). Post-hoc analyses showed that there was a significant main effect of *time interval* for the unilateral ( $F(2,28)=17.17$ ,  $p<0.001$ ,  $\eta^2p=0.55$ ) but not for the bilateral ( $F(2,28)=0.10$ ,  $p=0.91$ ,  $\eta^2p=0.007$ ) cue conditions. More specifically, in the unilateral cue condition, there was a significant difference between the 200 ms and the 400 ms time interval ( $t(14)=2.53$ ,  $p=0.024$ ,  $d=0.65$ ), between the 200 ms and the 600 ms time interval ( $t(14)=5.81$ ,  $p<0.001$ ,  $d=1.50$ ), as well as between the 400 ms and the 600 ms time interval ( $t(14)=3.78$ ,  $p=0.002$ ,  $d=0.97$ ). The data suggest therefore an increasing shift of PSS with decreasing time interval between the nociceptive cue and the visual targets.

### 3.3. Slope

The mean slope data for each condition are shown in Fig. 1. The two-way repeated measures ANOVA revealed a significant main effect of *cue condition* ( $F(1,14)=23.39$ ,  $p<0.001$ ,  $\eta^2p=0.63$ ) and a significant interaction between *cue condition* and *time interval* ( $F(2,28)=3.69$ ,  $p=0.038$ ,  $\eta^2p=0.21$ ). There was no significant main effect for the factor *time interval* ( $F(2,18)=0.88$ ,  $p=0.43$ ,  $\eta^2p=0.06$ ). Post-hoc analyses showed that the interaction between *cue condition* and *time interval* can be explained by the fact that there was a significant difference between the unilateral and the bilateral cue condition for the 200 ms interval ( $F(1,14)=21.41$ ,  $p<0.001$ ,  $\eta^2p=0.61$ ) but not for the 400 and 600 ms intervals (all  $F(1,14) \leq 2.47$ ,  $p \geq 0.14$ ). These results suggest that participants' judgments were less noisy, i.e. less variable, in the unilateral than in the bilateral cue conditions when the time interval between the nociceptive cue and the first visual stimulus was 200 ms. This finding supports the PSS results reported above, as a steeper slope for the unilateral cue conditions for the 200 ms time interval could suggest that participant's judgments were more systematically biased by the nociceptive cues in this specific condition and thus more precise than in the other conditions.

## Do nociception and pain affect the perception of peripersonal space?



**Fig.1.** Visual temporal order judgments (TOJs). The left part of the figure illustrates the data for the unilateral cue condition (1), the right part for the bilateral cue condition (2). For each part, the upper section illustrates the fitted logistic functions from the data of the 15 participants. For the unilateral cue condition (1), the x-axis represents different hypothetical SOAs between the two visual stimuli: negative values indicate that the visual stimulus occurring in the cued side of space was presented first, while positive values indicate that the visual stimulus occurring in the uncued side of space was presented first. The y-axis represents the proportion of trials in which the participants perceived the visual stimulus presented in the cued side of space as occurring first. For the bilateral cue condition (2) negative SOA values on the x-axis indicate that the visual stimulus occurring in the left side of space was presented first, while positive values indicate that the visual stimulus occurring in the right side of space was presented first. The y-axis represents the proportion of trials in which the participants perceived the stimulus presented in the left side of space as occurring first. The lower sections of the figure represent the PSS (a) and slope (b) values for their respective cue condition. Red curves and boxes represent the conditions in which the time interval between the nociceptive cue and the first visual stimulus was 200 ms, blue curves and boxes represent the 400 ms interval, and green curves and boxes represent the 600 ms interval. The arrows in (1) indicate the PSS values significantly different from zero. Significant differences are indicated with asterisks (\*  $p \leq .05$ , \*\*  $p \leq .01$ , \*\*\*  $p \leq .001$ ).

#### **4. Discussion**

In the present studies, we showed for the first time that shifts in attention can be induced by a spatially non-predictive somatosensory stimulus that is specifically coded and transmitted by the nociceptive system. Indeed, the main aim of these studies was to demonstrate, by means of TOJ tasks, that a nociceptive stimulus can attract spatial attention to the side of external space corresponding to the limb on which the nociceptive stimulus is applied and prioritize the perceptual processing of visual stimuli that occur subsequently in this same side of space. Attentional prioritization in TOJ tasks is usually highlighted by shifts in the PSS (Spence & Parise, 2010). In the present studies, participants judged the temporal order of pairs of visual stimuli, with one visual stimulus being presented next to either hand of the participants. With the aim to induce shifts in spatial attention, visual stimuli were shortly preceded by nociceptive stimuli which were applied on the participants' hands, either unilaterally on one of the two hands or bilaterally, on both hands simultaneously. The results showed that when both hands were stimulated simultaneously, none of the two visual stimuli were prioritized. Conversely, when only one hand was stimulated, temporal order was judged to the advantage of the visual stimuli that were presented close to the hand on which the nociceptive stimulus was applied, as indexed by a shift of the PSS towards visual stimuli that occurred close to the hand that was not stimulated, i.e. the uncued side of space. More precisely, these uncued visual stimuli had to be presented several ms before the visual stimuli that occurred close to the stimulated hand, i.e. in the cued side of space, in order to be judged as occurring first. In addition, we showed that this attentional effect grew more efficient with the reduction of the time delay between the nociceptive cue and the first stimulus of the visual pair. The most significant effect was indeed observed with an interval of 200 ms.

Importantly, since in the present paradigm all conditions were equivalently and randomly presented, the participants could not predict, based on the location of the unilateral nociceptive stimuli, the side of space in which the first stimulus of the visual pairs would appear. In other words, the location of the nociceptive stimuli was uninformative as to the location of the forthcoming visual stimulus, suggesting that attention was attracted automatically by the nociceptive stimuli to their location, independently of voluntary control or decision of the participants. In the classic spatial attention literature, especially the one about cueing paradigms (e.g. Luck et al., 1994; Posner & Petersen, 1990; Spence, McDonald, et al., 2004), attention can be spatially directed in two main ways: either endogenously, that is, by the participant's motivation, decision or anticipation, or exogenously, that is, driven by the stimulus itself, independently of the voluntary control of the participant. In endogenous cueing paradigms, attention displacements are manipulated by symbolic cues, i.e. cues that instruct the participant to shift his attention in one particular direction based on their meaning (such as an arrow), or, alternatively, by using lateralized cues based on which the participant can anticipate the most probable location of the forthcoming target. For instance, in the study of Favril et al.

(2014), after the application of a nociceptive stimulus on one hand, the visual stimuli appeared in the same side of space in 70% of the trials. Responses to these visual stimuli were characterized by faster reaction times and elicited evoked potentials (ERPs) of greater magnitude as compared to the responses to the 30% of visual stimuli that were delivered in the opposite side of space. One can imagine that if the proportion of trials “same vs. opposite sides of space” would have been reversed (i.e. visual stimuli occur in 70% of the trials in the space contralateral to the hand on which the nociceptive stimulus was applied), it could be highly expected that the results would also be reversed. In other words, faster reaction times and larger ERPs would have been observed for the visual stimuli presented in the opposite side, since, based on the location of the nociceptive stimulus, the participants would have predicted that it is most efficient to direct their attention to the opposite side of space. With exogenous cueing paradigms, in which all conditions are equiprobable, such predictions cannot be made and attention shifts are driven by the occurrence of the stimulus itself (Wright & Ward, 1994). Exogenous cueing paradigms are useful to investigate mechanisms underlying crossmodal interaction (Spence, McDonald, et al., 2004), as they allow investigating how sensory inputs arising from different sensory modalities interact with each other in order to build a multisensory representation of space that integrates the body space and the external space proximal to the body (see e.g. di Pellegrino & Làdavas, 2015; Holmes & Spence, 2004; Macaluso & Maravita, 2010). Such a multisensory representation is useful to adapt manipulation behaviors to innocuous stimuli (Rizzolatti et al., 1997) or defensive behaviors to noxious stimuli (Graziano & Cooke, 2006). The existence of such a crossmodal representation of the body and the space nearby is hypothesized to rely on multimodal neurons in fronto-parietal regions that can respond to both somatosensory and visual stimuli occurring in the proximity of the body, as shown in non-human primate studies (Dong et al., 1994; Rizzolatti et al., 1981a, 1981b). Surprisingly though, while visual-tactile interactions have been investigated extensively (e.g. Spence & Driver, 2004), visual-nociceptive interactions are still poorly studied (Legrain & Torta, 2015). For instance, besides the huge quantities of data regarding the recording of visual-tactile neurons in monkeys (see e.g. Graziano et al., 2004), only one study recorded the activity of neurons responding to both thermo-nociceptive and visual stimuli (Dong et al., 1994). Yet, such visual-nociceptive interactions are also clinically relevant, since it has been shown that some specific chronic pain conditions can impact the patients’ abilities to represent and perceive space (see e.g. Legrain et al., 2012; Reinersmann et al., 2013). In addition, targeting these cognitive difficulties has been suggested as a potentially useful method to treat chronic pain. In a recent study, De Paepe et al. (2014) used similar TOJ tasks but with pairs of nociceptive stimuli, applied one on either hand. They showed that the occurrence, in one side of space, of a visual stimulus presented slightly before the pairs of nociceptive stimuli positively biased the perception of the nociceptive stimuli applied on the hand placed in the same side of space, to the detriment of the nociceptive stimuli applied to the opposite hand. Importantly, the impact of the visual cues was more efficient when they were presented close to the stimulated hand, as compared to the conditions in which they were presented farther away. In addition, they also showed that these effects

were independent of the relative position of the hands in space (De Paepe et al., 2015). More precisely, when the participants crossed their hands over their body midline, the perception of the nociceptive stimuli applied to the left hand (but now located in right space) was positively impacted by right-sided visual stimuli. The reverse was shown for nociceptive stimuli applied to the right hand. These data strongly suggest that visual stimuli can affect the processing of nociceptive stimuli within the framework of a spatial representation integrating body space and proximal external space. The present studies showed the reverse effect, i.e. that nociceptive stimuli for their part can also positively impact spatially congruent visual stimuli. However, up to now, we are unable to conclude whether this effect is due to a general competition between the left and the right hemispace, or more specifically to the existence of a multisensory representation of the body that not only integrates tactile, but also nociceptive, stimuli.

Before addressing the former question, a main issue was to determine in which time window nociceptive stimuli can positively impact the processing of stimuli from other sensory modalities, since the optimal time window in which such effects could be observed was completely unknown. As already mentioned in the Introduction section, since the neural systems coding mechanical versus nociceptive information are anatomically and functionally different, such an estimation cannot rely on studies having used tactile stimuli as cues (e.g. Kennett, Eimer, et al., 2001; Spence, Nicholls, Gillespie, & Driver, 1998). Pre-testing trials revealed that when using time intervals of 100-150 ms between the nociceptive cues and the visual targets, some participants perceived the nociceptive stimuli after the visual stimuli. This effect could be accounted for by the long distance from the coding receptors to the cortex and the slow velocity of the transmission system conveying nociceptive inputs. As a consequence, nociceptive inputs probably arrived, or were at least fully processed, at the cortical level after the visual inputs. We tested three time intervals between the nociceptive cue and the visual targets: 200, 400 and 600 ms. Results showed that biases induced by the unilateral nociceptive cues were significant for all three time intervals. It seems, therefore, that nociceptive stimuli can impact the processing of visual stimuli within a time window ranging from 200 to 600 ms. Analyses however also revealed that there were significant differences between the three intervals with regard to their ability to orient attention, showing increasing biases with decreasing time interval. The 200 ms time interval between the nociceptive cue and the first visual target was thus the most efficient for the nociceptive cue to capture attention and facilitate the processing of subsequent visual stimuli presented in the same side of space. Now that we highlighted the optimal time window to obtain cueing effects from nociceptive stimuli on visual stimuli, future studies should also investigate whether the crossmodal influence of nociception on visual processing depends on a multisensory reference frame for the spatial perception of sensory events that is organized around the body.

Finally, another major contribution of the present studies is that we were able to demonstrate crossmodal shifts in spatial attention by using a TOJ task based on the adaptive

PSI procedure (Kontsevich & Tyler, 1999). The advantage of this method is that the PSS and the slope are estimated at each trial, and that the to-be-tested SOAs on each trial depend on the participant's own performance on all the previous trials, contrary to the classically used method of constant stimuli in which all the SOAs have to be presented several times to finally estimate the PSS and slope values. Since with the adaptive method not all of the possible SOAs have to be tested in order to derive the final measures for each participant, the number of necessary trials can be largely reduced. This can be of interest when an important number of conditions needs to be tested (e.g. see De Paepe et al., 2014). Maintaining a precise estimation of TOJ parameters while reducing the number of trials is also of particular interest for the assessment of perceptual difficulties in clinical populations, whose performance could, due to their clinical conditions, particularly be prone to be influenced by task-independent factors as fatigue or difficulties in sustained attention. Furthermore, using the adaptive method can also be of interest to minimize the risk of imprecise estimates of the measures due to inappropriately chosen stimulus levels (SOAs). With this method one can consider to include a broader range of SOAs levels (without extending the duration of the experiment) to minimize floor or ceiling effects when there is no a priori knowledge based on pilot studies or previous research as to the range of SOAs used to reliably estimate the measures of interest. For example, Van der Biest and colleagues<sup>2</sup> used a tactile TOJ paradigm based on the method of constant stimuli to assess perceptual deficits in chronic pain patients. They could however not reliably evidence any biases, since, for an important number of participants, the magnitude of the bias, as well as the SOA at which participants judge stimulus order correctly in 75% of trials was bigger than the highest presented SOA, which suggests that the chosen SOA levels were probably not adapted and that possible effects could have been masked by the difficulty of the task. By using the adaptive PSI method we recently succeeded to demonstrate subtle visuospatial biases in a TOJ task in patients suffering from unilateral chronic pain<sup>3</sup>. Using adaptive methods seems therefore to be efficient in minimizing undesired confounding effects in the interpretation of TOJ data, especially when comparing conditions with different levels of difficulty or different populations.

To conclude, the present studies succeeded to demonstrate the efficiency of our paradigm, that is, a crossmodal cueing temporal order judgment task based on an adaptive procedure, with the aim to further investigate multisensory interaction between nociception and vision, both in healthy volunteers and chronic pain patients.

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<sup>2</sup> Van der Biest, L., Legrain, V., Hollevoet, N., Van Tongel, A., De Wilde, L., Jacobs, H., De Paepe, A. L., Crombez, G. (unpublished manuscript). An investigation of perceptual biases in Complex Regional Pain Syndrome.

<sup>3</sup> Filbrich, L., Alamia, A., Verfaillie, C., Berquin, A., Barbier, O., Libouton, X., Fraselle, V., Mouraux, D. & Legrain, V. (submitted). Does Complex Regional Pain Syndrome impair the perception of body space and extra-body space?

## Study 1 : Orienting attention in visual space by nociceptive stimuli

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Do nociception and pain affect the perception of peripersonal space?

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## **Study 2**

# ***Shaping visual space perception through bodily sensations: testing the impact of nociceptive stimuli on visual perception in peripersonal space with temporal order judgments<sup>1</sup>***

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### **Abstract**

Coordinating spatial perception between body space and its external surrounding space is essential to adapt behaviors to objects, especially when they are noxious. Such coherent multisensory representation of the body extended into external space is conceptualized by the notion of peripersonal reference frame, mapping the portion of space in which somatic and extra-somatic inputs interact closely. Studies on crossmodal interactions between nociception and vision have been scarce. Here we investigated how the perception of visual stimuli, especially those surrounding the body, can be impacted by a nociceptive and potentially harmful stimulus inflicted on a particular body part. In two temporal order judgment tasks, participants judged which of two lateralized visual stimuli, presented either near or far from the body, had been presented first. Visual stimuli were preceded by nociceptive stimuli, either applied unilaterally (on one single hand) or bilaterally (on both hands simultaneously). In Experiment 1 participants' hands were always placed next to the visual stimuli in near space, while in Experiment 2 they could also be placed next to the far visual stimuli. In Experiment 1, the presence of unilateral nociceptive stimuli prioritized the perception of the visual stimulus presented in the same side of space as the stimulated hand, with a significantly larger effect when visual stimuli were presented in near space than when they were presented farther away. Results of Experiment 2 showed that these visuospatial biases were related to the spatial congruency between the hand on which nociceptive stimuli were applied and the visual stimuli, independently of the relative distance of both the stimulated hand and the visual stimuli from the body considered as a whole. Indeed, nociceptive stimuli mostly impacted perception of the closest visual stimuli. It is hypothesized that these crossmodal interactions may rely on peripersonal representations of particular body parts.

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<sup>1</sup> Based on: Filbrich, L., Alamia, A., Blandiaux, S., Burns, S., & Legrain, V. (submitted). Shaping visual space perception through bodily sensations: testing the impact of nociceptive stimuli on visual perception in peripersonal space with temporal order judgments.

Do nociception and pain affect the perception of peripersonal space?

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## **Study 2**

# ***Shaping visual space perception through bodily sensations: testing the impact of nociceptive stimuli on visual perception in peripersonal space with temporal order judgments***

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## **1. Introduction**

For any living organism, it is important to monitor the space surrounding the body in order to avoid stimuli that have the potential to inflict damage on the body. Pain represents the archetype of physical threat. It is an unpleasant sensory and emotional experience that acts as a warning signal about potential body damage, with the aim of triggering behaviors purposely oriented to defend or restore the physical integrity of the body. Pain is initiated, in normal conditions, by the activation of specific sensory receptors, the nociceptors, characterized by the ability to code high intensity, and, as a consequence, potentially harmful stimuli. In order to adapt the behavior to possibly harmful stimuli, we need to detect and localize the part of the body that is potentially being harmed, i.e. the body part on which the nociceptive stimulus is applied. The spatial position of sensory information can be coded according to different frames of reference, i.e. coordinate systems. Localizing the position of a nociceptive stimulus depends partly on projections of spatially organized sensory receptor fields on the body surface to specific spatially segregated groups of neurons in the cortex (Baumgartner et al., 2010; Bingel et al., 2004; Kenshalo & Isensee, 1983; Mancini et al., 2012). This somatotopic frame of reference, representing the skin surface anatomically, is however not sufficient to respond adequately to the potential threat. Localizing the position of the possibly harming object in external space is also of primary importance, in order to spatially guide defensive motor responses. It is therefore necessary to coordinate the representation and perception of the space of the body and its surrounding external space. Such a coherent multisensory representation of the body space and its surrounding space is conceptualized by the notion of peripersonal reference frames. The peripersonal reference frames are mapping systems coding the portion of space in which somatic and extra-somatic (e.g. visual) stimuli can interact closely (Cardinali et al., 2009; Rizzolatti et al., 1997; Rizzolatti et al., 1983; Rizzolatti et al., 1981a, 1981b). The existence of peripersonal frames of reference has largely been documented for touch (di Pellegrino & Làdavas, 2015; Holmes & Spence, 2004; Macaluso & Maravita, 2010; Maravita et al., 2003), but very poorly investigated for nociception and pain (Legrain & Torta, 2015). Studying the involvement of a peripersonal frame of reference in localizing nociceptive stimuli is not only important to apprehend how

nociception is integrated with other sensory information to build a full representation of physical threats, but also to broaden the understanding of chronic pain pathophysiology. Indeed, it has recently been suggested that chronic pain can impair the representation and the perception of external space, although the exact nature of these impairments is still unknown (see Legrain et al., 2012). For instance, it has been shown that the level of painfulness evoked by a nociceptive stimulus can depend on the posture and the vision of the body part on which the nociceptive stimulus is applied (Beck et al., 2016; Gallace et al., 2011; Longo et al., 2009; Longo et al., 2012; Mancini et al., 2011) (however, see Torta et al., 2015; Valentini et al., 2015). Similarly, Sambo et al. (2013) and De Paepe et al. (2015) showed that judgments about the occurrence of nociceptive stimuli depend on the relative position of the limbs. In both studies a temporal order judgement (TOJ) task was used (see Spence & Parise, 2010), and participants had to judge which of two nociceptive stimuli, one applied on either hand, was perceived as being presented first. The task was performed with the hands either in a normal, uncrossed posture or with the hands crossed over the body midline. In studies on the spatial perception of touch, the crossed posture is known to reveal a competition between somatotopic and spatiotopic reference frames, indexed by a deterioration of performance when the hands are placed in a crossed posture (see Heed & Azañón, 2014). Similarly, TOJs on nociceptive stimuli were also affected by the crossed posture, suggesting that space-based reference frames are also used to code nociceptive stimuli (De Paepe et al., 2015; Sambo et al., 2013). Even more compelling evidence was provided by De Paepe et al. (2014) who showed, also using TOJ tasks, that judgments about nociceptive perception were systematically biased by the presence of a visual stimulus shortly preceding the nociceptive stimuli in the same side of space. This visual cue facilitated indeed the perception of the nociceptive stimulus applied on the ipsilateral hand, to the detriment of the nociceptive stimulus applied on the opposite hand. Importantly, this effect of the visual cue on the perception of the nociceptive stimuli was most pronounced when the visual cue was presented close to the participant's hand, as compared to conditions in which the cue was presented farther away. They demonstrated furthermore that the effect of this close proximity between visual and nociceptive stimuli was independent of the relative posture of the body limb (De Paepe et al., 2015). Finally, De Paepe et al. 2016 showed that reaction times to nociceptive stimuli were differently influenced by the vision of a visual stimulus approaching the to-be-stimulated hand (that is, a stimulus that could possibly contact the body) vs. a receding visual stimulus (that is, a stimulus that will not contact the body).

If these studies demonstrated that the detection, the localization and the perception of a nociceptive stimulus depends on the perception of a visual stimulus that may have an impact on the body, it is also highly relevant to investigate the reverse link, that is, how the perception of visual stimuli around the body can be affected by a nociceptive and potentially harmful stimulus inflicted on a particular body part. In non-human primates, such links are thought to be based on, at least for innocuous tactile stimuli, the existence of multimodal neurons, that is, neurons able to respond to sensory inputs from different

sensory modalities (see Graziano & Cooke, 2006). For instance, Rizzolatti and colleagues (Rizzolatti et al., 1981a, 1981b) discovered neurons in the ventral premotor cortex (PMv) responding to tactile stimuli applied to a given body part, but also to visual stimuli. Importantly, for some of these PMv neurons, the visual receptive fields (RFs) are limited to the portion of external space immediately adjacent to the associated tactile RFs (Rizzolatti et al., 1981b). Moreover, the RFs of these neurons do not move with eye movement, but with movements of the limb to which they are anchored (Fogassi et al., 1996; Gentilucci et al., 1983; Graziano et al., 1997; Graziano et al., 1994). Similar neurons have been found in the ventral intraparietal sulcus (VIP), with the difference that their visual RFs are mostly head-centered (Avillac et al., 2005; Duhamel et al., 1998). In other words, as far as visuospatial perception is concerned, the function of such bimodal neurons would be to remap the location of visual inputs from a retinotopic to a spatiotopic frame of reference, but, crucially, by using body parts as coordinate references. Finally, direct electrical stimulation of neurons in the PMv and VIP elicit defensive motor reactions in the monkeys (Cooke & Graziano, 2004; Cooke et al., 2003), similar to those evoked by direct application of unpleasant somatosensory stimuli on the monkeys' skin (Cooke & Graziano, 2004), suggesting that such neurons could be involved in coding threat information (Graziano & Cooke, 2006). However, up to now, there is only one study that demonstrated the existence of neurons in the inferior parietal lobe, close to the secondary somatosensory area, coding both thermo-nociceptive inputs as well as visual inputs that approach the body part on which the nociceptive stimulus is applied (Dong et al., 1994).

In the present studies we investigated, in humans, how the perception of the visuospatial environment can be impacted by bodily sensations, especially when these sensations are conveyed through the nociceptive system, that is, the neural system coding and transmitting sensory information about potentially harmful somatosensory events. We hypothesized that applying a nociceptive stimulus would particularly influence the perception of visual stimuli surrounding the body, that is, stimuli that might have an immediate impact on the body, in order to prioritize their processing. To this aim, we used two TOJ tasks, similar to those used by De Paepe and colleagues (De Paepe et al., 2015; De Paepe et al., 2014) but with pairs of visual stimuli, one stimulus presented in each side of space. In a first experiment, visual stimuli were presented either close or far from the body, and the participants' hands were placed next to the closest visual stimuli. Visual stimuli were shortly preceded by nociceptive stimuli, which were either applied unilaterally on one hand or bilaterally on both hands simultaneously. We hypothesized that the unilateral nociceptive stimuli would positively bias the perception of the visual stimuli presented in the same side of space as the stimulated hand, especially when these visual stimuli were presented close to the body. In the second experiment, we added a condition during which participants were asked to place their hands next to the visual stimuli that were presented farther away from the body. This condition was aimed to disentangle whether nociceptive-visual interactions are driven by the proximity of the visual stimuli to the body considered as a whole vs. to the stimulated hand itself. Indeed, as animal studies revealed that the

visual RFs of multimodal neurons are anchored to particular body parts, we hypothesized that nociceptive stimuli would mostly impact the perception of visual stimuli in the immediate proximity of the hand on which the nociceptive stimuli were applied, independently of the distance of the visual stimuli from the trunk, and the relative position of the limbs. The results confirmed our hypotheses and strongly support the hypothesis that the perception of visual space, especially that of peripersonal space, can be shaped by nociceptive information.

## **2. Methods**

### **2.1. Experiment 1**

#### **2.1.1. Participants**

Eighteen participants volunteered to take part in the experiment. One participant was excluded before data analysis because of difficulties in perceiving the nociceptive stimuli. The mean age of the remaining 17 participants (9 women) was  $23.29 \pm 3.1$  years (range: 19-32 years). Exclusion criteria were non-corrected vision deficits, neurological, psychiatric, cardiac or chronic pain problems, regular use of psychotropic drugs, as well as a traumatic injury of the upper limbs within the six months preceding the experiment. Participants were asked to not use any analgesic substances (e.g. NSAIDs or paracetamol) within the 12 hours preceding the experiment and to sleep at least 6 hours the night before the experiment. According to the Flinders Handedness Survey (Flanders) (Nicholls et al., 2013), all of the participants were right-handed. The experimental procedure was approved by the local ethic committee in agreement with the latest version of the Declaration of Helsinki and was carried out in accordance with the corresponding guidelines and regulations. All participants signed a consent form prior to the experimental session. Participants received financial compensation for their participation.

#### **2.1.2. Stimuli and apparatus**

Nociceptive stimuli were applied at the hand dorsum using intra-epidermal electrical stimulation (IES) (DS7 Stimulator, Digitimer Ltd, UK) with stainless steel concentric bipolar electrodes (Nihon Kohden, Japan; Inui et al., 2006). These electrodes consist of a needle cathode (length: 0.1 mm, Ø: 0.2 mm) surrounded by a cylindrical anode (Ø: 1.4 mm). They were gently pressed against the skin to insert the needle in the epidermis of the sensory territory of the superficial branch of radial nerve. For each of the participants' hands, absolute detection thresholds to a single 0.5 ms square-wave pulse were determined using a staircase procedure (Churyukanov et al., 2012). The intensity of the electrical stimulation was then individually set to twice the absolute detection threshold to selectively activate nociceptors, with a limit of 0.5 mA (Mouraux et al., 2010). If necessary,

these intensities were individually adapted to guarantee that stimulus intensities were perceived as equivalent for both hands (see Favril et al., 2014 for details). Using this specific procedure, IES has been shown to selectively activate A $\delta$  nociceptors without co-activation of A $\beta$  mechanoreceptors (Mouraux et al., 2013; Mouraux et al., 2010; Mouraux et al., 2014). During the experiment, stimuli consisted of trains of three consecutive 0.5 ms square-wave pulses separated by a 5 ms interpulse interval, to increase intensity of perception while preserving the selectivity for nociceptors (Mouraux et al., 2013; Mouraux et al., 2014). Participants described the sensation as pricking but not necessarily as painful.

Visual stimuli were presented by means of four white light emitting diodes (LEDs) with a 17 lm luminous flux, a 6.40 cd luminous intensity, and a 120° visual angle (GM5BW97330A, Sharp Corporation, Japan). They were perceived as brief flashes. Before the experimental session participants were asked to report the position of the flashing LED (e.g. the left one in front, the right one in the back, etc.) to ensure the visibility of the LEDs. A yellow LED (min. 0.7 cd luminous intensity at 20 mA, 120° viewing angle) served as fixation point.

### 2.1.3. Procedure

Participants were sitting in front of a table in a dimly-illuminated testing room, with their arms placed on the table and their palms down. Their heads were stabilized with a chin-rest placed ~10 cm from the trunk, in order to minimize head movements. The four white LEDs were fixed on the table. A first pair of LEDs was placed at a distance of ~40 cm from the participants' trunk (near space), the other pair at a distance of 50 cm from the LEDs in near space (far space) (Fig 1, upper part). For each pair, one LED was placed to the participant's left, the other to the participant's right, with a distance of ~40 cm between them. The participants placed their hands next to the LEDs in near space (the left hand next to the left LED and the right hand next to the right LED), with a maximum distance of 1 cm between the LED and the metacarpophalangeal joint of the index finger. The fixation LED was placed equidistantly from the LEDs in near and far space and equidistantly from the left and right LEDs, at a distance of 65 cm in front of the body midline.

A trial started with the illumination of the fixation LED. After 500 ms, the nociceptive stimulus was applied either unilaterally, on the left or the right hand, or bilaterally, i.e. on both hands simultaneously. After an interval of 200 ms, the nociceptive stimulus was followed by a pair of visual stimuli of 5 ms duration each, either presented in near or in far space, depending on the block. This interval was chosen based on previous studies (Filbrich, L., Alamia, A., Burns, S., Legrain, V., submitted) in which we showed that a 200 ms interval was the most efficient, as compared to 400 and 600 ms, for the nociceptive cue to impact the processing of the visual target in the TOJ task. Ten possible time intervals (SOAs, i.e. stimulus onset asynchronies) were used between the two visual stimuli:  $\pm 200$ ,  $\pm 90$ ,  $\pm 55$ ,  $\pm 30$ ,  $\pm 10$  ms (negative values indicate that the left LED was illuminated first). Participants were instructed to keep their gaze at the fixation point during

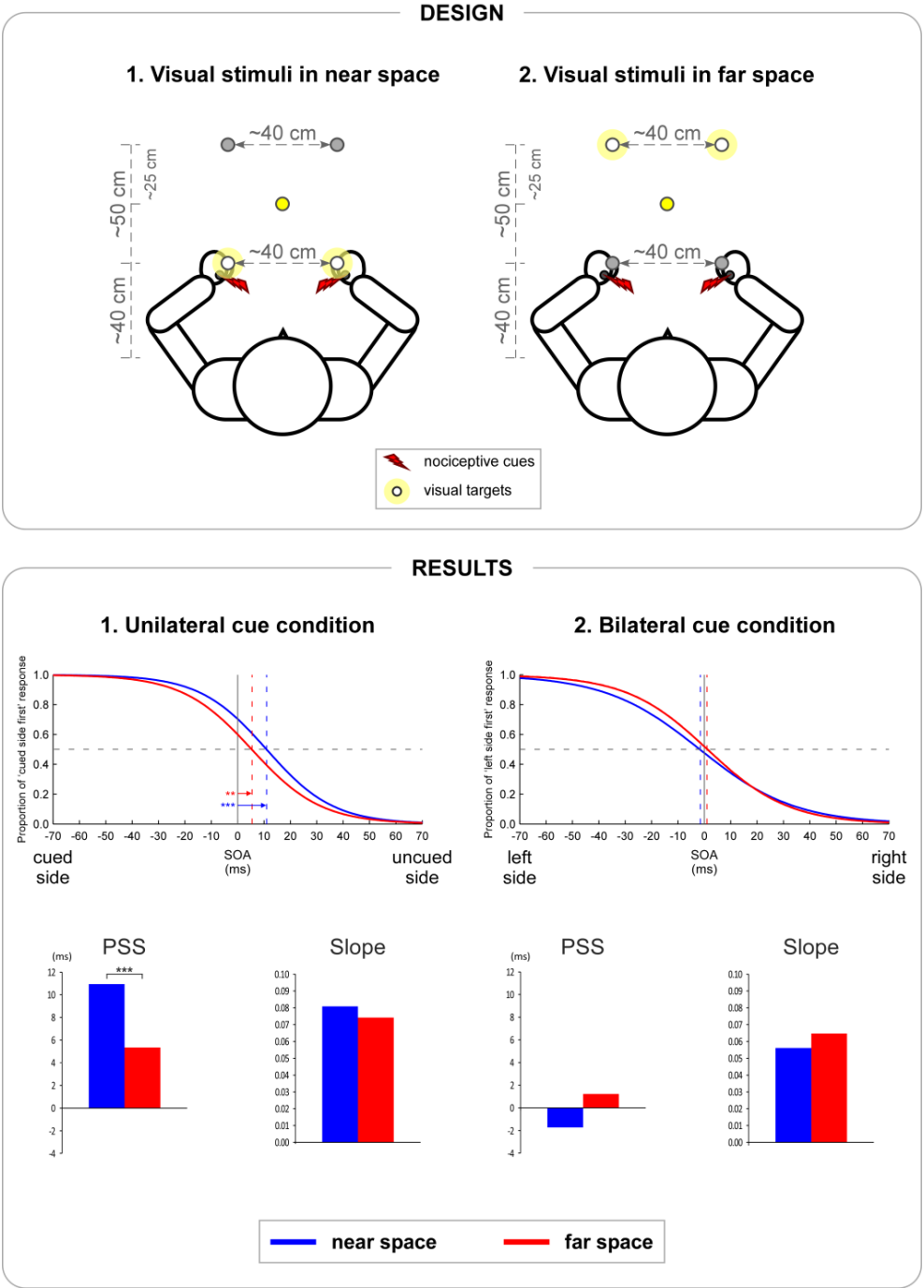
the whole trial. In half of the blocks they reported verbally which of the two visual stimuli they perceived as appearing first, while they reported which visual stimulus they perceived as appearing second in the other half of the blocks (by answering ‘left’ or ‘right’). By using these two response modalities, genuine perceptual spatial biases can be dissociated from more decisional biases (see Filbrich et al., 2016; Shore et al., 2001; Spence & Parise, 2010 for a discussion). The participants didn’t receive any specific instruction regarding response speed and no feedback regarding the accuracy of their performance was given. Illumination of the fixation point was switched off as soon as the response was encoded by the experimenter and the next trial started 2000 ms later.

The experiment was composed of four blocks resulting from the combination of the position of the visual stimuli (near space vs. far space) and the response factors (‘which is first’ vs. ‘which is second’). The order of the blocks was randomized. Each block consisted of three series of 20 trials, one for each cueing condition: unilateral left vs. unilateral right vs. bilateral nociceptive stimuli. The trials of the three series were randomly and equiprobably intermixed. Within each of the series, the presented SOAs were determined online trial by trial according to the adaptive PSI procedure (Kontsevich & Tyler, 1999), i.e. based on participants’ performance on all previous trials within one cueing condition (implemented through the Palamedes Toolbox, Prins & Kingdom, 2009).

Levels of perceived intensity of the nociceptive stimuli were assessed (on a scale from 0 to 10, with 0 = no sensation and 10 = very intense sensation) after each block, to ensure they were still perceived and that their intensities were rated as equivalent for both hands. If these criteria were not met, the intensities were adapted, or the electrodes were displaced and the absolute threshold measurements restarted (see Favril et al., 2014 for details). A rest period between the blocks was possible when requested. Duration of the whole experiment was approximately 45 min.



Study 2 : Shaping visual space perception through bodily sensations



**Fig 1.** Design and results of Experiment 1. The upper part of the figure illustrates the experimental design. Visual stimuli are presented by means of two pairs of LEDs, one placed near and the other placed far from the trunk. The participants' hands are positioned close to the LEDs in near space. In each block, participants perform the task only with one pair of LEDs, either in near (1) or in far (2) space. The task-relevant pair is considered as the visual targets and illustrated by the white circles with a slight yellow halo. Nociceptive stimuli are illustrated by the red flashes and, depending on the trial, they are either applied unilaterally on the left or the right hand or bilaterally, on both hands simultaneously. A centrally-placed yellow LED, represented by the yellow circles, serves as fixation point. The lower part of the figure illustrates the averaged results of the 17 participants. Data from left-sided nociceptive cue conditions and right-sided nociceptive cue conditions were averaged into a unilateral cue condition. The upper part of the results section depicts the fitted logistic functions for the (1) unilateral and the (2) bilateral cue condition. For the unilateral cue condition (1), the x-axis represents different hypothetical stimulus onset asynchronies (SOAs) between the two visual stimuli: negative values indicate that the visual stimulus occurring in the cued side of space was presented first, while positive values indicate that the visual stimulus occurring in the uncued side of space was presented first. The y-axis represents the proportion of trials in which the participants perceived the visual stimulus presented in the cued side of space as occurring first. For the bilateral cue condition (2), negative SOA values on the x-axis indicate that the visual stimulus occurring in the left side of space was presented first, while positive values indicate that the visual stimulus occurring in the right side of space was presented first. The y-axis represents the proportion of trials in which the participants perceived the stimulus presented in the left side of space as occurring first. In both (1) and (2), blue curves represent the conditions in which visual stimuli were presented in near space, with the corresponding PSS values indicated by the blue vertical dashed lines. Red curves represent the conditions in which visual stimuli were presented in far space, with the corresponding PSS values indicated by the red vertical dashed lines. The arrows in (1) indicate the PSS values significantly different from zero. The curves in the unilateral cue condition are significantly shifted to the uncued side of space, indicating that visual stimuli presented in the uncued side of space had to be presented several ms before the stimuli presented in the cued side of space to have the chance to be perceived as occurring first equally often. There are no significant shifts to either side of space in the bilateral condition. The lower part of the results section illustrates the mean PSS and slope values, for both the unilateral (1) and the bilateral (2) cue condition. Significant differences are indicated with asterisks (\*  $p \leq .05$ , \*\*  $p \leq .01$ , \*\*\*  $p \leq .001$ ). PSS values were significantly different between visual TOJs performed in near vs. far space, but only in the unilateral cue condition (asterisks in the bar graphs illustrate the p-value of the contrast resulting from the significant interaction between cue condition and visual stimuli position factors).

#### 2.1.4. Measures

We consider two measures to assess the performance of the participants in the TOJ task: the point of subjective simultaneity (PSS) and the slope. More in detail, we estimated these measures as the  $\alpha$  and  $\beta$  parameters of a logistic function. The  $\alpha$  defines the threshold of the function, which, in our study, corresponds to the SOA at which the two visual stimuli are perceived as occurring first equally often (i.e. the 0.5 criterion on the ordinate). Accordingly, this measure corresponds to the PSS which is defined as the amount of time one stimulus has to precede or follow the other in order for the two stimuli to be perceived as occurring simultaneously (Spence et al., 2001). The  $\beta$  parameter defines the slope of the logistic function, which describes the noisiness of the results and can be related to the precision of participants' responses during the experiment (Kingdom & Prins, 2010). The slope of the psychometric function is often used to derive the just noticeable difference (JND) in typical TOJ experiments. In order to estimate the logistic function we used the adaptive PSI method (Kontsevich & Tyler, 1999), in which the psychometric curve and its parameters are estimated at each trial. This specific method adapts the experimental procedure and the presented SOA's according to the performance of the participant to all the previous trials. This method is based on an algorithm that adopts a Bayesian framework, with the ultimate goal to estimate the parameters of interest without probing extensively all the SOAs.

The average of the PSS values for left sided cues and the PSS values (multiplied by -1) for right sided cues was calculated to derive a unilateral cue condition for each participant and each experimental condition. For the unilateral cue conditions, the proportion of trials in which the visual stimulus presented in the cued side of space was reported as appearing first was plotted as a function of SOA. For the bilateral cue conditions, it was the proportion of trials in which the left visual stimulus was reported as appearing first that was plotted as a function of SOA.

#### 2.1.5. Data analysis

Before statistical analyses data from the two response modalities ('which is first' vs. 'which is second?') were merged to reduce potential response biases. First, simple t-tests were performed, comparing each PSS value to 0, with the aim to characterize potential shifts in TOJs to one side of space in the different experimental conditions. The differences between PSS and slope values across conditions were tested using an analysis of variance (ANOVA) for repeated measures with *cue condition* (unilateral vs. bilateral) and *visual stimuli position* (near space vs. far space) as within-participant factors. Greenhouse-Geisser corrections of degrees of freedom and contrast analyses were used when necessary. Significance level was set at  $p \leq .05$ . Effect sizes were measured using Cohen's  $d$  for t-tests or partial Eta squared for ANOVAs.

## **2.2. Experiment 2**

### **2.2.1. Participants**

Twenty-six volunteers took part in the experiment. Three participants were excluded before data analysis, one because of a technical problem and two because of difficulties in perceiving the nociceptive stimuli. The remaining 23 participants (17 women) had a mean age of  $24.1 \pm 4.46$  years (range: 18-33 years). Exclusion criteria were the same as in Experiment 1. According to the Flanders questionnaire, 21 participants were right-handed and two left-handed. The experimental procedure was approved by the local ethic committee in agreement with the latest version of the Declaration of Helsinki and was carried out in accordance with the corresponding guidelines and regulations. All participants signed a consent form prior to the experimental session. Participants received financial compensation for their participation.

### **2.2.2. Stimuli and apparatus**

Nociceptive stimuli were applied in the same manner than in Experiment 1. Stimulation intensities were also determined as in Experiment 1. All the participants described the sensation as pricking.

Visual stimuli were presented by means of the four same white LEDs as in Experiment 1 and a yellow LED served as fixation point.

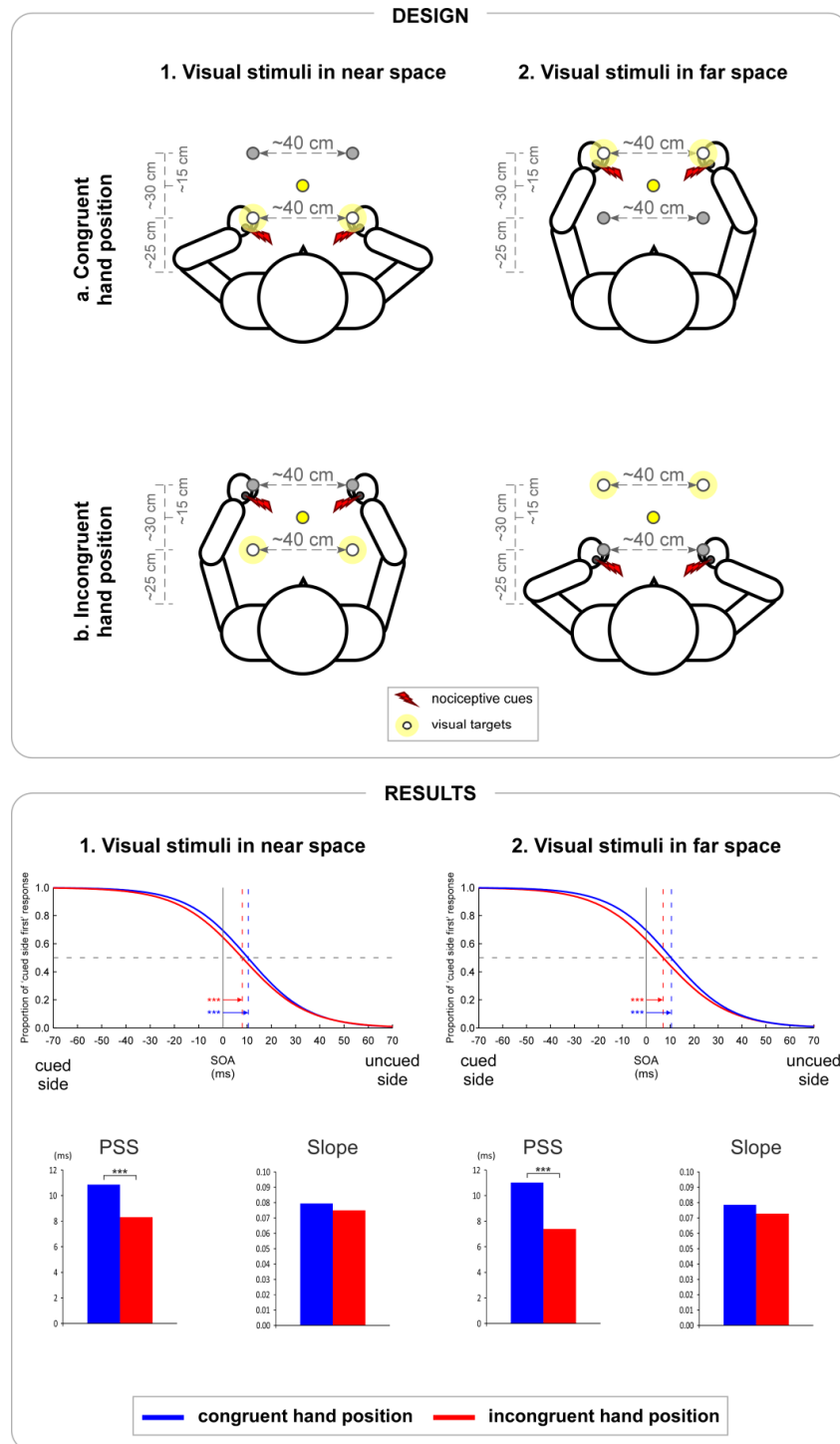
### **2.2.3. Procedure**

The experimental set-up and procedure were similar to Experiment 1. Participants were sitting in front of a table, their heads stabilized with a chin-rest and their hands placed on the table, palms down. The LEDs were fixated on the table. Two of the white LEDs were placed in near space,  $\sim 25$  cm from the trunk, and two LEDs in far space,  $\sim 30$  cm from the LEDs in near space. The distance between the left and right LED was  $\sim 40$  cm for stimuli in near space and stimuli in far space. The fixation LED was placed equidistantly from the LEDs in near and far space and equidistantly from the left and right LEDs, at a distance of  $\sim 40$  cm in front of the body midline. The participants placed their hands either next to the LEDs in near space, or next to the LEDs in far space (Fig 2, upper part), depending on the block. The left hand was always placed next to the left LED and the right hand next to the right LED.

A trial started with the illumination of the fixation LED. After 500 ms, a nociceptive stimulus was applied either unilaterally on the left or unilaterally on the right hand. As compared to Experiment 1, we did not use bilaterally applied nociceptive stimuli anymore, since we showed in previous studies and in Experiment 1 (see 3.1.2) that bilateral cues do not induce significant biases to any of the two sides of space. This allowed us to reduce the number of trials and therefore to double the number of conditions without

extending the duration of the experiment excessively. After 200 ms, the nociceptive stimulus was followed by a pair of visual stimuli of 5 ms duration each, either presented in near or in far space, depending on the block. Accordingly, the hands were placed in a position that was either congruent or incongruent to the position of the pair of visual stimuli on which the TOJ task was performed (congruent: visual stimuli in near space and hands next to LEDs in near space, visual stimuli in far space and hands next to the LEDs in far space; incongruent: visual stimuli in near space and hands next to LEDs in far space, visual stimuli in far space and hands next to the LEDs in near space) (Fig 2, upper part). Twenty possible SOAs were used between the two visual stimuli:  $\pm 200$ ,  $\pm 145$ ,  $\pm 90$ ,  $\pm 75$ ,  $\pm 60$ ,  $\pm 45$ ,  $\pm 30$ ,  $\pm 15$ ,  $\pm 10$ ,  $\pm 5$  ms (negative values indicate that the left LED was illuminated first). Since we used an adaptive method where only SOAs for which one might expect to gain the most information about the parameters of interest are presented (Kingdom & Prins, 2010), we decided to include more possible SOAs than in Experiment 1, to reduce the risk of errors due to inappropriately chosen SOA levels. Participants were instructed to keep their gaze at the fixation point during the whole trial. Depending on the block, they either reported which of the two visual stimuli they perceived as appearing first, or which of the stimuli they perceived as appearing second. No specific instruction regarding response speed and no feedback regarding the accuracy of the performance were given. Illumination of the fixation point was switched off as soon as the response was encoded by the experimenter and the next trial started 2000 ms later.

Do nociception and pain affect the perception of peripersonal space?



**Fig 2.** Design and results of Experiment 2. The upper part of the figure illustrates the experimental design. Visual stimuli are presented by means of two pairs of LEDs, one placed near and the other placed far from the trunk. The participants' hands are positioned either close to the LEDs in near space or close to the LEDs in far space. In each block, participants perform the task only with one pair of LEDs, either in near (1) or in far (2) space, and the position of the hands is either congruent (1a & 2a) or incongruent (1b & 2b) relative to the position of the visual stimuli. The task-relevant pair is considered as the visual targets and illustrated by the white circles with a slight yellow halo. Nociceptive stimuli are illustrated by the red flashes and, depending on the trial, they were applied unilaterally and randomly either on the left or the right hand. A centrally-placed yellow LED, represented by the yellow circles, serves as fixation point. The lower part of the figure illustrates the averaged results of the 23 participants. Data from left-sided cue conditions and right-sided cue conditions were averaged into a unilateral cue condition. The upper part of the results section depicts the fitted logistic functions for the (1) visual stimuli in near space and the (2) visual stimuli in far space condition. The x-axis represents different hypothetical stimulus onset asynchronies (SOAs) between the two visual stimuli: negative values indicate that the visual stimulus occurring in the cued side of space was presented first, while positive values indicate that the visual stimulus occurring in the uncued side of space was presented first. The y-axis represents the proportion of trials in which the participants perceived the visual stimulus presented in the cued side of space as occurring first. Blue curves represent the conditions in which the participants' hands were placed in a congruent position relative to the visual stimuli, with the corresponding PSS values indicated by the blue vertical dashed lines. Red curves represent the conditions in which the participants' hands were placed in an incongruent position relative to the visual stimuli, with the corresponding PSS values indicated by the red vertical dashed lines. The arrows indicate the PSS values significantly different from zero. In both (1) and (2) the curves are significantly shifted to the uncued side of space, indicating that visual stimuli presented in the uncued side of space had to be presented several ms before the stimuli presented in the cued side of space to have the chance to be perceived as occurring first equally often. The lower part of the figure illustrates the mean PSS and slope values, for both the visual stimuli in near space (1) and the visual stimuli in far space (2) condition. Significant differences are indicated with asterisks (\*  $p \leq .05$ , \*\*  $p \leq .01$ , \*\*\*  $p \leq .001$ ). PSS values were significantly different between visual TOJs performed in the congruent vs. incongruent conditions, for TOJs performed in both near and far space (asterisks in the bar graphs illustrate the p-value of the significant main effect of the hand congruency factor).

The experiment was composed of eight blocks resulting from the combination of the position of the visual stimuli (near space vs. far space), the congruency of the position of the hands relative to the visual stimuli (congruent vs. incongruent) and the response modalities ('which is first' vs. 'which is second'). The order of the blocks was randomized. Each block consisted of two series of 20 trials, one for each cueing condition: unilateral left vs. unilateral right. The trials of the two series were randomly and equiprobably intermixed. Within each of the series, the presented SOAs were chosen according to the adaptive PSI procedure (Kontsevich & Tyler, 1999), as explained for Experiment 1.

Levels of perceived intensity of the nociceptive stimuli were assessed after each block and the intensities adapted or the electrodes displaced and the threshold measurements restarted if necessary. A rest period between the blocks was possible when requested. Duration of the whole experiment was approximately 60 min.

#### 2.2.4. Measures

The measures were the same than for Experiment 1. PSS values for left sided cues and PSS values (multiplied by -1) for right sided cues were again averaged. The proportion of trials in which the visual stimulus presented in the cued side of space was reported as appearing first was plotted as a function of SOA.

#### 2.2.5. Data analysis

Analyses were similar to Experiment 1. Before statistical analyses data from the two responses ('Which stimulus appeared first' and 'Which stimulus appeared second?') were merged. Each PSS value was compared to 0 using simple t-tests. An ANOVA for repeated measures was performed with *visual stimuli position* (near space vs. far space) and *hand congruency* (congruent vs. incongruent) as within-participant factors, for both PSS and slope.

### 3. Results

#### 3.1. Experiment 1

##### 3.1.1. Intensity of nociceptive stimuli

The mean of the maximal intensities were  $0.35 \pm 0.08$  mA for nociceptive stimuli applied to the left hand and  $0.35 \pm 0.09$  for nociceptive stimuli applied to the right hand (no significant difference:  $t(16) = -0.39$ ,  $p = 0.97$ ). These intensities are in the range of values that have been shown to selectively activate skin nociceptors in previous studies (Mouraux et al., 2013; Mouraux et al., 2010; Mouraux et al., 2014).



### 3.1.2. PSS

Results of Experiment 1 are illustrated in the lower part of Fig 1. Simple t-tests showed that PSS values were significantly different from zero for the unilateral cue conditions, for both the near ( $t(16)=6.19$ ,  $p \leq 0.001$ ,  $d= 1.50$ ) and the far space ( $t(16)=3.46$ ,  $p= 0.003$ ,  $d= 0.84$ ). The visual stimuli appearing in the uncued side of space had thus to be presented significantly earlier than stimuli appearing in the cued side of space to have the chance to be perceived as occurring simultaneously. On the contrary, PSS values for the bilateral cue conditions were never significantly different from zero (all  $t(16) \leq 0.61$ ,  $p \geq 0.42$ ). These results suggest that unilateral cues can induce spatial biases.

The ANOVA showed a significant main effect of *cue condition* ( $F(1,16)=24.37$ ,  $p \leq 0.001$ ,  $\eta^2p= 0.60$ ) and a significant interaction between *cue condition* and *visual stimuli position* ( $F(1,16)=11.93$ ,  $p= 0.003$ ,  $\eta^2p= 0.43$ ). There was no significant main effect of the factor *visual stimuli position* ( $F(1,16)=0.84$ ,  $p= 0.37$ ,  $\eta^2p= 0.05$ ). Contrast analyses revealed that there was a significant difference between the near and the far visual stimuli position for the unilateral cue condition ( $F(1,16)=16.66$ ,  $p= 0.001$ ,  $\eta^2p= 0.51$ ), whereas such a difference was not significant for the bilateral cue condition ( $F(1,16)=1.61$ ,  $p= 0.22$ ,  $\eta^2p= 0.09$ ). This suggests that the spatial biases induced by unilateral nociceptive cues are significantly bigger when visual stimuli are presented in near space ( $M= 10.95$ ,  $SD= 7.29$ ) than when they are presented in far space ( $M= 5.34$ ,  $SD= 6.36$ ).

### 3.1.3. Slope

The ANOVA revealed a significant main effect of *cue condition* ( $F(1,16)=25.66$ ,  $p \leq 0.001$ ,  $\eta^2p= 0.62$ ). There was neither a significant main effect of *visual stimuli position* ( $F(1,16)=0.04$ ,  $p= 0.84$ ,  $\eta^2p= 0.04$ ) nor a significant *cue condition* x *visual stimuli position* interaction ( $F(1,16)=2.79$ ,  $p= 0.11$ ,  $\eta^2p= 0.15$ ). Slopes were in general steeper in the unilateral cue conditions than in the bilateral cue conditions, indicating that judgments were less noisy, i.e. less variable, when unilateral nociceptive cues were presented. This corroborates the PSS results reported in 3.1.2, since steeper slopes suggest that judgments were more systematically biased by unilateral cues and thus more precise than in the bilateral cue conditions.

## 3.2. Experiment 2

### 3.2.1. Intensity of nociceptive stimuli

The mean of the maximal intensities were  $0.31 \pm 0.08$  for the nociceptive stimuli applied to the left hand and  $0.30 \pm 0.1$  for nociceptive stimuli applied to the right hand (difference not significant:  $t(22)=0.63$ ,  $p= 0.53$ ).

### 3.2.2. PSS

Results of Experiment 2 are illustrated in the lower part of Fig 2. The PSS values of the four condition were all significantly different from zero (visual stimuli in near space, hands in congruent position :  $t(22)=5.96$ ,  $p \leq 0.001$ ,  $d= 1.24$ ; visual stimuli in near space, hands in incongruent position :  $t(22)=5.08$ ,  $p \leq 0.001$ ,  $d= 1.06$ ; visual stimuli in far space, hands in congruent position:  $t(22)=6.02$ ,  $p \leq 0.001$ ,  $d= 1.26$ ; visual stimuli in far space, in incongruent position:  $t(22)=5.52$ ,  $p \leq 0.001$ ,  $d= 1.15$ ). Judgments were biased to the advantage of visual stimuli presented in the same side of space than the nociceptive stimuli.

The ANOVA showed a significant main effect of *hand congruency* ( $F(1,22)=16.80$ ,  $p \leq 0.001$ ,  $\eta^2 p= 0.43$ ). Neither the main effect of *visual stimuli position* nor the interaction between *hand congruency* and *visual stimuli position* was significant (all  $F \leq 0.36$ ,  $p \geq 0.55$ ). These results suggest that the spatial biases induced by nociceptive lateralized cues were significantly more important when the hands were placed in a congruent position ( $M= 10.94$ ,  $SD= 8.33$ ) than when the hands were placed in an incongruent position ( $M= 7.85$ ,  $SD=6.64$ ) with regard to the visual stimuli.

### 3.2.3. Slope

The ANOVA revealed no significant main effects and no significant interaction (all  $F \leq 3.08$ ,  $p \geq 0.09$ ).

## 4. Discussion

The aim of the present studies was to demonstrate that the perception of visual space can be affected by somatosensory sensations felt on a limb occupying one particular location in space. Such crossmodal interactions are especially important when these somatosensory sensations indicate potential body damage and when the source of this potential damage has to be located in the external world. Concretely, by using TOJ tasks, we aimed at inducing biases in the perception of the visual stimuli elicited by nociceptive stimuli applied on one of the hands. Interpretation of performance during TOJ is based on the theory of prior entry (Titchener, 1908) according to which stimuli on which we focus our attention are perceived earlier than unattended ones. As a consequence, to get the chance to be perceived as appearing at the same time as the attended stimulus, the unattended stimulus has to be presented before the attended stimulus. In TOJ tasks, the time interval at which both stimuli are perceived as occurring first equally often (i.e. the PSS) can thus be used to index shifts in attention to one of the two stimuli. In our first TOJ experiment, participants judged the temporal order of pairs of lateralized visual stimuli, either presented near or far from the trunk, which were preceded by nociceptive stimuli applied either on one single hand, i.e. unilaterally or on both hands simultaneously, i.e.

bilaterally. The participants' hands were always placed next to the visual stimuli presented in near space. Results showed that the presence of unilateral nociceptive stimuli biased temporal order perception of the visual stimuli, with TOJs prioritizing the visual stimulus that was presented in the same side of space as the nociceptive stimuli. More precisely, visual stimuli presented in the uncued side of space had to be presented several ms before the visual stimuli presented in the cued side of space to have the chance to be perceived as occurring first equally often. When both hands were stimulated simultaneously with the nociceptive stimuli, no significant judgment biases to any of the two sides of space were observed, as attention was probably not shifted in one particular direction. Although biases were significant in the unilateral condition for visual stimuli presented in both near and far space, the magnitude of these biases was significantly larger when the visual stimuli were presented in near space than when they were presented farther away. In a second experiment, we tested whether this effect of the proximity between the nociceptive and visual stimuli was determined by the close distance of the visual stimuli to the hand on which the nociceptive stimuli were applied or rather by the general proximity to the body as a whole (i.e. the trunk). For this purpose we added conditions in which the participants' hands were also placed next to the visual stimuli in far space. Manipulating both the position of the visual stimuli and the position of the participants' hands allowed us to compare conditions in which the position of the hands was either congruent or incongruent with regard to the visual stimuli. The results revealed significant biases to the advantage of the visual stimuli presented in the same side of space as the stimulated hand in all conditions, but with a significantly larger effect when the hands were placed in a congruent position with regard to the visual stimuli. This suggests that the observed crossmodal effects between nociceptive and visual stimuli are rather related to the proximity of the visual stimuli to the hand on which the nociceptive stimuli are applied.

These findings further support the hypothesis that nociceptive and visual inputs are integrated to build a coherent multisensory representation of the body and the space immediately surrounding it (Haggard, Iannetti, & Longo, 2013; Legrain & Torta, 2015). Such multisensory representation would act as a coordinate system to code the spatial position of nociceptive stimuli on the body surface and the position of non-somatic, i.e. visual, stimuli immediately surrounding the body part on which the nociceptive stimuli are applied, that is, the body area potentially being damaged. Indeed, while interacting with proximal visual stimuli is of primary importance to optimize the manipulation of innocuous objects, it is even more important for optimizing defensive behaviors against potentially noxious objects (Graziano & Cooke, 2006; Legrain & Torta, 2015). Detecting physical threat is first of all a priority for survival, as illustrated, for instance, by individuals suffering from congenital analgesia, a condition characterized by an inability to feel pain, mainly due to a genetic mutation affecting voltage-gated sodium channels that are expressed in nociceptive neurons (see Cummins, Sheets, & Waxman, 2007; Nagasako, Oaklander, & Dworkin, 2003). Due to the absence of pain perception, these individuals are exposed to important body damages since they do not develop any sense of danger. It is

furthermore also important to monitor the space around the body to avoid stimuli that can induce pain, or, when a limb is already in pain, to avoid increasing the pain through the contact with external objects. This can be illustrated, for instance, by patients suffering from complex regional pain syndrome (CRPS), a chronic pain disorder predominantly characterized by sensory, trophic, motor and vegetative symptoms. Interestingly, deficits in perceiving and representing their own body, but also the visual external space have been reported in these patients (for a review see Legrain et al., 2012; Legrain & Torta, 2015). Moseley et al. (2009) for instance showed that the temporal order of pairs of tactile stimuli applied on the hands is judged to the disadvantage of tactile stimuli applied on the painful hand. When the hands were however crossed over the sagittal body-midline, patients' perceptual judgments were made to the disadvantage of the non-painful hand, now placed in the space previously occupied by the painful hand. TOJ performances of CRPS patients were thus not determined by the painful limb, but rather by the side of space in which that limb normally resides. These results suggest that pain can change other somatic sensations according to a personal reference frame that interacts also with proprioception, i.e. the relative position of the limbs in external space. Furthermore, there is evidence that extrapersonal space perception can also be affected in CRPS, as Sumitani, Shibata et al. (2007), for instance, showed that when CRPS patients judged the position of visual stimuli relative to their body midline, spatial perception was biased in favor of the side of space corresponding to the painful limb (see however Christophe et al., 2016; Reinersmann et al., 2012 for contrasting results). On the contrary, Filippopoulos et al. (2015) did not observe any visuospatial biases in CRPS patients, measured by saccade latencies towards lateralized visual stimuli on a screen. This would suggest that CRPS can affect the perception of visual space on condition that visual stimuli are processed according to a body reference. This hypothesis is even more corroborated by the results of a recent TOJ study, showing that in CRPS patients judging the temporal order of pairs of visual stimuli, spatial attention was significantly shifted towards the side of space corresponding to the non-painful hand, but only when visual stimuli were presented in the immediate vicinity of the hands (Filbrich, L., Alamia, A., Verfaillie, C., Berquin, A., Barbier, O., Libouton, X., Fraselle, V., Mouraux, D. & Legrain, V., submitted). These deficits in spatial perception observed in CRPS have been suggested to result from a maladaptive neuroplasticity consecutive to (implicit) behavioral strategies developed by the patients, aimed at avoiding an increase of pain of the pathological limb (e.g. Marinus et al., 2011). Finally, there are preliminary results suggesting that acting on visuospatial perception, for instance, by visual displacement with prismatic goggles combined with sensorimotor coordination, can reduce pain and other CRPS-related symptoms (Bultitude & Rafal, 2010; Christophe et al., 2016; Sumitani, Rossetti, et al., 2007) (for a review see Torta et al., 2016). Clarifying how nociceptive and visual inputs interact is therefore also of primary importance for the development of new rehabilitation techniques to reduce chronic pain.

Our results complement those observed by De Paepe and colleagues (De Paepe et al., 2015; De Paepe et al., 2014), who demonstrated in series of TOJ experiments that

nociception, like touch, is also likely to be integrated in a common, peripersonal, reference frame, by showing that visual inputs presented in the vicinity of the body can affect how we perceive nociceptive stimuli. Here we extend these results, by demonstrating that nociception, for its part, can also influence visual perception, suggesting that the way we perceive and represent our near visual surrounding is built on strict links with somatosensory, i.e. nociceptive perception.

Furthermore, we also showed that these crossmodal spatial interactions between nociception and vision rely on the close proximity between the visual stimulus and the hand on which the nociceptive stimulus is applied. Independently from the distance of the visual stimuli and the hands from the trunk, crossmodal influence was largest when visual stimuli were presented near the hands. This finding is in line with studies in the tactile modality suggesting the existence of spatial representations around specific body parts. Indeed, animal studies revealed the existence of bimodal neurons, for instance in the PMv, associating a tactile RF on a specific body part and a visual RF in the same spatial area, anchored to the tactile RF (e.g. Rizzolatti et al., 1981a; Rizzolatti et al., 1981b). Importantly, it has been shown that visual RF moves with the corresponding tactile one, independently of the gaze direction and eye movement, (e.g. Fogassi et al., 1996; Gentilucci et al., 1983; Graziano et al., 1997; Graziano et al., 1994). In humans, evidence comes from studies showing that crossmodal visual-tactile extinction depends on the proximity between the visual and the tactile stimuli, independently of the position of the visual stimuli with regard to the trunk or the retina. In other words, a tactile stimulus applied on a left limb can be extinguished by a visual stimulus presented in the contralateral space, but on condition that this visual stimulus occurs close to the homologous contralateral limb (e.g. Farné et al., 2005; Làdavas et al., 1998). In addition, recent neuroimaging studies in healthy participants showed increased blood-flow activity in premotor and parietal areas induced by a visual stimuli presented near the hand (e.g. Brozzoli et al., 2011; Makin et al., 2007). Similarly, a recent study showed that changing the hand posture during the application of mechanical nociceptive stimuli modulated the activity of the parietal cortex (Torta et al., 2013).

In conclusion, the present experiments further support the hypothesis that a nociceptive input can be integrated in the peripersonal representation of the limb on which the nociceptive stimulus is applied, in order to affect the perception of extra-somatic stimuli occurring in the space surrounding that limb.

Do nociception and pain affect the perception of peripersonal space?

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### Study 3

## ***Investigating the spatial characteristics of the crossmodal interaction between nociception and vision using gaze direction<sup>1</sup>***

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### **Abstract**

The mechanisms underlying crossmodal interaction between somatic and non-somatic stimuli have been suggested to rely on the ability to update the mapping coordinates from the initial anatomical reference frames of each sensory modality to an integrated mapping system using external space as main reference frame. This hypothesis was tested in the present experiments, investigating the influence of nociceptive stimuli on visual stimuli processing according to the relative spatial congruence between the location of the nociceptive stimuli (i.e. of the stimulated limb) and that of the visual stimuli. Participants performed temporal order judgments (TOJs) on pairs of visual stimuli. One visual stimulus of a pair was located close to one of the participants' hands on which nociceptive stimuli were occasionally applied. Across blocks, the other visual stimulus of the pair was presented either to the left or the right of the hand. Participants were instructed to direct their gaze between the two stimuli of the pair, that is, either to the left or the right of the hand. Using such a display, the nociceptive stimuli were always applied on the same hemibody, whereas the visual stimuli presented close to the stimulated hand were either seen in the left or the right visual hemifield. In other words, the anatomical alignment between the two respective receptive fields, i.e. somatotopic and retinotopic, could be either matching or mismatching. Despite the occasional mismatching of the anatomical alignment of the nociceptive and visual inputs, participants judgments were always biased in favor of the visual stimuli presented near the hand on which the nociceptive stimuli were applied. This indicates that crossmodal interaction between nociception and vision relies on a realignment of the initial modality-specific spatial reference frames according to an external, i.e. spatiotopic, frame of reference.

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<sup>1</sup> Based on: Filbrich, L., Halicka, M., Alamia, A., & Legrain, V. (in preparation). Investigating the spatial characteristics of the crossmodal interaction between nociception and vision using gaze direction.

Do nociception and pain affect the perception of peripersonal space?

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## Study 3

# ***Investigating the spatial characteristics of the crossmodal interaction between nociception and vision using gaze direction***

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### **1. Introduction**

The cognitive mechanisms, and their neuronal substrates, underlying crossmodal interaction between somatic and non-somatic stimuli have been largely investigated over the last decades (see e.g. di Pellegrino & Làdavas, 2015; Holmes & Spence, 2004; Macaluso & Maravita, 2010). For such crossmodal interactions between somatic and non-somatic stimuli to be possible, one needs to be able to coordinate and to integrate the representation and the perception of the space of the body and its surrounding space. Conceptualized by the notion of peripersonal reference frames (Rizzolatti et al., 1997), such integrated and multisensory representations are coordinate systems for the spatial coding of both somatic and extra-somatic (e.g. visual) stimuli occurring near the body. Such systems are thought to be used as interfaces to translate the perceptual characteristics of an object near the body into a motor schema to spatially guide actions toward that object, such as grasping and dexterous manipulation (Brozzoli et al., 2014). It has been furthermore hypothesized that such peripersonal representations could be used to the purpose of defensive actions against objects that threaten the physical integrity of the body (Cooke & Graziano, 2004; Graziano & Cooke, 2006). Supporting this latter hypothesis, recent studies in humans demonstrated a privileged interaction between visual stimuli occurring very close to the body, and nociceptive stimuli, that is, stimuli that selectively activate the nervous system specifically involved in coding and transmitting information about sensory events that have the potential to inflict body damage (see Legrain & Torta, 2015 for a review). Most of these studies used temporal order judgment (TOJ) tasks, which consist in presenting pairs of stimuli with various time delays between them, and participants have to report which of the two stimuli they perceived as having been presented first. In such tasks, the amount of time one stimulus has to follow or precede the other in order for the two stimuli to be perceived by the participant as occurring simultaneously is used as an index of attentional bias, and can be shifted to the advantage of one of the two stimuli (Spence & Parise, 2010). Indeed, according to the theory of prior entry (Titchener, 1908), paying attention to a stimulus speeds-up its processing as compared to a competing unattended stimulus. A first series of experiments in which pairs of nociceptive stimuli were used, one applied on each hand dorsum, showed that judgments about the occurrence of nociceptive stimuli was dependent of the relative position of the hands in external space (De Paepe et al., 2015; Sambo et al., 2013). When TOJ tasks were performed with the hands crossed

over the midsagittal plane of the body, judgments were much less accurate, as compared to conditions in which the task was performed with a normal, uncrossed hand posture. These results suggest that the ability of perceiving nociceptive stimuli is not only determined by the anatomical position of the stimuli on the body, but also relies on frames of reference that integrate the relative position of the stimulated limb in external space (see Smania & Aglioti, 1995). Similar effects have been reported for tactile stimuli (Shore et al., 2002; Yamamoto & Kitazawa, 2001). In further experiments, the nociceptive stimuli were preceded by a visual cue presented randomly in the same side of space as one of the hands (De Paepe et al., 2015; De Paepe et al., 2014). These studies showed that the occurrence of the visual stimulus biased judgments in favor of the perception of the nociceptive stimuli applied on the hand laying in the same side of space as the visual stimulus. The effects were shown to be stronger for the visual stimulus presented the closest to the stimulated hand (De Paepe et al., 2014), independently of the relative position of the hands and the visual stimuli according to the participant's trunk (De Paepe et al., 2015). In other words, the ability of a visual stimulus to impact the perception of a nociceptive stimulus depends on the proximity of the visual stimulus to the limb on which the nociceptive stimulus is applied and thus on the location of the stimulated hand in external space, irrespective of the fact which hand was stimulated according to an anatomical reference (De Paepe et al., 2015). Taken together, these studies suggest the existence of a peripersonal frame of reference for the localization of nociceptive stimuli, thus enabling close visual stimuli in external space to affect the perception of nociceptive stimuli applied on the body.

There are longstanding debates on the mechanisms underlying crossmodal interaction between somatic and proximal non-somatic stimuli (Macaluso, Frith, & Driver, 2001; McDonald, Teder-Sälejärvi, & Ward, 2001; Spence, McDonald, et al., 2004). One of the most popular theories postulates that such interactions rely on the existence of neurons able to respond to both somatic and non-somatic stimuli (see Graziano et al., 2004 for a review). More precisely, electrophysiological studies in monkeys have revealed, mostly in the ventral premotor cortex (PMv) and ventral intraparietal sulcus (VIP), the existence of neurons associating tactile and visual receptive fields (RFs). The particularity of these visual RFs is that they are mainly limited and anchored to the body parts which *host* their associated tactile RFs, thus following these limbs during their movements in space. In other words, the tactile and the visual RFs are aligned according to a frame of reference that takes into account external space, instead of their initial and respective anatomical frames of reference (i.e. somatotopic and retinotopic, respectively). Several studies have shown, for instance, that PMv neurons respond to both visual and tactile stimuli only when the position or the trajectory of the visual stimulus is spatially congruent with the limb on which it is anchored and thus with its associated tactile RF, irrespective of the posture of the body and the projection of the visual stimulus onto the retina (Fogassi et al., 1992; Fogassi et al., 1996; Gentilucci et al., 1983; Graziano et al., 1997; Graziano et al., 1994). Indeed, Graziano et al. (1997) have shown that visual stimuli were still able to activate such bimodal neurons even when the monkeys were trained to fixate their gaze at different

positions. Similar effects have been observed in neuroimaging studies performed in humans (see Macaluso & Maravita, 2010). For instance, Macaluso and colleagues investigated how cortical responses to a stimulus of one sensory modality can be influenced by the proximal occurrence of a stimulus of another sensory modality (Macaluso et al., 2000; Macaluso et al., 2002). In one of their studies, participants were asked to place one hand, on which tactile stimuli were applied, close to a visual stimulus, and, across conditions, to fixate their gaze either to the left or to the right of the visual stimulus (Macaluso et al., 2002). Using such a manipulation, the visual stimulus was alternately seen in different visual hemifields, while the tactile stimulus was always felt on the same hemibody. The occurrence of a tactile stimulus was shown to boost the cortical responses to the visual stimuli in the visual cortex contralateral to visual stimuli location, independently of the primary cortical projection of the tactile input to its contralateral hemisphere, and thus irrespective of the hemispheric correspondence between the visual and the tactile cortical projections (Macaluso et al., 2002).

The studies reviewed here above suggest that one of the mechanisms underlying crossmodal interaction between somatic and non-somatic stimuli relies on the ability to update the mapping coordinates from the initial anatomical reference frames of each sensory modality (i.e. somatotopic for somatosensory inputs and retinotopic for visual inputs) to an integrated mapping system using external space as main reference frame. They also suggest that such an updating takes into account the relative position of the limbs and the eyes, whatever the stimulated hemibody and hemifield. In the present study, we investigated whether nociceptive stimuli can influence the perception of visual stimuli, especially those presented close the limb on which the nociceptive stimuli are felt. This question is of particular importance when considering that it has been suggested that chronic pain states could change how patients perceive their visual environment (see e.g. Legrain et al., 2012). More specifically, we investigated whether such an interaction between nociceptive and visual stimuli depends on the relative spatial congruence between the location of the nociceptive stimuli (i.e. of the stimulated limb) and that of the visual stimuli, irrespective of their exact positions according to their respective sensory RFs. To this end, we manipulated the direction of the gaze so that visual stimuli and the body part on which nociceptive stimuli were applied could be seen in different areas of the visual field, while the cortical projections of the nociceptive inputs remained constant (as it was always the same limb that was stimulated). Participants performed TOJs on pairs of visual stimuli, one centrally positioned in front of the participant and one more laterally. One of the hands was placed close to the central visual stimulus, and nociceptive stimuli could occasionally be applied on that specific hand. Using such a setting, the central visual stimuli were therefore always the ones spatially congruent with the nociceptive stimuli. However, by changing gaze shift across the experimental blocks, central visual stimuli could either appear as left-sided stimuli (i.e. in the left visual hemifield) when participants' gaze was shifted toward the right side of space, or as right-sided stimuli (i.e. in the right hemifield) when gaze was shifted to the left side. We hypothesized that if nociception

influences vision based on their spatial correspondence in external space, nociceptive stimuli would bias visual TOJs in favor of the perception of the visual stimuli presented close to the stimulated hand, i.e., the centrally positioned visual stimuli, independently of left vs. right gaze direction. In other words, the visual hemifield (left vs. right) that would be prioritized by the occurrence of the nociceptive stimuli should be reversed as function of the change in gaze direction. Such a result would also corroborate the hypothesis that somatic, including nociceptive, and non-somatic stimuli are remapped from their respective initial frames of reference into a common frame that uses the space around the body as reference.

## **2. Methods**

### **2.1. Participants**

Twenty volunteers (14 women) took part in the experiment. The mean age was  $23.15 \pm 3.91$  years (range: 20-38 years). Exclusion criteria were non-corrected vision deficits, neurological, psychiatric, cardiac or chronic pain problems, regular use of psychotropic drugs, as well as a traumatic injury of the upper limbs within the six months preceding the experiment. Participants were asked to not use any analgesic substances (e.g. NSAIDs or paracetamol) within the 12 hours preceding the experiment and to sleep at least 6 hours the night before the experiment. According to the Flinders Handedness Survey (Flanders) (Nicholls et al., 2013), 18 participants were right-handed, one participant was left-handed and one participant ambidextrous. The experimental procedure was approved by the local ethic committee in agreement with the latest version of the Declaration of Helsinki and was carried out in accordance with the corresponding guidelines and regulations. All participants signed a consent form prior to the experimental session. Participants received financial compensation for their participation.

### **2.2. Stimuli and apparatus**

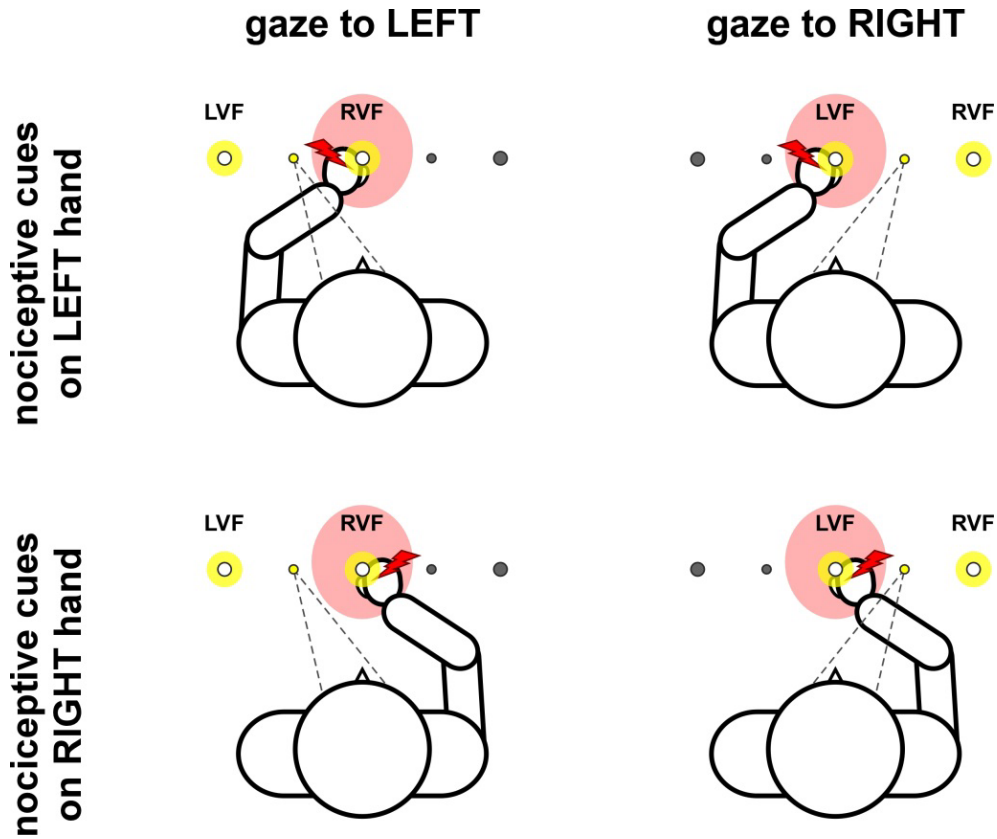
Intra-epidermal electrical stimulation (IES) (DS7 Stimulator, Digitimer Ltd, UK) was used to apply nociceptive stimuli on the hand dorsum with stainless steel concentric bipolar electrodes (Nihon Kohden, Japan; Inui et al., 2006). These electrodes consist of a needle cathode (length: 0.1 mm, Ø: 0.2 mm) surrounded by a cylindrical anode (Ø: 1.4 mm), and are gently pressed against the skin to insert the needle in the epidermis of the sensory territory of the superficial branch of radial nerve. Absolute detection thresholds to a single 0.5 ms square-wave pulse were determined using a staircase procedure (Churyukanov et al., 2012). The intensity of the electrical stimulation was then individually set to twice the absolute detection threshold to selectively activate nociceptors, with a limit of 0.5 mA (Mouraux et al., 2010). Using this specific procedure, IES has been shown to selectively activate A $\delta$  nociceptors without co-activation of A $\beta$  mechanoreceptors

(Mouraux et al., 2013; Mouraux et al., 2010; Mouraux et al., 2014). During the experiment, stimuli consisted of trains of three consecutive 0.5 ms square-wave pulses separated by a 5 ms interpulse interval, to increase intensity of perception while preserving the selectivity for nociceptors (Mouraux et al., 2013; Mouraux et al., 2014). Participants described the sensation as pricking but not necessarily as painful. Visual stimuli were presented by means of three white light emitting diodes (LEDs) with a 17 lm luminous flux, a 6.40 cd luminous intensity, and a 120° visual angle (GM5BW97330A, Sharp Corporation, Japan). They were perceived as brief flashes. Two yellow LEDs (min. 0.7 cd luminous intensity at 20 mA, 120° viewing angle) served as fixation points.

### **2.3. Procedure**

Participants were sitting in front of a table in a dimly-illuminated testing room. Their heads were stabilized with a chin-rest placed ~10 cm from the trunk, in order to minimize head movements. The three white LEDs were fixed on the table. One LED was placed centrally (centered on the chin rest), ~50 cm in front of the participants (central LED), one LED 40 cm to the left of the centrally placed LED (left LED), and one LED 40 cm to the right of the centrally placed LED (right LED). One yellow fixation LED was placed equidistantly between the left LED and the central LED (left fixation) and another one between the central LED and the right LED (right fixation). All the LEDs were aligned on a single line parallel to the edge of the table where the participants were seated. The participants placed one single hand (either the left or the right one, counterbalanced between participants), palm down, next to the central LED, with a maximum distance of 1 cm between the LED and the metacarpophalangeal joint of the index finger (see Fig. 1).

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**Fig. 1.** Experimental design of the experiment. Visual stimuli are presented by means of three white LEDs, one placed centrally in front of the participants and two other ones, one placed to the left and one placed to the right of the central LED. The task-relevant pair for each condition is represented by the white circles with a small yellow halo, and always consists in a visual stimulus seen in the left hemifield (LVF) and a visual stimulus seen in the right hemifield (RVF). Either the left or the right hand, counterbalanced between participants, is placed next to the central LED. Nociceptive cues are illustrated by the red flashes, and are occasionally applied on the centrally placed hand, shortly preceding the visual stimuli. Depending on the condition, participants either fixated their gaze, without moving their head, at a left or a right fixation point, which are both represented by the yellow circles. Accordingly, the potentially stimulated hand is either seen in the RVF or in the LVF, respectively. The LED expected to be prioritized during TOJs in the different conditions is encircled by the large rose halo.

Before each experimental block, participants were told whether to fixate their gaze at the left or the right fixation LED, so that the central LED and the hand on which nociceptive stimuli could be applied were seen either in the participants' right visual hemifield (RVF) in case of left fixation, or in their left visual hemifield (RVF) in case of right fixation. A trial started with the illumination of the fixation LED. After 500 ms, participants either received a nociceptive stimulus applied on the hand (cue condition) or no stimulation (no cue condition). Two hundred ms after the potential onset of the nociceptive stimulation, a pair of visual stimuli (the left LED and the central LED in case of left fixation or the central LED and the right LED in case of right fixation), both stimuli of 5 ms duration each, was presented. Twenty possible time intervals (SOAs, i.e. stimulus onset asynchronies) were used between the two visual stimuli:  $\pm 200$ ,  $\pm 145$ ,  $\pm 90$ ,  $\pm 75$ ,  $\pm 60$ ,  $\pm 45$ ,  $\pm 30$ ,  $\pm 15$ ,  $\pm 10$ ,  $\pm 5$  ms (negative values indicate that the LED in the LVF was illuminated first, positive values that the one in the RVF was illuminated first). Participants were instructed to keep their gaze at the fixation point during the whole trial. Depending on the block, they either reported verbally which of the two visual stimuli they perceived as appearing first, or they reported which visual stimulus they perceived as appearing second (by answering "left" or "right", corresponding to the LVF and the RVF, respectively). By using these two response modalities, genuine perceptual spatial biases can be dissociated from response and/or decision-related biases (see Filbrich et al., 2016; Shore et al., 2001; Spence & Parise, 2010 for a discussion). The participants didn't receive any specific instruction regarding response speed, as well as no feedback regarding the accuracy of their performance. Illumination of the fixation point was switched off as soon as the response was encoded by the experimenter and the next trial started 2000 ms later.

Participants started with a practice session of two blocks of 10 trials each (either two blocks of left fixation or two blocks of right fixation, one block per response modality) only with the two highest SOAs. The experimental session was composed of four blocks resulting from the combination of the gaze direction (left vs. right) and the response factors ('which is first' vs. 'which is second'). The order of the blocks was randomized. Each block consisted of two series of 30 trials, one for each nociceptive cueing condition (cue vs. no cue) presented in a random order. Within each of the series, the presented SOAs were determined online trial by trial according to the adaptive PSI procedure (Kontsevich & Tyler, 1999), i.e. based on participants' performance on all previous trials within one cueing condition (implemented through the Palamedes Toolbox, Prins & Kingdom, 2009).

Levels of perceived intensity of the nociceptive stimuli were assessed (on a scale from 0 to 10, with 0 = no sensation and 10 = very intense sensation) after each block, to ensure that they were still perceived. If this was not the case, the intensities were adapted, or the electrodes were displaced and the absolute threshold measurements restarted (see Favril et al., 2014 for details). A rest period between the blocks was possible when requested. Duration of the whole experiment was approximately 45 min.

## 2.4. Measures

We consider two measures to assess the performance of the participants in the TOJ task: the point of subjective simultaneity (PSS) and the slope, which were estimated as the  $\alpha$  and  $\beta$  parameters of a logistic function. The  $\alpha$  defines the threshold of the function, which, in our study, corresponds to the SOA at which the two visual stimuli are perceived as occurring first equally often (i.e. the 0.5 criterion on the ordinate). Accordingly, this measure corresponds to the PSS which is defined as the amount of time one stimulus has to precede or follow the other in order for the two stimuli to be perceived as occurring simultaneously (Spence et al., 2001). The  $\beta$  parameter defines the slope of the logistic function, which describes the noisiness of the results and can be related to the precision of participants' responses during the experiment (Kingdom & Prins, 2010). In order to estimate the logistic function we used the adaptive PSI method (Kontsevich & Tyler, 1999), in which the psychometric curve and its parameters are estimated at each trial. This specific method adapts the experimental procedure and the presented SOA's according to the performance of the participant in all the previous trials. This method is based on an algorithm that adopts a Bayesian framework, with the ultimate goal to estimate the parameters of interest without probing extensively all the SOA's.

For both left and right gaze direction conditions, the proportion of trials in which the visual stimulus presented in the LVF was reported as appearing first was plotted as a function of SOA.

## 2.5. Data analysis

Before statistical analyses data from the two response modalities ('which is first' vs. 'which is second?') were merged to reduce potential response biases. First, simple t-tests comparing each PSS value to 0 were performed, with the aim to characterize potential shifts in TOJs to one visual hemifield in the different experimental conditions. The differences between PSS and slope values across conditions were respectively tested using an analysis of variance (ANOVA) for repeated measures with *cue condition* (cue vs. no cue) and *gaze direction* (left vs. right) as within-participant factors, as well as *hand* (left vs. right) as between-participant factor. Greenhouse-Geisser corrections of degrees of freedom and contrast analyses were used when necessary. Significance level was set at  $p \leq .05$ . Effect sizes were measured using Cohen's d for t-tests or partial Eta squared for ANOVAs.



### 3. Results

#### 3.1. Intensity of nociceptive stimuli

The mean of the maximal intensities was  $0.30 \pm 0.09$  mA for nociceptive stimuli applied to the right hand and  $0.30 \pm 0.11$  for nociceptive stimuli applied to the right hand (no significant difference:  $t(18)=0.00$ ,  $p=1$ ). These intensities are in the range of values that have been shown to selectively activate skin nociceptors in previous studies (Mouraux et al., 2013; Mouraux et al., 2010; Mouraux et al., 2014).

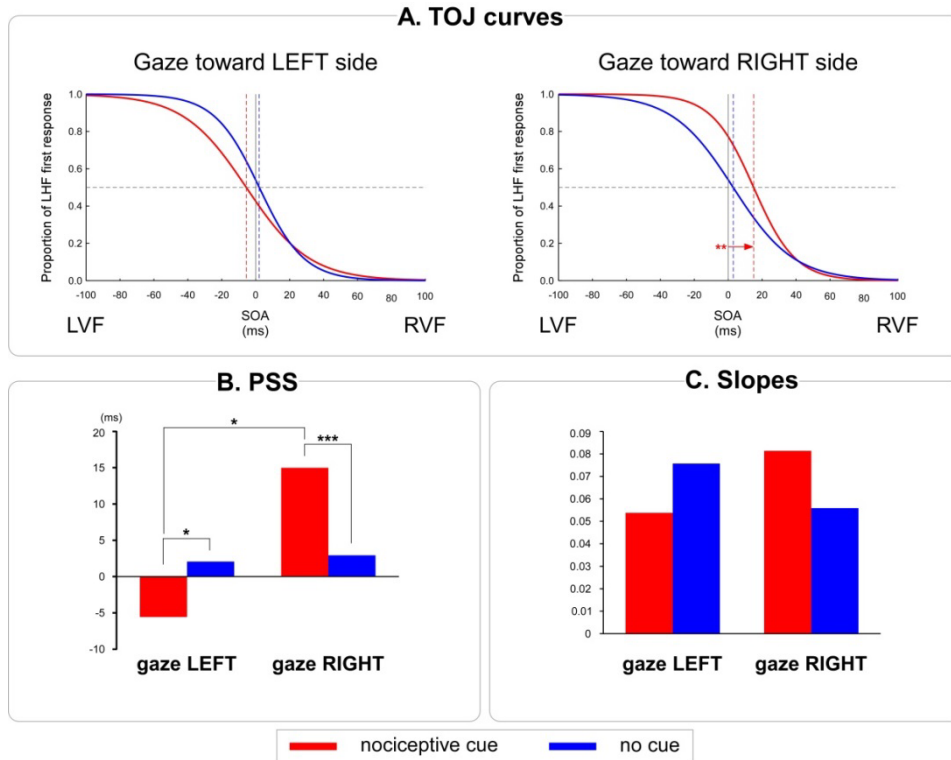
#### 3.2. PSS

Results are illustrated in Figure 2. In the conditions with nociceptive cue, simple t-tests showed that PSS values were positive ( $14.99 \pm 20.23$ ) and significantly different from zero ( $t(19)=3.31$ ,  $p=0.004$ ,  $d=0.74$ ) when gaze was directed to the right (and, therefore, central LED and hand in the LVF). However, when gaze was directed to the left (central LED and hand in RVF), PSS values tended to be more negative ( $-5.57 \pm 20.43$ ) but not significantly different from 0 ( $t(19)=-1.22$ ,  $p=0.283$ ). For the no-cue condition, neither PSS values for the left gaze direction nor for the right gaze direction were significantly different from zero (all  $t(19) \leq 0.81$ ,  $p \geq 0.43$ ). When gaze was directed to the right, visual stimuli appearing in the RVF (i.e. the uncued side of space) had thus to be presented significantly earlier than stimuli appearing in the LVF (i.e. cued side of space) to have the chance to be perceived as occurring simultaneously.

The ANOVA revealed a significant interaction between *cue condition* and *gaze direction* ( $F(1,18)=18.06$ ,  $p \leq 0.001$ ,  $\eta^2 p=0.50$ ). Contrast analyses showed that, during left fixation, the PSS value was significantly smaller in the cue than in the no cue condition ( $F(1,19)=5.62$ ,  $p=0.029$ ,  $\eta^2 p=0.23$ ). On the contrary, during right fixation, the PSS value was significantly larger in the cue than in the no cue condition ( $F(1,19)=18.13$ ,  $p \leq 0.001$ ,  $\eta^2 p=0.49$ ). In addition, the PSS values of the cue conditions were significantly different between left and right fixation conditions ( $F(1,19)=9.65$ ,  $p=0.006$ ,  $\eta^2 p=0.34$ ), whereas such a comparison revealed quite identical values in the no cue conditions ( $F(1,19)=0.02$ ,  $p=0.90$ ,  $\eta^2 p=0.00$ ). In the conditions during which nociceptive stimuli were applied on the hand, spatial biases changed direction according to gaze fixation: when the gaze was directed to the left, temporal order was judged to the advantage of stimuli in the RVF, whereas it was judged to the advantage of stimuli in the LVF when gaze was directed to the right. In other words, judgments were always biased to the advantage of the visual stimuli the closest to the hand on which the nociceptive stimuli were applied irrespective of the visual hemifield in which they were seen. The between-participant factor *hand* was also significant ( $F(1,18)=7.55$ ,  $p=0.013$ ,  $\eta^2 p=0.30$ ), suggesting that biases were larger when the left hand ( $M=10.30$ ,  $SD=23.05$ ) was placed next to the central LED than when the right hand ( $M=-3.09$ ,  $SD=15.90$ ) was placed there. None of the main effects and no interaction with the between-participant factor were significant (all  $F \leq 3.07$ ,  $p \geq 0.097$ ).

### 3.3. Slope

The ANOVA revealed a significant interaction between *cue condition* and *gaze direction* ( $F(1,18)=8.17$ ,  $p=0.010$ ,  $\eta^2p=0.31$ ). None of the main effects or any of the interaction with the between-participant factor *hand* were significant (all  $F \leq 1.96$ ,  $p \geq 0.178$ ). However, none of the contrasts we performed could explain the *cue x gaze direction* interaction (all  $F \leq 2.81$ ,  $p \geq 0.101$ ). This suggests that the precision of the participants' responses does not seem to be affected differently neither in the left vs. right fixation condition as a function of cue condition, nor in the cue vs. no cue conditions as a function of gaze direction.



**Figure 2.** Averaged results of the 20 participants. The upper part of the figure (A) depicts the fitted logistic functions for the left gaze direction and the right gaze direction conditions. The x-axis represents different hypothetical stimulus onset asynchronies (SOAs) between the two visual stimuli: negative values indicate that the visual stimulus in the left hemifield (LVF) was presented first, while positive values indicate that the visual stimulus in the right hemifield (RVF) was presented first. The y-axis represents the proportion of trials in which the participants perceived the visual stimulus in the LVF as occurring first. For both left gaze direction and right gaze direction conditions, blue curves represent the conditions in which no nociceptive cue was applied on the centrally placed hand, with the corresponding PSS values indicated by the blue vertical dashed lines. Red curves represent the conditions in which a nociceptive cue was applied on the hand, with the corresponding PSS values indicated by the red vertical dashed lines. The arrow in the left gaze direction condition indicates the PSS value significantly different from zero. In this condition, when a nociceptive cue was applied, curves are shifted to the RVF, indicating that visual stimuli presented in the RVF had to be presented several ms before the visual stimuli presented in the LVF (i.e. the one spatially congruent with the stimulated hand) to have the chance to be perceived as occurring first equally often. The lower parts of the figure illustrate the mean PSS (B) and slope (C) values, for both the left gaze direction and the right gaze direction conditions. Significant differences are indicated with asterisks (\*  $p \leq .05$ , \*\*  $p \leq .01$ , \*\*\*  $p \leq .001$ ).

#### **4. Discussion**

The aim of the present study was to investigate the effect of current gaze direction on nociceptive-visual crossmodal interactions, and more specifically on the influence of nociception on perceiving visual stimuli. Manipulating gaze direction while keeping the position of the head constant entails that in some trials spatially congruent nociceptive and visual stimulations occur in one visual hemifield, while in other trials such spatially congruent multimodal stimulations occur in the opposite hemifield, despite the fact that the physical positions of the visual stimuli and the hand on which the nociceptive stimulus were applied remained unchanged (see Macaluso et al., 2002 for a similar procedure with tactile stimuli). In the present study we aimed to demonstrate that the influence of nociception on visual perception is strongest when nociceptive and visual stimuli are congruent in external space, i.e. seen in the same hemifield, independently of the direction of gaze. This hypothesis was tested by using TOJ tasks. In the present experiment, shifts of the PSS in the perception of visual stimuli were aimed to be induced by nociceptive cues presented in one side of space. Participants judged the temporal order of pairs of lateralized visual stimuli. They fixated their gaze either to the left or the right without moving their head, and accordingly, performed the TOJ between a left-sided LED and a centrally placed LED in front of them or between the centrally placed LED and a right-sided LED (sides of space are defined according to their head). One of the participants' hands was positioned close to the centrally placed LED. Accordingly, a nociceptive stimulus applied on the hand, preceding the pairs of visual stimuli, was spatially congruent with the visual stimulus in the RVF when gaze was directed to the left, and congruent with the visual stimulus in the LVF when gaze was directed to the right. In half of the trials no nociceptive stimulus, i.e. cue, was applied on the centrally placed hand, with the aim to control for effects on visual perception due to the mere presence of a hand that could potentially attract attention to its position (e.g. Lloyd, Azanon, & Poliakoff, 2010; Reed, Grubb, & Steele, 2006) instead of the nociceptive cues. Results showed that for both gaze fixation conditions, biases were more important in the conditions with a nociceptive cue than in conditions without nociceptive cue, suggesting that a nociceptive stimulus can impact visual perception. Importantly, when a nociceptive cue was applied to the centrally placed hand, the direction of the bias changed according to the gaze fixation, showing that TOJ prioritized the perception of visual stimuli presented in the RVF when gaze was directed to the left (i.e. the stimulated hand is seen in the RVF), whereas TOJ prioritized the perception of visual stimuli presented in the LVF (i.e. the stimulated hand is seen in the LVF) when gaze was directed to the right. Thus, participants always prioritized the visual stimuli presented close to the stimulated hand, irrespective of the gaze direction.

It has to be noted however that, even if there was a significant difference in the biases between conditions with cue and conditions without cue for both left and right gaze conditions, biases to the advantage of visual stimuli presented close to the nociceptive stimulus in the cue conditions were only significantly different from zero when gaze was

directed to the right (i.e. when the stimulated hand was seen in the LVF). This could be explained by a slight *general* bias to the LVF that would even be present when spatial attention is not explicitly manipulated by the presence of nociceptive cues. Such systematic left-ward biases in visuospatial attention, termed *pseudoneglect*, are a well-described phenomenon in neurologically intact participants (see e.g. Bowers & Heilman, 1980; Brooks, Della Sala, & Darling, 2014; Jewell & McCourt, 2000; Voyer, Voyer, & Tramonte, 2012). Although the left-ward biases in the no cue condition were not significantly different from zero, one could still imagine a possible influence on the crossmodal effects. Such a *general* bias to the LVF could enhance biases to the advantage of the visual stimulus in the LVF, induced by the spatial correspondence of the nociceptive stimulus in the same hemifield, when gaze was directed to the right, while it could reduce biases to the advantage of the RVF, induced by the presence of the nociceptive stimulus in same hemifield, when gaze was directed to the left. Importantly however, we showed that a nociceptive stimulus seen in the RVF can induce biases to the advantage of visual stimuli in the RVF, thus counterbalancing the possible influence of a *general* bias to the LVF (by changing the direction of the bias). Thus, even if biases to the advantage of the visual stimuli presented close to the stimulated hand (in the RVF) when gaze was directed to the left were not significantly different from zero, this finding doesn't change the fact that we were able to demonstrate that the perception of a visual stimulus can be impacted by a nociceptive stimulus seen in the same hemifield, that is, when both stimuli are presented in the same location in external space.

It could also be argued that, in the conditions in which no nociceptive cue was applied on the hand, visuospatial biases could have been induced by the fact that participants could still have expected/anticipated the application of a nociceptive stimulus on the hand, since nociceptive stimuli were always applied on the same hand (for the same participant). Indeed, it has been suggested that anticipating pain at a particular body location could prioritize sensory input at that location (Vanden Bulcke, Crombez, Durnez, & Van Damme, 2015; Vanden Bulcke, Van Damme, Durnez, & Crombez, 2013). Since biases in the conditions without nociceptive cue were not significantly different from zero, the possibility of anticipating a nociceptive stimulus seems not to have contributed predominantly to the results, but a certain influence, e.g. by reducing the significance of the comparison between cue vs. no cue conditions, can however not be excluded.

An unexpected result was the main effect of the between-participant factor *hand*, showing that visuospatial biases were of larger magnitude when the nociceptive stimulus was applied to the left hand than when it was applied to the right hand. This factor did however not interact with the other manipulated variables of the experiment. Accordingly, the difference between biases induced by nociceptive stimuli applied on the left vs. right hand seemed not due to the main experimental manipulation in this study, i.e. gaze shift - possible interpretations of this effect should thus be considered within a larger framework and is beyond the scope of the present study.

The question raised in the present study, i.e. whether nociception influences visual perception based on their spatial correspondence in external space, can be considered in the more general context of studying the spatial nature of spatially specific crossmodal influences between stimuli of different sensory modalities. For instance, visual stimulus location is initially represented in retinal coordinates, whereas somatosensory (i.e. tactile or nociceptive) stimulation is initially represented in somatotopic coordinates. When the eyes move or arm posture is changed, the spatial alignment of these two representations will change relatively to each other (Macaluso & Maravita, 2010). In studies investigating crossmodal interactions between touch and vision, for instance, the spatial relation between tactile and visual stimuli is often fixed (see e.g. Macaluso et al., 2000), with a right tactile stimulation always occurring in the RVF or a left tactile stimulation always occurring in the LVF. In these studies, effects of spatial congruence on crossmodal visual-tactile influence could be due to bimodal stimulation of the same hemisphere or to the spatial alignment of tactile and visual stimuli in external space. The former case implies that irrespective of the position of the tactile and visual stimuli in external space, a tactile stimulus applied to the left hand, for instance, always interacts with visual stimuli presented in the LVF because both modalities activate the same hemisphere. The latter case implies that a tactile stimulus applied to the left arm can either interact with visual stimuli in the LVF or visual stimuli in the RVF, depending on the current position of the hand with regard to the retina, suggesting that, for instance, information regarding current posture is taken into account to update the mapping between spatial representations for different sensory modalities that initially use different coordinate systems (Macaluso et al., 2002). For the tactile modality, these two accounts of the spatial nature of spatially specific crossmodal interactions have been disentangled by manipulating the alignment of tactile and visual reference frames, i.e. by dissociating the position of the sensory inputs on the space of the sensory RFs (i.e. on the skin or the retina) from the position of the eliciting stimuli in external space, either by changing hand posture or gaze posture of participants without moving their head (Macaluso & Maravita, 2010). Several behavioral (e.g. Kennett et al., 2002), electrophysiological (Eimer, Cockburn, Smedley, & Driver, 2001; Kennett, Eimer, et al., 2001; Macaluso, Driver, van Velzen, & Eimer, 2005) and neuroimaging studies (Macaluso et al., 2002) demonstrated that crossmodal visual-tactile influence is rather dependent on the co-occurrence of both stimuli in external space rather than on the anatomical correspondence of the primary sensory projections in the cortex. Similarly for visual-nociceptive interactions, De Paepe et al. (2015) succeeded to demonstrate, by manipulating hand posture while keeping gaze constant, that visual stimuli affect the perception of nociceptive stimuli when both stimuli occur in the same external spatial position, irrespective of hand posture, suggesting that an initial somatotopic reference frame of the body space for the localization of nociceptive input is remapped into a spatiotopic reference frame, taking the relative position of body limbs in external space into account. Here, we extended these results, showing that, by using manipulation of gaze direction while keeping the position of the head constant, nociception, for its part, also influences visual perception based on their correspondence in external space. Combined with previous results showing that the way a

nociceptive stimulus affects visuospatial processing is related to the spatial congruency between the hand on which nociceptive stimuli were applied and the visual stimuli, independently of the relative distance of both the stimulated hand and the visual stimuli from the body considered as a whole, i.e. the trunk<sup>1</sup>, the present results could suggest that visual stimuli can be remapped according to their proximity to specific body parts into a peripersonal representation of external space.

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<sup>1</sup> Filbrich, L., Alamia, A., Blandiaux, S., Burns, S., & Legrain, V. (submitted). Shaping visual space perception through bodily sensations: testing the impact of nociceptive stimuli on visual perception in peripersonal space with temporal order judgments.

Do nociception and pain affect the perception of peripersonal space?

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## Study 4

### *Investigating peri-limb interaction between nociception and vision using spatial depth*<sup>1</sup>

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#### **Abstract**

In order to adapt behavior to a potentially body damaging threat, it is crucial to coordinate the perception of the location of the threat in external space and that of the location of the potential damage on the body surface. Such ability presupposes interactions between nociceptive stimuli and visual stimuli occurring close to the body. We hypothesized that these interactions would rely on the close proximity between the visual stimuli and the stimulated body part, with less influence of the distance of the visual stimuli from the body considered as a whole. In most studies investigating such interactions, spatial organization of the somatic and extra-somatic stimuli is made according to an egocentric frame of reference centered on the main axes of the participant's whole body, e.g. the midsagittal plane dissociating the left vs. the right side of space. Here, the contribution of the midsagittal plane reference was minimized, by placing participants' hands in front of them along their anteroposterior body axis, one at a proximal, the other at a distal location. They performed a temporal order judgment task on pairs of visual stimuli, one delivered close to each hand. Visual stimuli were preceded by nociceptive stimuli applied either on one hand, or on both hands simultaneously (control condition). Results showed that, as compared to the control condition, participants' judgements were biased in favor of the visual stimuli the closest to the stimulated hand, irrespective of their distance from the trunk. This finding supports the idea that the nociceptive-visual interactions depend on the proximity of the visual stimuli with regard to the stimulated hand rather than on a non-specific stimulation of the same hemispace which would be defined according to the anatomical axes of the whole body.

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<sup>1</sup> Based on: Vanderclausen, C.\*, Filbrich, L.\*, Alamia, A., & Legrain, V. (submitted). Investigating peri-limb interaction between nociception and vision using spatial depth. \*These two authors contributed equally as first authors to the present study.

Do nociception and pain affect the perception of peripersonal space?

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## **Study 4**

### ***Investigating peri-limb interaction between nociception and vision using spatial depth***

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#### **1. Introduction**

Monitoring the space of the body and the external space around the body is of primary importance to identify and react to stimuli that might inflict physical damage on the body. Such an ability is thought to rely on the existence of specific representations of the body, namely peripersonal representations, slightly extending their physical boundaries into external space in order to integrate somatic and non-somatic (e.g. visual) stimuli (Vallar & Maravita, 2009). Such multisensory peripersonal representations have been largely evidenced for the spatial perception of touch (di Pellegrino & Làdavas, 2015), and have also recently been shown to be involved in the processing of nociceptive stimuli (De Paepe et al., 2015, 2016; De Paepe et al., 2014; Sambo et al., 2013), that is, stimuli activating the neurophysiological system involved in transmitting inputs about potentially harmful sensory events to the cortical brain. Most of these studies used temporal order judgment (TOJ) tasks during which participants discriminate the temporal order of two stimuli presented in rapid temporal succession. These tasks are classically used to measure effects of selective attention, and are grounded on the theory of prior-entry according to which the processing of attended stimuli is speeded-up as compared to unattended ones (Spence & Parise, 2010). In these studies (De Paepe et al., 2015; De Paepe et al., 2014), pairs of nociceptive stimuli were presented to the participants, one on each hand, and they judged which of the two hands they perceived as having been stimulated first. Slightly before the nociceptive stimuli, a visual stimulus was presented in either the left or the right side of space, at different locations relative to the hands. It was shown that the participants' judgments were biased to the advantage of the perception of the nociceptive stimuli applied on the hand the closest to the visual stimulus, irrespective of the relative position of the hands and the visual stimuli in external space (De Paepe et al., 2015; De Paepe et al., 2014). Moreover, in a different set of experiments, it was shown that reactions to nociceptive stimuli were differently affected by visual stimuli approaching the stimulated hand as compared to those receding from it (De Paepe et al., 2016). These studies thus suggest that the perception of nociceptive stimuli depends on the vision of an object occurring in external space that might have an immediate impact on the body. However, investigating the reverse link, that is, how the perception of visual space can be influenced by bodily sensations, seems also ecologically, and, most notably, clinically relevant. Indeed, it has recently been shown that patients with unilateral chronic pain can be characterized by difficulties in representing and perceiving the affected limb (Legrain et al., 2012), and, in

addition, in perceiving visual stimuli presented in the side of space ipsilateral to the affected limb<sup>1</sup>. The aim of the present study was therefore to understand how a nociceptive stimulus applied to a specific limb could impact the perception of a visual stimulus occurring in the peripersonal space of that stimulated limb. The second aim was to disentangle whether nociceptive-visual interactions are mostly facilitated by the proximity between the visual stimuli and the hand on which the nociceptive stimuli are applied or by unspecific stimulation of the same hemispace such as for instance defined by the midsagittal plane splitting the body in two equal parts (i.e. the left and right side). In previous studies (De Paepe et al., 2015; De Paepe et al., 2014; Sambo et al., 2013), nociceptive-visual interactions were actually investigated using the main spatial organization of the body, dissociating the left and the right sides of space, which are always defined according to a global egocentric frame of reference, that is, the midsagittal plane of the participant's body (Vallar & Maravita, 2009). Indeed, although in these studies the largest significant effect was always observed for visual stimuli the most proximal to the hands, the results showed that nociceptive stimuli were in each case influenced by visual stimuli presented ipsilaterally to the stimulated hemibody, even those presented more distally from the hands. Here, in order to minimize a confusing contribution of the main anatomical axes of the body and to investigate the specific contribution of the spatial congruence between the visual stimuli and the stimulated hand, we avoided the classic left-right dimension usually used in TOJ tasks. Indeed, visual stimuli and the stimulated hands were not aligned anymore according to the left vs. right side of space, but along the midsagittal plane of the body. Therefore, the perception of visual space was not manipulated anymore according to the left vs. right side of space, but according to the depth along the anteroposterior axis of the body. Similarly, although nociceptive stimuli were still applied to the two opposite hemibodies, the left and right hands were placed *proximally* vs. *distally* from the participants' trunk. Concretely, participants were asked to perform a TOJ task on pairs of visual stimuli, one occurring close to (i.e. at a proximal location), the other one far from (i.e. at a distal location) the participants' body while one hand was placed close to each visual stimulus. Nociceptive stimuli were applied on one of the two hands. We hypothesized that participants would prioritize the perception of the visual stimuli occurring close to the stimulated hand, regardless of which hand was stimulated and of the distance of the visual stimuli and the participants' hands from the body.

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<sup>1</sup> Filbrich, L., Alamia, A., Verfaillie, C., Berquin, A., Barbier, O., Libouton, X., Fraselle, V., Mouraux, D. & Legrain, V. (submitted). Does Complex Regional Pain Syndrome impair the perception of body space and extra-body space?

## **2. Methods**

### **2.1. Participants**

Sixteen paid participants volunteered to take part in the study (mean age:  $21.87 \pm 3.42$ , range: 18-32 years, 13 women), with no prior history of neurological, psychiatric, heart and chronic pain disorders, no trauma of the upper limbs in the previous six months and no regular drug intake, including painkillers and anti-inflammatory within the 12 hours before the experiment. All of them had normal to corrected-to-normal vision and slept at least 6 hours the night preceding the experiment. According to the Flinders Handedness Survey (Nicholls et al., 2013), 14 participants were right-handed. Written informed consents were obtained and all experimental procedures were approved by the local ethics committee in agreement with the latest version of the Declaration of Helsinki.

### **2.2. Stimuli and apparatus**

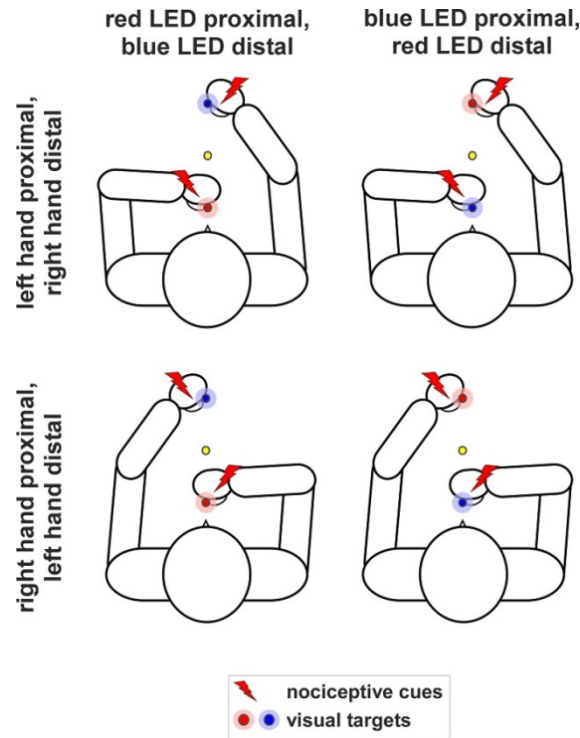
Visual stimuli were presented by means of two light-emitting diodes (LEDs), a red (625nm wavelength at 20mA, 756mcd luminous intensity, 120° viewing angle) and a blue (465nm wavelength at 20mA, 370mcd luminous intensity, 120° viewing angle) one (Multicomp, Farnell element14, Leeds, UK). A third yellow LED (591nm wavelength, 700mcd luminous intensity at 20mA, 120° viewing angle) was used as fixation point during the task. During the experiment, the red and blue LEDs were illuminated with a 5 ms duration and were perceived by the participants as brief flashes. Their colors were clearly discriminated by all participants. One of the two experimental LEDs was placed ~32 cm from the edge of a table in front of the participant (proximal location), the other one at a distance of ~60 cm (distal location), both on a straight line perpendicular to the table's edge. The order in which red and blue LEDs were placed either at the proximal or the distal location was counterbalanced across participants. The yellow fixation LED was placed equidistantly from the red and blue LEDs on the same line.

Nociceptive stimuli were applied on the hands' dorsa by means of intra-epidermal electrical stimulations (IES) using stainless steel concentric bipolar needle electrodes (Nihon Kohden, Tokyo, Japan) (Inui et al., 2006). The needle cathode was of 0.1mm in length and 0.2 mm in diameter and was surrounded by a cylindrical anode of 1.4 mm in diameter. By gently pressing the electrode against the skin, the needle cathode was inserted into the epidermis in the sensory territory of the superficial branch of the radial nerve. The absolute detection thresholds of the IES to a single 0.5 ms square-wave pulse were established for each hand separately using a staircase procedure (Churyukanov et al., 2012). Once they were determined, the threshold values were doubled. Using IES based on such a procedure has been shown to specifically and selectively activate skin nociceptors (Mouraux et al., 2010). IES intensities were adjusted if necessary so that they were perceived as equally intense between the two hands, but intensities were always set at values less than 0.5 mA (Favril et al., 2014). During the experiment, nociceptive stimuli

consisted of trains of 3 consecutive 0.5 ms IES pulses separated by an interpulse interval of 5 ms. Sensations were described by the participants as pricking. After each experimental block, participants were asked to rate the perceived intensity of the nociceptive stimuli on a scale ranging from 0 (=not perceived) to 10 (=very intense) by giving a verbal response, in order to ensure that the stimuli were still perceived and their intensities qualified as equivalent between the two hands. If this was not the case, stimulus intensities were adjusted before starting the next block, with 0.5 mA as a limit. If these criteria were still not met, the electrodes were displaced and the threshold measurement restarted (Favril et al., 2014). Stimuli presentation was remotely controlled using Matlab 2012.

### **2.3. Procedure**

The participants were sitting on a chair placed in front of a table in a dimly illuminated testing room. Their arms rested on the table and their head was placed in an individually adapted chin-rest to avoid head movements. Participants sat in a way that the three LEDs were positioned along their body's midsagittal plane, in front of them. After the threshold measurements, the participants were asked to place their hands on the table, palms down, one close to each of the target LEDs, so that the LEDs were placed between the thumb and the index finger of each hand. Hence, one of the hands was positioned proximally to the body trunk, whereas the other one was placed distally to it, according to the anteroposterior axis (i.e. in line with the body sagittal plane). The position of the hands were counterbalanced across participants, with half of the participants placing their left hand at the proximal location and the right hand at the distal location, and the other half of participants doing the reverse (see Figure 1).



**Fig. 1.** Illustration of the experimental set-up. Participants performed a temporal order judgment task on two colored LEDs, red and blue, placed equidistantly from a yellow fixation LED along the participants' anteroposterior body axis. Participants placed each hand close to one of the target LEDs, so that both the hands and the targets LEDs were positioned at a proximal vs. distal location. Slightly before the presentation of visual stimuli, nociceptive stimuli (represented by red flashes) were applied either on both hands simultaneously or on one single hand. The positions of the colored target LEDs and of the hands were counterbalanced across participants.

The participants were presented with one practice block of 10 trials, with only the two largest time intervals (i.e. SOAs, stimulus onset asynchronies, see below) between the two visual stimuli, and two experimental blocks of 90 trials each. One experimental block lasted about 8 min. A trial started with the illumination of the yellow fixation LED, which remained illuminated during the whole trial. The participants were asked to maintain their gaze on that LED. Five hundred ms after the fixation light onset, a nociceptive stimulus was applied either on one of the hands (*single cueing condition*) or on both hands at the same time (*simultaneous cueing condition*). In the single cueing condition, the nociceptive stimulus was applied either on the hand the closest to the trunk (i.e. the hand next to the

proximal visual stimuli) or on the hand the furthest from the trunk (i.e. the hand next to the distal visual stimuli). The three conditions, *single proximal cueing*, *single distal cueing* and *simultaneous cueing*, were equiprobably and randomly presented across trials. After 200 ms, the pair of visual stimuli was presented, one stimulus flashed close to each hand. The two visual stimuli were separated in time by twenty possible stimulus onset asynchronies (SOAs):  $\pm 200, \pm 145, \pm 90, \pm 75, \pm 60, \pm 45, \pm 30, \pm 15, \pm 10, \pm 5$  ms. Negative values indicate that the proximal visual stimulus was presented first, while positive values indicate that the distal visual stimuli were presented first. The presented SOAs were determined according to the adaptive PSI method, and selected trial by trial considering the performance of the participant in all the previous trials within one cueing condition (Kingdom & Prins, 2010; Kontsevich & Tyler, 1999). This method mainly aims to estimate the parameters of interest without probing extensively all the SOAs. The participants were instructed to not respond to the nociceptive stimuli but to verbally report the color of the visual stimulus that was perceived as being presented first (*'which color is first?'* condition) in one block and the color of the one that was perceived as being presented second (*'which color is second?'* condition) in the other block. These two different response conditions were used to prevent that any potential response bias could be mistaken for a perceptual spatial bias (Spence & Parise, 2010). The order of the two blocks was counterbalanced across participants. The participants' responses were encoded by the experimenter by pressing a key that switched off the fixation LED and triggered the next trial 2000 ms later. Participants were instructed to be as accurate as possible and that speed was not relevant for the task. The participants were not given any feedback regarding the accuracy of their responses. The whole experiment took on average 30 to 45 min.

## 2.4. Measures

Data were fitted online during the experiment with a logistic function from which the parameters of interest ( $\alpha$ , the threshold, and  $\beta$ , the slope) were derived. The parameter estimates correspond to the values of the last update computed by the function during the adaptive procedure (Kingdom & Prins, 2010; Kontsevich & Tyler, 1999). The first parameter is the  $\alpha$  of the logistic function, which corresponds to the point of subjective simultaneity (PSS) and refers to the SOA at which participants report the two events (i.e. the illumination of the proximal and the distal LEDs) as occurring first equally often (i.e. the 0.5 criterion on the ordinate). The PSS is thus the amount of time by which one stimulus has to precede or follow the other one in order to be perceived as occurring simultaneously (Spence et al., 2001). For each participant, the final PSS values for each cue condition (i.e., the *single proximal cueing*, the *single distal cueing* and the *simultaneous cueing*) correspond to the last PSS value estimated by the psychometric function. The slope of the function, i.e. the  $\beta$ , describes the noisiness of the participant's performance, and corresponds to the precision of the participant's responses during the experiment (Kingdom & Prins, 2010). For all cueing conditions, the proportion of proximal visual stimuli having been reported as perceived first was plotted as a function of SOA.



## 2.5. Data analysis

Preliminary statistical analyses did not reveal any significant effect or interaction of the response modalities (i.e. “*which color is first?*” vs. “*which color is second?*”), the posture of the hands (left vs. right hand at proximal vs. distal location) and the position of the colored target LEDs (red vs. blue color at proximal vs. distal location). Therefore, data from these conditions were merged and excluded from further analyses. Variables referring to the hands’ and LEDs’ position were coded according to the distance from the trunk (i.e. proximal vs. distal). Regarding the PSS, in order to test the presence of biases in the participants’ judgments, PSS values were compared to 0 by using t-tests. Next, to compare the different experimental conditions, a repeated measures analysis of variance (ANOVA) was performed on PSS and slope values with *cueing condition* (*single proximal* vs. *single distal* vs. *simultaneous*) as within-subject factor. Greenhouse-Geisser corrections and contrast analyses were used if necessary. Significance level was set at  $p \leq .05$ .

## 3. Results

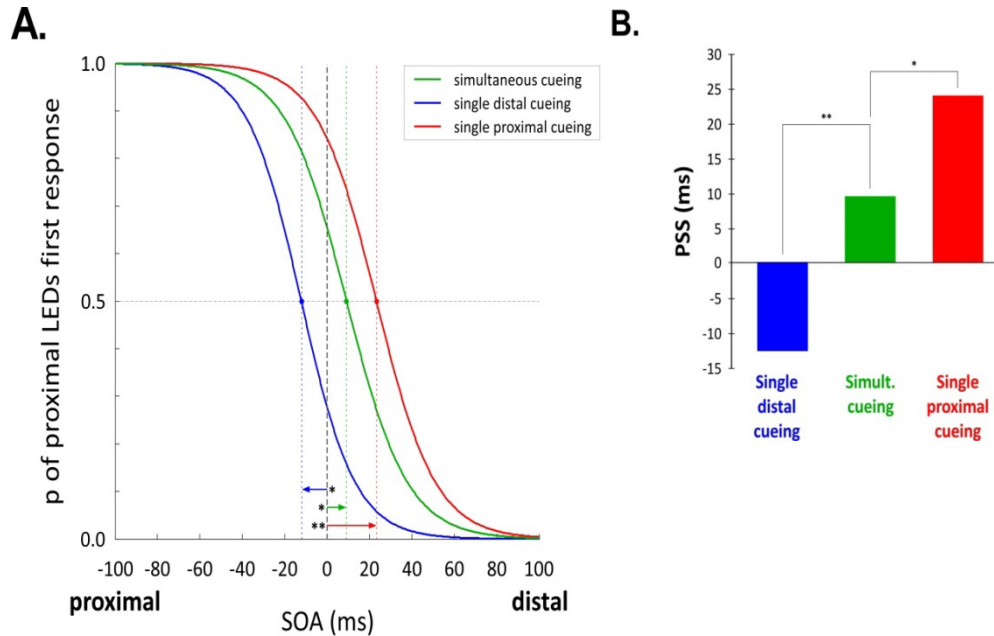
### 3.1. Intensity of nociceptive stimuli

The mean values of the maximal intensity of the nociceptive stimuli applied on the proximal hand and the distal hand were  $0.30 \pm 0.9$  mA and  $0.25 \pm 0.08$  mA, respectively. These values are in the range of those used in previous studies to activate selectively skin nociceptors without concomitant activation of mechanoreceptors (Favril et al., 2014; Mouraux et al., 2010). The self-reported intensities were on average  $4.94 \pm 1.78$  and  $5 \pm 1.81$  for proximal and distal hands, respectively. The mean value of the maximal intensity of the nociceptive stimuli applied to the proximal hand was significantly greater than the one applied to the distal hand ( $t(15)=2.66$ ,  $p=.018$ ). However, the self-reported intensities of the nociceptive stimuli applied on the proximal vs. the distal hands were not significantly different ( $Z=-0.82$ ,  $p=.414$ ).

### 3.2. PSS and slope

The fitted psychometric curves of the TOJ performances averaged across participants per condition are shown in Figure 2. The t-tests revealed that the PSS values from the *single proximal cueing* ( $M = 23.00 \pm 23.85$ ) and *simultaneous cueing* ( $M = 9.58 \pm 13.04$ ) conditions were significantly larger than 0 ( $t(15)=4.03$ ,  $p=.001$ ,  $t(15)=2.94$ ,  $p=.010$ , respectively), while the PSS value for the *single distal cueing* condition ( $M = -12.76 \pm 19.65$ ) was significantly smaller than 0 ( $t(15)=-2.60$ ,  $p=.020$ ). This indicates that judgments were biased in all three conditions, towards the visual stimuli presented close to the hand at a proximal location for the single proximal and simultaneous cueing conditions, and towards the visual stimuli presented close to the hand at a distal location in the single

distal cueing condition. The ANOVA performed on the PSS values revealed a significant main effect of the factor *cueing condition* ( $F(2,14)=15.59$ ,  $p=.001$ ,  $\eta^2p=.56$ ). Contrasts analyses showed that the PSS in the *single proximal cueing* condition was significantly larger than the PSS in the *simultaneous cueing* condition ( $t(15)=2.84$ ,  $p=.013$ ). The PSS in the *single distal cueing* condition was significantly smaller than the PSS in the *simultaneous cueing* condition ( $t(15)=-4.15$ ,  $p=.001$ ) (Figure 2). The ANOVA performed on the slopes did not reveal any significant effect of the factor *cueing condition* ( $F(2,14)=0.16$ ,  $p=.852$ ).



**Fig. 2.** Visual temporal order judgements (TOJs). (A) Fitted curves of the psychometric function from the data of the 16 participants according to the cueing conditions. The x-axis represents different possible SOAs. A negative value indicates that the proximal visual stimulus was flashed first and a positive value indicates that the distal visual stimulus was flashed first. The y-axis represents the proportion of trials in which the proximal visual stimulus was perceived as occurring first. The lines represent the fitted curves for the single distal cueing condition (blue), the simultaneous cueing condition (green), and the single proximal cueing condition (red), respectively. The 0.5 point of the y-axis represents the point at which the participants have equal chances to perceive the proximal and distal visual stimuli as being presented first. The respective points of subjective simultaneity (PSS) were obtained by deriving the x values of the points of the fitted curves with (x, 0.5) as coordinate. All the PSS values were significantly different from 0 (larger than 0 for the single proximal and simultaneous cueing conditions and smaller than 0 for single distal cueing condition), as indicated in the graph by means of the arrows (\*  $p \leq .05$ , \*\*  $p \leq .001$ ). (B) Mean values of the PSS for each cueing condition. The mean PSS value for the single proximal cueing condition (red) was significantly larger than the one for the simultaneous cueing condition (green). The mean PSS value for the single distal cueing condition (blue) was reversed with regard to that of the simultaneous cueing condition, indicating a significant change in bias direction (\*  $p \leq .05$ , \*\*  $p \leq .001$ ).

#### **4. Discussion**

This study aimed to investigate the ability to represent a spatial extension of the body space in order to prioritize the processing of external stimuli that might have an impending impact on the body's integrity. More specifically, we demonstrated that a nociceptive stimulus inflicted onto one hand impacts the perception of visual stimuli presented in the vicinity of the stimulated hand. The participants performed a TOJ task on two visual stimuli placed along the anteroposterior axis in front of them, at two different distances from the body, proximally vs. distally from it. One hand was placed next to each visual stimulus. This specific experimental setting allows investigating the effect of the peripersonal representation of the limb, i.e. the peri-limb representation, on crossmodal interaction between somatic and non-somatic stimuli, while minimizing the effect of the classic spatial dissociation into left vs. right sides of space. Opposing left and right sides of space often involves an egocentric frame of reference, which is defined by the main axes of the body such as the midsagittal plane, mainly represented by the body trunk. Therefore, by placing the hands and the visual stimuli along the anteroposterior axis in front of the participants, we limited the contribution of the main anatomical axes of the body in remapping the visual, i.e. extra-somatic, stimuli according to the spatial proximity of nociceptive, i.e. somatic, stimuli. Indeed, although nociceptive stimuli were still applied to the left vs. right hand according to an anatomical reference frame, their position in external space, the position of the visual stimuli, as well as the spatial congruence between the locations of the stimuli from both modalities, were completely independent of the classic lateral spatial organization, and rather defined in terms of spatial depth (i.e. proximal vs. distal). In addition, participants' responses in the task were given according to the color of the visual stimuli, and not their location, so that space was irrelevant for the response mode, avoiding any confounding effects of non-orthogonal response modalities (Spence & Parise, 2010). In a first condition, which served as a control condition, nociceptive stimuli were applied on both hands simultaneously, a few milliseconds before the visual targets. Attentional prioritization in TOJ tasks is usually highlighted by shifts in the PSS (Spence & Parise, 2010). We observed that PSS values in this control condition were shifted towards the visual stimulus at a distal location. Visual stimuli presented distally had thus to be presented about 10 ms before the ones presented proximally in order to be perceived as being stimulated first equally often. In other words, judgments were biased to the advantage of the proximal visual stimuli, suggesting that the perception of visual stimuli occurring close to the body received more attentional weight than those presented far from it. This supports the idea that we prioritize the processing of sensory events occurring close to our body because they might have a greater behavioral relevance due to their potential impending impact on the body. Many studies support the dissociation between the peripersonal frame of reference, coding the near space close to the body, and the extrapersonal frame of reference, coding the far out-of-reach space, which probably rely on different cortical networks (Vallar & Maravita, 2009). Paying more attention to sensory events arising near the body would optimize contacts and manipulation of innocuous

objects, but also defensive behaviors against noxious objects in order to protect the physical integrity of the body (Graziano & Cooke, 2006). However, the priority for proximal visual stimuli after simultaneous nociceptive stimulation could also be explained in terms of a difference between lower and upper visual hemifields. Indeed, our participants were asked to fixate their gaze right in the middle between the proximal and the distal visual stimuli, so that the proximal visual stimuli were presented in the lower hemifield, and distal visual stimuli in the upper hemifield. Experiments have demonstrated the dominance of the lower visual field in several aspects of visual perception, such as contrast sensitivity, visual acuity and spatial resolution (Intriligator & Cavanagh, 2001; Karim & Kojima, 2010). Nevertheless, the most striking result of the present study is that, as compared to the simultaneous cueing condition, in the single cueing conditions, the direction of the PSS and, consequently, of the perceptual bias, depended on the hand on which the nociceptive stimulus was applied (i.e. the one in proximal vs. distal location), independently of the stimulated hand according to the anatomical reference (i.e. left or right hand). When a nociceptive stimulus was applied on the hand proximal from the body trunk, visual PSS were shifted towards the distal visual stimuli, and PSS values were significantly larger than the ones obtained in the simultaneous cueing condition, although the direction of the bias was the same. Conversely, when the nociceptive stimulus was applied on the hand distal from the trunk, PSS values were completely reversed as compared to the PSS in the simultaneous cueing condition and were shifted towards proximal visual stimuli. In other words, applying a nociceptive stimulus on one hand facilitated the perception of visual stimuli presented in the close vicinity of the stimulated hand, irrespective of the distance of both the hand and the visual stimuli from the trunk. Our results support the existence of peripersonal representations that integrate somatic inputs, including nociceptive ones as previously suggested and non-somatic inputs such as visual stimuli, when these visual stimuli are presented close to the limb or approach it. Moreover, our results support the idea that peri-limb representations play a primary role in nociceptive-visual interactions, while minimizing the effects of non-specific influences due to the occurrence of both stimuli in the same hemispace as defined according to the main axes of the body as a whole. Such a conclusion is in line with similar studies investigating visual-tactile interactions. For instance, single-cell recordings in monkeys have revealed the existence of bimodal neurons, mainly in the ventral parts of the premotor (PMv) cortex and the intraparietal sulcus (VIP) (Duhamel et al., 1998; Graziano & Cooke, 2006; Graziano et al., 1997; Rizzolatti et al., 1981b). More specifically, some PMv neurons were found to associate both a tactile receptive field (RF) and a visual RF, with the particularity that the visual RF of these neurons is independent of the eye position, and is, instead, anchored to the tactile RF, moving with it during limb displacement. In humans, such peri-limb spatial representations have been studied, amongst others, in patients with cortical lesions who are characterized by an inability to report a stimulus presented in the side of space contralateral to the damaged cortical hemisphere, when presented simultaneously with a stimulus in the ipsilateral side. Indeed, in these patients, the perception of a touch applied on one limb was extinguished by a touch applied on the opposite limb, as well as by a visual stimulus, but

only if it was presented close to the opposite and homologous limb (Làdavas, 2002). In other words, patients' perceptual abilities were characterized by a pathologically unbalanced competition between spatial peripersonal representations of the two hemibodies, restricted to specific limbs.

Our results are also of clinical relevance for the understanding of cognitive biases observed in chronic pain, such as complex regional pain syndrome (CRPS). CRPS is an affection mainly characterized by pain, vegetative, motor and trophic symptoms in one limb. However, recent studies demonstrated a disrupted perception of tactile stimuli, which could not be explained by peripheral mechanisms, but rather by a distortion of body representation (Legrain et al., 2012). Very recent studies have furthermore shown, using similar visual TOJ tasks, that CRPS patients can also present perceptual biases affecting the perception of external visual stimuli, especially those presented close to the affected limb, suggesting that they “neglected” the side of space around the affected limb<sup>2</sup>. Moreover, preliminary studies suggest that manipulating visuospatial perception combined with visuomotor coordination could be used as an efficient rehabilitation technique to alleviate pain and other related symptoms in CRPS (Torta et al., 2016). Therefore, dissociating different spatial representations of the body, as well as investigating which of them could be affected by chronic pain, is also of primary importance in the context of the adaptation of cognitive rehabilitation techniques to treat chronic pain.

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<sup>2</sup> Filbrich, L., Alamia, A., Verfaille, C., Berquin, A., Barbier, O., Libouton, X., Frassel, V., Mouraux, D. & Legrain, V. (submitted). Does Complex Regional Pain Syndrome impair the perception of body space and extra-body space?

#### Study 4 : Peri-limb interaction between nociception and vision using spatial depth

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Do nociception and pain affect the perception of peripersonal space?

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**Part 2**  
**Peripersonal space perception in CRPS**

Do nociception and pain affect the perception of peripersonal space?

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## Study 5

### ***Does Complex Regional Pain Syndrome impair the perception of body space and extra-body space?<sup>1</sup>***

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#### **Abstract**

Complex regional pain syndrome (CRPS) is a chronic pain condition associating sensory, motor, trophic and autonomic symptoms in one limb. Cognitive difficulties have also been reported, affecting the patients' ability to mentally represent, perceive and use their affected limb. However, the nature of these deficits is still a matter of debate. Recent studies suggest that cognitive deficits are limited to body-related information and body perception, while not extending to external space. Here we challenge that statement, by using temporal order judgment (TOJ) tasks with tactile (i.e. body) or visual (i.e. extra-body) stimuli in patients with upper-limb CRPS. TOJ tasks allow characterizing cognitive biases to the advantage of one of the two sides of space. While the tactile TOJ tasks did not show any significant results, significant cognitive biases were observed in the visual TOJ tasks, affecting mostly the perception of visual stimuli occurring in the immediate vicinity of the affected limb. Our results clearly demonstrate the presence of visuospatial deficits in CRPS, corroborating the cortical contribution to the CRPS pathophysiology, and supporting the utility of developing rehabilitation techniques modifying visuospatial abilities to treat chronic pain.

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<sup>1</sup> Based on: Filbrich, L., Alamia, A., Verfaillie, C., Berquin, A., Barbier, O., Libouton, X., Fraselle, V., Mouraux, D. & Legrain, V. (submitted). Does Complex Regional Pain Syndrome impair the perception of body space and extra-body space?

Do nociception and pain affect the perception of peripersonal space?

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## **Study 5**

### ***Does Complex Regional Pain Syndrome impair the perception of body space and extra-body space?***

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#### **1. Introduction**

Complex regional pain syndrome (CRPS) is a chronic pain condition associating sensory, motor, trophic and autonomic symptoms in one limb (for a review see e.g. Marinus et al., 2011). The pathophysiology of CRPS is complex and difficult to understand as it can involve different mechanisms such as neurogenic inflammation, vasomotor dysfunction as well as structural and functional changes at the cortical level (Juottonen et al., 2002; Krause et al., 2006; Maihofner et al., 2007; Maihofner et al., 2003, 2004; Pleger et al., 2014; Pleger et al., 2006; Pleger et al., 2005; Pleger et al., 2004). Probably as a consequence of these cortical changes, unilateral cognitive symptoms have also been described in CRPS, affecting the patients' abilities to represent, use and perceive their affected limb (see e.g. Legrain et al., 2012; Legrain & Torta, 2015 ; Reinersmann et al., 2013 for a review). Although there is no clear definition for the concept of body representation, as it encompasses different notions which are often used in different manners and sometimes with opposite meanings by different authors (Berlucchi & Aglioti, 2010), disturbances in mentally representing their affected limb have been increasingly recognized as being part of the symptomatology in an important subset of CRPS patients (Reinersmann et al., 2013). For instance, patients regularly report feelings of disownership over the affected limb (Forderreuther et al., 2004; Galer et al., 1995; Galer & Jensen, 1999; Lewis et al., 2007), as well as distortions in representing its size, shape (Lewis et al., 2007; Moseley, 2005; Peltz et al., 2011) and position (Lewis et al., 2010). Furthermore, altered laterality recognition for the affected limb has been repeatedly demonstrated (Moseley, 2004; Reid et al., 2016; Reinersmann et al., 2010; Schwoebel et al., 2001). At the motor level, patients described struggling in order to voluntarily move their limb, with movements that are difficult to initiate (hypokinesia) and slower (bradykinesia) (Galer et al., 1995; Galer & Jensen, 1999; Lewis et al., 2007). Because there are similarities of the aforementioned symptoms with those reported in hemispatial neglect, the cognitive symptoms observed in CRPS have often been considered as "neglect-like" symptoms (Galer et al., 1995; Galer & Jensen, 1999; however, see Legrain et al., 2012; Punt et al., 2013 for discussion). Hemispatial neglect is a cognitive disorder consecutive to lesions in one cortical hemisphere, characterized by an inability to orient to, explore and report sensory events from the side of space contralateral to the damaged hemisphere, which cannot be attributed to peripheral sensory or motor loss (Driver & Vuilleumier, 2001; Heilman & Valenstein, 1979; Vallar, 1998). Despite the fact the hemispatial neglect can affect different sensory modalities, as well as representational

(e.g. Bisiach & Luzzatti, 1978; Salvato et al., 2014) and motor processing (e.g. Coulthard et al., 2006; Husain et al., 2000), patients' symptoms are often, if not almost exclusively, characterized by tests investigating their perceptual abilities in the visuospatial domain, that is, their abilities to perceive and locate stimuli in extra-body space (Brozzoli et al., 2006; Hach & Schutz-Bosbach, 2014; Jacobs et al., 2012). However, neuropsychological tests classically used to investigate disrupted visuospatial perception were generally not able to highlight the presence of neglect symptoms in CRPS patients (Christophe et al., 2016; Forderreuther et al., 2004; Kolb et al., 2012; Reid et al., 2016; Reinersmann et al., 2012). There are some perceptual difficulties in CRPS that have been reported for the tactile modality, such as decreased tactile acuity of the affected limb (Lewis & Schweinhardt, 2012; Peltz et al., 2011), and referred sensations between stimulated body parts (Maihofner et al., 2006; McCabe, Haigh, Halligan, et al., 2003), but it is difficult to disentangle the cortical from the peripheral origins of these unilateral tactile perceptual symptoms. For these reasons, the "neglect-like" nature of the cognitive symptomatology in CRPS was called into question. Punt et al. (2013), for example, argued that the perceptual difficulties of CRPS patients only emerged from specific laboratory-based measures, suggesting that they might not be clinically relevant. However, some clinical trials successfully alleviated CRPS pain and other related symptoms by using cognitive rehabilitation techniques based on visual perception and visuomotor coordination manipulation (Bultitude & Rafal, 2010; Christophe et al., 2016; McCabe, Haigh, Ring, et al., 2003; Sumitani, Rossetti, et al., 2007). It could thus be counter-argued that cognitive testing instruments classically used to diagnose hemispatial neglect after hemispheric damage are not sensitive enough to clearly characterize spatial perception deficits in CRPS (Legrain et al., 2012; Legrain & Torta, 2015). Furthermore, Moseley et al. (2009) and Moseley, Gallace, and Iannetti (2012) succeeded to demonstrate, using a TOJ task, that some tactile perceptual deficits observed in CRPS can obviously be attributed to neuro-cognitive deficits affecting spatial perception. TOJ tasks consist in discriminating the temporal order of two sensory events presented in a rapid temporal succession. Concretely, pairs of stimuli are presented with various delays between them, and participants have to report which of the two stimuli was perceived as presented first. One important parameter of the participants' performance is the *point of subjective simultaneity* (PSS) and corresponds to the delay between the two stimuli at which the two stimuli have an equal chance to be perceived as being presented first. Significant changes in the PSS can be related to a shift in judgment toward one of the two stimuli, and allow characterizing cognitive biases to the advantage of the perception of one of the two stimuli. Moseley et al. (2009) applied pairs of tactile stimuli, one on either hand, and showed that CRPS patients' perceptual judgments were biased to the detriment of the stimulation on the affected hand. However, this was only observed when the patients' hands were in a normal, i.e. uncrossed posture. When patients were asked to cross their hands over their body midline, perceptual judgements were biased to the detriment of the unaffected hand, as if the patients' performance did not rely on the actual stimulation of the affected hand, but rather on the side of space in which the affected hand normally resides. These results clearly show that somatosensory perceptual difficulties in CRPS, as illustrated

by TOJ tasks, cannot be attributed to altered peripheral coding or spinal transmission of somatosensory inputs, but rather to deficits in their cognitive processing. In a recent study, Reid et al. (2016) replicated these results in the tactile modality, but also showed, with the same TOJ task, that spatial perception of auditory stimuli, i.e. stimuli occurring outside the body space, was not impaired. Auditory stimuli were delivered using speakers placed close to the patients' hands. The authors concluded that cognitive difficulties in CRPS are limited to the representation of body-related information and the perception of body space, and do not extend to the perception of external space. It can however be argued that the auditory modality is not the ideal modality to test lateralized perceptual difficulties in external space, since audition, conversely to touch and vision, is not primarily spatially coded. Indeed, because both ears are stimulated (especially with external speakers), sound localization is extracted from interaural intensity or time differences (Pickles, 2012). Importantly, presuming that CRPS-related perceptual deficits are limited to the somatosensory modalities would invalidate neuropsychological techniques that use visuospatial attention as a useful method to treat chronic pain.

The aims of the present studies were to replicate the results obtained with tactile TOJ as well as to test the hypothesis according to which perceptual deficits in CRPS patients can actually extend to external space, by using TOJ tasks with the presumably more indicated -visual- modality. In addition, we manipulated the distance of the visual stimuli from the patients' hands, as dissociations in perceiving the proximal and the more distal external space have been shown (see Vallar & Maravita, 2009 for a review).

## **2. Methods**

### **2.1. Participants**

Sixteen participants affected by upper-limb CRPS took part in this study (Table 1). Exclusion criteria were any neurological and severe psychiatric disorders, unresolved orthopedic injuries, as well as uncorrected vision difficulties. For the tactile task only, nerve damage (CRPS type II) or any medical condition disrupting somatosensory perception were also considered as exclusion criteria. Six participants were diagnosed according to the Budapest criteria for research, seven according to the clinical Budapest criteria (Harden et al., 2010) and three according to non-specified criteria by orthopedic surgeons based on clinical examination and bone scintigraphy. For the visual task, two participants were excluded because of visual impairments (one case of glaucoma and one of amblyopia). The mean age of the remaining 14 participants (10 women) was 49 years ( $SD = 9$ , range: 37-65 years). Half of them presented with a left-side CRPS. All but one of the participants were right-handed according to the Flinders Handedness Survey (Flanders) (Nicholls et al., 2013). For the tactile task, four participants were excluded, one participant because of nerve damage associated with the CRPS and three participants based on their poor performance

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(see Measures section for details). The remaining 12 participants (nine women) had a mean age of 50 years ( $SD = 9$ , range: 37-65 years), six of them presenting with a CRPS of the left side. Eleven participants were right-handed and one was ambidextrous according to the Flanders questionnaire. The experimental procedure was approved by the local ethic committee in agreement with the latest version of the Declaration of Helsinki, and all participants signed an informed consent form prior to the experimental session. Participants received financial compensation for their participation.



Study 5 : Does CRPS impair the perception of body space and extra-body space?

Table 1

Participant characteristics

| ID | Age/sex/<br>handedness | Inciting injury  | CRPS<br>limb | Diagnosis | Dur. | Current treatment/medication           | Other pain      | Other     | Task |
|----|------------------------|------------------|--------------|-----------|------|----------------------------------------|-----------------|-----------|------|
| 01 | 37/F/R                 | STI wrist        | L            | NS        | 15   | PT                                     | /               | /         | V,T  |
| 02 | 47/F/R                 | STI wrist        | L            | CRPS-R    | 32   | PT/OT/Amitriptyline                    | /               | Glaucoma  | T    |
| 03 | 44/M/R                 | Frac thumb       | L            | NS        | 5    | PT                                     | /               | /         | V,T  |
| 04 | 46/M/R                 | Frac-PS wrist    | R            | NS        | 3    | PT                                     | /               | /         | V,T  |
| 05 | 65/F/R                 | Frac-PS wrist    | L            | CRPS-C    | 6    | PT/Paracetamol,Ibuprofen               | /               | /         | V,T  |
| 06 | 52/F/R                 | STI cut nerve-PS | L            | CRPS-C II | 3    | PT/Paracetamol,Pregabalin              | /               | /         | V    |
| 07 | 49/M/R                 | Frac fingers     | R            | CRPS-C    | 2.5  | PT                                     | /               | /         | V,T  |
| 08 | 38/F/R                 | STI wrist        | R            | CRPS-C    | 6    | PT                                     | L hand, R ankle | /         | V,T  |
| 09 | 63/F/R                 | Frac-PS wrist    | R            | CRPS-C    | 7    | Ibuprofen                              | /               | /         | V,T  |
| 10 | 56/F/ambi              | Frac shoulder    | R            | CRPS-R    | 3    | PT/Amitriptyline,Tramadol              | L thumb         | Amblyopia | T    |
| 11 | 54/F/L                 | Frac wrist       | L            | CRPS-R    | 4    | PT                                     | R shoulder      | /         | V    |
| 12 | 38/M/R                 | Frac wrist       | R            | CRPS-R    | 9    | PT                                     | /               | /         | V    |
| 13 | 47/F/R                 | PS wrist         | R            | CRPS-C    | 18.5 | PT/OT/Pregabalin,Topiramate,Duloxetine | /               | /         | V    |
| 14 | 48/F/R                 | STI hand         | L            | CRPS-R    | 17   | PT/OT/Amitriptyline                    | /               | /         | V,T  |
| 15 | 61/F/R                 | Frac-PS wrist    | L            | CRPS-R    | 6    | PT/OT/Tramadol                         | L foot          | /         | V,T  |
| 16 | 54/F/R                 | PS hand          | R            | CRPS-C    | 10   | PT/OT/Tramadol                         | /               | /         | V,T  |

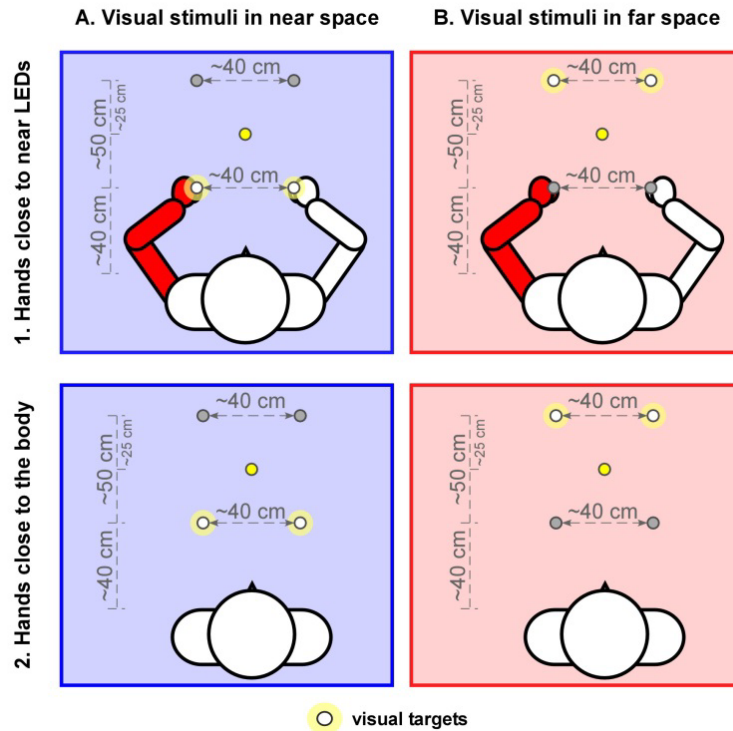
Note. Age in years; F= female; M= male; R= right; ambi= ambidextrous; L= left; STI= soft tissue injury; Frac= fracture; PS= post-surgery; NS= not specified; CRPS-R= Budapest research criteria for CRPS; CRPS-C= Budapest clinical criteria for CRPS; II= CRPS due to nerve injury; Dur.= duration since inciting injury in months; PT= physical therapy; OT= occupational therapy; V= participated in visual task; T= participated in tactile task.

## **2.2. Stimuli and apparatus**

Visual stimuli were presented by means of four white light emitting diodes (LEDs) with a 17-lm luminous flux, a 6.40-cd luminous intensity, and a 120° visual angle (GM5BW97330A, Sharp Corporation, Japan). They were illuminated for 5 ms and perceived as brief flashes. Participants were familiarized with the stimuli by reporting the position of the flashing LED (i.e. the left or the right one, close to the body or farther away). An additional yellow LED (min. 0.7 cd luminous intensity at 20mA, 120° viewing angle) was used as fixation point during the visual task (Multicomp, Farnell element14, UK).

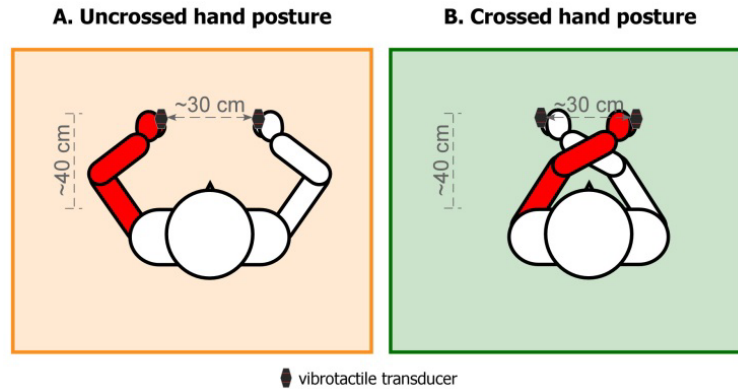
The LEDs were fixated on the surface of a table. Two of the white LEDs were placed ~40 cm away from the participant's trunk and with a distance of ~40 cm between them (visual stimuli in near space). The other two LEDs were positioned ~50 cm from the LEDs in near space, with a distance of ~40 cm between them (visual stimuli in far space). The yellow fixation LED was placed equidistantly from the four white LEDs at a distance of ~65cm in front of the participants' trunk (Fig. 1).

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**Fig. 1.** Illustration of the experimental set-up for the visual TOJ task. Visual stimuli are presented by means of two pairs of LEDs, one placed near and the other placed far from the trunk. The participants' hands are either positioned close to the LEDs in near space (1) or close to the body (2). In each block, participants performed the task only with one pair of LEDs, either in near (A, in blue) or in far (B, in red) space. The task-relevant pair is considered as the visual targets and illustrated by the white circles with a slight yellow halo. A centrally-placed yellow LED, represented by the yellow circles, serves as fixation point. The figure depicts a participant affected by left-sided CRPS.

Vibrotactile stimuli were generated by two vibrotactile transducers driven by standard audio amplifiers (TL-002-14R Haptuator Redesign, Tactile Labs, Inc., Montreal, Canada). Stimulus vibration were lasting 10 ms, at 440 Hz. Participants were familiarized with the stimulations and, if necessary, signal amplitude was adapted individually, in order to match the perceived sensation and intensity between the left and right hand stimuli. During the task, participants held a vibrotactile transducer between the thumb and the index fingers of each hand. The two transducers were held with a distance of ~30 cm between them, at a distance of ~40 cm from the trunk and without touching the table (Fig. 2).



**Fig. 2.** Illustration of the experimental set-up for the tactile TOJ task. Tactile stimuli are generated by two vibrotactile transducers held between the thumb and the index finger of each hand. The hands are either held in an uncrossed posture (A) or crossed over the sagittal body midline (B). Participants are blindfolded and presented with white noise. The figure depicts a participant affected by left-sided CRPS.

### 2.3. Procedure

General assessments and measures that were taken before the experimental session, as well as between the different experimental blocks, are reported in Supplementary materials. The two TOJ tasks were always administered during the same day (with a break of at least 30 min between them) and the order of presentation of the two tasks was counterbalanced across participants.

*Visual TOJ task.* Participants were sitting in a dimly-illuminated testing room, in front of the table with the LEDs. In half of the blocks their hands were placed on the table with palms down next to the LEDs in near space (i.e. the left hand placed next to the left LED and the right hand next to the right LED). Each of these two LEDs was positioned at a maximum distance of 1 cm from the metacarpophalangeal joint of the index finger. In the other half of the blocks, the participants held their hands in a comfortable position close to their body (Fig. 1). Their heads were stabilized with a chin-rest placed at approximately 10 cm from the trunk, in order to minimize head movement. A trial started with the illumination of the fixation point. After 500 ms a pair of visual stimuli appeared, one stimulus presented in either side of space. Depending on the block, the pair of stimuli was presented either in near or in far space. Twenty possible time intervals (SOAs for stimulus onset asynchronies) were used between the two visual stimuli of the pair:  $\pm 200$ ,  $\pm 145$ ,  $\pm 90$ ,  $\pm 75$ ,  $\pm 60$ ,  $\pm 45$ ,  $\pm 30$ ,  $\pm 15$ ,  $\pm 10$ ,  $\pm 5$  ms (negative values indicate that the left LED was

illuminated first). Participants were instructed to keep their gaze at the fixation point during the whole trial. In half of the blocks participants had to respond verbally which stimulus they perceived as occurring first, whereas they had to respond which stimulus was perceived as occurring second in the other half of the blocks (by answering '*left*' or '*right*'). These two response modalities were used to minimize response biases that can be confounded with genuine perceptual biases (for a discussion see Filbrich et al., 2016; Scharlau, 2004; Shore et al., 2001; Spence & Parise, 2010). No specific instruction was given regarding response speed. Illumination of the fixation point was switched off as soon as the participant's response was encoded by the experimenter. The next trial started 2000 ms later. No feedback regarding the accuracy of the participant's performance was given.

Participants started with a practice session of four blocks of 10 trials each, one block per condition (i.e., LEDs in near vs. far space, and '*which is first*' vs. '*which is second*' responses), but only with the two highest SOAs. The experimental session consisted of eight blocks, resulting from the combination of the factors *hand position* (close to near LEDs vs. close to the body), *visual stimuli position* (near space vs. far space) and *response modality* ('*which is first*' vs. '*which is second*'). The order of the blocks was counterbalanced for the two hand positions (half of the participants started the experiment with all the blocks *hands close to near LEDs*, the other half with all the blocks *hands close to the body*), and randomized for the visual stimuli positions and response modalities. Each block was composed of 40 trials and for each trial the presented SOA was determined online according to the adaptive PSI procedure (Kontsevich & Tyler, 1999), i.e. based on participants' performance on all previous trials (implemented through the Palamedes Toolbox, Prins & Kingdom, 2009). With this procedure the parameters of interest (see Measures) are estimated validly and reliably without probing extensively all the possible SOAs, and presented SOAs are adapted to each participant's own performance.

A rest period between the blocks was possible when requested. Duration of the visual TOJ experiment was ~60 min.

*Tactile TOJ task.* Participants were sitting in front of the same table and held a vibrotactile transducer between the thumb and the index finger of each hand. In half of the blocks their hands were in an uncrossed posture, while in the other half of the blocks they held their hands crossed over the sagittal body midline. For the crossed posture, all participants placed their affected arm over the unaffected arm, since the reverse was too painful for the majority of participants (Fig. 2). Participants' heads were placed in a chin-rest as for the visual TOJ experiment. To mask any sound produced by the vibrotactile stimulators, white noise was presented continuously through headphones. Participants were also blindfolded throughout the different blocks to avoid any visual distraction. On each trial two vibrotactile stimuli were presented, one on each hand. Twenty possible SOAs were used between the two stimuli:  $\pm 200, \pm 145, \pm 90, \pm 75, \pm 60, \pm 45, \pm 30, \pm 15, \pm 10, \pm 5$  ms (negative values indicate that the left hand was stimulated first). Participants had to respond verbally which hand they perceived as being stimulated first in half of the blocks,

whereas they had to respond which hand was perceived as being stimulated second in the other half of the blocks (by answering ‘*left*’ or ‘*right*’). No specific instruction was given regarding response speed. The response was encoded by the experimenter and the next trial started 2000 ms later. No feedback regarding the accuracy of participants’ performance was given.

Participants started with a practice session of 4 blocks of 10 trials each, one block per condition (i.e., uncrossed vs. crossed and ‘*which is first*’ vs. ‘*which is second*’) only with the two highest SOAs. The experimental session consisted of 4 blocks, of 40 trials each, resulting from the combination of the factors *hand posture* (*uncrossed* vs. *crossed*) and *response modality* (‘*which is first*’ vs. ‘*which is second*’). The order of the blocks was counterbalanced for the two hand postures (half of the participants started with the uncrossed hand posture, whereas the other half started with the crossed hand posture) and randomized for the response modalities. As for the visual TOJ, presented SOAs were determined according to the adaptive PSI procedure (Kontsevich & Tyler, 1999).

A rest period between the blocks was possible when requested. Duration of the tactile TOJ task was ~ 30 min.

## 2.4. Measures

Data were fitted with a logistic function for each participant and for each condition in order to compute two parameters of interest,  $\alpha$  and  $\beta$ . The  $\alpha$  defines the overall position of the curve along the abscissa (Kingdom & Prins, 2010), i.e. the threshold of the function. In our study, the threshold corresponds to the SOA at which the proportion of trials in which the visual stimulus presented at the same side as the affected limb (or the tactile stimulus applied to the affected hand) was reported as presented first, reaches the 0.5 criterion<sup>1</sup>. The  $\alpha$  corresponds to the PSS reported in typical TOJ experiments, defined as the amount of time one stimulus has to precede or follow the other in order for the two stimuli to be perceived by the participant as occurring simultaneously (Spence et al., 2001). The  $\beta$  parameter defines the slope of the logistic function, which describes the noisiness of the results and can be related to the precision of participants’ responses during the experiment (Kingdom & Prins, 2010)<sup>2</sup>. In order to estimate the logistic function we used the adaptive PSI method (Kontsevich & Tyler, 1999), which adopts a Bayesian framework, with the ultimate goal of estimating the posterior probability of the parameters of interest without probing extensively all the SOAs. Since a Bayesian approach is used, a prior probability distribution also needs to be postulated, i.e. the researcher’s knowledge/ beliefs regarding

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<sup>1</sup> Stimuli that were initially presented on the left during the tasks were recoded as corresponding to stimuli presented in the affected side of space/on the affected limb. Accordingly, data from participants affected by right-sided CRPS were transformed (multiplied by -1) to facilitate data display and statistical analyses.

<sup>2</sup> In most TOJ experiments, the  $\beta$ , i.e. slope of the psychometric function, is used to derive the just noticeable difference (JND). The JND denotes the delay/SOA between two stimuli needed for participants to perceive the correct order of presentation of the two stimuli in a certain percentage of trials (Spence and Parise, 2010).

the values of the parameters of interest (Kingdom & Prins, 2010). Based on previously conducted pilot studies and existing literature (e.g. Moseley *et al.*, 2009; Moseley *et al.*, 2012) we used a prior distributions of  $0 \pm 20$  and  $0.06 \pm 0.6$  for the threshold and slope parameters, respectively.

For each condition of the visual TOJ task, the proportion of trials in which the visual stimulus presented at the same side as the affected limb was reported as appearing first was plotted as a function of SOA. For the tactile TOJ, the proportion of trials during which the tactile stimulus applied on the affected hand was reported as being presented first was plotted as a function of SOA for each condition.

## 2.5. Data analysis

Participants' data were excluded from statistical analyses if the slope of the psychometric function couldn't be reliably estimated during the 40 trials, indexing that their performance was below chance level.

Before statistical analyses, data from the two response modalities ('*which is first*' & '*which is second*') were merged to reduce potential response biases. Firstly, simple t-tests were performed to compare the different PSS values to 0, in order to test the presence of a significant bias related to the affected limb. Next, the PSS and slope values from the different conditions were compared using an ANOVA for repeated measures. Regarding the visual TOJ, the ANOVA was performed with *visual stimuli position* (near space vs. far space), *hand position* (close to near LEDs vs. close to the body) as within-participant factors. As for the tactile TOJ, *hand posture* (uncrossed vs. crossed) was defined as within-participant factor. These ANOVAs were initially performed with a group factor characterizing which hand was affected (either left vs. right or dominant vs. non-dominant). Since the group factors did not differently impact the results, these analyses are reported in the Supplementary materials.

Greenhouse-Geisser corrections of degrees of freedom and contrast analyses were used when necessary. Effect sizes of the ANOVA were measured using partial Eta squared. Significance level was set at  $p \leq .05$ .

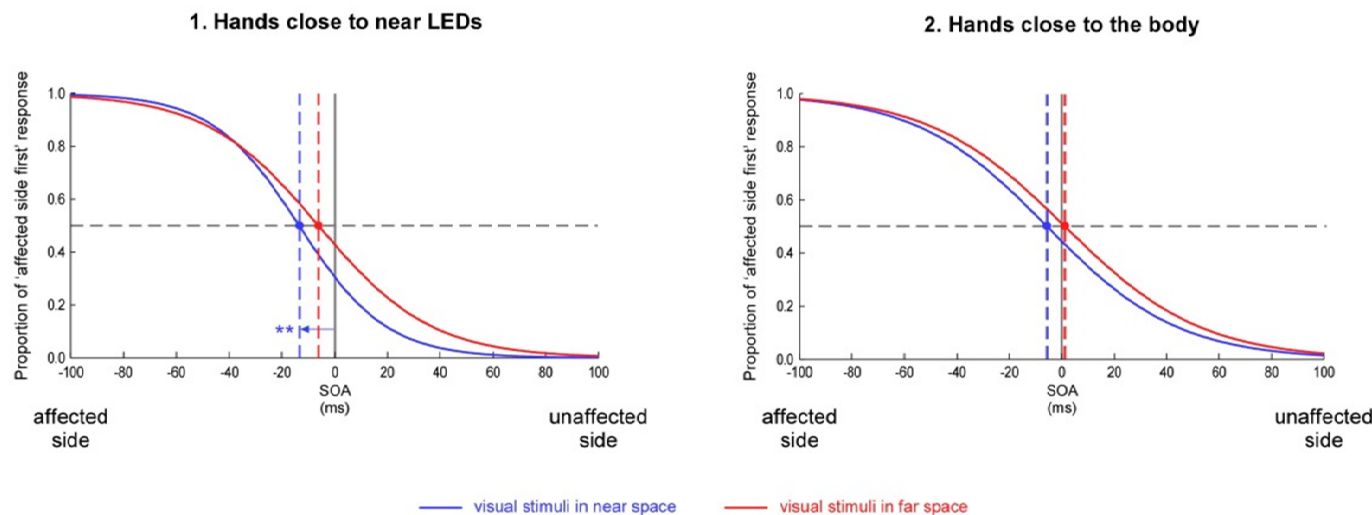
## 3. Results

### 3.1. Visual TOJ task

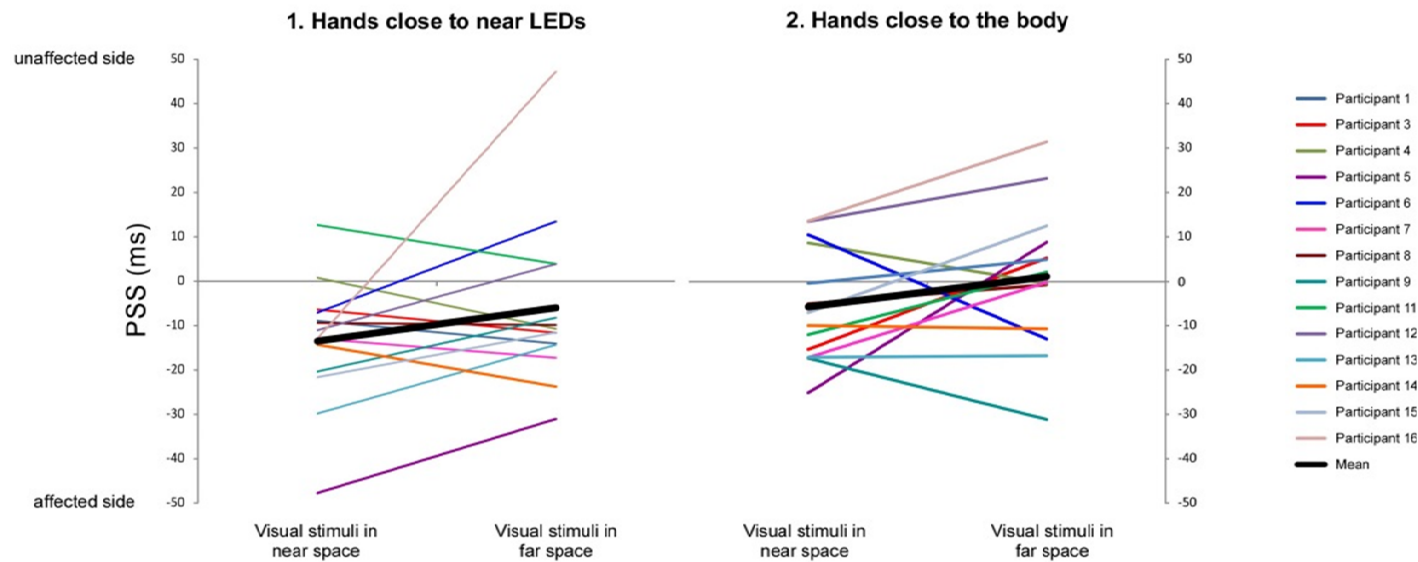
The fitted psychometric curves for each condition are shown in Fig. 3. The individual and mean PSS scores are illustrated in Fig. 4. Simple t-tests revealed that the PSS value was significantly different from zero only when visual stimuli were presented in near space and the hands placed next to them ( $t(13)=-3.582$ ,  $p=.003$ ,  $d=-0.96$ ), showing

that, in this condition, the visual stimulus appearing close to the affected limb had to be presented significantly earlier than the stimulus appearing close to the unaffected limb to be perceived as occurring simultaneously. This suggests a significant bias at the advantage of the perception of the visual stimulus presented close to the unaffected hand and at the detriment of the visual stimulus presented close to the affected hand. The PSS values of all the other conditions were not significantly different from zero (all  $t \leq -1.64$ ,  $p \geq .125$ ). When comparing the different conditions, repeated measures ANOVA showed a significant main effect of *hand position* ( $F(1,13)=5.578$ ,  $p=.034$ ,  $\eta^2p=.300$ ): PSS values were larger (more negative) when the hands were placed close to the LEDs in near space ( $M=-9.739$ ,  $SD=13.854$ ) than when they were placed close to the body ( $M=-2.236$ ,  $SD=12.335$ ). The main effect of *visual stimuli position* approached significance ( $F(1,13)=4.395$ ,  $p=.056$ ,  $\eta^2p=.253$ ), suggesting a trend for larger (more negative) PSS values for visual stimuli presented in near space with regard to the trunk ( $M=-9.897$ ,  $SD=11.546$ ) than for visual stimuli presented further away ( $M=-2.401$ ,  $SD=14.893$ ). In addition to the results of the t-tests, these findings suggest larger biases at the detriment of the visual stimuli presented in the affected side when the hands are placed close to them. The interaction between these two factors was not significant ( $F(1,13)=.012$ ,  $p=.914$ ,  $\eta^2p=.001$ ).





**Fig. 3.** Visual TOJs. The figure illustrates the fitted logistic functions from the data of the 14 participants for the (1) hands close to near LEDs and the (2) hands close to the body position. The x-axis represents different hypothetical SOAs between the two visual stimuli: negative values on the left side indicate that the visual stimulus occurring in the side of space of the affected limb was presented first, while positive values indicate that the visual stimulus occurring in the side of space of the unaffected limb was presented first. The y-axis represents the proportion of trials in which the participants perceived the stimulus presented in the side of space of the affected limb as occurring first. Blue curves represent the conditions in which visual stimuli were presented in near space, with the corresponding PSS values indicated by the blue dashed lines. Red curves represent the conditions in which visual stimuli were presented in far space, with the corresponding PSS values indicated by the red dashed lines. The arrow in (1) indicates the PSS value significantly different from zero (\*\*  $p \leq .01$ ) for the condition during which visual stimuli were presented in near space with the hands placed next to them.



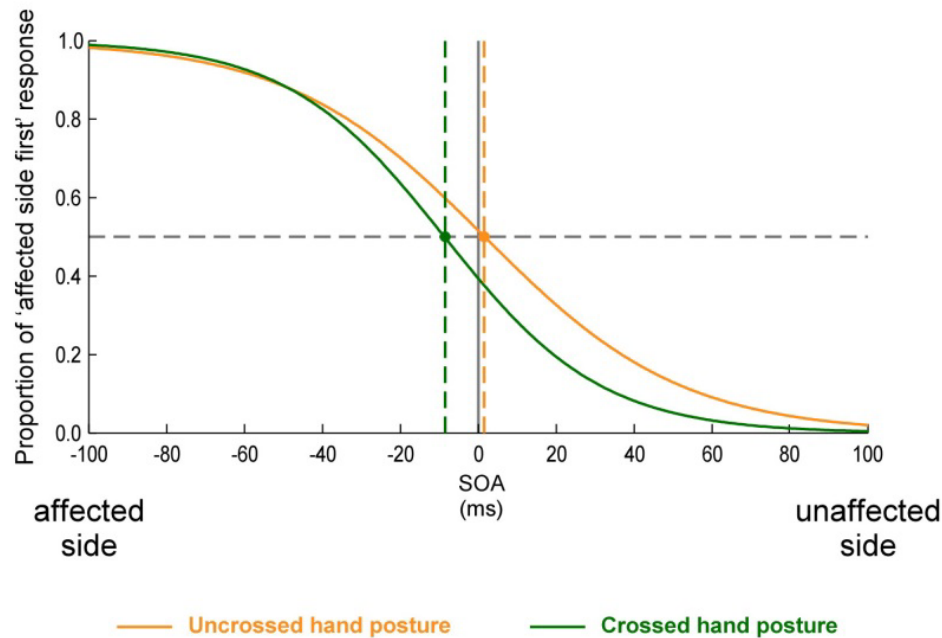
**Fig. 4.** Individual and mean PSS values for the visual TOJ tasks. The left graphic illustrates the PSS values for the conditions with the hands close to the near LEDs (1), and the right graphic the PSS values for the conditions with the hands close to the body (2). Within each graphic, the left side illustrate the PSS of the tasks performed with the visual stimuli in near space, the right side those with the visual stimuli in far space. Each color line represents one of the 14 participants who participated in the visual TOJ tasks; the thick black lines represent the mean of the PSS values across these 14 participants.

As for the slope values, the repeated measures ANOVA did not reveal significant main effects or interactions (all  $F \leq 1.032$ ,  $p \geq .328$ ), with an exception for the factor *hand position* which approached significance ( $F(1,13)=4.518$ ,  $p=.053$ ,  $\eta^2p=.258$ ). These results suggest that participants' judgments were less noisy, i.e. less variable, in the conditions during which the hands were placed close to the LEDs in near space than when they were placed close to the body. This finding support the PSS results reported above, as a steeper slope for the conditions in which the hands are placed on the table, i.e. close to the LEDs in near space, suggests that participant's judgments were more systematically biased in these specific conditions and thus more precise than in the other conditions.

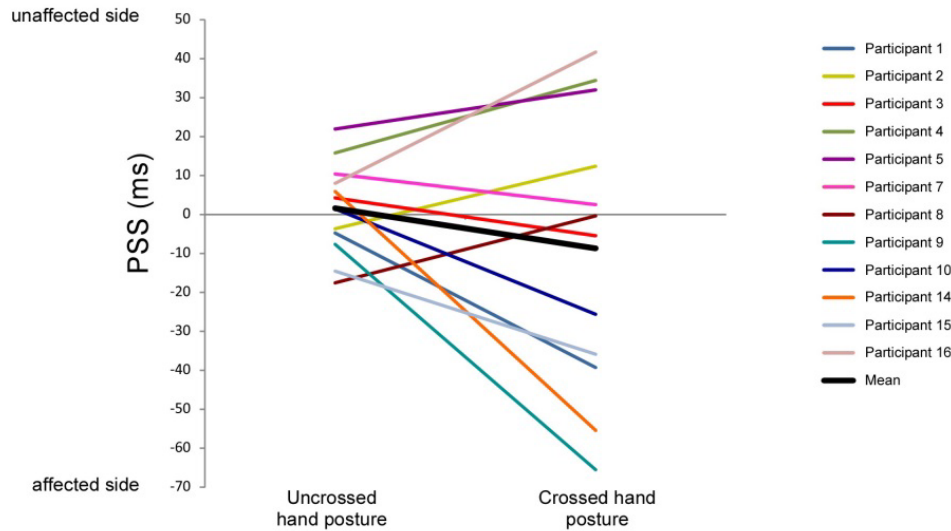
### **3.2. Tactile TOJ task**

The fitted psychometric curves for each condition are shown in Fig. 5. The individual and average PSS scores are illustrated in Fig. 6. None of the PSS values were significantly different from 0 (all  $t(11) \leq -.841$ ,  $p \geq .418$ ). There was no significant difference between the two hand postures as shown by the repeated measures ANOVA ( $F(1,11)=1.342$ ,  $p=.271$ ,  $\eta^2p=.109$ ). Regarding the slope values, this difference also didn't reach significance ( $F(1,11)=.351$ ,  $p=.565$ ,  $\eta^2p=.031$ ).

Do nociception and pain affect the perception of peripersonal space?



**Fig. 5.** Tactile TOJs. The figure illustrates the fitted logistic functions from the data of the 12 participants. The x-axis represents different hypothetical SOAs between the two tactile stimuli: negative values on the left side indicate that the affected limb was stimulated first, while positive values indicate that the unaffected limb was stimulated first. The y-axis represents the proportion of trials in which the participants perceived the affected limb as being stimulated first. The orange curve represents the conditions in which the hands were held in an uncrossed posture, with the corresponding PSS value indicated by the orange dashed line. The green curve represents the conditions in which the hands were crossed over the sagittal body midline, with the corresponding PSS value indicated by the green dashed line. None of the two PSS values were significantly different from 0.



**Fig. 6.** Individual and mean PSS values for the tactile TOJ tasks. Within the graphic, the left side illustrates the PSS values for the tasks performed with the hands in an uncrossed posture, the right side those with the hands in a crossed posture. Each color line represents one of the 12 participants who participated in the tactile TOJ tasks; the thick black line represents the mean of the PSS values across these 12 participants.

#### 4. Discussion

In the present studies, we investigated whether CRPS affects spatial perception, i.e. induces attentional biases to one side of space, by means of TOJ tasks. Attentional effects on TOJ have been explained by the law of prior entry, which postulates that attended stimuli are perceived earlier than unattended ones (for a review see Spence & Parise, 2010). When stimuli are presented in opposite sides of space, prior-entry related spatial biases in TOJ are typically evidenced by shifts in PSS values. These shifts indicate that, in order to have the chance to be perceived as stimulated first equally often, one side of space has to be stimulated before the opposite side, resulting from a facilitated perception of the stimuli presented in the latter one. In the present experiments we used two series of TOJ tasks, one with tactile stimuli applied to CRPS patients' hands and another one with visual stimuli presented at various distances from the patients' hands. The aim was to clarify whether CRPS patients' perceptual biases are limited to stimuli applied to the patients' body, as previously shown (Reid et al., 2016), or if they also extend to stimuli occurring in external space. In contrast to previous studies (Moseley, Gallace, & Iannetti,

2012; Moseley et al., 2009; Reid et al., 2016) we did not evidence any systematic changes in the PSS values in tactile TOJs, neither in the uncrossed nor in the crossed hand posture. We did however succeed to demonstrate significant changes in visual TOJs. More specifically, we showed that visual stimuli directly surrounding the affected limb were perceived significantly later than stimuli that were presented next to the unaffected hand, suggesting that participants paid less attention to visual stimuli occurring close to the affected hand. Furthermore, PSS shifts were in general more important when the hands were placed on the table (i.e. close to the nearest visual stimuli) than when they were placed close to the body. The difference between the near and far position of the visual stimuli only approached significance, but taken all together the results of the visual TOJs indicate that the perception of external stimuli is affected, especially when they occur in the space immediately surrounding the CRPS patients' hands. These deficits affect the perception of visual stimuli occurring close to the affected limb, as if the patients positively biased the perception of the visual stimuli occurring in the opposite side of space.

Spatial perception is a complex cognitive ability as it encompasses different cognitive mechanisms with distinct underlying neural processes (see Vallar & Maravita, 2009). These cognitive mechanisms are based on specific frames of reference that are defined as coordinate systems to map the position of a stimulus in a particular portion of space. For instance, the position of a somatosensory stimulus on the cutaneous space can be located based on anatomical projection of the receptors fields to spatially organized subgroups of neurons in somatosensory cortical areas (somatotopic reference frame), but also based on the relative position of each limb in external space (spatiotopic reference frame). The latter one allows recognizing that, when the hands are for instance crossed and the eyes closed, a touch applied to the left hand is produced by the contact of an object coming from the right part of space (e.g. Smania & Aglioti, 1995; Yamamoto & Kitazawa, 2001). Similarly, the ability to perceive visual stimuli in external space is also regulated by dissociated reference frames, with the peripersonal frame for external stimuli occurring in the proximity of the body, and the extrapersonal frame for stimulus occurring farther away (e.g. Graziano & Gross, 1998; Halligan & Marshall, 1991). The peripersonal reference frame is of primary importance as it allows integrating bodily and extra-bodily information to form a coherent representation of the body space and its immediate surrounding space. This multimodal representation of the body and the space nearby facilitates the interaction with objects in contact with the body, such as the manipulation of non-threatening objects (Holmes & Spence, 2004) and defensive reactions against threatening objects (Legrain & Torta, 2015). Indeed, to adequately react to a potential damaging stimulus, it is necessary to locate the part of the body that is potentially being harmed, the position of the threat in external space, as well as the relative postural position of the threatened limb in space. It has been shown, for example, that the perceived pain induced by a nociceptive stimulus can depend on the body posture and the vision of the limb on which the nociceptive stimulus is applied (Beck et al., 2016; Gallace et al., 2011; Longo et al., 2009; Longo et al., 2012; Mancini et al., 2011) (however, see Torta et al., 2015; Valentini et al., 2015). For these

reasons the existence of a spatial coding for nociceptive stimuli according to a peripersonal reference frame has been suggested and highlighted in recent studies (De Paepe et al., 2015, 2016; De Paepe et al., 2014). For instance, De Paepe et al. (2014) have shown that the temporal perception of nociceptive stimuli applied on the hands of healthy volunteers is affected by the occurrence of visual stimuli, especially when they are presented close to the stimulated hands. Similarly, we recently demonstrated, still with healthy volunteers, that TOJs of visual stimuli can be biased to the advantage of the visual stimulus presented close to the hand on which a nociceptive stimulus is applied<sup>3</sup>. These results support the idea that visual experience of the immediate surrounding of the body influences how we perceive bodily sensations and represent our body, as well as that the way we perceive our environment can also be shaped by bodily information like pain. The present studies indicate that the development of a chronic pain condition such as CRPS can also have an impact on how patients perceive their environment (see Bassolino, Finisguerra, Canzoneri, Serino, & Pozzo, 2015; Canzoneri et al., 2013; Makin et al., 2010 for similar conclusions in limb immobilization and amputation).

Our results are at odds with those observed in previous studies. Reid et al. (2016) showed that CRPS affects TOJs of tactile stimuli applied on the hands, but not those of auditory stimuli presented close to the hands. They concluded that spatial cognitive deficits were limited to bodily-specific sensations and do not affect the perception of external space. However, as outlined in the introduction, tones delivered by means of external speakers are not ideal to explore subtle spatial biases, as both ears are stimulated by all tones, independently of the original speaker. Measuring saccade latencies in a visuospatial attentional cueing task, Filippopoulos et al. (2015) come to the same conclusion as Reid et al. (2016), since they didn't observe any differences between CRPS patients' and controls' performances. However, in Filippopoulos et al. (2015)'s study, visual stimuli were presented on a screen placed at a distance of 68.5 cm from the participant's body. This distance is even greater than the distance of the visual stimuli presented in far space in our studies and for which attentional biases were not significantly different from 0. Since, in our studies, spatial attention was only significantly shifted towards the unaffected side when visual stimuli were presented in the immediate vicinity of the limbs, it seems conceivable to postulate that spatial perception of external stimuli is distorted in CRPS if the stimuli are processed according to frames of reference that include interactions with the body.

The most striking difference relative to previous experiments is that we did not succeed to replicate the tactile biases observed with similar TOJ tasks (Moseley, Gallace, & Iannetti, 2012; Moseley et al., 2009; Reid et al., 2016). However, the lack of significant results doesn't allow us to conclude that there is no somatosensory perceptual bias in CRPS patients. Instead, we were not able to evidence a systematic bias toward one of the two

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<sup>3</sup> Filbrich *et al.* (2015). Investigating crossmodal influence between nociception and vision using temporal judgments. Communication presented at the 16<sup>th</sup> International Multisensory Research Forum, Pisa. A publication is currently in preparation.

sides of space at the group level, as some of our patients displayed biases in opposite directions. One reason for these discrepant results could be that, compared to the other studies, the participants of our study seem on average less chronic, a fact that could imply differences at the level of cortical reorganization. However, this does not appear to be the main reason since even less chronic patients showed some signs of cortical reorganization, as demonstrated by the significant visuospatial biases. Symptoms in CRPS are thought to “centralize” gradually, with a time frame that varies from patient to patient (Birklein & Schlereth, 2015). Furthermore, duration of CRPS did not significantly predict the results of our TOJ tasks. Some of the patients we tested also presented with pain in other parts of the body (Table 1), which could have influenced their performance in the different tasks. However, all of them described these sensations as rather minor and much less constraining as compared to the pain in the CRPS limb. Furthermore, these participants didn’t seem to perform differently from the others.

The observed discrepancies, not only between TOJ studies, but also in the literature about CRPS-related cognitive deficits in general, raise the question of important inter-individual differences in the cognitive symptomatology of CRPS. Looking carefully at the literature on post-stroke hemispatial neglect, it appears that the symptomatology is highly variable. Neglect can affect different sensory modalities separately or concurrently and visuospatial deficits can impact or spare motor exploration (Brozzoli et al., 2006; Vallar, 1998). Dissociation have also been observed between the different frames of reference (for a summary see Halligan et al., 2003; Vallar, 1998), as well as between perceptual and representational abilities (Guariglia, Padovani, Pantano, & Pizzamiglio, 1993; Salvato et al., 2014). The variability of the symptoms may be accounted for by the variability of the location and the extent of the lesions. Similar dissociations can also be observed in CRPS patients, as Sumitani, Shibata, et al. (2007) and Sumitani, Rossetti, et al. (2007) demonstrated biases in visuospatial attention *in favor* of the affected limb when patients judged the position of a visual stimulus according to their own body midline (see however Christophe et al., 2016; Reinersmann et al., 2012 for different results). We would thus like to propose that the observed discrepancies across studies might be the result of an extreme variability of cognitive difficulties in CRPS, with possible dissociations between different cognitive abilities. Indeed, it has been suggested that cognitive deficits in CRPS are the result of a maladaptive cortical reorganization induced by (implicit) behavioral strategies developed by the patients to avoid the provocation of pain. It seems moreover reasonable to suppose that various strategies can be developed across CRPS patients, which, in turn, might impact cortical plasticity differently. This emphasizes the need to move to a more individual approach rather than a global one when investigating cognitive reorganization in CRPS in the future.

To conclude, the present experiments demonstrated the presence of the visuospatial deficits in CRPS patients. Conversely to previous statements (e.g. Punt et al., 2013), our results highlight the need to develop more specific empirical designs to uncover



cognitive difficulties in CRPS patients. Similar conclusions have been proposed for hemispatial neglect, since it has been observed that some post-stroke patients still display difficulties in their daily life while standard tests of neglect don't reveal any symptoms (e.g. Bonato, 2012; Bonato & Deouell, 2013). This is particularly important for the development and individual orientation of rehabilitation strategies which aim at integrating physiotherapeutic and neuropsychological aspects to treat chronic pain.

## 5. *Supplementary materials*

### 5.1. **Additional assessments and measures**

Before and during the experiments, other parameters were measured with the aim to investigate potential relationships between CRPS symptoms/characteristics and cognitive deficits.

**Methods.** Participants were assessed with a clinical interview and the Budapest criteria were (re)verified (with the exception of the 5 first participants we tested) (supplementary table S1). Before the experimental session, several additional clinical measures were taken, with the aim to relate them to the cognitive data during statistical analyses (supplementary table S2). The volume of the two hands was used as an index of swelling, measured by means of a hand volumeter (FEI 12-3504 Baseline<sup>®</sup> Volumetric Measuring Device, Forearm Set, 6X6X24 Inch Cavity). Participants were instructed to put their hand up to the crease of the wrist for 15 sec into the water. The mean of three consecutive measures of displaced water was calculated and converted in ml for both the affected and the unaffected hand<sup>1</sup>. Skin temperature of both the affected and unaffected hand was measured from the hands' dorsa (at the location of the first dorsal interosseous muscle) with an infrared thermometer (Tempett, SENSELab, Sweden). The absolute difference between the affected and the unaffected hand for hand volume as well as for skin temperature was used for statistical regression analyses. Participants also completed the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire (Institute for Work & Health, Canada) to assess physical symptoms and participants' abilities to perform daily-life activities. The final score calculated from the 30 items was used for statistical analyses. Average pain over the last 2 days was rated on a visually presented numeric rating scale (NRS) (ranging from 0-10, with 0= no pain and 10= worst pain imaginable). Degree of immobilization and physical activity was assessed with accelerometers (ActiGraph ASP-BTLE 2GB Activity Monitor, ActiGraph, United States) for 7 of the participants. Only participants who returned to the laboratory for other measures and tasks (not reported in this paper) wore the accelerometers for 3 consecutive days. Average vector magnitude count for the affected side minus that for the unaffected side was calculated.

Furthermore, for both the visual and the tactile task, subjective pain intensity and skin temperature of both hands were assessed before and after each block. Pain intensity was assessed by means of a visually presented NRS (ranging from 0-10, with 0= no pain and 10= worst pain imaginable). Skin temperature was measured from the hands' dorsa by means of an infrared thermometer (Tempett, SENSELab, Sweden).

**Analyses.** Linear regression was used to test if significant PSS values, i.e. PSS values significantly different from 0, could be predicted by the additional clinical measures, i.e. differences in hand volume or temperature of the hands, average pain over the two last days, disability score of the DASH, degree of immobilization and CRPS duration. Differences in hand temperature before and after the different conditions for each hand were tested using a repeated measures ANOVA, with *hand* (unaffected vs. affected), *time* (before vs. after), *visual stimuli position* (near space vs. far space) as well as *hand position* (close to near LEDs vs. close to the body) as within-participant factors and *side of symptoms* (left vs. right) as between-participants factor for the visual TOJ task. *Hand* (unaffected vs. affected), *time* (before vs. after) as well as *hand posture* (uncrossed vs. crossed) were used as within-participant factors and *side of symptoms* (left vs. right) as between-participant factor for the tactile TOJ task. The differences in pain intensity ratings before vs. after the experimental blocks were compared between the different conditions using the non-parametric Friedman test.

**Results.** For the visual TOJ tasks, PSS values for the condition in which visual stimuli were presented in near space and the hands placed next to them were not related to any of the additional clinical measures (all  $r^2 \leq .095$ ,  $F \leq 1.264$ ,  $p \geq .283$ ), with an exception for the measure "difference in hand volume" which approached significance ( $r^2 = .260$ ,  $F(1,12)=4.223$ ,  $p=.062$ ). None of the visual and tactile PSS values, neither the one that was significantly different from 0, nor the other ones, were related to the duration of the disease (all  $r^2 \leq .091$ ,  $F \leq 1.205$ ,  $p \geq .294$ ).

Regarding hand temperatures during the visual TOJ task, the ANOVA revealed a significant main effect of *time* ( $F(1,12)=19.042$ ,  $p=.001$ ,  $\eta^2p=.613$ ) and a significant *time*  $\times$  *hand position* interaction ( $F(1,12)=18.151$ ,  $p=.001$ ,  $\eta^2p=.602$ ). Contrast analyses showed that the two hands were in general warmer after the blocks than before, but only when the hands were placed close to the body (all  $t \geq -1.628$ ,  $p \leq .021$ ). None of the other main effects or interactions reached significance (all  $F \leq 3.943$ ,  $p \geq .070$ ). The difference in pain intensity ratings between the different conditions was not significant ( $\chi^2(3) = 2.444$ ,  $p=.485$ ). For the tactile TOJ tasks, the ANOVA performed on hand temperatures did not show any significant main effects or interactions (all  $F \leq 2.409$ ,  $p \geq .152$ ). There were also no significant differences in pain intensity ratings between the two hand postures ( $\chi^2(1)=1.286$ ,  $p=.257$ ).

## 5.2. Additional analyses of the TOJ tasks

The ANOVAs of the TOJ parameters were initially performed by adding a group factor to assess whether the side of the affected hand (either left vs. right or dominant vs. non-dominant) could impact the other factors.

**Analyses.** The group factor was defined as either *affected hand* (left vs. right) or *dominance of the affected hand* (dominant vs. non-dominant). The ANOVAs for the visual TOJ tasks were therefore performed with *visual stimulus position*, *hand position* and one of the two group factors successively. Similarly, the ANOVAs for the tactile TOJ tasks were performed with *hand posture* and one of the group factors successively.

**Results.** Since the results were mostly the same whatever the added group factor, the reported results combine the two analyses and the values of the statistical tests relate to the analyses with the added factor *affected hand* and the factor *dominance of the affected hand*, respectively. Regarding the PSS values of the visual TOJ tasks, there was a significant main effect of *hand position* ( $F(1,12)=5.153$ ,  $p=.042$ ,  $\eta^2p=.300$ ;  $F(1,12)=6.219$ ,  $p=.028$ ,  $\eta^2p=.341$ ) and an effect of *visual stimuli position* that approached significance ( $F(1,12)=4.081$ ,  $p=.066$ ,  $\eta^2p=.254$ ;  $F(1,12)=3.927$ ,  $p=.071$ ,  $\eta^2p=.247$ ). The *hand position*  $\times$  *visual stimuli position* interaction was not significant ( $F(1,12)=.013$ ,  $p=.912$ ,  $\eta^2p=.001$ ;  $F(1,12)=.000$ ,  $p=.995$ ,  $\eta^2p=.000$ ). There was no significant group difference ( $F(1,12)=.428$ ,  $p=.525$ ,  $\eta^2p=.034$ ;  $F(1,12)=1.073$ ,  $p=.321$ ,  $\eta^2p=.082$ ), as well as no significant interaction with this factor (all  $F \leq 1.674$ ,  $p \geq .220$ ; all  $F \leq 1.084$ ,  $p \geq .318$ ). Regarding the slope values, the repeated measures ANOVAs did not show significant main effects or interactions (all  $F \leq 1.167$ ,  $p \geq .301$ ; all  $F \leq 1.165$ ,  $p \geq .302$ ), with an exception for the factor *hand position* which approached significance ( $F(1,12)=4.565$ ,  $p=.054$ ,  $\eta^2p=.276$ ) when using the *affected hand* group factor and which was significant when using the *dominance of the affected hand* group factor ( $F(1,12)=5.446$ ,  $p=.038$ ,  $\eta^2p=.312$ ). As for the PSS data, there was no significant difference between the groups ( $F(1,12)=.154$ ,  $p=.701$ ,  $\eta^2p=.013$ ;  $F(1,12)=.000$ ,  $p=.985$ ,  $\eta^2p=.000$ ), nor any significant interaction with this factor (all  $F \leq 3.313$ ,  $p \geq .094$ ; all  $F \leq 3.794$ ,  $p \geq .075$ ). Regarding the PSS values for the tactile tasks, the ANOVAs did not show any significant difference, neither between the two conditions, nor between the groups, and no significant interaction between the factors (all  $F \leq 1.281$ ,  $p \geq .284$ ; all  $F \leq 1.117$ ,  $p \geq .315$ ). Regarding the slope values, none of the effects tested in the repeated measures ANOVA were significant (all  $F \leq 1.415$ ,  $p \geq .262$ ; all  $F \leq 2.663$ ,  $p \geq .134$ ).

## 5.3. References

Lewis, J. S., & Schweinhardt, P. (2012). Perceptions of the painful body: the relationship between body perception disturbance, pain and tactile discrimination in complex regional pain syndrome. *Eur J Pain*, **16**, 1320-1330, 10.1002/j.1532-2149.2012.00120.x.

Supplementary table S1

Number of fulfilled criteria per symptom category and per sign category according to the Budapest criteria for all participants

| ID | Reported Symptoms |           |                 |                 |         |           | Signs           |                 |     |  |
|----|-------------------|-----------|-----------------|-----------------|---------|-----------|-----------------|-----------------|-----|--|
|    | Sensory           | Vasomotor | Sudomotor/Edema | Motor/Trophic   | Sensory | Vasomotor | Sudomotor/Edema | Motor/Trophic   |     |  |
| 01 | n/a               | n/a       | n/a             | n/a             | n/a     | n/a       | n/a             | n/a             | n/a |  |
| 02 | 1/1               | 1/2 t°    | 1/2 E           | 1/3 range       | 1/2 H   | 1/2 color | 1/2 E           | 2/3 motor+range |     |  |
| 03 | n/a               | n/a       | n/a             | n/a             | n/a     | n/a       | n/a             | n/a             | n/a |  |
| 04 | n/a               | n/a       | n/a             | n/a             | n/a     | n/a       | n/a             | n/a             | n/a |  |
| 05 | n/a               | n/a       | n/a             | n/a             | n/a     | n/a       | n/a             | n/a             | n/a |  |
| 06 | 1/1               | 2/2       | 0/2             | 2/3 troph+motor | 0/2     | 1/2 color | 0/2             | 2/3 troph+motor |     |  |
| 07 | 0/1               | 2/2       | 2/2             | 3/3             | 1/2 H   | 1/2 color | 1/2 E           | 2/3 troph+range |     |  |
| 08 | 1/1               | 0/2       | 1/2 E           | 2/3 motor+range | 1/2 A   | 0/2       | 0/2             | 2/3 motor+range |     |  |
| 09 | 0/1               | 1/2 t°    | 2/2             | 3/3             | 1/2 A   | 1/2 t°    | 1/2 E           | 3/3             |     |  |
| 10 | 1/1               | 2/2       | 1/2 E           | 2/3 motor+range | 2/2     | 2/2       | 1/2 E           | 2/3 motor+range |     |  |
| 11 | 1/1               | 2/2       | 1/2 E           | 3/3             | 2/2     | 0/2       | 1/2 E           | 3/3             |     |  |
| 12 | 1/1               | 2/2       | 2/2             | 2/3 motor+range | 2/2     | 2/2       | 2/2             | 2/3 motor+range |     |  |
| 13 | 0/1               | 1/2 color | 2/2             | 3/3             | 0/2     | 1/2 color | 1/2 E           | 3/3             |     |  |
| 14 | 1/1               | 2/2       | 1/2 E           | 3/3             | 1/2 A   | 1/2 color | 1/2 E           | 2/2 motor+range |     |  |
| 15 | 1/1               | 2/2       | 2/2             | 3/3             | 1/2 A   | 1/2 t°    | 2/2             | 3/3             |     |  |
| 16 | 1/1               | 1/2 t°    | 0/2             | 2/3 motor+range | 2/2     | 0/2       | 0/2             | 2/3 motor+range |     |  |

Note. n/a= data not available; t°= temperature asymmetry; color= skin color changes; E= edema, range= decreased range of motion; troph= trophic changes; motor= motor dysfunction; H= hyperalgesia; A= allodynia.

Supplementary table S2

*Additional clinical measures*

| ID | Pain <sup>2days</sup> | T° affected (C°) | T° unaffected (C°) | Volume affected (ml) | Volume unaffected (ml) | DASH score | Activity affected-<br>unaffected |
|----|-----------------------|------------------|--------------------|----------------------|------------------------|------------|----------------------------------|
| 01 | 4                     | 31.7             | 30.3               | 164.7                | 185                    | 30.8       | n/a                              |
| 02 | 3                     | 24.5             | 26.5               | 156.6                | 151.3                  | 54.2       | n/a                              |
| 03 | 5                     | 31.2             | 32.6               | 328.3                | 345                    | 60.8       | n/a                              |
| 04 | 5                     | 33.2             | 33.5               | 156                  | 165                    | 47.5       | n/a                              |
| 05 | 5                     | 24.6             | 25.8               | 121.6                | 126.6                  | 40.8       | -858.4                           |
| 06 | 2                     | 29.2             | 29.4               | 170                  | 156.6                  | 15.8       | -816                             |
| 07 | 1                     | 28.2             | 27.2               | 318.3                | 278.3                  | 54.1       | -201.7                           |
| 08 | 4                     | 32               | 33.2               | 151.3                | 150                    | 52.5       | -83.1                            |
| 09 | 4                     | 33.1             | 34.5               | 148.3                | 160                    | 60.8       | n/a                              |
| 10 | 4                     | 29.6             | 30.9               | 255                  | 191.6                  | 59.2       | n/a                              |
| 11 | 2                     | 33.5             | 33                 | 191.6                | 146.6                  | 60.8       | n/a                              |
| 12 | 7                     | 29.4             | 30                 | 383.3                | 363.3                  | 63.3       | n/a                              |
| 13 | 7                     | 35.6             | 34.3               | 216.6                | 225                    | 81.7       | -702.5                           |
| 14 | 4                     | 28.3             | 31.2               | 303.3                | 291.6                  | 39.1       | -1359.6                          |
| 15 | 8                     | 34.4             | 34.5               | 121.6                | 140                    | 69.2       | n/a                              |
| 16 | 8                     | 30.8             | 30.9               | 186.6                | 173.3                  | 44.1       | 113.7                            |

*Note.* Pain<sup>2days</sup> = average pain over the last 2 days rated on a visually presented numeric rating scale ranging from 0-10; T° affected= temperature of the affected hand; T° unaffected= temperature of the unaffected hand; Volume affected= volume of the affected hand, Volume unaffected= volume of the unaffected hand; DASH score = score calculated from the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire, smaller score= less impairment; n/a= data not available; Activity affected-unaffected= Average vector magnitude count of the affected minus the unaffected hand, as assessed with accelerometers.

Do nociception and pain affect the perception of peripersonal space?

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## **General discussion**

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Do nociception and pain affect the perception of peripersonal space?

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## General discussion

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To efficiently react to stimuli that might be of potential harm to our body, we not only need to identify the part of the body that is potentially being harmed, but also its position and the position of the potentially harming stimulus in external space. This implies the necessity to coordinate and to integrate the representation of the space of the body and the representation of the external space surrounding the body, an ability that is thought to rely on the construction of a common multisensory spatial representation of the body slightly extending its physical boundaries into external space, which has been conceptualized by the notion of peripersonal reference frame.

Such an integrated peripersonal coordinate system for spatial perception and its role in protecting the integrity of the body is not only important in the sense that it allows to identify and react efficiently against a potentially noxious stimulus that is already in contact with the body, but also because it allows to monitor the external space for the presence of sensory events that might potentially contact the body and inflict harm on it. In this sense, peripersonal spatial representations would be multisensory by essence, and imply that stimuli from different sensory modalities can interact closely with each other, which, in turn, could affect perception.

Within this general context, the present dissertation was aimed to investigate whether nociception and pain can have a significant impact on the perception of the visual space close to the body. The first part of the experimental section investigated the possible influence of applying a nociceptive stimulus on the body of healthy participants on their processing of visual stimuli presented in external space, and under which conditions such influence might eventuate. The second part focused on the clinical implications of such crossmodal influence, by investigating to which extent the presence of chronic pain could impact the perception of the visuospatial environment.

In this general discussion, the main findings of the performed experiments will firstly be summarized, before being interpreted and integrated within the context of the existing literature. The limitations of these studies will also be discussed and directions for future research will be proposed.

## **1. Main findings**

### **1.1. Part 1**

In **Study 1** we tested whether a nociceptive stimulus can attract attention to its location, in order to prioritize the processing of a visual stimulus occurring in the same side of space as the nociceptively stimulated limb. Since the optimal time window in which such effects could be observed was completely unknown, we also tested different time intervals between the onset of the nociceptive stimulus and the first visual stimulus. Participants judged the temporal order of pairs of lateralized visual stimuli, one visual stimulus presented next to either hand of the participants. Visual stimuli were shortly preceded by nociceptive stimuli (by 200, 400 or 600 ms) which were applied on the participants' hands, either unilaterally on one of the two hands, or bilaterally, on both hands simultaneously. Results showed that when only one hand was stimulated, temporal order was judged to the advantage of the visual stimuli that were presented close to the hand on which the nociceptive stimulus was applied. When both hands were stimulated simultaneously, none of the two visual stimuli were prioritized. In addition, we showed that this attentional effect became more efficient with the reduction of the time delay between the nociceptive cue and the first stimulus of the visual pair, with the most significant effect being observed with an interval of 200 ms. These findings suggest that nociceptive stimuli can positively impact the processing of spatially congruent visual stimuli.

In **Study 2** we investigated whether nociceptive stimuli primarily impact the perception of visual stimuli occurring near the body as compared to visual stimuli occurring farther away, and whether such an influence would rely on the proximity between the visual stimuli and the stimulated hand rather than between the visual stimuli and the body considered as a whole. In a first experiment, participants judged the temporal order of pairs of lateralized visual stimuli, either presented near or far from the trunk, which were preceded by nociceptive stimuli either applied unilaterally, on one single hand, or bilaterally, on both hands simultaneously. The participants' hands were always placed next to the visual stimuli presented in near space relative to the trunk. Results showed that when both hands were stimulated simultaneously with the nociceptive stimuli, no significant judgment biases to any of the two sides of space were observed. However, when nociceptive stimuli were applied unilaterally, TOJs were made to the advantage of the visual stimulus that was presented in the same side of space as the nociceptive stimuli. These biases were significant for visual stimuli presented in both near and far space, but bias magnitude was significantly larger when the visual stimuli were presented in near space than when they were presented farther away. In a second experiment, we added conditions in which the participants' hands were also placed next to the visual stimuli in far space, allowing us to compare conditions in which the position of the hands was either congruent or incongruent with regard to the visual stimuli. The results revealed significant biases to the advantage of the visual stimuli presented in the same side of space as the

stimulated hand in all conditions, but with larger effects when the hands were placed in a congruent position with regard to the visual stimuli, which were thus independent of the relative distance of both the stimulated hand and the visual stimuli from the body considered as a whole. Taken together, these findings suggest that the influence of nociception on visual stimuli processing depends on the proximity of the visual stimulus to the hand on which the nociceptive stimulus is applied.

In **Study 3** we tested whether the influence of nociception on visual processing depends on the relative congruence between the location of the nociceptive stimulus and the location of the visual stimulus in external space, independently of their position with regard to their respective sensory RFs. Participants judged the temporal order of pairs of visual stimuli. They fixated their gaze either to the left or the right without moving their head, and accordingly, performed the TOJ task between a left-sided visual stimulus and a centrally placed visual stimulus in front of them or between the centrally placed visual stimulus and a right-sided visual stimulus. One of the participants' hands was positioned close to the centrally placed visual stimulus. Accordingly, a nociceptive stimulus occasionally applied on this hand, preceding the pairs of visual stimuli, was spatially congruent with the visual stimulus in the RVF when gaze was directed to the left, and congruent with the visual stimulus in the LVF when gaze was directed to the right. Results showed that TOJs prioritized visual stimuli presented in the RVF when gaze was directed to the left. When gaze was however directed to the right, TOJs prioritized visual stimuli presented in the LVF. When no nociceptive stimulus was applied on the hand, none of the two visual hemifields was prioritized. Participants thus always prioritized the visual stimuli presented close to the stimulated hand, irrespective of the gaze direction. This finding suggests that nociception influences visual perception based on their correspondence in external space, independently of the positions of both nociceptive and visual stimuli registered according to their initial anatomical reference frames. Crossmodal nociceptive-visual interactions would thus rely on a realignment of the initial modality-specific reference frames according to an external, i.e., spatiotopic, frame of reference.

In **Study 4** we further investigated the hypothesis that the effects of nociceptive stimuli on the processing of visual stimuli rely rather on the proximity of the visual stimuli to the stimulated hand rather than on the occurrence of both stimuli in the same hemispace as defined by the midsagittal plane of the body. Participants placed their hands along the anteroposterior axis in front of them, one hand at a proximal, the other one at a distal location with regard to the trunk. They performed a TOJ task on pairs of visual stimuli, one delivered close to either the proximal or the distal hand. Visual stimuli were preceded by nociceptive stimuli applied either on both hands simultaneously or on one hand unilaterally. Using such a stimulus placement, we avoided a manipulation of visual space perception according to the classic left vs. right side dimension, which is defined by the main axes of the body, such as its midsagittal plane, mainly represented by the trunk. Results showed that when nociceptive stimuli were applied on both hands simultaneously, judgments were

biased to the advantage of the proximal visual stimuli with regard to the trunk, suggesting that visual stimuli occurring close to the body receive in general more attentional weight than those presented far from it. More importantly however, when a unilateral stimulus was applied, TOJs always prioritized the visual stimuli presented close to the stimulated limb, irrespective of both the location of the hand and the visual stimulus with regard to the trunk. In accordance with the results of study 2, this finding suggests that nociception influences visual perception based on the close proximity between the visual stimulus and the hand on which the nociceptive stimulus is applied.

## **1.2. Part 2**

In **Study 5** we investigated whether the observed deficits in space representation and perception in CRPS patients can also extend to external, peripersonal, space perception. Patients performed two series of TOJ tasks, one on pairs of tactile stimuli and another one on pairs of visual stimuli. In the tactile task, one tactile stimulus was applied on either hand and patients performed the task with their arms either in an uncrossed or a crossed posture. In the visual task, visual stimuli were presented either near or far from the body, with the hands placed either close to the nearest visual stimuli or close to the body. In contrast to previous studies, we did not observe any spatial biases in the tactile task, neither in the uncrossed nor in the crossed hand posture. For the visual task we showed that patients' TOJs prioritized visual stimuli presented in the same side of space as the unaffected limb, with biases that were only significant when the visual stimuli occurred in the direct vicinity of the patient's hands. These results suggest that cognitive deficits in upper-limb CRPS patients can also affect the perception of the space external to the body, and more specifically, the space directly surrounding the patients' hands.

## **2. Interpretation and theoretical implications**

### **2.1. Nociception influences visual perception according to a peripersonal reference frame**

Whereas visual-tactile interactions and the underlying principles for their occurrence have been abundantly studied these past years (Spence, McDonald, et al., 2004)<sup>1</sup>, in healthy and brain-damaged participants as well as non-human primates, studies relating to the mechanisms underlying the link between nociceptive and visual processing are relatively scarce. Only recently De Paepe and colleagues (De Paepe et al., 2015; De Paepe et al., 2014) suggested that the occurrence of visual-nociceptive interactions might be grounded on similar principles than those that govern visual-tactile interactions, by

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<sup>1</sup> One has to note however that the majority of studies relating to visual-tactile interactions investigated the crossmodal influence of visual stimuli on touch processing and perception, with considerably less studies that investigated the reverse link.

demonstrating that the perception of nociceptive stimuli depends on the occurrence of visual stimuli, and that such crossmodal influence depends more specifically on the close proximity of the visual stimuli to the nociceptively stimulated limb, as well as on their relative co-localization in external space. These studies considerably extended our knowledge as to the ability to locate nociceptive, and thus potentially harmful, stimuli on the space of the body as well as in external space, and how such spatial processing could be influenced by external non-somatic stimuli. However, one question that still remains unanswered within this context is how the integration of nociceptive stimuli into such a peripersonal representation of the body might impact the processing of visual stimuli occurring close to the body, which might to some extent also be of potential threat to body integrity. While the few studies concerned with such potential influence of nociceptive and painful stimuli on the perception of visual stimuli can be questioned with regard to the specificity of the used stimulation method in activating the nociceptive system or to their specificity in studying purely stimulus-driven effects (as opposed to confounding effects of decision-related processes), they did also generally not manipulate the distance of the visual stimuli with regard to the body, making any conclusion as to the involved reference frames for such nociceptive-visual interactions difficult (see e.g. Favril et al., 2014; Filippopoulos et al., 2015; Van Damme et al., 2007). Therefore, the first part of my thesis was focused on investigating whether, and under which spatial conditions, a specifically nociceptive stimulus can impact the perceptual processing of visual stimuli occurring outside the body.

In **Study 1** we succeeded to demonstrate that a stimulus specifically activating the nociceptive system can actually positively impact the processing of visual external stimuli presented in the same side of space as the stimulated hand. We did so by showing effects of shifts in spatial attention induced by spatially non-predictive nociceptive cues on the facilitation of visual stimuli presented in the same location as the stimulated limb, as compared to visual stimuli in another location. We used an unspeeded TOJ task, which, as compared to classic detection and reaction tasks, offers the advantage of measuring more pure behavioral effects on perception, by avoiding the confound of faster response selection and/or execution (Spence, 2010; Spence, McDonald, et al., 2004; Zampini et al., 2007). Importantly, cueing effects were induced exogenously, so that the location of the nociceptive stimuli was uninformative as to the location of the first visual stimulus, suggesting that attention was attracted automatically by the nociceptive stimuli to their location, independently of voluntary control or decision of the participants, thus further minimizing the confounding effects of decision-related processes in the interpretation of the results. However, since in this first study, we only used visual stimuli presented close to the body, we were unable to conclude whether the crossmodal effects we observed in this study were due to a general competition between the left and the right hemispaces (i.e. both stimuli are presented in the same side of space), or more specifically to the close proximity between the visual stimuli and the nociceptively stimulated hand, and thus to the existence of a multisensory representation of the body in which both nociceptive and visual stimuli would be integrated. For this reason, we used the same task in **Study 2**, but, importantly, by

manipulating both the distance of the visual stimuli and of the stimulated hands with regard to the body. We demonstrated that the observed influence of nociceptive stimuli on the perception of visual stimuli was predominantly related to the proximity of the visual stimuli to the stimulated hand, independently of both the distance of the visual stimuli and the hands with regard to the body as a whole (i.e. the trunk). However, although the most significant effects were always observed for visual stimuli the most proximal to the stimulated hands, the results also showed that nociceptive stimuli, in either case, significantly influenced the visual stimuli presented ipsilaterally to the stimulated hand, even those presented farther away from the hands. Indeed, in Studies 1 and 2, nociceptive-visual interactions were always investigated using the main spatial organization of the body, dissociating the left and the right sides of space, which are defined according to a global egocentric frame of reference, that is, the midsagittal plane of the participant's body, mainly centered on the trunk or the head (Vallar & Maravita, 2009). With the aim to minimize the contribution of effects due to a non-specific stimulation of the same hemispace as defined by the midsagittal plane of the body, we avoided the classic left-right dimension usually used in TOJ tasks by aligning the visual stimuli and the stimulated hands with the midsagittal plane of the body in **Study 4**. Visual stimuli position was thus not perceived according to left vs. right side of space, but rather as a function of spatial depth (proximal vs. distal with regard to the trunk). An unexpected result was that in the conditions in which bilateral simultaneous nociceptive stimuli were applied, and in which no specific attentional bias was expected, TOJs were biased to the advantage of the visual stimuli presented proximal to the trunk. It could be hypothesized that visual stimuli occurring close to the body receive more attentional weight than those presented farther away, possibly due to their behavioral relevance. However, an explanation in terms of dominance of the lower visual field for some aspects of spatial perception can also not be excluded (e.g. Intriligator & Cavanagh, 2001; Karim & Kojima, 2010). Most importantly however, we showed that such a *default* preference for visual stimuli occurring close to the body could be “counterbalanced” when unilateral nociceptive cues were applied, since in these conditions visual stimuli presented close to the stimulated hand were always prioritized, independently from their distance and the one of the hand from the trunk, and thus from a reference centered on the whole body. This study thus corroborated the results of Study 2, suggesting the primary importance of the occurrence of visual stimuli in the space surrounding the stimulated limb for nociceptive-visual interactions. Finally, in **Study 3** we demonstrated that such interactions specifically rely on the correspondence between the relative locations of nociceptive and visual stimuli as defined according to external space, rather than by their relative locations as defined according to their respective initial sensory receptors. We did so by manipulating the relative spatial alignment between nociceptive and visual stimuli, via changes in gaze direction without movements of the head, showing a systematic prioritization of the visual stimuli occurring close to the stimulated hand, independently of the projection of these visual stimuli onto the retina, i.e. gaze direction. This suggests that the mechanisms underlying the crossmodal influence from nociception on vision rely on the ability to update mapping coordinates from the

initial anatomical reference frames of each sensory modality (i.e. somatotopic for nociceptive inputs and retinotopic for visual inputs) to an integrated mapping system using external space as main reference frame.

Our results complement those observed by De Paepe and colleagues (De Paepe et al., 2015, 2016; De Paepe et al., 2014), who demonstrated, using, amongst others, similar TOJ tasks than we did, that nociceptive stimuli are likely to be integrated in a common, peripersonal, reference frame, by showing that visual inputs presented in the vicinity of the body can affect how we perceive nociceptive stimuli. Here we extend these results, by demonstrating that nociception, for its part, can also influence visual perception.

They also fit well with the already well-established literature on stimulus-driven visual-tactile interactions in healthy participants, which demonstrated for instance, with behavioral and/or neuroimaging techniques, that the effects of one modality on the perception of the other modality are modulated by the proximity between the visual and tactile stimuli (see e.g. Macaluso & Maravita, 2010; Maravita et al., 2003; Spence, Pavani, et al., 2004), and that such space-specific effects depend of the co-localization of both stimuli in external space, independently of gaze or hand posture (e.g. Kennett, Eimer, et al., 2001; Kennett et al., 2002; Macaluso et al., 2002; Spence, Pavani, et al., 2004). Similar conclusions have been drawn by studying the phenomenon of extinction in brain damaged patients (see e.g. Ládavas, 2002), showing, for instance, that a visual stimulus presented close to the right hand can extinguish the perception of a left tactile stimulus, but not, or at least to a lesser extent, a visual stimulus presented farther away. These studies furthermore highlighted the importance of the position of the visual stimulus with regard to the hand, rather than with regard to the trunk or the retina for the phenomenon of crossmodal visual-tactile extinction to arise (e.g. di Pellegrino et al., 1997; Farné et al., 2005), thus bridging this part of human research and the research performed at the single-cell level in animals, which demonstrated that some visual responses of bimodal neurons in the macaque brain are to some extent anchored to specific body parts (e.g. Graziano et al., 2004).

There is a longstanding debate in the literature about the mechanisms that might underlie these crossmodal spatial interactions between somatic and non-somatic stimuli, at least when stimulus-driven effects are observed (see Spence, McDonald, et al., 2004). Indeed, mainly two different possible mechanisms have been proposed to explain that a non-predictive cue of one modality presented at one specific spatial location might facilitate the responses to a subsequent target of another modality at that same location. A first account that has been predominantly considered in the cognitive psychology literature is a shift of spatial attention induced by the spatially non-predictive cue to its location. Another account refers to multisensory integration, proposing that such crossmodal spatial cueing effects might rely on the integration of the sensory responses to both stimuli (cue and target) into an unified perceptual object at the single-cell level (McDonald et al., 2001). According to this account, the integration of both stimuli appearing around the same location and time would induce greater responses of multisensory neurons, which would

result in improved sensory information processing. It has furthermore been proposed that these two accounts could be differentiated based on the relative timing of the stimuli in the two sensory modalities, with simultaneous or near-simultaneous stimulation that would be required for maximal crossmodal integration, but not for crossmodal effects due to spatial attention. It has however also been argued that such a distinction based on relative timing might not be decisive for the differentiation between the two accounts for crossmodal spatial interactions (for a discussion see Spence, McDonald, et al., 2004). Another possible distinction between these two accounts relates to the different neural mechanisms of crossmodal spatial attention and integration. According to Spence, McDonald, et al. (2004), the co-occurrence of signals from different sensory modalities within a common multisensory brain area would not be necessary for crossmodal effects to occur if they were due to shifts in spatial attention. Such effects would thus not rely on feedforward convergence from the two sensory-specific areas to multisensory regions, but rather on back-projections from a supramodal attentional system to sensory specific areas. Importantly, such back-projections could be induced by the sole presence of the cue, even before the target stimuli in the other modality occurs. On the contrary, according to the putative model proposed by Spence, McDonald, et al. (2004), crossmodal effects due to multisensory integration might only arise when feedforward projections of *both* the cue and the target from their respective sensory modality specific areas (temporally) converge in multisensory brain areas, without however excluding further feedback projections from the multimodal level to sensory specific areas. It has also been proposed that a combination of both mechanisms could be possible, since attention has been shown to be involved in outcomes of multisensory integration and vice-versa (see Chen & Spence, 2016; Macaluso et al., 2016).

In any case, we hypothesize that such crossmodal nociceptive-visual interactions as observed in our studies could not simply be explained by shifts of spatial attention to the visual stimulus presented in the previously nociceptively cued location. Instead, for such interactions between somatosensory and non-somatosensory stimuli to occur, the brain would need to construct a multisensory representation of the space of the body and the external space nearby, in which both somatosensory and visual stimuli would be integrated, so that they could both be localized and interact with each other according to their position (and hence, their alignment) in external space, independently from their initial position relative to their respective sensory RFs and associated coordinate systems (i.e. somatotopic for nociceptive stimuli and retinotopic for visual stimuli). Somatosensory and visual stimuli would thus be integrated spatially, i.e. to form an integrated multisensory representation of space allowing them to be localized with regard to each other in external space, without being integrated in the sense that they would constitute a unified percept. In other words, they would still be perceived as two different stimuli, but which would be processed according to a common spatial reference frame allowing them to interact, which in turn would enable the nociceptive stimulus to influence the perception of the visual stimulus (and vice-versa). Such mechanisms explaining the observed interactions between stimuli of



different sensory modalities explicitly take into account how the brain registers the spatial (re)alignment of two stimuli that are initially coded according to different frames of reference. It has been proposed that the use of such space-based representations is not innate and develops during childhood (e.g. Bremner, Mareschal, Lloyd-Fox, & Spence, 2008; Pagel, Heed, & Röder, 2009), and that early experience of vision may play a role, since differences as to the use of such external reference frames, at least for tactile localization, have been shown between sighted as well as late blind and congenitally blind individuals (e.g. Collignon, Charbonneau, Lassonde, & Lepore, 2009; Röder, Rösler, & Spence, 2004). Such an integrated representation of space fits well with an often proposed third mechanism possibly underlying crossmodal interactions between somatosensory and non-somatosensory stimuli: the existence of bimodal neurons in fronto-parietal areas as discovered with single-cell recordings in the monkey (e.g. Dong et al., 1994; Graziano et al., 2004). As already mentioned previously, such neurons have associated somatosensory and non-somatosensory RFs. In the case of bimodal neurons that respond both to tactile and visual sensory input, the visual RFs are anchored to the tactile RFs and their corresponding body parts, and are mainly limited to the portion of external space immediately adjacent to their associated tactile RF. In such, these visual RF do not move with eye-movements, but rather with movements of the body parts on which they are anchored, and thus independently of their initial retinotopic reference frame (Fogassi et al., 1992; Gentilucci et al., 1983; Graziano et al., 1997; Graziano et al., 1994). The role of such bimodal neurons could be to underlie the remapping of sensory inputs from their initial anatomical to common spatiotopic reference frames.

Without such a coherent peripersonal representation of space which integrates somatosensory and visual stimuli, it would be difficult to explain the finding that, for instance, a left-sided visual stimulus influenced a nociceptive stimulus applied on the right hand when the hands were crossed over the body midline in the study of De Paepe et al. (2015), or that a nociceptively stimulated hand remaining in the same external position in our study could either influence the perception of a visual stimulus in the left hemifield or of a stimulus in the right hemifield, when gaze was shifted from one side to the other.

Based on our series of experiments, we can thus postulate that a nociceptive stimulus can influence the perception of a visual stimulus, on the condition that this latter one is presented in a very specific part of space, that is, the space just surrounding the stimulated limb. Importantly, this influence is independent of the fact which hemibody is stimulated and its exact position, as well as of the exact position of the visual stimulus in the visual field, as long as both the nociceptive and the visual stimulus are presented in close proximity to one another.

Our studies, combined with the results of De Paepe and colleagues, give further support to the hypothesis that nociceptive and visual inputs are integrated to build a coherent multisensory representation of the body and the space immediately surrounding it (Haggard et al., 2013; Legrain & Torta, 2015). Spatially congruent somatosensory and non-

somatosensory stimuli would therefore interact and be integrated for an efficient stimulus processing and selection in peripersonal space, possibly as a function of the possible limb–object interactions occurring in this space (Brozzoli et al., 2014). While interacting with proximal visual stimuli is of primary importance to optimize the manipulation of innocuous objects, this would be even more important for optimizing defensive behaviors against potentially noxious objects (Graziano & Cooke, 2006; Legrain & Torta, 2015). To protect the body from harm, it is first of all important to detect the physical threat on the body, but it seems furthermore at least equally important to monitor the space around the body, with the aim to avoid stimuli that can induce pain before they even reach the body, or, when a limb already is in pain, to avoid increasing pain through the contact with external objects. This leads to the question of how space, and especially the peripersonal space close to the body, would be perceived in the context of maladaptive, e.g. chronic, pain, a question that will be considered in the second part of this discussion.

## **2.2. Impaired peripersonal space perception in CRPS**

Whereas the first part of my thesis highlighted the influence of brief nociceptive stimulation on visual perception, the second part focused on the possible links between pain and perception of visual space in a clinical context. This is of particular relevance since it has been suggested that patients suffering from CRPS, a unilateral chronic pain disorder, might be affected by cognitive difficulties in mentally representing, perceiving and using their affected limb, that might possibly even extend to external space perception (see e.g. Legrain et al., 2012; Reinersmann et al., 2013). This clinical situation offers thus a unique occasion to investigate how a limb in pain might influence the perception of its visual surrounding space.

Whereas the observed cognitive difficulties in mentally representing and using the affected limb are increasingly recognized as being a typical feature of the CRPS symptomatology, a consensus as to the nature and the extent of perceptual difficulties in CRPS seems currently missing. When such perceptual difficulties have been reported in past studies, they were mainly related to tactile sensations, such as decreased tactile acuity and referred sensations (Lewis & Schweinhardt, 2012; Maihofner et al., 2006; McCabe, Haigh, Halligan, et al., 2003; Peltz et al., 2011), as well as attentional biases to the detriment of vibrotactile stimuli applied on the affected limb, as measured by TOJ tasks (Moseley, Gallace, & Iannetti, 2012; Moseley et al., 2009; Reid et al., 2016). Importantly, in these last-mentioned studies, it was furthermore observed that the deficits in tactile processing were rather defined by the space in which the affected limb usually resides than by the affected limb itself. Indeed, these studies revealed that attentional biases shifted to the detriment of the *unaffected* hand when the hands were crossed over the body midline, with the unaffected hand laying in the location previously occupied by the affected hand, thus emphasizing the existence of disrupted spatial processing related to external coordinates in CRPS. However, there is currently no clear answer to the question whether CRPS can actually also affect the perception of external, i.e. non-somatic, visual stimuli.

Studies that actually succeeded to demonstrate biases in perceiving external visual stimuli when far visual stimuli were judged with regard to the body midline<sup>2</sup> are not consistent as to the direction of such biases (see Jacquin-Courtois et al., In Press; Reinersmann et al., 2012; Sumitani, Rossetti, et al., 2007; Sumitani, Shibata, et al., 2007), and also contrast with studies using the same task that showed no biases at all (Christophe et al., 2016; Kolb et al., 2012). Recently, some authors suggested that cognitive difficulties in CRPS would be limited to the representation of body-related information and personal space perception, without extending to external space (Filippopulos et al., 2015; Reid et al., 2016). Presuming that CRPS-related perceptual deficits are limited to the somatosensory modalities would not be without important consequences, as it would invalidate neuropsychological techniques that use visuospatial attention as a useful method to treat chronic pain. However, as already mentioned in the theoretical section, the results and interpretations of these studies can be questioned, with regard to the sensory modality that was used in Reid et al. (2016), as well as to the fact that they are not informative about the perception of the space close to the body in Filippopulos et al. (2015).

In any case, our results challenge these statements, as we succeeded to demonstrate significant cognitive biases in visual TOJs in a population of upper-limb CRPS patients. Furthermore, since we explicitly manipulated the relative distance of the visual stimuli from the hands and the trunk, we were able to observe that it was mostly the perception of visual stimuli presented close to the affected hand that was affected, suggesting a possible distorted perception of peripersonal space in CRPS. Our results are in line with the results of a very recent study (Bultitude, Walker, & Spence, 2017), which compared visual TOJs of upper and lower-limb CRPS patients to those of healthy controls and demonstrated that judgments of CRPS patients were made to the detriment of the visual stimuli presented in the same side of space as the affected hand, whereas healthy controls did not show any significant biases in spatial perception.

Furthermore, our result that visual stimuli presented close to the affected hand received *less attention* seems not compatible with the view that sensitization-related changes in the central nervous system, enhancing not only cortical responses to nociceptive but also to non-nociceptive inputs, may be involved in the observed cognitive difficulties observed in CRPS (Birklein & Schlereth, 2015). Indeed, our findings of *impaired processing* of visual stimuli presented close to the affected hand are in contrast with studies which demonstrated an *enhancement* in the cortical processing of visual stimuli presented on the sensitized arm after experimentally induced central sensitization by a previous sustained and intense activation of nociceptors in healthy participants (Torta et al., 2017). They also differ from results obtained in fibromyalgia patients which showed a possibly central-sensitization related *hypersensitivity* to a broad range of sensory stimuli, including non-somatosensory ones (e.g. Geisser et al., 2008; Wilbarger & Cook, 2011).

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<sup>2</sup> It is worthwhile to note that this task could be considered as rather relating to the assessment of body representation and their impact on space perception than of the processing of external space per se.

This suggests that our results may be mediated by other mechanisms, involving possibly higher level representations responsible for the mapping of external space in higher order brain areas such as the parietal cortex (e.g. Cohen et al., 2013; Maihofner & Peltz, 2011), rather than cortical changes in primary somatosensory and motor cortices as those that have been suggested to be related to disturbed body representation (see e.g. Lewis & Schweinhardt, 2012; Reinersmann et al., 2013). In this sense, CRPS might affect brain networks that extend beyond the classic nociceptive cortical network.

Some of our findings need some specifications. Firstly, the fact that spatial biases were not significantly different between visual stimuli presented close to the patients' hands and those farther away from the hands, as revealed by the repeated measures ANOVA, should not be taken as a demonstration of unspecific deficits in space perception. On one hand, it is important to note that the only biases that were significantly different from zero were those observed in the conditions in which visual stimuli were presented directly next to the patients' hands. Furthermore, the difference between visual stimuli in near vs. far space approached significance, suggesting that the absence of such a significant effect could simply be due to a lack of statistical power. On the other hand, one has also to consider the possibility that the spatial boundary between near and far extrapersonal space might be less clear in CRPS than in healthy participants. Indeed, it has been suggested that the size of the peripersonal space and its representation can be perceptually changed by the experience with stimuli in this specific part of space, for instance, when regularly confronted with painful and threatening stimuli (e.g. Coello, Bourgeois, & Iachini, 2012; Taffou & Viaud-Delmon, 2014), or after limb amputation (Canzoneri et al., 2013). It has for example recently been observed that fibromyalgia patients seem to react differently to visual stimuli approaching the body than do healthy controls, suggesting that these patients perceived their surrounding space differently, as if the safety margin between near and far space had changed<sup>3</sup>. One should thus at least consider the possibility that a prolonged and permanent experience of pain in one limb might change how CRPS patients perceive spatial boundaries.

Secondly, it has been argued that the observed perceptual difficulties of CRPS patients only emerged from specific laboratory-based measures, suggesting that they might not be clinically relevant (Punt et al., 2013). For that matter, it seems likely that such discrete deficits in spatial perception may not even be noticed by CRPS patients (however, for an exception see Jacquin-Courtois et al., *In Press*), much less directly impair their quality of every-day life. However, it has also been suggested that cognitive disturbances in CRPS might not only be a consequence of having CRPS and its associated cortical changes, but might also exert a direct top-down effect on the limb itself (see Marinus et al., 2011). For instance, Moseley, Parsons, and Spence (2008) showed that movement-evoked pain and swelling of the affected limb is more severe when patients see a magnified image of

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<sup>3</sup> De Paepe, A.L., Crombez, G., & Legrain, V. (in preparation). Can far become near? The effect of approaching visual stimuli on tactile processing in fibromyalgia patients and controls.

their affected limb. Based on such studies, it seems reasonable to assume that difficulties related to spatial perception might also exert such top-down influences on pain or even movement in CRPS. Such an idea is supported by the results of studies that used experimental procedures acting on visuospatial perception, such as induced lateral displacements of the visual field and subsequent mismatches between the seen and the felt positions of the limbs by prismatic goggles. Moseley, Gallace, Di Pietro, Spence, and Iannetti (2013), for instance, succeeded to modulate the temperature of the affected limb simply by manipulating visuospatial perception with prismatic goggles, without actually moving the limb. Furthermore, preliminary studies using prismatic adaption, a procedure in which patients perform a visuomotor pointing task while wearing prismatic goggles shifting their visual field, also reported, besides a normalization of visuospatial biases, a reduction in pain and improvement of other CRPS-related symptoms, such as edema, discoloration and range of movement (for a review see Torta et al., 2016). Despite the raised objections, investigating and highlighting even subtle changes in spatial perception abilities in patients can thus be considered as being of high clinical relevance, especially in the context of the treatment of CRPS.

Third, the fact that we were not able to replicate tactile biases observed with similar TOJ tasks (Moseley, Gallace, & Iannetti, 2012; Moseley et al., 2009; Reid et al., 2016) does not allow us to conclude that there is no somatosensory perceptual bias in CRPS patients. Instead, we were not able to evidence a systematic bias toward one of the two sides of space at the group level, as some of our patients displayed biases in opposite directions. Since the variability of biases was quite important between participants, one reason for these discrepant results could be the duration of the CRPS. Indeed, compared to the other studies, the participants of our study were on average less chronic, a fact that could imply differences at the level of cortical reorganization. However, since even less chronic patients showed some signs of cortical reorganization as witnessed by the significant visuospatial biases, this does not appear to be the main reason of the observed discrepancies. Symptoms in CRPS are thought to “centralize” gradually, with a time frame that varies from patient to patient (Birklein & Schlereth, 2015). Furthermore, duration, as well as pain intensity of CRPS did not significantly predict the results of our TOJ tasks.

In conclusion, we were able to demonstrate that the presence of chronic pain, at least in CRPS, can not only entail difficulties in perceiving the body, but also visual stimuli in external space directly surrounding the affected limb. However, since one cannot deny the discrepancies that have been observed in the literature, not only between different TOJ studies, but also between studies investigating CRPS-related spatial deficits with other tasks, it seems relevant to consider the possibility of important inter-individual differences in the cognitive symptomatology of CRPS. As already highlighted in the context of hemispatial neglect in the theoretical section of this dissertation, such possible dissociations could possibly be observed for different sensory modalities and/or different frames of reference. Since it has been suggested that cognitive difficulties in CRPS might be the

result of a maladaptive cortical reorganization induced by (implicit) behavioral strategies developed by the patients to avoid the provocation of pain (see e.g. Marinus et al., 2011), it seems reasonable to suppose that various strategies can be developed across CRPS patients, which, in turn, might impact cortical plasticity differently and lead to the observed discrepancies. This emphasizes the need to consider a more individual approach rather than a global one when investigating cognitive reorganization in CRPS in the future.

### **3.     *Limitations and challenges for future research***

The experiments performed in the context of the present thesis allowed us to gain more insight into the mechanisms underlying nociceptive-visual interactions, as well as into the effects of chronic pain on the perception of the visuospatial environment. However, there are still some aspects that could be improved in future studies. There are moreover many questions that remain unanswered and aspects that need to be specified, leading to some interesting and exciting possibilities for future research.

Throughout the different studies investigating nociceptive-visual interactions, IES was used to deliver nociceptive stimuli. It has been argued in the past that such electrical stimulation could not be considered as a reliable method to selectively activate nociceptors, since it would also co-activate low-threshold mechanoreceptors and their associated faster-conducting non-nociceptive A $\beta$ -fibers responsible for tactile sensation (e.g. de Tommaso et al., 2011; Perchet et al., 2012). This statement can however be rebutted, since Mouraux et al. (2010) provided convincing evidence that IES can be used to selectively activate nociceptive afferents, on the condition that very *low* intensities of stimulation are used. However, since very low current intensities have to be used if one wants to avoid the co-activation of non-nociceptive fibers, this also entails that the stimulation only generates a very weak percept, which was described as pricking and sometimes unpleasant, but not necessarily painful. Although the strength of the elicited nociceptive percept was already increased through temporal summation, by using short trains of IES (Mouraux et al., 2014), the perceived sensation was still very weak. In some participants the perception fluctuated between the stimulated hands and the experimental blocks and even disappeared completely sometimes, which necessitated a displacement of the electrode. However, despite such drawbacks of the IES method, we were still able to reliably demonstrate crossmodal interactions between nociception and vision. Nonetheless, although the induction of a painful sensation is certainly not necessary to apprehend the implications of such crossmodal links between nociception and vision, it would be interesting to consider the use of nociceptive stimuli that induce a stronger and painful percept in the future, such as thermal stimuli generated by laser stimulation which are indisputably selective for heat-sensitive nociceptors, notably to circumvent the possible drawbacks of using IES stimulation.

An important issue that has to be considered when using TOJ tasks is to avoid, or at least minimize, the contribution of response and decisional-level biases that could be mistaken for genuine perceptual biases induced by the attentional manipulation, such as, in our case, spatially non-predictive cues. When studying spatial perception abilities with a cueing paradigm as in our studies, such non-perceptual biases can, for instance, arise when participants, unsure about the exact temporal order, decide (not necessarily explicitly) to report the location they guess to be the most task-relevant, e.g. the cued location, even though the stimulus presented in this location was actually not perceived as occurring first (e.g. Frey, 1990; Jaskowski, 1993; Scharlau, 2004; Shore et al., 2001). For that reason, it has been proposed that such possible confounding effects could be minimized by adding blocks of stimulation in which participants have to judge which of the two stimuli was presented second, instead of first<sup>4</sup> (e.g. Scharlau, 2004; Shore et al., 2001; Spence et al., 2001; Yates & Nicholls, 2009), a procedure that we used throughout all our experiments. However, there are also other strategies that can be used to further minimize response and decisional biases, such as using response modalities that are orthogonal to the spatial dimension of the stimuli (Shore et al., 2001), as well as using simultaneity judgments (Zampini, Shore, & Spence, 2005) rather than order judgments or a combination of the two (Zampini et al., 2007). Another interesting proposition has been to use TOJ models that explicitly consider response biases by including decisional parameters, with the aim to *directly* distinguish perceptual from response and/or decisional accounts (Garcia-Perez & Alcalá-Quintana, 2012a, 2012b). Study 4 was the only one of our studies in which participants also used a response modality that was orthogonal (i.e. the color of the LEDs) to the spatial dimension of the stimuli set-up, in addition to the “which is second” modality. Since we already used one of these control conditions to minimize the confounding influence of potential responses biases, we are confident as to the perceptual nature of the results we obtained. However, in future studies, several of these strategies should ideally be used, to dismiss any last doubts that could be raised as to presence of genuine, non-exaggerated perceptual biases in the context of nociceptive-visual interactions.

One of the aims of our studies on crossmodal nociceptive-visual interactions in healthy participants was to demonstrate that such interactions rely on the existence of peripersonal reference frames, which would allow the prioritized processing of visual stimuli that occur in the immediate vicinity of a nociceptively stimulated hand. Such representations would be particularly important for the optimization of specific actions against stimuli that might be of potential threat for the integrity of the body, even before they can contact the body. In Study 2 and 4 we explicitly tested the hypothesis that the observed nociceptive-visual interactions were due to the occurrence of the visual stimuli in the immediate vicinity of the stimulated hand, rather than to their proximity to the body

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<sup>4</sup> Using such a procedure, perceptual biases induced by attentional manipulation can be evidenced by reversed judgments in the “which is second” conditions relative to the “which is first” conditions. On the contrary, decisional biases can be highlighted by the fact that participants would more likely report the same stimulus (i.e. the same cued location), irrespective of the fact which question (“which is first” or “which is second”) was asked.

considered as a whole or simply their occurrence in the same hemispace as the stimulated limb. As predicted, our results suggest that nociceptive-visual interactions specifically depend on the close proximity between the visual stimuli and the hand on which the nociceptive stimuli are applied. However, our studies are not able to disentangle whether these interactions rely on the existence of a specific limb-centered peripersonal representation which uses the stimulated hand itself as a coordinate system rather than on a global peripersonal representation centered on the whole body which uses, for instance, the trunk, as a coordinate system. Even though we succeeded in Study 4 to avoid the classic left-right dimension in the stimulus set-up which relates to a coordinate system centered on the trunk and which might have contributed to the effects observed in Study 2, some of the results obtained in Study 4 could still be compatible with a default use of a whole-body peripersonal reference frame (i.e. observed biases to the advantage of the visual stimuli presented proximal to the body when nociceptive cues were applied on both hands simultaneously). To be able to demonstrate the existence of a peri-limb reference frame using the limb itself as reference and that is mainly independent of a global peripersonal representation of the body as a whole, future studies should investigate whether, for instance, a hand can effectively serve as its own reference to define the left and right sides of its own space. Furthermore, such studies should also include an investigation of the effects of dynamic and plastic properties of peri-hand representations on nociceptive-visual interactions. As already briefly mentioned before in the context of changed boundaries between near and far extrapersonal space in chronic pain, peripersonal space representation is not static, and can change, for instance, as a function of our possibilities to act in space, such as, for example, after amputation (Canzoneri et al., 2013), or, on the other extreme, after tool-use. Indeed, tool-use procedures have been extensively used to demonstrate the plasticity of the peri-hand space and its repercussions on visual-tactile interactions, in healthy participants as well as in brain-damaged patients (see Bonifazi, Farnè, Rinaldesi, & Làdavas, 2007; Macaluso & Maravita, 2010; Martel, Cardinali, Roy, & Farne, 2016). The plasticity of the peri-hand space has initially been demonstrated in the context of parietal (IPS) bimodal neurons in the monkey, by showing that visual RFs, initially confined to the space immediately adjacent to its associated tactile RF, can extend to elongate along the axis of a rake that was previously used to retrieve distant food pellets (Iriki, Tanaka, & Iwamura, 1996). This tool-use procedure has subsequently been used repeatedly to demonstrate that actively using a tool linking the hand and far out-of-reach visual stimuli allows these latter ones to impact the perception of tactile stimuli applied on the acting hand, in the same manner as near visual stimuli do. Of particular interest for our question as to the existence of specific peri-hand representations, is the finding that when the tools are held in a crossed position, without crossing the hands, reactions to a tactile stimulus perceived on one hand are modulated by a visual stimulus presented close to the tip of the tool in the hemispace contralateral to the stimulated hand (e.g. Maravita, Spence, Kennett, & Driver, 2002). This suggests an actual extension of the peri-hand representation, rather than of a global peripersonal representation within one hemispace (centered on the body). In future research, crossmodal interactions between nociception and vision and their



underlying mechanisms should thus also be considered in the context of the dynamic properties of peripersonal representations.

With regard to peripersonal space perception in the context of CRPS, the picture might seem relatively clear at first glance, with cortical reorganizations inducing difficulties in representing and perceiving the body and near external space and the development of neuropsychological interventions to reduce these cognitive difficulties, but also pain, as well as other related symptoms. However, there are still many inconsistencies and unanswered questions, leading to a much more blurry picture. Firstly, one has to consider that the CRPS-related cortical reorganization might also be the cause rather than simply the consequence of the presence of pain. Such an idea would be supported by the aforementioned studies reporting top-down effects of the cognitive disturbances (and thus of the cortical reorganization) or visuospatial experimental manipulation on pain and other related symptoms (e.g. Bultitude & Rafal, 2010; Christophe et al., 2016; Moseley et al., 2013; Moseley et al., 2008; Sumitani, Rossetti, et al., 2007). Furthermore, the widespread cortical reorganization and the related cognitive deficits could also be the consequence (or the cause?) of initial post-trauma immobilization and/or the non-use of the affected limb, possibly due to (implicit) behavioral strategies to avoid the provocation of pain (Marinus et al., 2011). Indeed, limb immobilization after the initiating event has been suggested to be a potential risk factor to develop CRPS (Pons, Shipton, Williman, & Mulder, 2015). In this sense, one has to seriously consider that the observed cognitive difficulties and especially the observed biases in spatial perception in our and in other studies might not be due to the sustained experience of pain, but rather to initial immobilization and/or reduced activity of the affected limb. In healthy participants, short-term immobilization (1-2 days) with a splint or a cast has already been shown to induce deficits in body representation of the immobilized limb (e.g. in a hand laterality judgment task, see Meugnot, Almecija, & Toussaint, 2014) similar to those observed in CRPS patients (e.g. Moseley, 2004; Reinersmann et al., 2010; Schwoebel et al., 2001). Furthermore, experimental immobilization of 12h (Huber et al., 2006) as well as cast immobilization of several weeks after bone fracture without any pain and signs of CRPS (Lissek et al., 2009) can also impair somatosensory processing. As to deficits in spatial perception, a recent study suggested that 10h of immobilization can affect tactile-audio integration, by reducing the area in which auditory stimuli can facilitate the processing of touch (Bassolino et al., 2015). In future research it could thus be important to study whether, and to which extent, short-term immobilization can also induce deficits in the perception of non-somatic stimuli, as those we observed in CRPS.

Furthermore, with regard to the specific findings of deficits in spatial perception, there are still many open questions as to the affected sensory modalities, direction of the bias(es) and implicated reference frame(s). Further studies should, for instance, investigate whether the observed biases to the detriment of visual stimuli presented in the same side of space as the affected limb are due to an impaired limb-centered representation and thus

follow the limb when it moves, or rather due to an altered representation of space organized along the midsagittal plane of the body, i.e. a body-centered representation, as suggested by Moseley, Gallace, and Spence (2012). Although our results suggest that these deficits might be limb-centered, since significant biases were only observed for visual stimuli presented close to the hands, this has to be confirmed by manipulating stimulus mapping according to different frames of reference, as it has been done in the context of the investigation of nociceptive-visual interactions in the first part of this thesis. Thoroughly defining the spatial deficits of CRPS patients is a prerequisite for developing and assessing the effectiveness of rehabilitation techniques based on the manipulation of visuospatial perception, such as prismatic adaptation. Even though there are preliminary results suggesting that such techniques can, besides its positive effects on visuospatial perception, also reduce pain and improve other CRPS-related symptoms, it is not clear how exactly these procedures should be (individually) configured for the use with CRPS patients, such as, for instance, the choice of the direction of the prismatic displacement (see Torta et al., 2016).

Finally, it would also be interesting to investigate in future studies whether the difficulties in spatial perception observed in CRPS can also be generalized to other (chronic) pain populations (for contrasting results, see e.g. Kolb et al., 2012; Moseley, Gallagher, & Gallace, 2012; Reinersmann et al., 2012), or whether they could specifically be involved in the symptomatology of CRPS.

#### **4. Conclusion**

The studies presented in this dissertation were conducted within the general context of understanding the functioning of a peripersonal coordinate system for spatial perception that integrates the space of the body and external space, as well as its role in protecting body integrity. Such a representation would not only be important for the identification and efficient reaction to potentially noxious stimuli that are already in contact with the body, but also for the monitoring of external space close to the body in order to detect and react to sensory events that might potentially contact the body and inflict harm on it. Importantly, such an integrated representation also implies that somatic and non-somatic stimuli can interact closely, which in turn, could affect perception. Within this context, the aim of this dissertation was more specifically to clarify to which extent the perception of external space would be dependent on nociceptive and pain-related body sensations, by investigating whether and under which conditions the occurrence of nociceptive stimuli on the body as well as the presence of chronic pain states affects the perception of the visual space outside the body.

In a first approach we investigated in several experiments the effects of brief nociceptive stimulation on the processing of visual stimuli in healthy participants. Our

results demonstrated that nociceptive stimuli can actually facilitate the processing of visual stimuli, when they are *spatially congruent*. Furthermore, we showed that this facilitation depends mainly on the proximity of the visual stimuli to the hand on which the nociceptive stimuli are applied, independently of both the position of the stimulated hand and the visual stimuli from the body considered as whole. Finally, we demonstrated that these interactions depend on the relative spatial congruence of nociceptive and visual stimuli in *external space*, indicating a realignment of the initial modality-specific anatomical spatial reference frames according to an external, i.e. spatiotopic, reference frame. In a second approach we studied the abilities of patients suffering from upper-limb CRPS, a chronic pain disorder, in perceiving visual stimuli occurring in external space, presented at various distances from the body. Results showed that patients paid less attention to visual stimuli occurring in the same side of space as their affected limb, especially when stimuli were presented in the immediate vicinity of the hands, i.e. in peripersonal space.

It seems thus that the way we perceive and represent our near visual surrounding is built on strict links with somatosensory, i.e. nociceptive perception, and that pain is processed in spatial frames of reference that are not limited to the frontiers of the body. Clarifying which spatial representations are affected by nociception and pain will contribute to further develop neuropsychological rehabilitation techniques acting on multisensory perception to treat chronic pain, and to understand the exact mechanisms on which these techniques rely to efficiently alleviate sensorimotor symptoms.

Do nociception and pain affect the perception of peripersonal space?

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