

WHERE IS MY PAIN?
A NEUROCOGNITIVE INVESTIGATION OF THE
SPATIAL PERCEPTION OF PAIN.

ANNICK DE PAEPE

PROMOTOR: PROF. DR. GEERT CROMBEZ

COPROMOTOR: PROF. DR. VALÉRY LEGRAIN

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GENERAL INTRODUCTION

*“It is a shame that we possess such
insufficient knowledge concerning the
character of pain—those symptoms which
represent the essential part of all bodily
suffering of man”*

(Alfred Goldscheider)

1 THIS FUNNY THING CALLED PAIN

1.1 EVERYBODY EXPERIENCES IT...

Everybody regularly experiences pain in the course of his/her life. It is a distressing feeling often (but not always) caused by intense or damaging stimuli. Pain is adaptive as it motivates the individual to withdraw from damaging situations, to protect the body against threats and to avoid similar experiences in the future (Chapman, Tuckett, & Song, 2008; Dawkins, 1995; Eccleston & Crombez, 1999). However, for some individuals pain persists after the noxious stimulus is removed. A distinction has been made between 'acute' and 'chronic' pain. Acute pain generally comes on suddenly, and is accompanied by anxiety and emotional distress. Its cause can often be diagnosed and treated, and the pain is confined to a given period of time (i.e. less than three months, e.g., Renton, 2008; Saastamoinen, Leino-Arjas, Laaksonen, & Lahelma, 2005; Suri et al., 2011). Chronic pain, however, persists over a longer period of time (i.e. longer than three or sometimes six months, e.g., Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Català et al., 2002; Gatchel, Peng, Peters, Fuchs, & Turk, 2007) and is persistent to almost any kind of medical treatment. The prevalence of acute and chronic pain differs widely across studies depending upon the population, settings and the definition used. Among three of the more recent studies investigating the presence of both acute and chronic pain (Català et al., 2002; Chung & Wong, 2007; Saastamoinen et al., 2005), the overall presence of pain (at the time of the interview, the day before or the week before the interview) varied between 30% and 45%. Acute pain (i.e. pain with a duration of less than 3 months) was present in about 15% to 20% of the respondents, while 20% to 40% of the respondents reported to have chronic pain (i.e. pain with a duration of more than 3 months). Breivik et al. (2006) investigated the prevalence of chronic pain in 46,394 people within 15 European countries and found that 19% of the respondents had experienced moderate or severe pain of at least 6 months duration. Pain is more prevalent in women than in men (Català et al., 2002; Chung & Wong, 2007; Saastamoinen et al., 2005) and its prevalence is found to increase with age (Català et al., 2002; Chung & Wong, 2007).

1.2 ...BUT HOW TO EXPLAIN IT?

The conceptualization of pain has proved to be difficult. Over the centuries a number of theories have been postulated to describe mechanisms underlying pain perception, and the conceptualization of pain has changed. For many years, pain was conceived as a sensory process that informs the brain about tissue damage. One of the influential theories was the

specificity theory, which stated that each somatosensory modality (e.g., mechanoreception, thermoreception, nociception) has a specific receptor and associated sensory fiber that is sensitive to one specific stimulus (Dubner, Sessle, & Storey, 1978). This idea has its foundations in the mechanistic view on the body of Descartes (1664), who proposed that a specific pain pathway carries the messages from a pain receptor in the skin to a pain center in the brain, much like a cord attached to a bell: By pulling on the other end of a cord, the bell will ring. Pain is thus addressed in purely mechanistic terms where pain intensity is thought to be a direct function of the degree of tissue damage¹. Other theories state that pain is not an unique sensory experience, but rather an emotion that occurs when a stimulus is stronger than usual (*intensity theory*, cited in Dallenbach, 1939), or that the pain experience results from a specific and particular pattern of neural firing (*pattern theory*, Sinclair, 1955; Weddell, 1955).

The theories mentioned above, all assume a one-to-one relationship between tissue damage and the pain experience. However, in reality there can be tissue damage without pain experience. One of the classic examples to illustrate this distinction is offered by Beecher (1959), who studied soldiers returning from the battlefield with extensive wounds. Remarkably he observed that there was no clear relationship between the extent of the wound and the pain experienced. Many of the soldiers even barely noticed their wounds. Further findings that the aforementioned theories are unable to explain, are the observation that amputees can experience pain in a limb that is no longer there (Melzack, 2005), and that innocuous stimuli, such as tender touch or soft sounds, cause excruciating pain in some individuals (Katzenell & Segal, 2001). These examples illustrate that pain is a complex and highly variable phenomenon that can be influenced by several psychological and physiological factors.

The *gate-control theory* of Melzack and Wall (1965) is the first theory that allows for psychological factors to influence the pain perception. In this theory, a mechanism in the dorsal horn of the spinal cord is proposed to act as a gate, which modulates or blocks nociceptive information to be processed by the central nervous system. This gate mediates the relationship between tissue damage and pain perception, and may be activated in different ways. First, it can be influenced by peripheral afferent nerve activity: It is further opened by activation of fibers responding to noxious stimuli, and it tends to close by activation of fibers responding to non-noxious stimuli. Second, central pathways,

¹ It is noteworthy that, despite the specificity of the transmission of sensory inputs, Descartes had already suggested that the different sensory inputs are integrated at the cortical level to form one single perceptual representation.

descending from the brain, modulate the transmission of nociceptive information at the spinal cord level. Affective and cognitive factors, such as anxiety, depression, and expectation can exert an influence on pain perception via this pathway. Later on, Melzack and Casey (1968) elaborated this idea adding sensory-discriminative and motivational-affective systems to the model. These ideas had a large impact on pain research, going towards the conceptualization of pain as a multidimensional experience, and moving from a strict biomedical perspective to a biopsychosocial perspective (Engel, 1977). Within the biopsychosocial perspective it is assumed that in order to fully understand a person's perception and response to pain and illness, the interrelationships among biological variables, psychological states, and the sociocultural context need to be considered (Gatchel et al., 2007). This gave rise to the investigation of the involvement of psychological and cognitive factors in the pain experience.

1.3 THE DEFINITION OF PAIN

Currently, pain is 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). First, this definition implies that a distinction should be made between pain and nociception (Figure 1). Nociception refers to the reception of signals in the central nervous system evoked by the activation of specialized sensory receptors (nociceptors) that provide information about tissue damage. Pain, however, is a product of activity in higher order brain areas and is a subjective experience. Although the perception of pain is related to the activation of nociceptors, there is no one-to-one relationship. Indeed, as mentioned above, not every pain experience is the result of a noxious stimulus or an injury, nor do all noxious stimuli that activate the nociceptors lead to the experience of pain. This is also related to a second facet of pain, namely that the pain experience can be influenced by top-down variables, such as expectations or anxiety. Third, the definition implies that pain has both an emotional component as well as unique sensory and perceptual characteristics. The emotional and sensory components are to some extent correlated, but can also be differentiated (Fernandez & Turk, 1992).

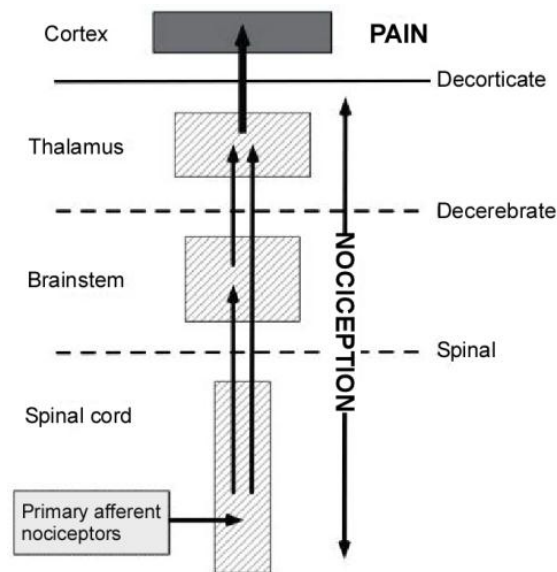


FIGURE 1. ANATOMICAL DISTRIBUTION OF NOCICEPTION AND PAIN. THE FIGURE SCHEMATIZES THE MAJOR NEUROANATOMICAL STRUCTURES THAT DIFFERENTIATE NOCICEPTION AND PAIN. FROM NATIONAL RESEARCH COUNCIL (US) COMMITTEE ON RECOGNITION AND ALLEVIATION OF PAIN IN LABORATORY ANIMALS (2009).

2 FROM PAIN AS A UNIQUE SENSATION TOWARDS A COGNITIVE PERSPECTIVE ON PAIN

2.1 THE “PAIN MATRIX”

A large number of studies have focused on the sensory characteristics of pain and have tried to unravel what is unique and unitary about pain. These studies have relied on a variety of non-invasive neuroimaging techniques (going from electroencephalography [EEG], magnetoencephalography [MEG] to positron emission tomography [PET], and functional magnetic resonance imaging [fMRI]) to measure the neural activity evoked by various kinds of nociceptive stimuli. Findings show the involvement of multiple subcortical and cortical areas in the processing of nociceptive stimuli, such as the primary (SI) and secondary (SII) somatosensory cortices, the insula, and the anterior cingulate cortex (ACC) (Apkarian, Bushnell, Treede, & Zubieta, 2005; Bushnell et al., 1999; Garcia-Larrea, Frot, & Valeriani, 2003; Ingvar, 1999; Peyron, Laurent, & García-Larrea, 2000; Porro, 2003; Rainville & Rainville, 2002; Tracey & Mantyh, 2007; Treede, Kenshalo, Gracely, & Jones, 1999). Because the same brain structures were consistently found to be involved in nociceptive processing across different studies (Garcia-Larrea et al., 2003; Tracey & Mantyh, 2007) and because the perceived intensity of the pain sensation correlates strongly with the activity in these brain areas (Bornhövd et al., 2002; Coghill, Sang, Maisog, & Iadarola, 1999; Iannetti, Zambreanu, Cruccu, & Tracey, 2005), it has been hypothesized that these cortical areas constitute a “pain

matrix”, a constellation of brain areas that are preferentially involved in the generation of pain from nociception (Bornhövd et al., 2002; Coghill et al., 1999; Iannetti et al., 2005). It should be noted that other brain structures also respond to nociceptive stimuli, such as the amygdala, the prefrontal and parietal cortices, various parts of the brainstem and the cerebellum (Figure 2). However, these are not explicitly included in the “pain matrix” either because they did not consistently respond to nociceptive input across studies (Peyron et al., 2000), or because of the a-priori assumption that they reflect brain processes that are unspecific for pain (Apkarian et al., 2005). The conceptualization of the “pain matrix” has led to the idea that the pain experience would result from the activity elicited in the network of brain areas that constitute the “pain matrix”. Therefore, measuring the activity within this network would provide a direct and objective measure of the actual pain experience (Borsook, Sava, & Becerra, 2010).

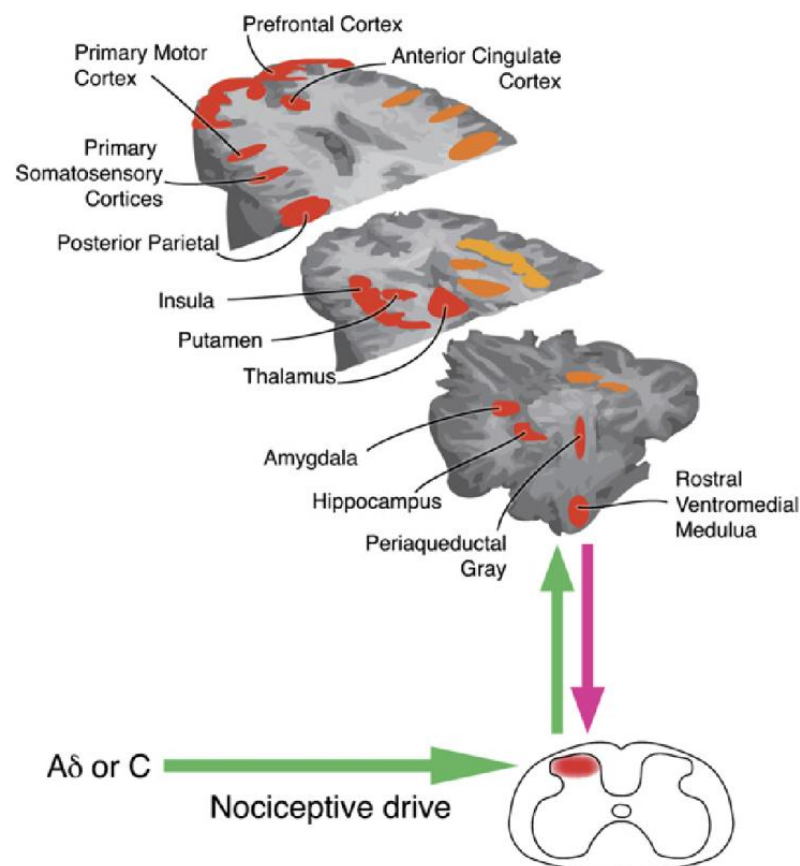


FIGURE 2. THE CORTICAL AND SUBCORTICAL STRUCTURES ACTIVATED DURING A PAINFUL EXPERIENCE. FROM TRACEY & MANTYH (2007).

2.2 TOWARDS A “SALIENCE DETECTION SYSTEM”

Several studies have challenged the idea of the “pain matrix” as a specific and unique “signature” (Tracey & Mantyh, 2007) of pain in the brain. First, it has been shown that the activity in the “pain matrix” can be dissociated from the perceived pain and the physical intensity of the nociceptive stimulus (Clark, Brown, Jones, & El-Dereby, 2008; Iannetti, Hughes, Lee, & Mouraux, 2008). For example, Iannetti et al. (2008) delivered trains of three identical laser pulses at four different energies and explored the modulation of the temporal expectancy of the stimulus on the relationship between intensity and pain perception, and on the magnitude of the laser-evoked brain responses (LEPs). They found that increasing the temporal expectancy of the stimulus, through stimulus repetition at a constant inter-stimulus interval, did not affect the intensity of the elicited pain sensation. In contrast, it significantly reduced the magnitude of the LEPs. These results show that the relationship between the perceived pain intensity and the brain responses evoked by the painful stimulus can be disrupted.

Second, the activity within the brain areas that constitute the “pain matrix” seems to be dependent on the context in which the nociceptive stimulus appears, as well as the attention allocated to it, and not merely on the intensity of the nociceptive stimulus. It has been demonstrated that the effect of stimulus repetition (Iannetti et al., 2008) is dependent on the inter-stimulus interval: the shorter the interval, the larger the decrease in amplitude of the LEPs following stimulus repetition (Truini, Galeotti, Cruccu, & Garcia-Larrea, 2007). However, when inter-stimulus intervals vary randomly, and the presentation of the stimulus becomes unpredictable, the length of the inter-stimulus interval no longer has an effect on the amplitude of the LEPs (Wang, Mouraux, Liang, & Iannetti, 2010). This indicates that contextual information has a crucial impact on the brain activity elicited by nociceptive stimuli. Moreover, also the novelty of the nociceptive stimulus has an influence on the brain responses it elicits (Legrain, Guérit, Bruyer, & Plaghki, 2002; Legrain, Perchet, García-Larrea, & Garcia-Larrea, 2009). When long, monotonous sequences of nociceptive laser stimuli are randomly interspersed with a small amount of new stimuli (< 20%), this rare nociceptive stimulus evokes an increased LEP compared to the standard stimuli. This was true irrespective of the physical property distinguishing the rare from the standard stimuli: the same results were found both when the intensity (Legrain et al., 2002) and when the spatial location of the stimulus was changed (Legrain, Perchet, et al., 2009). Moreover, the effect was also observed when attention was directed towards another body location (Legrain et al., 2002), or to stimuli belonging to a different sensory modality (Legrain et al., 2009). This indicates that the effect of novelty on the magnitude of the ERPs is driven by the ability of

the nociceptive stimulus to involuntarily capture attention from its current focus (Legrain et al., 2009), and not by the participant's expectations or his intention to direct attention towards the nociceptive stimulus.

Third, activity in the "pain matrix" is not only elicited by nociceptive stimuli, but can also be elicited by stimuli in other modalities. Both EEG (Mouraux & Iannetti, 2009) and fMRI (Mouraux, Diukova, Lee, Wise, & Iannetti, 2011) studies have shown that nociceptive, tactile, auditory and visual stimuli can elicit brain responses that are indistinguishable from each other in brain areas associated with the "pain matrix". These studies indicate that most of the brain responses to nociceptive stimuli reflect multimodal neural activity, i.e. activity that can be triggered by any stimulus, irrespective of its sensory modality.

Taken together these studies show that, although it is likely that nociceptive-specific neurons exist, discovering these may prove to be difficult. The brain areas constituting the "pain matrix", such as the SII, the insula, and the ACC, can be activated by various kinds of sensory stimuli and cognitive settings (Corbetta & Shulman, 2002; Macaluso & Driver, 2005). The probability of finding neurons whose activity reliably triggers pain might be very low, considering the very low proportion of nociceptive-specific neurons in these brain areas (Dong, Chudler, Sugiyama, Roberts, & Hayashi, 1994). The studies mentioned above point out that the bulk of brain responses to nociceptive stimuli identified using fMRI and EEG, reflect a system involved in the extraction and processing of sensory information from the environment, independently of sensory modality.

Therefore, the activity in this network of brain areas seems more related to the concept of *saliency* (Iannetti et al., 2008; Legrain, Perchet, et al., 2009; Legrain, Van Damme, et al., 2009). The saliency of a stimulus is defined as its ability to stand out relative to other, neighboring stimuli, and is determined by how much it contrasts, along one or more physical dimensions, from its surroundings (Yantis, 2008). Moreover, saliency is also determined by the past context and memories (Näätänen, Paavilainen, Rinne, & Alho, 2007). In this case, novel events are salient, because they are completely new or because they deviate from the expectations built from past experiences. The brain activity evoked by nociceptive stimuli would then not reflect a "pain matrix", but instead a *saliency detection system*, detecting and orienting attention towards any event in the sensory environment that may have a significant impact on the organism (Legrain, Iannetti, Plaghki, & Mouraux, 2011). This function would be important to guarantee coherent and adaptive behavior, and stresses the affective-motivational aspects of pain.

2.3 A COGNITIVE PERSPECTIVE ON PAIN

The search for what is unique about pain has led to a restrictive focus on the sensory aspects of pain, neglecting the role of attentional and affective-motivational characteristics of pain on an organism that behaves within and interacts with its natural environment (Eccleston & Crombez, 1999). Indeed, pain is more than “*an unpleasant sensory and emotional experience caused by actual or potential tissue damage (...)*” (IASP, 1994, p 210). Instead it can be seen from a cognitive perspective as a “*warning signal allowing detection, localization and reaction against a stimulus potentially meaningful for the physical integrity of the body*” (Legrain & Torta, 2015). This definition points out the important role of three distinct cognitive processes in the processing of nociceptive stimuli: (1) selective attention, to detect and orient towards the most salient or relevant stimuli in order to prioritize its processing, (2) spatial perception, to localize stimuli on the space of the body and the external space, (3) action selection, to select and prepare the most appropriate (defensive) motor response. These processes are not specifically involved in nociception. Therefore, emphasis is no longer on the quality of the sensation evoked by noxious stimuli, but on the action prompted by the occurrence of potential threats. In order to understand how the brain adapts to meaningful changes and defends the body against potentially harmful stimuli, one should thus investigate how selective attention, spatial perception and action selection are involved in the processing of nociceptive inputs (Legrain & Torta, 2015). In this PhD thesis the focus lies on the involvement of one of these cognitive processes, namely the *spatial perception*, in the processing of nociceptive stimuli.

3 SPATIAL PERCEPTION

The localization of a nociceptive stimulus on the body surface is essential if an organism is to make a swift and appropriate response to bodily threat (Legrain, Mancini, et al., 2012; Mancini, Longo, Iannetti, & Haggard, 2011). Think about a lazy afternoon in the park. You are sitting and chatting with friends, enjoying the fresh air, the sun on your face, and the sound of the water that gurgles out of the fountain in the lake beside you. Oh yes, there is also the sound of children playing football, just a little bit too close to you to be completely at ease. So you will probably be more alert than you would normally be, dividing your attention between the conversation in your group and scanning the environment for possible projectiles approaching you. The moment one of the children (probably the one with the ‘Lionel Messi’ shirt) uncontrollably spins the ball towards your group, you will automatically put your arm up in defense and swipe the ball away.

This mindless act of swiping the ball away seems simple, but it poses a remarkable challenge for the brain. The ability to localize a nociceptive stimulus on the body depends partially on a direct relationship between the spatial organization of the skin receptors and the spatial organization of neurons in the cerebral cortex (Kenshalo & Isensee, 1983). However, this only allows the identification of their position on the skin surface. It is also of primary importance to perceive the position of objects, that might be the cause of damage, in external space in order to guide defensive motor responses towards the location of threat. The space around us is represented many times in the brain, and these multiple representations encode locations and objects of interest in several reference frames (Vallar & Maravita, 2009). Stimulus representations are transformed from coordinates of receptor surfaces, such as the retina, into the coordinates of effectors, such as the eyes. The brain constructs multiple spatial representations, with each representation linked to a different action or region of space (Fogassi et al., 1996; Graziano, Yap, & Gross, 1994; Jeannerod, Arbib, Rizzolatti, & Sakata, 1995). These multiple spatial reference frames or spatial coordinate systems are used to guide behavior, and are thought to be constructed within the parietal cortex (Colby & Goldberg, 1999). Indeed, patients with lesions in the parietal lobe exhibit a variety of spatial deficits, with one of the most striking being unilateral neglect, the tendency to ignore objects in half of the space contralateral to the site of the lesion (Vallar, 1997). In what follows a distinction will be made between several frames of reference that can be used to code the position of sensory stimuli.

4 SPATIAL FRAMES OF REFERENCE

4.1 EGOCENTRIC VERSUS ALLOCENTRIC

A distinction can be made between *egocentric* and *allocentric* frames of reference (Figure 3). Within an egocentric frame of reference, the location of stimuli in the environment are represented relative to the observer's body or relative to their body parts. Conversely, objects represented in an allocentric frame of reference are represented independently of the observer's current position. Instead they are represented relative to other objects and thus in object-centered coordinates. Egocentric representations can be found in the dorsal stream brain areas, subserving goal-directed actions (Goodale & Milner, 1992). Single cell recordings in monkeys and fMRI studies in humans have shown that coding of space in parietal (Andersen, 1995; Carey, 2000; Connolly, Andersen, & Goodale, 2003; Medendorp, Goltz, Crawford, & Vilis, 2005), subcortical (Meredith, Nemitz, & Stein, 1987) and (pre)motor (Kalaska & Crammond, 1992) structures takes place relative to a particular

effector, such as the current gaze (retinotopic), head orientation, or even body (or trunk) orientation. Conversely, areas holding allocentric representations of space are thought to subserve conscious perception of objects, or memory functions, and are found mainly along the ventral processing stream (Goodale & Milner, 1992). Evidence for the existence of these two separate spatial reference frames for coding spatial coordinates in humans have been provided by showing that these two reference frames can be differentially affected in patients with unilateral neglect (Marsh & Hillis, 2008).

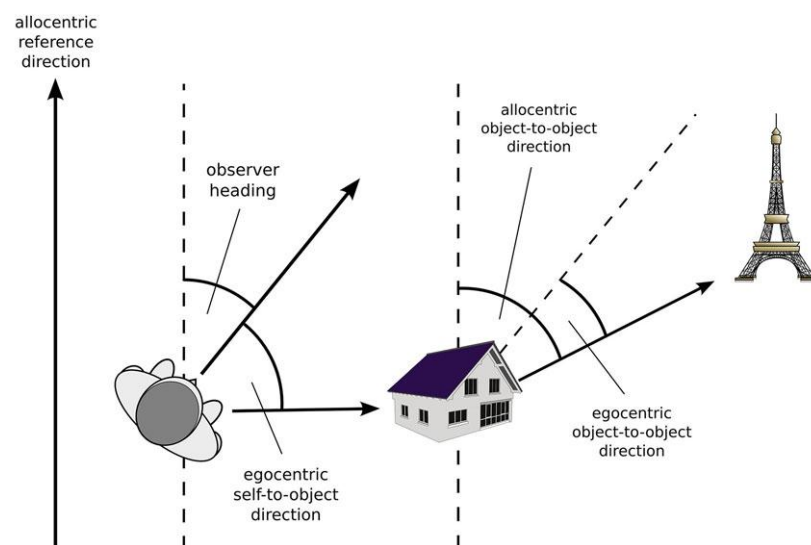


FIGURE 3. ILLUSTRATION OF THE DIFFERENCE BETWEEN THE EGOCENTRIC AND ALLOCENTRIC FRAME OF REFERENCE. THE EGOCENTRIC FRAME OF REFERENCE IS CENTERED ON THE OBSERVER, AND ITS ORIENTATION IS DEFINED BY THE OBSERVER'S HEADING. IN CONTRAST, AN ALLOCENTRIC REFERENCE FRAME SPECIFIES AN OBJECT'S POSITION WITHIN A FRAMEWORK EXTERNAL TO THE OBSERVER AND INDEPENDENT OF ITS POSITION AND ORIENTATION. FROM WOLBERS & WIENER (2014) .

4.2 SOMATOTOPIC VERSUS SPATIOTOPIC

The space of the body (also called the *personal space*) can be dissociated in a *somatotopic* and a *spatiotopic* frame of reference. The somatotopic reference frame provides an anatomical representation, based on the ordered projection of receptor fields² to segregated subgroups of neurons, or in other words a representation of the body parts as provided by somatotopic maps in the somatosensory cortex. The spatiotopic reference frame on the other hand, provides a space-based representation of the body space. This latter

² The receptive field of a neuron is the region of space in which the presence of a stimulus will alter the firing of that neuron

representation depends upon a representation of external space, i.e. the representation of your body or body-part locations relative to other external objects, or representations coding the position of your body parts relative to each other or relative to the body midline (Vallar, 1997).

The distinction between these two reference frames can be demonstrated by applying a stimulus (e.g., tactile or nociceptive) to one of the hands while your hands are either uncrossed or crossed over the body midline (Figure 4). If hands are uncrossed, the two reference frames cannot be dissociated from each other. When for example the left hand is stimulated, the representation in both reference frames will guide your attention to the left side of space. However, when hands are crossed over the body midline, the left hand now lies in the right side of space (and vice versa for the right hand). The somatotopic frame of reference does not take this information into account. A stimulation to the left hand is still processed in the contralateral (right) hemisphere, and therefore this reference frame would guide your attention to the left side of space. To the contrary, the space-based frame of reference acknowledges the position of your hands relative to the body midline and relative to each other (i.e. proprioceptive information). Therefore, when the left hand is stimulated, it will now guide your attention towards the right side of space. We will refer to this procedure as the '*crossing hands procedure*', that is when the relative position of the hands in external space is manipulated according to the sagittal midline of the body.

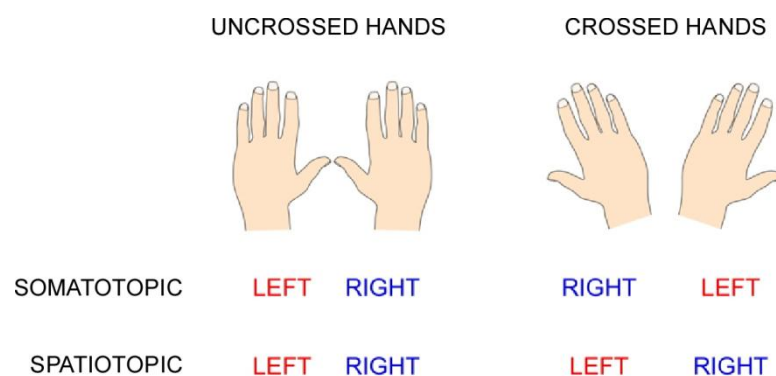


FIGURE 4. THE DISTINCTION BETWEEN SOMATOTOPIC AND SPATIOTOPIC FRAMES OF REFERENCE ILLUSTRATED WITH THE *CROSSING HANDS PROCEDURE*. A STIMULUS (E.G., TACTILE OR NOCICEPTIVE) IS APPLIED TO THE LEFT OR RIGHT HAND WHILE HANDS OR EITHER UNCROSSED (LEFT PART FIGURE) OR CROSSED OVER THE BODY MIDLINE (RIGHT PART FIGURE). IN UNCROSSED POSTURE, BOTH REFERENCE FRAMES WILL GUIDE YOUR ATTENTION TO THE LEFT WHEN THE LEFT HANDS IS STIMULATED (AND VICE VERSA FOR THE RIGHT HAND), MAKING IT IMPOSSIBLE TO DISSOCIATE BETWEEN THE TWO REFERENCE FRAMES. HOWEVER, WHEN HANDS ARE CROSSED OVER THE BODY MIDLINE, A STIMULUS APPLIED TO THE LEFT HAND WILL STILL GUIDE YOUR ATTENTION TO THE LEFT SIDE OF SPACE (AND VICE VERSA FOR THE RIGHT HAND) BASED ON THE SOMATOTOPIC FRAME OF REFERENCE (UPPER PART FIGURE). TO THE CONTRARY, THE SPATIOTOPIC FRAME OF REFERENCE (LOWER PART FIGURE) WILL TAKE PROPRIOCEPTIVE INFORMATION INTO ACCOUNT, AND WILL GUIDE YOUR ATTENTION THE RIGHT SIDE OF SPACE (AND VICE VERSA FOR THE RIGHT HAND).

Smania & Aglioti (1995) were able to demonstrate a dissociation between the somatotopic and the spatiotopic frames of reference using the crossing hands procedure in patients with right brain damage and somatosensory extinction, hemispacial neglect or both. Extinction is the phenomenon that a simple sensory stimulus (e.g., a light touch or a flash of light) delivered contralaterally to a cerebral lesion may be detected when presented alone, but when an ipsilesional stimulus is simultaneously presented, the contralesional stimulus remains undetected. Extinction can occur in patients with peripheral lesions (Heilman et al., 1993) and in callosotomy patients (Sparks, 1968; Milner et al., 1968), but it is mostly observed in patients with cerebral lesions, particularly those involving the parietal lobe (Schwartz et al., 1979; Gainotti et al., 1989). In their study, Smania & Aglioti (1995) asked patients to verbally report light touches delivered to the left hand, the right hand or both hands simultaneously, while their hands were either uncrossed or crossed over the body midline. Under both single and double stimulation conditions, patients detected stimuli delivered to the contralesional hand with lower accuracy in the uncrossed than in the crossed condition. These results suggest that symptoms of neglect are defined not only in terms of somatotopic frames of reference, but in terms of spatiotopic frames of reference, i.e. they demonstrate that the lesion affected the orienting of attention in the contralesional side of *space*.

The dissociation between the somatotopic and spatiotopic reference frame has also been demonstrated in healthy volunteers both for the localization of tactile and nociceptive stimuli. For *tactile* stimuli several studies used tactile temporal order judgment (TOJ) tasks to investigate this matter (Yamamoto & Kitazawa, 2001; Shore, Spry, & Spence, 2002; Röder, Rösler, & Spence, 2004; Pagel et al., 2009; Azañon et al., 2015). In these tasks, participants were presented with two tactile stimuli, one to each hand, and participants had to decide which hand was stimulated first. Importantly, they had to perform this task while their hands were either uncrossed or crossed over the body midline. Participants could correctly report the temporal order of the tactile stimuli when hands were uncrossed, but they often misreported the order when hands were crossed over the body midline (Yamamoto & Kitazawa, 2001; Shore, Spry, & Spence, 2002; Röder, Rösler, & Spence, 2004; Pagel et al., 2009; Azañon et al., 2015). It is argued that this lower temporal sensitivity in the crossed hands condition results from a competition between the somatotopic reference frame and a remapping of the tactile stimulus according to spatiotopic coordinates (Yamamoto & Kitazawa, 2001). Interestingly, a recent study suggests that the temporal sensitivity in the unfamiliar, crossed posture improves rapidly throughout trials, indicating that the mapping from the skin to external space also relies on spatial information from preceding touches

(Azañon et al., 2015). This improvement in tactile localization required neither performance feedback, nor explicit localization of the preceding tactile events.

Similar results have been found for *nociceptive* stimuli. Crossing the hands over the body midline affects judgments concerning the temporal order of nociceptive stimuli applied to either hand (Sambo et al., 2013), and it might even influence the perception of their intensity (Gallace et al., 2011). Gallace et al. (2011) asked participants to rate the perceived intensity of a low, medium and high energy nociceptive laser pulse and non-nociceptive somatosensory stimulus on a 0 to 100 numerical rating scale while their arms were uncrossed or crossed over the body midline. They found that crossing the arms reduced the intensity of the sensation evoked by the stimuli, irrespective of the energy and the sensory modality of the stimulus (i.e. nociceptive or non-nociceptive). Taken together, these studies demonstrate that nociceptive processing is influenced by the conflict between a somatotopic representation of the body, and a spatiotopic representation, generated by the crossing hands procedure.

4.3 PERIPERSONAL VERSUS EXTRAPERSONAL

The representation of external space can be dissociated into *peripersonal* and *extrapersonal* frames of reference, coding respectively the position of stimuli arising close to versus far from the body (see Figure 5) (Halligan & Marshall, 1991). These frames of reference are defined according to an egocentric perspective, that is relative to the observer's own body. The peripersonal frame of reference is of particular interest, because it codes both the position of somatosensory stimuli on the body surface and the position of stimuli in external space (e.g., visual stimuli), when they are close to the body (Holmes & Spence, 2004; Maravita, Spence, & Driver, 2003). It therefore allows an individual to coordinate the map of the body and the map of external close space into an integrated multisensory representation of space (Cardinali, Brozzoli, & Farnè, 2009; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981; Spence & Driver, 2004). The peripersonal frame of reference is specifically relevant to help guide direct manipulation of objects (Rizzolatti, Fadiga, Fogassi, & Gallese, 1997), unlike the extrapersonal frame of reference, which is more useful to explore the space by eye movements and to prepare reaching movements. Moreover, the peripersonal space is believed to be crucial for the organization of defensive motor actions (Graziano & Cooke, 2006).

In what follows, we will further focus on the peripersonal frame of reference and its role in the localization of tactile and nociceptive stimuli. In the next section, we discuss some of

the studies providing evidence for a peripersonal frame of reference for the localization of tactile stimuli.

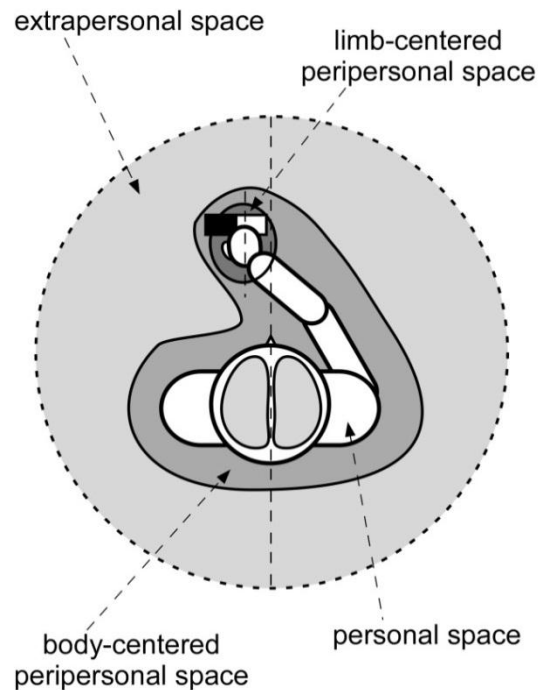


FIGURE 5. DIFFERENT FRAMES OF REFERENCE TO PERCEIVE THE BODY AND THE SPACE SURROUNDING THE BODY. THE PERSONAL REFERENCE FRAME CORRESPONDS TO THE SPACE OF THE BODY. THE PERIPERSONAL FRAME OF REFERENCE IS THE SPACE CLOSELY SURROUNDING THE BODY, IN WHICH SOMATOSENSORY INFORMATION IS INTEGRATED WITH VISUAL AND AUDITORY INFORMATION WHEN THEY APPEAR NEAR THE BODY. THE PERIPERSONAL FRAME OF REFERENCE CAN BE CENTERED ON THE BODY WITH THE SAGITTAL MIDLINE OF THE BODY AS A COORDINATE TO SEPARATE THE LEFT AND RIGHT SIDE OF SPACE (BODY-CENTERED PERIPERSONAL SPACE). IT CAN ALSO BE CENTERED ON EACH LIMB WITH THE LIMB ITSELF AS COORDINATE (LIMB-CENTERED PERIPERSONAL SPACE). THE EXTRAPERSONAL FRAME OF REFERENCE IS USED TO EXPLORE THE FAR SPACE BY MOVEMENTS OF THE EYES AND THE LIMBS. FROM LEGRAIN & TORTA, 2015.

5 EVIDENCE FOR A PERIPERSONAL FRAME OF REFERENCE FOR THE LOCALIZATION OF TACTILE STIMULI

5.1 BIMODAL NEURONS IN MONKEYS

The existence of a peripersonal frame of reference has been well-documented to map the position of tactile stimuli, by showing that tactile stimuli are integrated with external stimuli (e.g., visual or auditory) when they appear near the body (for a review, see Spence & Driver, 2004). In monkeys, it has been shown that this ability relies on bimodal neurons found in the ventral premotor cortex and the ventral intra-parietal sulcus. These bimodal neurons respond both to the stimulation of a specific body-part and to stimuli or events that occur

close to that body part (Graziano & Gross, 1994). For example, Graziano and Gross (1998) demonstrated that neurons in the ventral premotor cortex of monkeys fire both for tactile and visual stimuli, and that their visual receptive field (RF) extends from the approximate region of the tactile RF into the immediate adjacent space. Moreover, it has been shown that the region of space within which visual stimuli are effective in exciting these bimodal neurons is modulated by the positions of the arms in space (Fogassi et al., 1996; Graziano, Hu, & Gross, 1997). Graziano et al. (1997) recorded the activity of bimodal neurons while the arm position, the head position and the gaze direction were manipulated. They found that for most bimodal neurons with a tactile response on the arm, the visual RF moved when the arm was moved. Conversely, most bimodal cells with a tactile response on the face had a visual RF anchored to the head, moving as the head was rotated. The visual RFs did not move when gaze direction was manipulated. Furthermore, after training monkeys to retrieve distant objects with a rake, the visual RFs of the bimodal neurons was altered to include the entire length of the rake (Iriki, Tanaka, & Iwamura, 1996), indicating that the peripersonal space is constructed around the modified representation of the hand. These studies provide evidence for a peripersonal frame of reference for the mapping of tactile stimuli in monkeys. Moreover, they show that the peripersonal frame of reference is spatially locked to the stimulated body part, moving with it in space, providing evidence for a *limb-centered* peripersonal frame of reference, taking the limb as coordinate to separate left and right space, as opposed to a *body-centered* peripersonal frame of reference, which takes the sagittal midline of the body as coordinate (see Figure 5).

5.2 NEUROPSYCHOLOGICAL STUDIES IN PATIENTS

In humans, some neuropsychological studies provided evidence to support multimodal interactions between tactile stimuli and external (e.g., visual, or auditory) stimuli in the peripersonal space. These studies have investigated the perception of somatosensory stimuli in patients with lesions in the frontal and parietal cortices, mostly in the right hemisphere. As mentioned before, these patients often demonstrate a phenomenon called extinction: they can feel a tactile stimulus to the left hand in isolation, but when their right hand is concurrently stimulated, they fail to report the stimulation to their left hand (unimodal extinction). Remarkably, extinction can also occur when a visual stimulus is presented near the ipsilesional hand (crossmodal extinction) (di Pellegrino, Làdavas, & Farnè, 1997; Mattingley, Driver, Beschin, & Robertson, 1997). This crossmodal extinction was attenuated when the relative distance to the hand was increased, even when the distance to the body was kept constant (di Pellegrino et al., 1997), providing evidence for a

limb-centered peripersonal frame of reference for the mapping of tactile stimuli. This was also demonstrated with studies investigating the effect of tool-use on crossmodal extinction in brain damaged patients. Farnè & Ladavas (2000) assessed crossmodal extinction far from the patients' ipsilesional hand, at the distal edge of a hand-held rake. They found that following the use of a rake to retrieve distant, otherwise non-reachable objects, the peri-hand multisensory area extended to include the distal part of the rake (Farnè & Ladavas, 2000). This re-sizing of the peri-hand space seems selective for tool-use, as the mere pointing without the tool, and passive exposure to the tool did not modulate the multisensory area around the hand (Farne, Bonifazi, & Ladavas, 2005).

5.3 THE CROSSMODAL CONGRUENCY TASK IN HEALTHY VOLUNTEERS

In healthy volunteers similar results were found using a visuo-tactile crossmodal congruency task. In this task, participants make speeded discrimination responses ('left' hand versus 'right' hand; or elevation judgments: 'upper' versus 'lower' location on either hand) to vibrotactile targets, while trying to ignore nearly simultaneous visual distractor stimuli. The effect of the congruency of the visual distractor to the vibrotactile target is then assessed. If multisensory interactions between tactile and visual stimuli occur, one would expect that reaction times would be shorter on congruent than on incongruent trials. Using this task, Spence, Nicholls, Gillespie, & Driver (1998) found that tactile discriminations were faster for targets presented at the same location as a shortly preceding visual distractor than when they were presented at the opposite side.

Some studies investigated the effect of crossing the hands on performance in a visuo-tactile crossmodal congruency task. These studies found that in the crossed posture, the discrimination of tactile stimuli applied to the left hand was more influenced by right - than left-sided visual stimuli, and vice versa (Holmes, Sanabria, Calvert, & Spence, 2006; Kennett, Eimer, Spence, & Driver, 2001; Kennett, Spence, & Driver, 2002; Spence, Pavani, & Driver, 2004; van Elk, Forget, & Blanke, 2013). This provides evidence for a space-based frame of reference for the localization of tactile stimuli, in which the position of the limbs (proprioception) and the position of external objects with respect to limb position is taken into account. It was further shown that the influence of the visual distractors on tactile discrimination is stronger when the visual distractors are presented near the body, as opposed to far from the body (Sambo & Forster, 2009), providing evidence for a peripersonal frame of reference. Moreover, other studies showed that after active tool-use visuo-tactile interactions are stronger at the tip of the tool (Holmes, Calvert, & Spence, 2004;

Maravita, Spence, Kennett, & Driver, 2002). This indicates that the tip of the tool in extrapersonal space are incorporated in the brain's visuotactile representation of the body and the peripersonal space, suggesting that the peripersonal space might be limb-centered, rather than body-centered.

5.4 DYNAMICAL STIMULI IN THE PERIPERSONAL SPACE

The above-mentioned studies in humans have, unlike the animal studies, focused on external stimuli at two fixed locations (i.e. one position near the participants, and one far from the participants), instead of dynamical, moving stimuli. Nevertheless, some studies have shown that the neural systems representing the peripersonal space show a preference for moving stimuli, both in humans and in monkeys (Bremmer, Schlack, Duhamel, Graf, & Fink, 2001; Duhamel, Colby, & Goldberg, 1998; Fogassi et al., 1996; Graziano et al., 1997; Makin, Holmes, & Zohary, 2007). Neurophysiological studies in monkeys have shown that bimodal neurons in the premotor cortex and the ventral intraparietal cortex are more effectively activated when objects are approaching or receding from the animal's body, compared to static stimuli. Some of these neurons also show direction-selective and velocity dependent response patterns, with increasing firing rates in function of the velocity of approaching stimuli (Colby, Duhamel, & Goldberg, 1993). In humans, similar results were found, with increased neural activity in the intraparietal sulcus and the ventral premotor cortex evoked by approaching visual, auditory and tactile stimuli (Bremmer, Schlack, Shah, et al., 2001). The preference for moving stimuli fits with the sensory-to-motor function of the peripersonal space representation. This representation would code for the spatial position of external stimuli with respect to the body parts, enabling interaction with it. This can consist of planning defensive reactions to potentially threatening objects approaching us (Graziano & Cooke, 2006), or an approaching movement towards an interesting object (Rizzolatti et al., 1997).

More recently, studies have begun to investigate the influence of moving stimuli on tactile processing (Brendel, DeLucia, Hecht, Stacy, & Larsen, 2012; Canzoneri, Magosso, & Serino, 2012; Taffou & Viaud-Delmon, 2014; Teneggi, Canzoneri, di Pellegrino, & Serino, 2013; Vagnoni, Lourenco, & Longo, 2012; Van der Biest, Legrain, De Paepe, & Crombez, 2015). An additional advantage of the use of moving stimuli is that it allows to investigate the influence of external stimuli along a spatial continuum (from near to far space). These studies have found that the spatially-dependent effects of external stimuli on tactile processing is stronger for approaching than for receding stimuli (e.g., Bremmer, Duhamel,

Ben Hamed, & Graf, 2002; Canzoneri et al., 2012; Colby et al., 1993; Kandula, Hofman, & Dijkerman, 2014). Moreover, this effect is dependent on the perceived threat of the stimuli. Some studies have shown that individuals underestimate the time it takes for an approaching visual stimulus to collide with them, when the stimulus is threatening (snakes, spiders, threatening face), compared to when it is non-threatening (Coello, Bourgeois, & Iachini, 2012). Finally, by using moving stimuli it has also been shown that the distance at which multimodal interactions with stimuli approaching the body are observed can be modulated by e.g., anxiety (Taffou & Viaud-Delmon, 2014) or satisfying social interactions (Teneggi et al., 2013).

5.5 THE NEURAL MECHANISMS OF VISUO-TACTILE INTERACTIONS

Visual and tactile stimuli are initially processed in different regions of the brain and the positions of these stimuli are registered according to different frames of reference. Tactile inputs activate somatosensory regions in the post-central gyrus (the primary (SI) and secondary (SII) somatosensory cortices), where the body surface is represented somatotopically (Disbrow, Roberts, & Krubitzer, 2000; Kurth et al., 1998). Visual responses activate the occipital visual cortex, where responses follow a retinotopic organization (Sereno, McDonald, & Allman, 1994; Tootell et al., 1998). The different sensory-specific areas project to common high-level associative regions in the parietal, frontal and temporal cortices (Jones & Powell, 1970; Lewis & Van Essen, 2000). Electrophysiological recordings in monkeys have revealed neurons responding both to vision and touch in ventral intraparietal area (VIP, Duhamel et al., 1998), the posterior parietal cortex (area 7, Leinonen, Hyvärinen, Nyman, & Linnankoski, 1979; Leinonen & Nyman, 1979), in the posterior part of the superior temporal sulcus (cSTP, Bruce, Desimone, & Gross, 1986) and in the premotor cortex (Graziano et al., 1997). Multimodal activation of corresponding brain areas has been identified in humans (Bremmer, Schlack, Shah, et al., 2001). Multisensory interactions might appear via feed-forward convergence from sensory-specific visual and tactile regions to associative regions, and on the other hand these interactions are likely to be influenced by feed-back projections from multisensory to modality-specific brain areas (Kennett et al., 2001; Macaluso, Frith, & Driver, 2000). For example, Kennett et al. (2001) showed that non-predictive tactile stimulation of the hands speeded reaction times and enhanced the magnitude of the ERPs elicited by visual stimuli presented near the stimulated hand. Similarly, Eimer & Van Velzen (2005) showed that enhancement of the visual N1 component at the cued side was dependent on the spatial proximity between the stimulated body limb and the visual stimulus. The modulation of visual ERPs as early as the N1 component

confirms that the location of a tactile stimulus can modulate the sensory processing of visual inputs and is compatible with the hypothesis of a crossmodal modulation of unimodal processing (Eimer, Cockburn, Smedley, & Driver, 2001; Macaluso & Driver, 2001; Macaluso, Frith, & Driver, 2005). Sambo & Forster (2009) investigated the opposite, namely the modulation of tactile ERPs by visual cue stimuli. They found an enhancement of ERPs recorded over and close to the somatosensory cortex as early as 100 ms (i.e. the P100) after the onset of the stimuli, when visual stimuli were presented near the site of tactile stimulation, compared to when they were presented far from the site of stimulation. The modulation of the P100 component, assumed to be generated in the secondary somatosensory cortex (SII, Frot & Maugière, 1999), suggests that sensory-specific areas can be modulated by spatially congruent visual-tactile stimulation. These ERP results are in line with fMRI studies, showing that activity in modality-specific brain regions (i.e. parietal operculum, corresponding to SII, and occipital cortex) can be modulated by crossmodal interactions between visual and tactile stimuli (Macaluso et al., 2000, 2002, 2005).

6 WHAT ABOUT THE LOCALIZATION OF NOCICEPTIVE STIMULI?

Although well established for touch, the mapping of nociceptive stimuli in a peripersonal frame of reference has received less attention. Dong et al. (1994) found multimodal neurons, analogously to the ones found for tactile stimuli (Graziano et al., 1997) that respond both to nociceptive stimuli and to dynamical visual stimuli moving towards the RF of neurons or static visual stimuli presented in vicinity of the somatosensory RF, in area 7b in the inferior parietal lobe of monkeys. In humans, most studies have focused on the description of the somatotopic organization of the neuronal responses to nociceptive and painful stimuli (Andersson et al., 1997; Baumgärtner et al., 2010; Bingel et al., 2004; Henderson, Gandevia, & Macefield, 2007). Only recently, studies have started to investigate the ability to localize pain according to non-somatotopic frames of reference. As mentioned above, some studies provided evidence for a spatiotopic frame of reference for the mapping of nociceptive stimuli (Gallace, Torta, Moseley, & Iannetti, 2011; Sambo et al., 2013). Other studies have shown that the hand blink reflex (HBR) triggered by high-intensity stimulations of the median nerve was enhanced when the stimulated hand was close to the eyes (Sambo, Forster, Williams, & Iannetti, 2012; Sambo & Iannetti, 2013; Sambo, Liang, Cruccu, & Iannetti, 2012). However, as visual stimuli were not presented beyond the personal space in these experiments, it is still a matter of debate whether the enhancement of the HBR by somatic threats is supported by the integration of the somatic threat into a head-centered

peripersonal frame of reference. Other studies have found evidence for crossmodal links in spatial attention between nociceptive or painful stimuli and proximal visual stimuli (Favril, Mouraux, Sambo, & Legrain, 2014; Van Ryckeghem et al., 2011). However, it is difficult to disentangle whether these effects are due to the lateralization of the stimuli (left vs. right space) or to their occurrence in proximity of the body.

Despite the lack of studies investigating the issue, the ability to quickly localize stimuli on the body and in external space seems especially relevant in the context of pain. Indeed, the peripersonal space is a multisensory motor interface between our body and the environment (Graziano & Cooke, 2006; Rizzolatti et al., 1997) enabling interaction with the world. While crossmodal interactions between external and tactile stimuli especially serve the grasping and manipulation of objects, the crossmodal interactions between external and nociceptive stimuli may serve the localization and initiation of defensive actions against potentially harmful objects approaching our body. Moreover, it has been shown that some chronic pain syndromes (e.g., complex regional pain syndrome, CRPS) are associated with cognitive deficits altering the ability to represent and perceive the body and the surrounding space (for a review, see Legrain, Bultitude, De Paepe, & Rossetti, 2012; Legrain & Torta, 2015). This highlights the importance of spatial perception to understand not only the normal processing of pain, but also to understand the pathophysiology and treatment of chronic pain.

7 AIMS AND OBJECTIVES

The aim of this PhD thesis is to investigate how the human brain constructs a multimodal and peripersonal schema of the body in order to localize nociceptive stimuli on the bodily space, and to swiftly react to potential physical threats approaching the body.

First, we investigate whether nociceptive stimuli are indeed mapped into a peripersonal frame of reference. We hypothesize that if a peripersonal frame of reference is used for the localization of nociceptive stimuli, nociceptive processing would be *multimodal*, (i.e. it would be influenced by the occurrence of visual stimuli occurring near the body) (De Paepe, Crombez, Spence, & Legrain, 2014), *spatiotopic* (i.e. it would depend on the position of the stimulated body part in external space) (De Paepe, Crombez, & Legrain, 2015), and *limb-centered* (i.e. the peripersonal space would be spatially locked to the stimulated body part and would move with it in space) (De Paepe, Crombez, & Legrain, in preparation [a]).

Second, we aim to investigate the neural correlates underlying the crossmodal interactions between vision and nociception in the peripersonal space with event-related potentials (ERPs). We hypothesize that visual stimuli occurring in the peripersonal space can modulate the early sensory-perceptual processing of nociceptive stimuli (De Paepe, Crombez, & Legrain, in preparation [b]).

Third, we are interested in the effect of moving visual stimuli, either approaching or receding from the body, on nociceptive processing in healthy volunteers. We expect that visual stimuli will influence nociceptive processing more when they are presented near as opposed to far from the body, and that approaching stimuli will have a larger spatially dependent effect on nociceptive processing than receding stimuli (De Paepe, Crombez, & Legrain, under review).

Fourth, we investigate the differential influence of moving visual stimuli on tactile processing for fibromyalgia (FM) patients compared to healthy controls. By doing this, we aim to test whether chronic pain, and more specifically FM, can alter spatial perception. We chose to investigate FM patients, because these patients demonstrate an exaggerated response not only to noxious stimuli, but also to stimuli in other modalities (e.g., sound) (Crombez, Van Damme, & Eccleston, 2005; McDermid, Rollman, & McCain, 1996). We want to investigate whether this over-responsiveness of FM patients could be associated with a heightened attention for stimuli entering the peripersonal space or whether they scan a larger share of the external space for salient and potentially threatening information (De Paepe, Crombez, & Legrain, in preparation [c]).

For the purpose of this PhD, three different paradigms were developed and used: (1) a temporal order judgment (TOJ) task, (2) a crossmodal cueing paradigm, and (3) a crossmodal cueing paradigm with dynamical stimuli.

7.1 THE TEMPORAL ORDER JUDGMENT TASK

According to the notion of prior entry, “*the object of attention comes to consciousness more quickly than the objects which we are not attending to*” (Titchener, 1908, p 251). The attended stimulus should have prior entry to awareness (Figure 6A). As a consequence, unattended stimuli have to be presented prior to attended stimuli in order to be perceived as simultaneous (for a review, see Spence & Parise, 2010). The difference in onset needed in order for unattended stimuli to be perceived at the same time as attended stimuli is a measure of the attentional bias (Figure 6B).

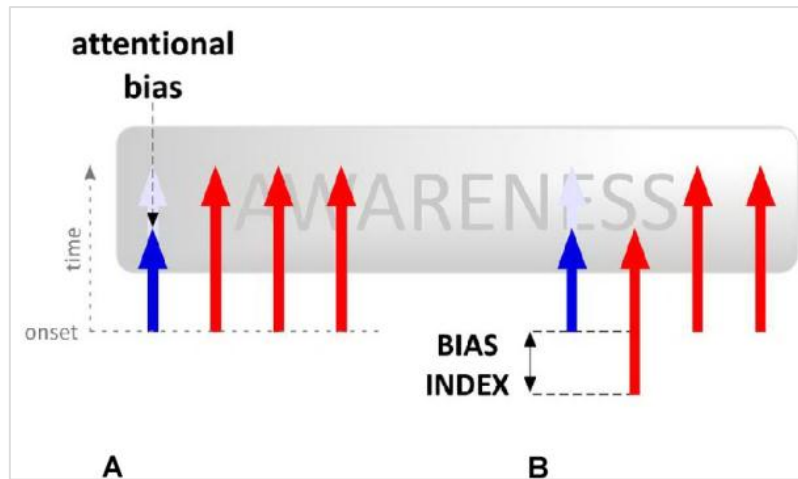


FIGURE 6. ILLUSTRATION OF THE PRIOR ENTRY EFFECT (TITCHENER, 1908). [A] ACCORDING TO THE NOTION OF PRIOR ENTRY, AN ATTENDED STIMULUS (BLUE ARROW) WILL COME EARLIER INTO AWARENESS COMPARED TO UNATTENDED STIMULI (RED ARROWS). [B] IN ORDER FOR THE UNATTENDED STIMULI (RED ARROWS) TO COME INTO AWARENESS AT THE SAME TIME AS THE ATTENDED STIMULUS (BLUE ARROW), IT HAS TO BE PRESENTED A CERTAIN TIME BEFORE THE ATTENDED STIMULUS. THE DIFFERENCE IN ONSET NEEDED IN ORDER FOR THE UNATTENDED AND THE ATTENDED STIMULI TO BE PERCEIVED AT THE SAME TIME IS A MEASURE FOR THE ATTENTIONAL BIAS.

The TOJ task allows to measure the prior entry effect (Pieron, 1952). In a typical TOJ task, two stimuli are presented at two different locations, for example one on each hand, with variable stimulus onset asynchronies (SOAs) between both hands. Participants have to judge which hand they perceived as being stimulated first (e.g., Shore, Gray, Spry, & Spence, 2005; Shore, Spence, & Klein, 2001).

We adapted this paradigm to investigate under which conditions nociceptive processing could be influenced by external visual stimuli. In the basic paradigm, participants are asked to make TOJs concerning which of two nociceptive stimuli, one presented to each hand, had been presented first. Each pair of nociceptive stimuli is preceded by unilateral or bilateral visual stimuli. We investigate whether participants' TOJs are affected by the visual stimuli. We may expect that an unilateral visual stimulus will draw attention towards its location. Consequently, the nociceptive stimulus at the cued side of space will come earlier into awareness than the uncued nociceptive stimulus. A bilateral stimulus on the other hand should not draw attention to one of both sides and consequently should have no influence on TOJs. Analysis of responses across the range of SOAs allows one to calculate the average time that one stimulus has to lead another in order for the two stimuli to be judged as simultaneous. This has been labeled the *point of subjective simultaneity* (PSS) (Figure 7). We expect that in the unilateral cue condition the PSS will be shifted towards the uncued side of space, indicating that the uncued hand has to be presented several milliseconds before the

cued hand in order to be perceived as simultaneous. In the bilateral cue condition the PSS should be near 0 ms, indicating that no attentional bias was induced by the cues.

Another parameter of the TOJ task is the *just noticeable difference* (JND). The JND indicates the interval needed to achieve 75% correct performance, and as such provides a standardized measure of the sensitivity of participants' temporal perception. The larger the JND interval, the more difficult the task, and the poorer the performance. The JND is conventionally calculated as half the temporal interval between the 25% and the 75% points on the psychometric function depicted in Figure 7. We do not expect that the JND will be affected by the position of the visual stimuli.

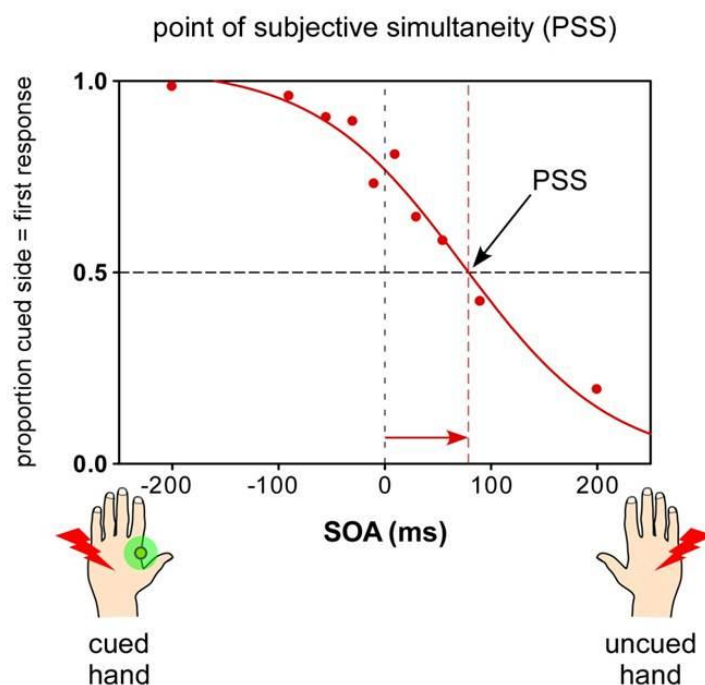


FIGURE 7. ILLUSTRATION OF THE POINT OF SUBJECTIVE SIMULTANEITY (PSS) IN A TEMPORAL ORDER JUDGMENT (TOJ) TASK. PAIRS OF NOCICEPTIVE STIMULI ARE APPLIED, ONE TO EACH HAND, WITH SEVERAL STIMULUS ONSET ASSYNCHRONIES (SOA) BETWEEN EACH HAND. SLIGHTLY BEFORE THE PRESENTATION OF THE FIRST NOCICEPTIVE STIMULUS, A VISUAL CUE STIMULUS IS PRESENTED NEAR ONE OF THE HANDS. THE DIFFERENT SOA'S ARE REPRESENTED ON THE X-AXIS. NEGATIVE VALUES INDICATE THAT THE CUED HAND WAS PRESENTED FIRST, POSITIVE VALUES INDICATE THAT THE UNCUED HAND WAS PRESENTED FIRST. THE PROPORTION OF TIME THAT THE PARTICIPANTS JUDGED THAT THE CUED HAND WAS PRESENTED FIRST IS SHOWN ON THE Y-AXIS. THE POINT ON THE X-AXIS THAT CORRESPONDS WITH A VALUE OF 0.5 (OR 50%) ON THE Y-AXIS HAS BEEN LABELED THE PSS. THIS IS THE POINT WHERE BOTH HANDS ARE PERCEIVED TO BE PRESENTED SIMULTANEOUSLY. IF NO ATTENTIONAL BIAS IS INDUCED BY THE CUES, WE WOULD EXPECT THE PSS TO BE 0, I.E. WHEN BOTH HANDS ARE INDEED STIMULATED SIMULTANEOUSLY (SOA IS 0 MS). HOWEVER, IN THIS EXAMPLE WE SEE THAT THE PSS IS SHIFTED TOWARDS THE UNCUED HAND, INDICATING THAT THE UNCUED HAND HAS TO BE PRESENTED SEVERAL MILLISECONDS (HERE APPROXIMATELY 80 MS) BEFORE THE CUED HAND IN ORDER TO BE PERCEIVED AS SIMULTANEOUS.

7.2 CROSSMODAL CUING PARADIGM

This paradigm is based on the classic ‘exogenous cuing paradigm’ introduced by Posner (Posner, 1978). Posner (1978) has shown that people can focus their attention covertly (i.e. without head or eye movement) on a particular location, and so enhance the processing of stimuli occurring there. At least two different attentional mechanisms can be involved in this effect. *Exogenous* orienting is elicited automatically by the presentation of spatially uninformative peripheral cues, which need not to predict the likely target location. This is an involuntary mechanism that is activated by suddenly occurring stimuli anywhere in the visual field. *Endogenous* orienting on the other hand is elicited by informative cues, which indirectly predict the likely target location, such as e.g., a central arrow. This mechanism is activated by expectancies about where in space a relevant visual stimulus will appear. In this PhD dissertation we will use an *exogenous* crossmodal cuing paradigm, in which the position of the cues will be completely unpredictable for the position of the forthcoming target.

The exogenous orienting of attention has been demonstrated in different sensory modalities, such as vision (Klein, Brennan, & Gilani, 1992), audition (Spence & Driver, 1994) and touch (Bradshaw, Howard, Pierson, Phillips, & Bradshaw, 1992), suggesting that spatial attention mechanisms might be shared among the various spatial senses. More recent studies have addressed the modality specificity of spatial attention by examining whether directing spatial attention to stimuli appearing in one sensory modality affects responses to targets appearing in other modalities (e.g., Spence & Driver, 1997). Such effects indicate strong crossmodal interactions in the control of spatial attention. Moreover, several ERP studies have shown that crossmodal effects included modulations of early components arising from modality-specific cortex, indicating that the mechanisms of the orienting of attention involves supramodal, or at least linked brain mechanisms (e.g., Eimer & Schroger, 1998; McDonald & Ward, 2000).

We adapted the paradigm used in Favril et al. (2014) to make the task suitable to investigate the influence of visual cue stimuli on nociceptive ERPs. On each trial a nociceptive stimulus is applied to one of both hands. Slightly before the nociceptive stimulus a visual cue stimulus is presented either at the same side (congruent) or the opposite side (incongruent). In some trials, the nociceptive stimulus is replaced by a tactile stimulus. Participants are instructed to react as fast and as accurately as possible which hand was stimulated, but only when a tactile (target) stimulus was presented. When a nociceptive (non-target) stimulus was presented they do not have to react. This is done to avoid contamination of the EEG signal by decision and movement related processes. Behavioral

responses to the tactile targets are analyzed both in terms of reaction times and accuracy. For the nociceptive non-targets ERPs are analyzed. The influence of the visual cue stimuli both on the behavioral results and on the ERP results are assessed. We expect reaction times to the tactile targets to be faster on congruent as opposed to incongruent trials. This should also be reflected by a larger amplitude of the ERP components evoked by the nociceptive (non-target) stimuli for congruent as opposed to incongruent trials.

7.3 CROSSMODAL CUING PARADIGM WITH DYNAMICAL STIMULI

The crossmodal cuing paradigm was adapted by Canzoneri et al. (2012) to encompass dynamical cue stimuli instead of static cue stimuli at different locations. We adapted this paradigm to investigate the influence of dynamical visual stimuli on nociceptive processing. In this paradigm, a visual stimulus is either approaching or receding the participant's left or right hand. At different temporal delays from the onset of the visual stimulus, a nociceptive stimulus is applied either at the same or the opposite hand, so that it is presented when the visual stimulus is perceived at varying distances from the hand. Participants are asked to respond as fast as possible at which side they perceive a nociceptive stimulus. The accuracy and reaction times to the nociceptive target stimuli are assessed in function of the distance of the visual stimuli to the hand. Moreover, by determining the best fitting curve of the reaction times in function of the perceived position of the visual stimulus in space, crossmodal interactions between visual and nociceptive stimuli can be assessed along a spatial continuum, from near to far space.

8 OUTLINE DISSERTATION

8.1 PART 1

In the first part of this PhD, several studies were conducted in healthy volunteers to investigate whether nociceptive stimuli are mapped into a peripersonal frame of reference.

In **Chapter 1**, we investigated whether nociceptive processing is influenced by the occurrence of visual stimuli occurring near the body, as opposed to far from the body. This was investigated in two experiments using a TOJ task, in which participants received pairs of nociceptive target stimuli, one to each hand. Slightly before the presentation of the first nociceptive stimulus, unilateral or bilateral visual stimuli were presented. These stimuli were presented either near (on the hand of the participants) or far from (in Experiment 1:

60 or 40 cm in front of the near visual stimuli; in Experiment 2: 70 cm in front of the near visual stimuli) the participants' body. We tested whether nociceptive TOJs would be influenced by the occurrence of the lateralized visual stimuli, and not by the bilateral visual stimuli. Importantly, we expected the lateralized visual stimuli to influence nociceptive processing more when they were presented near the body, compared to when they were presented far from the body.

In **Chapter 2**, we investigated whether nociceptive processing is influenced by the position of the stimulated body part in external space. Two experiments were conducted in which a crossing hands procedure was used in a TOJ task. Participants had to decide which of two nociceptive stimuli, one applied to each hand, had been presented first while their hands were either uncrossed, or crossed over the body midline. The occurrence of the nociceptive stimuli was preceded by uninformative visual cue stimuli, presented unilaterally or bilaterally (Experiment 1 and 2), and near or far from the participants (Experiment 1). We expected that the lateralized visual cue stimuli (and not the bilateral visual stimuli) would prioritize the perception of the nociceptive stimuli applied to the hand laying in the cued side of space. In other words, a visual stimulus in the left side of space would prioritize the perception of a nociceptive stimulus applied to the left hand when hands were uncrossed, but to the right hand when hands were crossed (and vice versa for a visual stimulus in the right side of space). Moreover, we expected that the influence of the visual stimuli would be larger when they were presented near as opposed to far from the participants' body. Finally, we expected that participants' temporal sensitivity would be reduced in the crossed hands posture, compared to the uncrossed posture.

In **Chapter 3**, we investigated whether the influence of visual stimuli on nociceptive processing depends on the proximity of the external stimuli to the stimulated body part, or merely to the distance to the body trunk as a whole. In other words, are nociceptive stimuli mapped in a frame of reference that is spatially locked to the stimulated body part, and that moves with it in space, or is it locked to the body trunk? Three TOJ experiments were conducted, in which the influence of unilateral visual stimuli was measured on the perceived temporal order of pairs of nociceptive stimuli, one applied to each hand. Crucially, both the position of the visual stimuli and the position of the hands was manipulated, so that visual and nociceptive stimuli occurred on adjacent or non-adjacent spatial positions. Hands and visual stimuli were displaced according to the anteroposterior axis (i.e. in depth in front of the trunk, Experiment 1), the mediolateral axis (i.e. eccentricity relative to the body midline, Experiment 2) and the longitudinal axis (i.e. according to elevation positions, Experiment 3). We expected that the influence of the visual stimuli would be largest when visual stimuli

were presented adjacent to the hands, irrespective of their distance to the body trunk. This would provide evidence for a limb-centered peripersonal frame of reference for the mapping of nociceptive stimuli.

8.2 PART 2

In the second part, we aimed at investigating the neural correlates of the crossmodal interactions between vision and nociception in the peripersonal space in healthy volunteers.

In **Chapter 4**, two experiments were conducted in which the neural correlates underlying the crossmodal interactions between visual and nociceptive stimuli in the peripersonal space were investigated with event-related potentials (ERPs). To this end, an exogenous crossmodal cuing paradigm with single nociceptive non-target stimuli, tactile (Experiment 1) or double nociceptive (Experiment 2) target stimuli, and visual cue stimuli, was used, as described above. Crucially, the position of the visual cue stimuli was manipulated, so that in some blocks the visual stimuli were presented near the participants (i.e. in between thumb and index finger), whereas in other trials they were presented far from the participants (i.e. 50 cm in front of the cues in near space). Behavioral responses to tactile stimuli (Experiment 1) or to double nociceptive stimulation (Experiment 2), and ERPs to single (non-target) nociceptive stimuli were investigated. We expected that the reaction times to the target stimuli would be faster on congruent than on incongruent trials, and that this effect would be stronger when the visual stimuli were presented near the participants. Moreover, we expected that the amplitude of the nociceptive ERPs would be higher on congruent than on incongruent trials. Again, we expected this effect to be larger when visual cue stimuli were presented near, as opposed to far from the participants.

8.3 PART 3

In the third part of this PhD, two studies were conducted. The first study investigated the influence of moving visual stimuli, either approaching or receding from the body, on nociceptive processing in healthy volunteers. The other study assessed potential differences of the influence of approaching visual stimuli on tactile processing for fibromyalgia (FM) patients, compared to healthy control participants.

In **Chapter 5**, a crossmodal cuing study with dynamical visual stimuli was used (as described above) to investigate the influence of moving visual stimuli on nociceptive

processing in healthy volunteers. Participants had to react as fast and as accurately as possible at which hand they received a nociceptive stimulus, while ignoring visual stimuli that were either approaching or receding at the same side (congruent) or the opposite side (incongruent) of space. First, we were interested to investigate at which distance the visual stimuli had the largest impact on nociceptive processing. We expected that reaction times would be fastest when the visual stimuli were presented near the stimulated hand. Next, we were interested in comparing the impact of the visual stimuli along a spatial continuum (from near to far space) between approaching and receding visual stimulus trials. We expected that the approaching visual stimuli would have a stronger spatially dependent effect on nociceptive processing compared to the receding visual stimuli.

In **Chapter 6**, we used a crossmodal cuing study with dynamical visual stimuli, but now with tactile targets and visual cue stimuli, to investigate whether chronic pain can alter spatial perception. This study was conducted with FM patients and matched control participants. First, we investigated the effect of the distance of the visual cues on tactile processing within each group. For both groups, we expected that tactile processing would be most affected when visual cue stimuli were presented near as compared to far from the stimulated hand. Next, we compared the influence of the approaching visual stimuli on tactile processing between both groups. We expected that FM patients would have a heightened attention for approaching stimuli, or that they would scan a larger share of the external space for potentially threatening stimuli, compared to healthy control participants. The former would be reflected by a stronger spatially dependent effect of the visual stimuli on tactile processing for FM patients, compared to healthy controls. The latter would be reflected by faster reaction times to the tactile stimuli for FM patients, at a further distance, where reaction times for healthy controls still remained high.

8.4 GENERAL DISCUSSION

Finally, in the general discussion the main findings of the different studies are presented, interpreted and integrated. Furthermore, theoretical and clinical implications are discussed. Finally, limitations and ideas for future research are reviewed.

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PART 1

**ARE NOCICEPTIVE STIMULI MAPPED IN A
PERIPERSONAL FRAME OF REFERENCE?**

CHAPTER 1

MAPPING NOCICEPTIVE STIMULI IN A PERIPERSONAL FRAME OF REFERENCE: EVIDENCE FROM A TEMPORAL ORDER JUDGMENT TASK.¹

ABSTRACT

The ability to localize nociceptive stimuli on the body is essential for an organism to respond appropriately to potential physical threats. This ability not only requires a representation of the space of the body, but also of the external space with respect to our body. Therefore, localizing nociceptive stimuli requires coordinating multiple senses into an integrated frame of reference. The peripersonal frame of reference allows for the coding of the position of somatosensory stimuli on the body surface and the position of stimuli occurring close to the body (e.g., visual stimuli). Intensively studied for touch, this topic has been largely ignored for nociception. Here, we investigated, using a temporal order judgment task, whether the spatial perception of nociceptive stimuli is coordinated with that of proximal visual stimuli into an integrated representation of peripersonal space. Participants judged which of two nociceptive stimuli, one presented to either hand, had been presented first. Each pair of nociceptive stimuli was preceded by lateralized visual cues presented either unilaterally or bilaterally, and either close to or far from the participant's body. The perception of the nociceptive stimuli was biased in favor of the stimulus delivered on the hand adjacent to the unilateral visual cue, especially when the cue was presented near the hand. These results suggest that a peripersonal frame of reference is used to map the position of nociceptive stimuli in a multisensory space. We propose that the peripersonal space constitutes a kind of margin of safety around the body to alert an organism to possible threats.

¹ Based on : De Paepe, A.L., Crombez, C., Spence, C., & Legrain, V. (2014). Mapping nociceptive stimuli in a peripersonal frame of reference : Evidence from a temporal order judgment task. *Neuropsychologia*, 56, 219-228.

1 INTRODUCTION

The localization of a nociceptive stimulus on the body surface is essential if an organism is to make a swift and appropriate response to bodily threat (Legrain et al., 2012; Mancini, Longo, Iannetti, & Haggard, 2011a). The ability to localize a somatosensory stimulus on the body depends partially on a direct relationship between the spatial organization of the skin receptors and the spatial organization of the neurons in the cerebral cortex (Penfield & Boldrey, 1937). However, adequate localization also requires the observer to perceive the position of the object in external space in contact with the body. Indeed, different frames of reference can be used to code the position of sensory stimuli (Vallar & Maravita, 2009). A first distinction can be made between somatotopic and spatiotopic personal frames of reference, the latter involving the integration of the position of the limbs in space (e.g., Smania & Aglioti, 1995).

Furthermore, the representation of external space can be dissociated into peripersonal and extrapersonal frames of reference, coding respectively the position of stimuli arising close to vs. far from the body (Halligan & Marshall, 1991). Interestingly, the peripersonal frame of reference codes both the position of somatosensory stimuli on the body surface and the position of stimuli in external space (e.g., visual stimuli), when they are seen close to the body; it therefore allows an individual to coordinate the map of the body and the map of external close space into an integrated multisensory representation of space (Cardinali, Brozzoli, & Farnè, 2009; Rizzolatti, Scandolara, & Gentilucci, 1981). Whereas the external frame of reference is particularly relevant to guide the preparation of reaching movements, the representation of peripersonal space is believed to be involved in the direct (i.e., without reaching movement) manipulation of objects in external space (Rizzolatti, Fadiga, Fogassi, & Gallese, 1997). Moreover, it is also believed to be part of a cortical defensive system, designed to trigger defensive motor actions (Graziano & Cooke, 2006).

The existence of a peripersonal frame of reference has been well-documented for the mapping of tactile stimuli (see Spence & Driver, 2004). It is supposed to rely on the existence of multisensory neurons that respond to the stimulation of a specific body-part and to stimuli/events that occur close to that body-part (see Graziano & Gross, 1994). However, as yet, there is no experimental evidence to demonstrate that nociceptive inputs are integrated with visual information into a peripersonal representation of the body and the space that surrounds it (Haggard, Iannetti, & Longo, 2013). Such integration is important because, while touch provides information about object features such as shape and contrasts, nociception warns the brain about potential harm of the body, and about the

occurrence of threats in external space. Surprisingly, most studies that have investigated the abilities to localize pain rely on the description of the somatotopic organization of the neuronal responses to nociceptive and painful stimuli (Andersson et al., 1997; Baumgartner et al., 2010; Bingel et al., 2004; Henderson, Gandevia, & Macefield, 2007). Only recently have authors started to investigate the ability to localize pain according to non-somatotopic frames of reference. For instance, Sambo et al. (2013) have demonstrated that crossing the hands over the body midline affects judgments concerning the temporal order of nociceptive stimuli delivered to the left and right hand (Sambo et al., 2013). Moreover, it has also been shown to reduce the perception of pain (Gallace, Torta, Moseley, & Iannetti, 2011). These effects suggest that nociception and pain are sensitive to the conflict, induced by crossing the hands, between a somatotopic representation of the body (defining the anatomical identity of the stimulated body limbs) and a spatiotopic representation (defining the position of the stimulated limbs in external space; see Shore, Spry, & Spence, 2002). Similarly, Moseley, Gallace and Spence (2009) have shown that unilateral chronic pain, such as in complex regional pain syndrome (CRPS), a chronic pain disorder characterized by unilateral sensory, autonomous, vasomotor and motor/trophic dysfunctions, affects the spatiotopic representation of the personal space. Other experiments (Sambo, Forster, Williams, & Iannetti, 2012; Sambo, Liang, Cruccu, & Iannetti, 2012; Sambo & Iannetti, 2013) indicated that the hand blink reflex (HBR), triggered by high-intensity stimulations of the median nerve, was enhanced when the stimulated hand was close to the eyes. However, as no *external* visual stimuli (i.e. outside the personal space) were used in these experiments, it is still a matter of debate as to whether the HBR enhancement by somatic threats is supported by integration of the somatic threat into a peripersonal frame of the face. Using a different experimental paradigm, Van Ryckeghem et al. (2011) and Favril, Mouraux, Sambo and Legrain (2014) have both shown crossmodal links in spatial attention between nociceptive/painful stimuli and proximal visual stimuli. However, up until now, it has been difficult to disentangle whether these effects are due to the lateralization of the stimuli (left vs. right space) or to their occurrence in the proximity of the body.

In the present study we investigated whether the spatial localization of nociceptive stimuli can be processed according to a peripersonal frame of reference. We tested whether the processing of nociceptive inputs is influenced by the occurrence of external, e.g., visual stimuli, especially when these external stimuli are delivered in the proximity of the stimulated body part. To this end, participants made temporal order judgments (TOJs) concerning which of two nociceptive stimuli, one presented to either hand, had been presented first. Analysis of the resulting data allows for the determination of the stimulus

onset asynchrony (SOA) at which two stimuli are perceived to be presented simultaneously. This is known as the Point of Subjective Simultaneity (PSS; Spence, Shore, & Klein, 2001).

According to the notion of prior entry (Titchener, 1908), attending to a stimulus will speed-up perceptual processing relative to when the same stimulus is unattended. The attended stimulus should then have prior entry to awareness. As a consequence, unattended stimuli normally have to be presented prior to attended stimuli in order to be perceived as simultaneous (see Spence & Parise, 2010, for a review), leading to a shift of the PSS to the unattended side. In the present study, each pair of nociceptive stimuli was preceded by visual stimuli presented either unilaterally or bilaterally, either close to or far from the participant's body. We investigated whether participant's TOJs were affected by the visual stimuli. Importantly, we expected that TOJs would be more affected by visual stimuli presented in close (peripersonal) as opposed to far space. Two experiments were conducted, diverging by the position of the fixation point to exclude potential effects of the gaze (Graziano, Hu, & Gross, 1997). In Experiment 1, we chose to actively manipulate the position of the fixation point, while in Experiment 2 we kept the fixation point constant at an intermediate distance between the close and far cues.

2 METHODS.

2.1 EXPERIMENT 1

2.1.1 PARTICIPANTS.

Twenty-four undergraduate students volunteered to take part in this study. Three of the participants were excluded, due to their poor performance (see section 2.1.5). The mean age of the 21 remaining participants (11 women; 20 right-handed) was 19 years (ranging from 18 to 23 years). All of the participants had normal to corrected-to-normal vision, did not report any neurological, psychiatric, or chronic pain problems, and were not currently using any psychotropic drugs. The experimental procedure was approved by the local ethics committee. All of the participants provided informed consent prior to taking part in the study.

2.1.2 STIMULI AND APPARATUS.

The nociceptive stimuli were delivered by means of intra-epidermal electrical stimulation (IES) (DS7 Stimulator, Digitimer Ltd, UK), with stainless steel concentric bipolar electrodes (Nihon Kohden, Japan; Inui, Tsuji, & Kakigi, 2006). The electrodes

consisted of a needle cathode (length: 0.1 mm, \emptyset : 0.2 mm) surrounded by a cylindrical anode (\emptyset : 1.4 mm). By gently pressing the device against the participant's skin, the needle electrode was inserted into the epidermis of the dorsum of the hand in the sensory territory of the superficial branch of the radial nerve. This method was shown to activate selectively the free nerve endings of the A δ fibers (Inui et al., 2006; Mouraux, Iannetti, & Plaghki, 2010). In order to guarantee the selective activation of the free endings of the nociceptive fibers, and in order to avoid co-activation of non-nociceptive A β fiber mechanoreceptors, a strict procedure was used to individually adjust the intensity of the stimulus to two times the detection threshold with an electrical current intensity that was as low as possible (Legrain & Mouraux, 2012; Mouraux et al., 2013; Mouraux et al., 2010). Each participant's detection threshold was determined with single-pulse stimuli (0.5 ms square wave pulse) using a staircase procedure (Churyukanov, Plaghki, Legrain, & Mouraux, 2012). Detection thresholds were established separately for each of the participant's hands. Next, the stimulus intensity was set at twice the detection threshold. If necessary, the intensity of the stimuli were adjusted so that the stimuli delivered to each hand were perceived as being equally intense. During the course of the experiment itself, the stimuli consisted of trains of three consecutive 0.5 ms square-wave pulses separated by a 5-ms inter-pulse interval. This method has been shown to increase the stimulus strength (Inui et al., 2006) without changing the type of activated fibers (Mouraux, Marot, & Legrain, 2014). Using a selection of pain words from the Dutch McGill Pain questionnaire (Vanderiet, Adriaensen, Carton, & Vertommen, 1987), it was found that the experience of the stimuli was best described as pricking and slightly unpleasant (see also Colon, Nozaradan, Legrain, & Mouraux, 2012; Favril et al., 2014; Inui et al., 2006; Mouraux et al., 2010). After each experimental block, the participants were asked to estimate the intensity elicited by the nociceptive stimuli on a numerical graphic rating scale (10 cm) with the following labels selected from the Dutch version of the McGill pain questionnaire (Vanderiet et al., 1987) (0 = felt nothing, 2.5 = lightly intense, 5 = moderately intense, 7.5 = very intense, 10 = enormously intense). This scale was used in order to ensure that: (1) the stimuli were still perceived, and (2) the percept elicited by the IES delivered to each of the participant's hands was still equivalent. If one of these two criteria was not met, the stimulus intensities were modified accordingly (with a maximum increase of 0.10 mA). If the adaptation proved to be unsuccessful, the electrodes were displaced and the procedure was restarted.

The visual stimuli were presented by means of four green light-emitting diodes (LEDs). The LEDs were illuminated for 20 ms, and these stimuli were perceived by

participants as a green light that briefly flashed. In a practice phase, the visibility of each of the LEDs was tested by asking the participants to report on the location of the LED that was illuminated (e.g., 'left near', 'right far').

The participants sat on a chair in a dimly illuminated, sound-attenuated room. They rested their arms on the table in front of them. The participants placed their hands, palm downward, on the table in front of a 16 inch CRT monitor used to present a fixation stimulus. The participant's head was immobilized in a chin-rest positioned at 10 cm from the trunk, in order to prevent the vision of the hands. The height of the chin rest was individually adapted. The distance between the participant's hands and their trunk, as well as the distance between the participant's index fingers was 40 cm. Two of the LEDs were situated in near/peripersonal space, and two in far/extraperpersonal space. The LEDs in near space were placed on the dorsum of the participant's hands, close to the IES electrodes (the distance between the two LEDs was therefore also approximately 40 cm). To dissociate any effects attributable to the distance of the LEDs from the participant's body (i.e., peripersonal vs. extraperpersonal space) from any effects attributable to the distance of the LEDs from the fixation point, the location of the screen and the LEDs in far space varied across participants (between-participant factor: *fixation distance*). For 11 of the participants, the LEDs in far space and the screen were positioned 100 cm from the participant's trunk (*far fixation* condition, see Figure 1A). The distance between the two LEDs in far space was 60 cm. For the other 10 participants, the LEDs in far space were positioned 80 cm from the participant's trunk, and the screen at a distance of 40 cm, i.e., close to the LEDs in near space (*near fixation* condition, see Figure 1B). The distance between the two LEDs in far space was 70 cm.

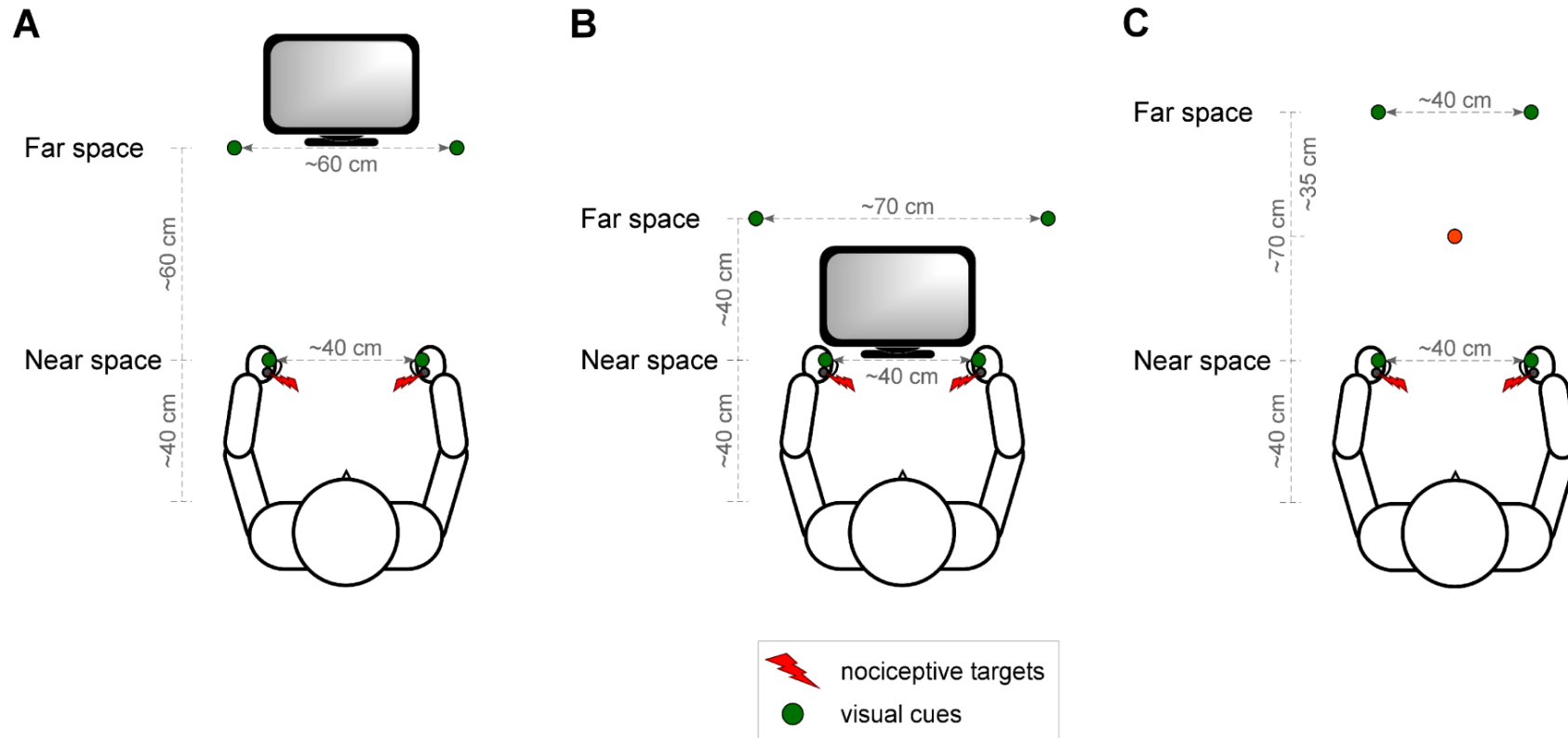


FIGURE 1. ILLUSTRATION OF THE EXPERIMENTAL SET-UP FOR EXPERIMENT 1 (A AND B) AND EXPERIMENT 2 (C). NOCICEPTIVE STIMULI, REPRESENTED BY THE RED LIGHTNING SYMBOLS, WERE APPLIED TO BOTH OF THE PARTICIPANT'S HANDS. VISUAL CUE STIMULI, REPRESENTED BY THE GREEN CIRCLES, WERE PRESENTED AT FOUR DIFFERENT LOCATIONS IN EACH TRIAL: EITHER UNILATERALLY OR BILATERALLY, AND EITHER ON THE PARTICIPANT'S HANDS (IN NEAR SPACE) OR IN FRONT OF THE PARTICIPANT'S HANDS (IN FAR SPACE). IN EXPERIMENT 1, HALF OF THE PARTICIPANTS FIXATED ON A COMPUTER SCREEN THAT WAS LOCATED 100 CM IN FRONT OF THEIR TRUNK (A), FOR THE OTHER HALF OF THE PARTICIPANTS THE SCREEN WAS LOCATED 40 CM IN FRONT OF THEIR TRUNK (B). IN EXPERIMENT 2, PARTICIPANTS FIXATED ON A RED LED THAT WAS SITUATED EQUIDISTANT BETWEEN THE NEAR AND FAR VISUAL CUES (C).

2.1.3 PROCEDURE

After a practice session of 2 blocks of 15 trials (with visual feedback on task performance; replacement of the fixation cross by a green 'correct' or a red 'incorrect'), the participants were presented with 4 blocks of 120 trials (Figure 2). Each trial started with a fixation cross presented in the center of the screen. 500 ms thereafter, the visual stimulus was presented in either near or far space. The visual stimulus consisted of either a single unilateral flash occurring in left space, a single unilateral flash occurring in right space, or two flashes resulting from the bilateral and simultaneous illumination of the LEDs on both sides at the same given distance. The visual stimulus was followed 80 ms after its onset by a pair of nociceptive stimuli, one applied to either hand. The time delay between the onset of the visual stimulus and the onset of the first nociceptive stimulus was motivated by the minimal time delay used to observe significant crossmodal attentional effects between a visual cue and a somatosensory target (e.g., 150 ms; Kennet, Spence, & Driver, 2002). However, these latter data were observed with tactile stimuli. Taken into account the difference in conduction velocity between non-nociceptive A β and nociceptive A δ fibers (~80 ms; see Mouraux & Plaghki, 2007), we adapted the time delay from 150 to 80 ms. This way the A δ -fiber inputs are expected to arrive at their cortical targets after the visual input at a latency similar to the time delay used in the study of Kennett et al. (2002) between visual cues and tactile targets.

The first nociceptive stimulus could be applied either to the left hand or the right hand. There were five possible SOAs between the nociceptive stimuli for each order of stimulation (left hand first vs. right hand first): ± 120 , ± 60 , ± 30 , ± 15 , ± 5 ms (where positive values indicate that the participant's right hand was stimulated first, and negative values indicate that the left hand was stimulated first). The fixation cross remained on-screen until participants had responded, whereupon it was replaced by a text prompt to respond ("Provide a response").

The trials were created combining 3 spatial locations of the visual stimuli x 2 visual cue distances x 2 orders for the nociceptive stimuli x 5 SOAs. Trials were randomly presented within each block of stimulation. The visual cues were not spatially informative and the location of any forthcoming nociceptive stimulus could thus not be predicted by the cue.

The participants were instructed to maintain their gaze on the fixation cross throughout each block of trials. In two blocks of trials, the participants had to indicate verbally which one of their hands had been stimulated first (right vs. left hand). In the

other two blocks, they had to indicate which of their hands had been stimulated second, instead. By using both a “Which came first?” and a “Which came second?” task, we were able to control for any response bias (that is, any tendency of participants to respond with the side on which the unilateral cue had been presented; see Cairney, 1975; Drew, 1896; Shore, Spence, & Klein, 2001; Spence et al., 2001). The instruction was alternated between blocks of trials and the order of presentation was counterbalanced across participants. Participants’ responses were provided verbally and were registered by the experimenter by pressing one of two keys on a keyboard. As soon as the response was given, the screen turned blank. The next trial started 1000 ms later. The experiment took approximately 60 minutes to complete.

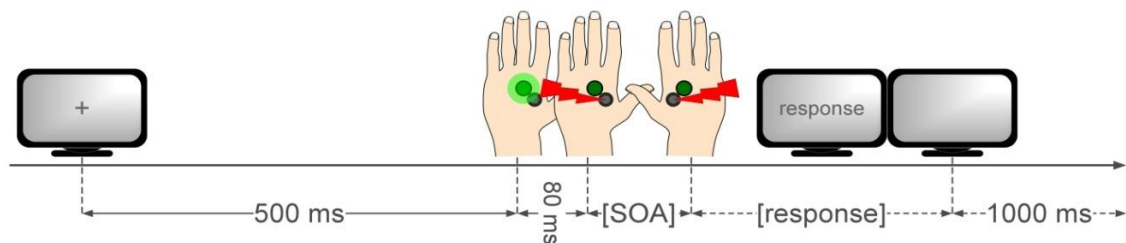


FIGURE 2. TIME-COURSE OF ONE TRIAL IN EXPERIMENT 1. IN EXPERIMENT 2, THE TIME-COURSE WAS IDENTICAL, BUT THE COMPUTER SCREEN WAS REPLACED BY A RED LED. THIS FIXATION LED STAYED ON DURING THE ENTIRE TRIAL, AND WAS TURNED OFF AFTER THE PARTICIPANT HAD MADE A RESPONSE.

2.1.4 MEASURES.

The procedure followed that reported in Spence et al. (2001; see also Shore, Gray, Spry, & Spence, 2005; Van Damme, Gallace, Spence, Crombez, & Moseley, 2009). For each participant, and for each SOA for each of the 8 within-participant conditions (bilateral vs. unilateral cues x close vs. far space x which first? vs. which second?), the proportion of trials on which participants perceived the cued hand as being stimulated first, was calculated. A sigmoid function was fitted to these proportions (see Figure 3). Subsequently, the proportion of *left/right hand first responses* (left hand first when the cue was presented on the left side, and right hands first when cues were presented on the right side) was converted into a z-score by means of a standardized cumulative normal distribution (probits). The best-fitting straight line was computed for each participant and each condition, and the derived slope and intercept values were used to compute the point of subjective simultaneity (PSS) and the just noticeable difference (JND).

The PSS refers to the point at which a participant reports the two events (i.e., the nociceptive stimuli presented to the right and left hand) as occurring first equally often. This is equivalent to the SOA value corresponding to a proportion of *left/right hand first responses* of 0.5 (Spence et al., 2001). The PSS is computed as the opposite of the intercept divided by the slope from the best-fitting straight line. In the unilateral cue condition, the sign of the PSS for the conditions in which the cues were presented on the right hand was reversed, and for each subject the final PSS value was calculated by taking the average of the PSS values for cues presented on the left side, and the reversed PSS value for cues presented on the right side. Hence, the PSS reflects how much time the *uncued* side has to be presented before/after the *cued* side in order to be perceived at the same time. In the bilateral cue condition, there was no “cued” or “uncued” side, as cues were always presented bilaterally. We decided to calculate the PSS from the amount of *left hand first* responses. The PSS for the bilateral cue trials thus reflects how much time the *right* side has to be presented before/after the *left* side in order to be perceived at the same time. In sum, the PSS provides information concerning biases in spatial attention resulting from the presentation of the visual cues.

The JND was measured as $0.675/\text{slope}$ (Spence et al., 2001). This corresponds to the value achieved by subtracting the SOA at which the best fitted line crosses the 0.75 point from the SOA at which the same line crosses the 0.25 point, and dividing this by 2, and indicates the interval needed to achieve 75% correct performance, and, as such, provides a standardized measure of the sensitivity of participant’s temporal perception.

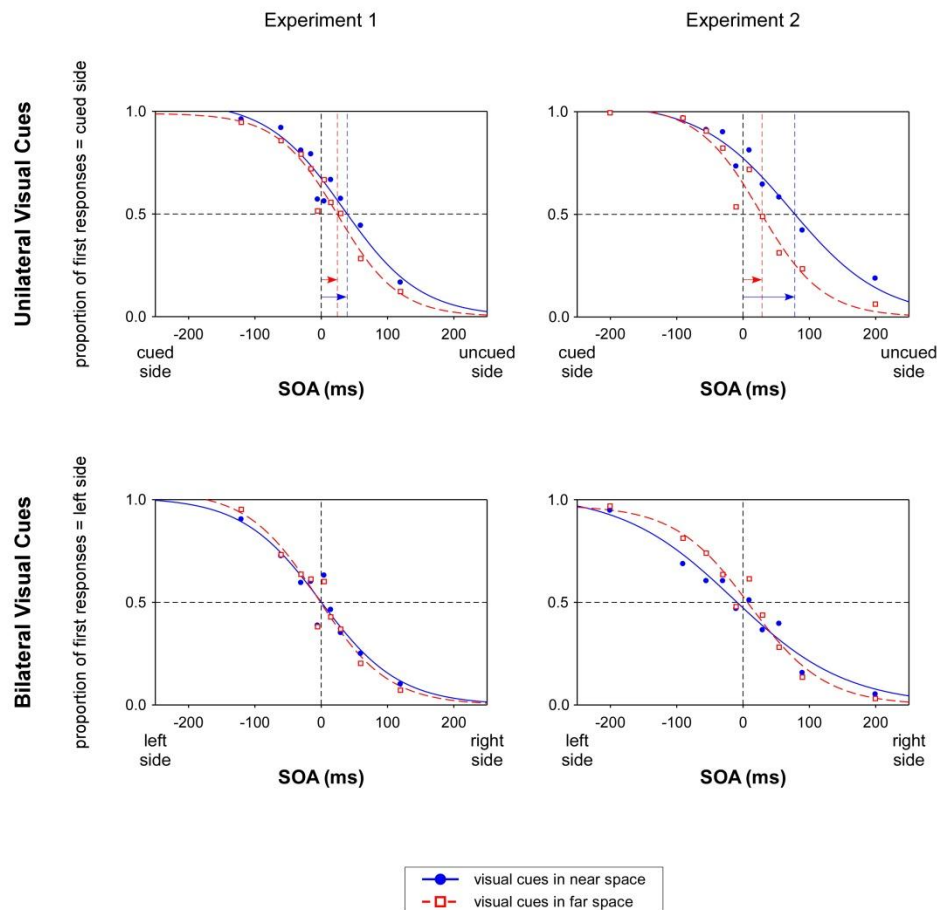


FIGURE 3. NOCICEPTIVE TEMPORAL ORDER JUDGMENTS (TOJ'S) IN EXPERIMENTS 1 AND 2. THE FIGURE ILLUSTRATES THE FITTED CURVES FROM CUMULATIVE DATA FROM THE 19 AND 12 PARTICIPANTS HAVING SUCCESSFULLY PARTICIPATED TO EXPERIMENT 1 AND EXPERIMENT 2 RESPECTIVELY. THE DATA FROM THE TWO SUBGROUPS OF PARTICIPANTS HAVING PARTICIPATED TO EXPERIMENT 1 (FIXATION FAR VS. CLOSE) AND THE DATA FROM THE TWO TASKS IN EACH EXPERIMENT ('WHICH IS FIRST' VS. 'WHICH IS SECOND') ARE MERGED. THE GRAPHS IN THE UPPER PART OF THE FIGURE REPRESENT THE PERFORMANCE TO THE TRIALS DURING WHICH A SINGLE VISUAL STIMULUS WAS PRESENTED UNILATERALLY. THE X-AXIS REPRESENTS THE DIFFERENT SOA'S BETWEEN THE TWO NOCICEPTIVE STIMULI PRESENTED IN A TRIAL. AS THE AIM OF THE STUDY WAS TO EVALUATE THE CROSSMODAL EFFECT OF UNILATERAL VISUAL CUES ON THE TOJ FOR NOCICEPTIVE STIMULI, THE RESPONSES WERE RECODED SO THAT NEGATIVE VALUES ON THE LEFT SIDE OF THE X-AXIS INDICATE THAT THE CUED HAND WAS STIMULATED FIRST, WHILE POSITIVE VALUES INDICATE THAT THE UNCUED HAND WAS STIMULATED FIRST. THE Y-AXIS REPRESENTS THE MEAN PROPORTION OF RESPONSES ACCORDING TO WHICH THE CUED HAND WAS PERCEIVED AS HAVING BEEN STIMULATED FIRST. THE GRAPHS IN THE LOWER PART OF THE FIGURE REPRESENT THE PERFORMANCE ON THOSE TRIALS WHERE TWO VISUAL STIMULI WERE PRESENTED BILATERALLY. AS, IN THIS CASE, BOTH SIDES WERE ALWAYS CUED SIMULTANEOUSLY, THE DISTINCTION BETWEEN LEFT HAND AND RIGHT HAND WAS MAINTAINED: NEGATIVE VALUES ON THE LEFT SIDE OF THE X-AXIS INDICATE THAT THE PARTICIPANT'S LEFT HAND WAS STIMULATED FIRST, WHILE POSITIVE VALUES INDICATE THAT THEIR RIGHT HAND WAS STIMULATED FIRST. THE Y-AXIS REPRESENTS THE MEAN PROPORTION OF RESPONSES ACCORDING TO WHICH THE LEFT HAND WAS PERCEIVED AS STIMULATED FIRST. SOLID BLUE LINES ILLUSTRATE THE FITTED CURVES TO THE TRIALS DURING WHICH THE VISUAL STIMULI WERE PRESENTED IN NEAR SPACE, THE BROKEN RED LINES REPRESENT THE FITTED CURVES TO THE TRIALS DURING WHICH THE VISUAL STIMULI WERE PRESENTED IN FAR SPACE. AS COMPARED TO THE BILATERAL CUE CONDITIONS, THE CURVES IN THE UNILATERAL CUE CONDITIONS WERE SHIFTED TOWARD THE UNCUED SIDE, INDICATING THAT THE NOCICEPTIVE STIMULUS PRESENTED ON THE UNCUED SIDE HAD TO BE PRESENTED SEVERAL MILLISECONDS BEFORE THE CUED STIMULUS IN ORDER TO HAVE AN EQUAL CHANCE OF BEING PERCEIVED FIRST. THE PSS VALUES THAT DIFFERED SIGNIFICANTLY FROM 0 ARE DEPICTED IN THE FIGURES WITH ARROWS. THE JND CAN BE INSPECTED BY LOOKING AT THE SLOPE OF THE CURVES. A STEEP SLOPE INDICATES THAT PARTICIPANTS' JUDGMENTS WERE CONSISTENTLY RIGHT, WHILE A FLATTER SLOPE INDICATES THAT THE PARTICIPANTS FOUND THE TASK HARDER TO PERFORM, AND CONSEQUENTLY MADE MORE MISTAKES. AS THE JND CORRESPONDS TO $0.675/\text{SLOPE}$, THE STEEPER THE SLOPE, THE SMALLER THE JND.

2.1.5 ANALYSES.

Participants were excluded from the data analysis if one of their PSS scores was greater/smaller than twice the maximum SOA (i.e. ± 240 ms), or if they had an average of less than 80% correct answers to the trials with the maximum SOA (i.e. ± 120 ms). In Experiment 1, two of the participants had poor task performance ($< 80\%$ correct at the ± 120 -ms SOAs) and one participant had a PSS value exceeding ± 240 ms. These participants were excluded from the analyses. To address the question of whether there was any attentional bias (due to the capture of attention by the occurrence of the lateralized visual cues), i.e., if the PSS differed significantly from 0 ms, one-sample t-tests were performed for each value. Next, in order to compare the PSS across the different experimental conditions, a repeated measures analysis of variance (ANOVA) was performed with *visual cue type* (unilateral vs. bilateral), *cue distance* (near vs. far space) and *task* ("which first?" vs. "which second?") as the within-participant factors and *fixation distance* (fixation near vs. far) as the between-participant factor. The same ANOVA was also performed on the JND data. The significance level was set at $p < 0.05$. Cohen's d was calculated for significant effects. For between-subject comparisons, the effect size was Cohen's d for independent samples. For within-subject comparisons, we calculated effect sizes for independent samples using the formula of Dunlap, Cortina, Vaslow, and Burke (1996). We determined whether Cohen's d was small (0.20), medium (0.50) or large (0.80) (Cohen, 1988).

2.2 EXPERIMENT 2.

2.2.1 PARTICIPANTS.

Thirteen paid volunteers took part in this experiment. One participant was excluded based on the same exclusion criteria as in Experiment 1 (see section 2.2.4). The mean age of the remaining 12 participants (9 females; 11 right-handed) was 22 years (ranging from 18 to 29 years). All of the participants had normal to corrected-to-normal vision, reported no neurological, psychiatric, or chronic pain problems, and were not currently using psychotropic drugs. The experimental procedure was approved by the local ethics committee. All of the participants provided informed consent prior to taking part in the study.

2.2.2 APPARATUS AND STIMULI.

The experimental set-up was largely the same as in Experiment 1. The computer screen was replaced by a red LED, positioned equidistantly from the LEDs in near and far space, and equidistant from the left and right LEDs (see Figure 1C). The distance between the participant's hands and their trunk, as well as the distance between their index fingers was again 40 cm. The LEDs in near space were positioned on the dorsum of each hand in close proximity of the IES electrode attached over the sensory territory of the superficial radial nerve. The two LEDs located in far space were positioned at a distance of 70 cm from the participant's hands. The distance between left and right LEDs, in both near and far space, was approximately 40 cm.

Compared with Experiment 1, during which three participants had to be excluded, we took some measures to reduce the number of rejected values from the dataset. First, we decreased the difficulty of the task by increasing the strength of the sensory afferent. More specifically, nociceptive stimuli consisted of trains of four consecutive 0.5 ms square-wave IES pulses separated by a 5-ms inter-pulse interval (Mouraux et al., 2014). Second, to avoid flat slopes of the estimated function, which could impair the estimation of the PSS, larger SOAs were used between the two nociceptive targets: ± 200 , ± 90 , ± 55 , ± 30 , ± 10 . The procedure used to determine the detection threshold remained the same of in the first experiment.

2.2.3 PROCEDURE.

The practice session contained a block of 12 trials with visual stimuli only in order to ensure correct detection, and 2 blocks of 24 trials with nociceptive stimuli only with the three largest SOAs in order to ensure correct task performance (80% correct response on the maximum SOA). The experiment consisted of 8 blocks of 60 trials. In this experiment, trial types were not mixed within each block, as was the case for Experiment 1. In Experiment 2, four blocks contained visual stimuli in near space only, and four blocks contained visual stimuli in far space only. The order in which the blocks were presented was randomized for the first 4 blocks, and the reverse order was used for the remaining 4 blocks. A trial started with the fixation LED being illuminated. This fixation LED stayed on during the entire trial. 500ms after the onset of the fixation LED, a single unilateral visual flash (either on the right or the left side), or paired bilateral visual flashes were presented. The visual stimulus was followed 80 ms after its onset by a pair of nociceptive stimuli, one applied to either hand. Ten possible SOAs were used between the two nociceptive stimuli: ± 200 , ± 90 , ± 55 , ± 30 , ± 10 ms (positive values indicate that the right hand was stimulated first, negative values indicate that the left hand was stimulated

first). Each block of trials was made up of three positions of the visual stimuli (bilateral, unilateral/left side, unilateral/right side), two orders of nociceptive stimuli (left hand first, right hand first) and five SOAs. The different resulting trials were equiprobable and randomly presented.

The participants were instructed to keep their gaze on the fixation LED and to indicate verbally which hand they perceived as having been stimulated first during four blocks, and which hand they perceived as having been stimulated second in the four other blocks (again with the order alternated over blocks and counterbalanced across participants). After the participants had made their response, the fixation LED was turned off. The verbal responses were encoded by the experimenter. After 1000 ms, the next trial started. The experiment took on average 75 minutes to complete.

2.2.4 MEASURES AND ANALYSES.

The measures and the analyses of the data were identical to the first experiment. The exclusion criteria were also the same. In Experiment 2, one participant exhibited poor task performance (< 80% correct at ± 200 ms SOAs). This participant was excluded from the analyses.

The difference of each PSS value from 0 was evaluated using one-sample t-tests. Two repeated measures ANOVAs, with *visual cue type* (unilateral vs. bilateral), *cue distance* (near vs. far space) and *task* (which first? vs. which second?) as within-participant factors were performed on the PSS and JND data, respectively. Cohen's *d* was calculated for significant effects.

3 RESULTS

3.1 INTENSITY OF THE NOCICEPTIVE STIMULI.

The mean current intensities used during Experiment 1 were 0.92 ± 0.33 mA and 0.87 ± 0.31 mA for left and right hands respectively. During Experiment 2, current intensities were 0.79 ± 0.31 mA and 0.69 ± 0.26 mA for left and right hands respectively. The differences between left and right hands were not significant (Experiment 1: $t(20) = 0.93$; $p = 0.36$; Experiment 2: $t(11) = 0.99$; $p = 0.34$). The mean self-reported intensities (VAS) were, during Experiment 1, 4.52 ± 1.87 for left hand and 4.59 ± 1.79 for right hand, and, during Experiment 2, 3.89 ± 1.41 for left hand and for right hand 3.80 ± 1.34 . These

differences were also not significant (Experiment 1: $t(20) = -0.72$; $p = 0.48$; Experiment 2: $t(11) = 0.79$; $p = 0.45$).

3.2 PSS.

Mean responses and mean PSS values are shown in Figure 3 and 4 respectively. In Experiment 1, the t-tests revealed that, in the group for which the fixation distance was far, all PSS values from trials with an unilateral cue were different from 0 (all $t(10) > 3.90$, all $p < 0.004$). In the group for which the fixation distance was near, the PSS values for unilateral cue trials were significantly different from 0 (all $t(9) > 2.80$, all $p < 0.04$), but not when the visual cue was in far space, and participants had to indicate which hand was stimulated first ($t(9) = 1.81$; $p = 0.10$). By contrast, none of the PSS values from trials with bilateral cues were significantly different from 0, nor for the trials where the fixation distance was far (all $t(10) < 1.5$, $p > 0.15$), nor for the trials where the fixation distance was near (all $t(9) < 1.7$, all $p > 0.13$). This result indicates that the PSS is only biased by the presence of an unilateral visual cue, and never by the presence of bilateral cues. In addition, these results suggest that the bias is always significant in the presence of a unilateral visual cue in near space, while it could depend on the position of the fixation point if a bias is present for the unilateral visual cues in far space.

The ANOVA revealed a main effect of *visual cue type* ($F(1,19) = 28.05$, $p < 0.001$, $d = 1.76$) suggesting that PSS values were larger for unilateral than bilateral cue conditions. The ANOVA also revealed a main effect of *cue distance* ($F(1,19) = 7.66$, $p = 0.01$, $d = 0.57$), suggesting that PSS values were larger when cues were presented in near space than in far space. However, the significant interaction between *visual cue type* and *cue distance* ($F(1,19) = 7.97$, $p = 0.01$, $d = 0.51$) suggests that the effect of the distance of the cue on the PSS depended on the type of cue presented. Indeed, the spatial location of the cue had a significant impact in trials with an unilateral cue ($F(1,19) = 14.69$, $p = 0.001$, $d = 0.68$), but not in trials with a bilateral cue ($F(1,19) = 0.046$, $p = 0.83$) (Figure 4). In addition to the results of the t-tests, this suggests that, an unilaterally presented visual cue, gave rise to an attentional bias to the side of the cue, and, more crucially, this bias was more pronounced when the visual cue occurred in near space than when it occurred in far space. The factors of *task* and *fixation distance* had no effect on participants' performance, except for a significant interaction between *task*, *cue distance*, and *fixation distance* ($F(1,19) = 7.42$; $p = 0.01$, $d = 1.17$), and a significant interaction between *visual cue type*, *task*, *cue distance*, and *fixation distance* ($F(1,19) = 8.40$, $p = 0.009$, $d = 1.28$). The

four-way interaction can be attributed to the fact that, while the PSS values in the unilateral cue condition were not dependent on the task nor on the fixation distance (*task*cue distance*fixation distance* interaction: $F(1,19) = 0.28$; $p = 0.60$), these latter factors influenced the PSS in the bilateral cue condition (*task*cue distance*fixation distance* interaction: $F(1,19) = 12.74$, $p = 0.002$, $d = 1.56$). This result was not further investigated because previous analyses showed that none of the PSS values for the bilateral cue conditions were significantly different from 0 ms, and the interaction included procedural variables that were of no further theoretical interest. None of the other comparisons were significant (all $F < 1.30$, $p > 0.25$).

The results of Experiment 2 were similar (see Figures 3 and 4). First, the t-tests revealed the presence of a bias significantly affecting the PSS in all trial types having an unilateral cue (all $t > 3.33$, all $p < 0.007$), whereas such a bias was not significantly different from 0 ms in those trials with bilateral cues (all $t < 1.26$, all $p > 0.23$). The repeated measures ANOVA revealed a significant main effect of *visual cue type* ($F(1,11) = 14.08$, $p = 0.003$, $d = 1.78$), a main effect of *cue distance* ($F(1,11) = 10.04$, $p = 0.009$, $d = 0.82$), and a significant interaction between these factors ($F(1,11) = 12.74$, $p = 0.004$, $d = 0.93$). This result confirmed that the bias was more pronounced when unilateral cues were presented in near space than when they were presented in far space (main effect of *cue distance* in those trials with an unilateral cue: $F(1,11) = 14.80$, $p = 0.003$, $d = 0.80$). In those trials with bilateral cues, there was no difference between cues in near vs. far space ($F(1,11) = 2.49$, $p = 0.14$).

3.3 JND.

The mean JND data are shown in Figure 4. The only noticeable result was a main effect of *cue distance* which reached significance in Experiment 2 ($F(1,11) = 7.05$, $p = 0.02$, $d = -0.54$), but which was not significant in Experiment 1 ($F(1,19) = 3.11$, $p = 0.09$). This result suggests that participants found it more difficult to identify which of the IES was the first/last when visual cues were presented in near space as opposed to when cues were presented in far space. None of the other effects were significant (all $F < 3.70$, $p > .08$).

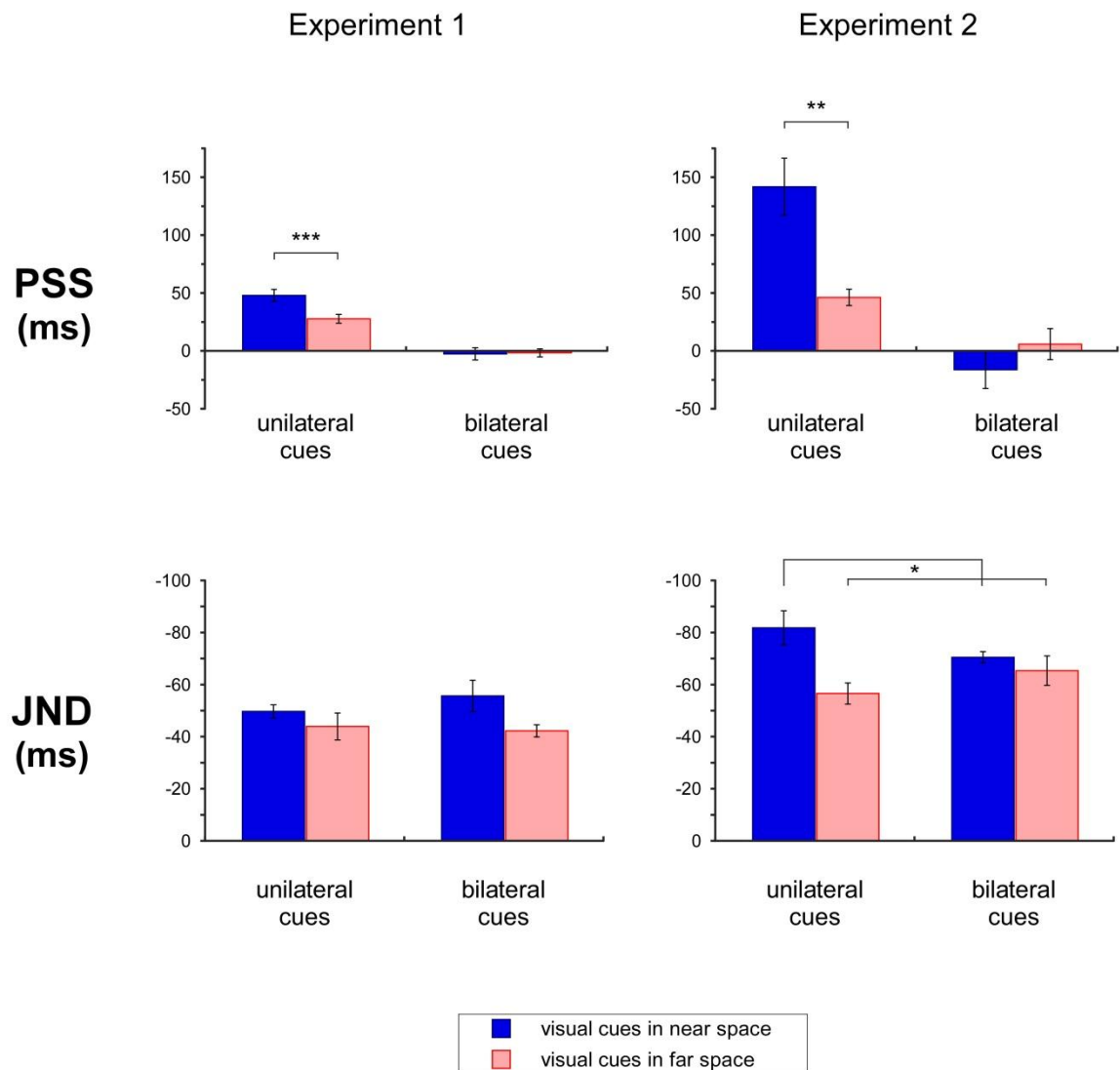


FIGURE 4. MEANS AND STANDARD DEVIATIONS FOR THE POINT OF SUBJECTIVE SIMULTANEITY (PSS) AND THE JUST NOTICEABLE DIFFERENCE (JND) FOR EXPERIMENTS 1 AND 2. THE PSS AND JND SCORES WERE CALCULATED FOR EACH PARTICIPANT AND EACH CONDITION SEPARATELY. THE DATA FROM THE TWO GROUPS OF PARTICIPANTS HAVING PARTICIPATED TO EXPERIMENT 1 (FIXATION FAR VS. CLOSE) AND THE DATA FROM THE TWO TASKS IN EACH EXPERIMENT (WHICH IS FIRST VS. WHICH IS SECOND) ARE MERGED. IN BOTH EXPERIMENTS, PSS VALUES WERE SIGNIFICANTLY DIFFERENT FROM 0 MS DURING TRIALS WITH UNILATERAL VISUAL CUES, BUT NOT DURING THE TRIALS WITH BILATERAL CUES. IN THE FORMER CONDITION, THE PSS WAS LARGER WHEN THE UNILATERAL CUE WAS PRESENTED IN NEAR SPACE AS COMPARED TO WHEN IT WAS PRESENTED IN FAR SPACE. THE JND VALUES WERE SIGNIFICANTLY LARGER WHEN THE VISUAL CUES WERE PRESENTED IN NEAR SPACE THAN WHEN THEY WERE PRESENTED IN FAR SPACE (IN EXPERIMENT 2 ONLY). ERROR BARS REPRESENT STANDARD ERRORS CORRECTED ACCORDING TO THE METHOD OF COUSINEAU (2005).

4 DISCUSSION

This study investigated the existence of a peripersonal frame of reference for the mapping of nociceptive stimuli. Two TOJ experiments were conducted involving the presentation of nociceptive stimuli, one applied to either hand and preceded by a visual cue. The cues were presented either close to or far from the participant's hands. The use of a TOJ task was motivated by the fact that TOJ responses are typically unsped and thus enable the investigation of the genuinely perceptual component of information processing, relatively unbiased by any response-related effects. The results of both experiments demonstrated a shift in the PSS towards the uncued hand, i.e., the hand opposite the location of the visual cue. Importantly, this shift was larger when the visual cue was presented close to than far from the hands. This result suggests that the processing of nociceptive stimuli was affected by the occurrence of visual stimuli located in peripersonal space.

An intriguing question concerns how people localize nociceptive stimuli on their body. Humans have the ability to localize cutaneous pain almost flawlessly (Koltzenburg, Handwerker, & Torebjörk, 1993; Mancini et al., 2011a; Moore & Schady, 1995; Trojan et al., 2006). However, a physical threat is rarely unisensory, and a purely anatomical frame of reference might be insufficient to localize which of the objects in external space is damaging the body (Moseley, Gallace, & Spence, 2012). Indeed, the ability to localize somatosensory stimuli not only relies on the adequate representation of the space of the body, but also on the ability to represent external space with respect to that body. Non-somatotopic frames of reference are, then, necessary to rapidly attend to, or direct actions toward, objects that could have a potential impact on the body. In the context of pain, this was illustrated by Moseley et al. (2009) in CRPS patients. Using a TOJ task with two concurrent tactile stimuli being applied sequentially, one to either hand, these authors showed that, in CRPS patients, the perception of the stimuli applied to the affected hand tends to be extinguished when the hands are in normal posture. However, when the patient's hands were crossed over the sagittal midline of the body, the reverse pattern was observed: The perception of the stimuli applied to the unaffected hand tended to be extinguished (Moseley et al., 2009). This result suggests that the deficits in spatial perception observed in CRPS are not related to the pathological limb but rather to the space normally inhabited by the pathological limb. In other words, neglect-like symptoms induced by unilateral pain, such as in the case of CRPS, revealed the existence of a *spatiotopic* reference frame (Smania & Aglioti, 1995), integrating the processing of both somatosensory and proprioceptive information. Even more striking, the same authors have shown that the skin temperature on the hands was not only dependent of their relative position in external space (Moseley, 2012) but also on the visual

perception of their position (Moseley, Gallace, Di Pietro, Spence, & Iannetti, 2013). Indeed, they demonstrated that when the pathological hand was viewed through prism glasses to appear in the healthy side of the body, the temperature of that hand warmed up. This latter study illustrates a potential role of vision in the deficits observed in CRPS. Similar crossmodal effects between nociceptive processing, proprioception and vision were also observed in healthy volunteers (Lloyd, Morrison, & Roberts, 2006; Longo, Betti, Aglioti, & Haggard, 2009; Mancini, Longo, Kammers, & Haggard, 2011b; Martini, Valentini, & Aglioti, 2013; Sambo et al., 2012a; Sambo et al., 2012b, Sambo & Iannetti, 2013). Other studies support the idea that such integration is made according a spatiotopic representation of the space of the body (Gallace et al., 2011; Sambo et al., 2013).

One further step made by the present study involved addressing the question of whether a peripersonal frame of reference can be used to code the spatial localization of nociceptive stimuli. Peripersonal space can be defined as a frame of reference coding the position of somatosensory stimuli on the body surface and the position of stimuli in external space (e.g., visual stimuli) *if* they appear in close proximity to the body. The present study specifically manipulated the distance of the cues relative to the body, and revealed that external visual stimuli presented close to the body are integrated with nociceptive stimuli applied to the hand. Indeed, the shift of the PSS towards the uncued side demonstrates that cuing a particular location in external space by a visual stimulus, prioritizes the processing of a subsequent nociceptive stimulus presented at the same location. Importantly, this is especially the case when the visual stimulus is presented close to the body, and to a lesser extent when the visual stimulus is presented further away from the body. In addition, because each visual cue was spatially non-informative and did not predict the location of the forthcoming nociceptive stimulus, the effects seem independent of the voluntary control of attention. This suggests an automatic coordination between nociceptive and proximal visual inputs for mapping peripersonal space (Spence & Driver, 2004a).

The existence of a peripersonal frame of reference has already been demonstrated for the mapping of tactile stimuli and supposedly relies on the existence, at least in monkeys, of bimodal neurons mostly in the ventral premotor cortex and the ventral intra-parietal sulcus (Graziano & Gross, 1994). For example, Graziano and Gross (1998) demonstrated that neurons in the ventral premotor cortex of monkeys fire both for tactile and visual stimuli, and that their visual receptive fields (RF) extends from the approximate region of the tactile RF into the immediate adjacent space. Similarly, Dong, Chudler, Sugiyama, Roberts, and Hayashi (1994) found in area 7b, in the inferior parietal lobe of monkeys, neurons that respond to nociceptive stimuli and to dynamical visual stimuli moving towards the RF of

these neurons and static visual stimuli presented in the vicinity of the somatosensory RF. Dong et al. (1994, p 561) suggested that this area would provide “(...) *dynamic visual-somatic information about an approaching noxious stimulus and impending tissue damage, respectively, which may be necessary for directing motor adjustments (...) to minimize body exposure and contact with the offending stimulus*”.

In humans, there is considerable evidence for the existence of an integration of tactile inputs in a peripersonal representation of the body. This idea is supported by neuropsychological data showing that the perception of somatosensory stimuli in patients with lesions, predominantly in the frontal and parietal cortices, is largely determined by the occurrence of visual stimuli close vs. far from the stimulated body part (e.g., Di Pellegrino & Làdavas, 1997; Farnè & Làdavas, 2000; Làdavas, Di Pellegrino, Farnè, & Zeloni, 1998; Làdavas, Farnè, Zeloni, & di Pellegrino, 2000). Neuroimaging studies also provide support for the role of the frontal cortex (Lloyd, Shore, Spence, & Calvert, 2003) and parietal cortex (Makin, Holmes, & Zohary, 2007) in the multisensory representation of the body. This fronto-parietal network might in turn boost the activity of unisensory areas, facilitating the processing of sensory inputs from each modality (Kennett, Eimer, Spence, & Driver, 2001; Macaluso, 2000; Taylor-Clarke, Kennett, & Haggard, 2002).

Based on the present results, it is reasonable to hypothesize that premotor and parietal areas play an important role in nociceptive processing and pain perception both in healthy individuals (Legrain, Iannetti, Plaghki, & Mouraux, 2011) and in chronic pain patients (Maihofner et al., 2007). Indeed, nociceptive inputs that are perceived as painful activate a large array of cortical areas such as mainly operculo-insular and cingulated areas, but also frontal and parietal areas (Tracey & Mantyh, 2007). Recently, the common view according to which some of these areas could be specifically involved in nociceptive processing and pain perception was challenged. Some authors have argued that such an activity reflects instead the detection, the localization and the reaction to sensory events that are meaningful for the integrity of the body (Legrain et al., 2011). As such, areas like frontal and parietal areas may be involved in the integration of nociceptive information into a multisensory representation of the body and the space nearby. By using peripersonal frames of references to code the spatial location of nociceptive stimuli, the brain can form an integrated representation of the part of the body in pain and the location of the external object causing that pain. Nociceptive inputs are integrated into a multisensory system that monitors the space of the body and the region of external space immediately surrounding the body, detects any sensory information having a potential impact on the body, and informs the individuals about changes in the representations of the body. The ultimate aim of the system would be to

facilitate the processing of physical threat and to select and prepare the most appropriate response (Graziano & Cooke, 2006). Therefore, the coding of nociceptive information in a peripersonal frame of reference may constitute a safety margin around the body to protect it against potential physical threats and represent a mechanism for preserving homeostatic control over the body (Moseley, Gallace, & Iannetti, 2012).

Furthermore, the present findings point at the potential relevance of spatial perception to the understanding of the pathophysiology and the treatment of chronic pain. For example, an etiology close to hemispatial neglect was described in CRPS patients (see Legrain, Bultitude, De Paepe, & Rossetti, 2012). As already explained, a phenomenon similar to tactile extinction is observed in these patients when a TOJ task is used (Moseley et al., 2009). Intriguingly, this pattern of sensory deficits tends to be reversed by changing the posture. Similarly, displacing the position of the CRPS hand either *proprioceptively* (by the crossing hands procedure; Moseley et al., 2012) or visually (by prism glasses; Moseley et al., 2013) also modifies the skin temperature of the CRPS hand. This illustrates that sensory and vegetative symptoms in chronic pain may be determined by higher-order cognitive processes involved in the representation of the body (Moseley et al., 2012). Sumitani et al. (2007) showed in CRPS patients a displacement of the body midline estimation towards the affected side of the body (however see Kolb, Lang, Seifert, & Maihofner, 2012; Reinersmann et al., 2012). Using prismatic visuomotor adaptation, these authors succeeded to reduce the displacement of the body representation. Importantly, they also showed that prismatic adaptation can alleviate pain and reduce associated CRPS symptoms such as edema, discoloration and motor impairment. Bultitude and Rafal (2010) reproduced these results in one patient showing that the benefits of the procedure were dependent of the use of the pathological hand during the prism adaptation. These latter studies illustrate the importance of understanding the mechanisms underlying the integration of nociceptive information in the multisensory representation of the bodily space for the rehabilitation of chronic pain patients.

The primary outcome of our study was the PSS. Nevertheless, we also observed effects on another parameter of TOJ tasks, namely the JND (which was not of primary interest; see Shore et al., 2005; Van Damme et al., 2009). More specifically, the JND had larger values (indicating less discriminating performance) when the visual cues were presented in near space, albeit only significant in Experiment 2. This effect was also present with bilateral cues, although the difference between close and far space was much smaller in this case. This pattern of results suggests that participants were more distracted by the occurrence of proximal visual stimuli regardless of their laterality relative to the somatosensory target,

thus resulting in poorer task performance. This result is difficult to interpret, and further research will be needed in order to reveal the mechanisms underlying this modulation of the JND (Shore et al., 2005; Van Damme et al., 2009).

The present study has a number of limitations that the reader should be made aware of. First, further studies are needed in order to determine whether crossmodal shifts in the PSS between vision and nociception reflect exogenous shifts of spatial attention from one space (i.e., external proximal space) to another space (i.e., bodily space) or intrinsic multisensory integration (Spence, McDonald, & Driver, 2004). Second, although the participant's head was fixed to minimize head and eye movements and to prevent vision of the hands, we cannot completely rule out the possibility that spatial attention was overtly shifted towards the location of the unilateral cues, and therefore to the hand positioned close to the cue, if cues were presented in near space. In this case, an alternative interpretation of our results would be that the selective vision of one of the hands primed the processing of nociceptive stimuli applied to that hand. However, this interpretation seems unlikely. Given that the distances between the hands and the trunk and the chin-rest and the trunk were respectively 40 cm and 10 cm, rapid gaze shifts from the fixation point towards the hands seem highly unlikely. Furthermore, it is commonly acknowledged that fast eye movements such as saccades take 200 ms to initiate and 20 to 200 ms to reach the target (depending on its eccentricity) (Kandel, Schwartz, & Jessell, 2000), a total duration largely superior to the delay between the visual cue and the second nociceptive stimulus, even in the conditions with the largest SOAs. Third, replications are also needed in order to circumvent the loss of participants due to their inability to perform the task at the required level. This could be attributable (1) to the low intensity of the nociceptive stimuli, which was needed to guarantee the selectivity for nociceptor activation (Mouraux et al., 2010), and (2) to jitter in input transmission due to the variability of the conduction velocity of A δ fibers (Adriaensen Gybels, Handwerker, & Van Hees, 1983). Indeed, according to the Erlanger-Gasser classification of sensory fibers, the conduction velocity of A δ fibers goes from 3 to 30 m/s. This variability in peripheral transmission might have made the temporal judgments more difficult, especially for trials with short SOAs. Nevertheless, it is worth noting that this loss did not prevent the observation of significant crossmodal shifts of the temporal order judgment of nociceptive stimuli.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest related to the present article.

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CHAPTER 2

FROM A SOMATOTOPIC TO A SPATIOTOPIC FRAME OF REFERENCE FOR THE LOCALIZATION OF NOCICEPTIVE STIMULI.¹

ABSTRACT

To react efficiently to potentially threatening stimuli, we have to be able to localize these stimuli in space. In daily life we are constantly moving so that our limbs can be positioned at the opposite side of space. Therefore, a somatotopic frame of reference is insufficient to localize nociceptive stimuli. Here we investigated whether nociceptive stimuli are mapped into a spatiotopic frame of reference, and more specifically a peripersonal frame of reference, which takes into account the position of the body limbs in external space, as well as the occurrence of external objects presented near the body. Two temporal order judgment (TOJ) experiments were conducted, during which participants had to decide which of two nociceptive stimuli, one applied to either hand, had been presented first while their hands were either uncrossed or crossed over the body midline. The occurrence of the nociceptive stimuli was cued by uninformative visual cues. We found that the visual cues prioritized the perception of nociceptive stimuli applied to the hand laying in the cued side of space, irrespective of posture. Moreover, the influence of the cues was smaller when they were presented far in front of participants' hands as compared to when they were presented in close proximity. Finally, participants' temporal sensitivity was reduced by changing posture. These findings are compatible with the existence of a peripersonal frame of reference for the localization of nociceptive stimuli. This allows for the construction of a stable representation of our body and the space closely surrounding our body, enabling a quick and efficient reaction to potential physical threats.

¹ Based on: De Paepe, A.L., Crombez, G., Legrain, V. (2015). From a somatotopic to a spatiotopic frame of reference for the localization of nociceptive stimuli. *PLoS one*, 10, e0137120.

1 INTRODUCTION

To react efficiently to stimuli that affect the integrity of the body, we have to localize them precisely. Thanks to a good spatial acuity, the nociceptive system seems finely-tuned for the localization of noxious stimuli on the body surface (Mancini et al., 2013; Mancini, Haggard, Iannetti, Longo, & Sereno, 2012). However, the localization of noxious stimuli requires not only the identification of their position on the body, but also the identification of their position in external space (Longo, Azanon, & Haggard, 2010). Information from the body surface and information from the external world are believed to be integrated in peripersonal frames of reference, which code both the position of somatosensory stimuli on the body surface *and* the position of stimuli in external space (e.g., visual stimuli) *if* presented in close proximity to the body. This idea has been investigated for touch (see Spence & Driver, 2004). Regarding nociception, we suggested the existence of such a peripersonal frame of reference for the localization of nociceptive stimuli (De Paepe, Crombez, Spence, & Legrain, 2014). In that study participants had to perform temporal order judgments (TOJs) on pairs of nociceptive target stimuli, one applied to either hand at various stimulus onset asynchronies (SOAs). Participants had to decide which hand was stimulated first. Slightly before the presentation of the first nociceptive stimulus, a visual stimulus was presented either in close proximity of one of the hands, or far from the hands (i.e. 70 cm in front of the hands). It was found that the visual stimulus speeded the perception of the nociceptive stimulus applied to the ipsilateral hand, at the detriment of the nociceptive stimulus applied to the opposite hand. More importantly, this effect was stronger when the visual stimulus was presented near the participants' hands, as compared to trials in which it was presented far away. These results suggest that the processing of nociceptive stimuli is affected by the occurrence of visual stimuli located in the peripersonal space of the body. Based upon these findings, we suggested that nociceptive stimuli can be mapped according a peripersonal frame of reference.

In the present study we wanted to confirm this hypothesis by showing that the spatial perception of nociceptive stimuli is made through a remapping of the body space according a spatial frame of reference which takes into account the relative position of the body limbs in external space. Indeed, when hands are in normal posture (as was the case in the study of De Paepe et al., 2014), the somatosensory and the visual maps are merely aligned, in the sense that the visual and the nociceptive inputs are sent to the same hemisphere. Therefore, our previous results were not able to completely dissociate between effects resulting from crossmodal displacement of spatial attention on the somatotopic representation of the skin surface from effects resulting from a remapping of nociceptive processing according to

external space coordinates (i.e. a spatiotopic frame of reference) (see Azañón & Soto-Faraco, 2008). Such spatiotopic frame of reference allows taking into account the relative positions of body parts in external space, enabling us to recognize that when the left hand is displaced toward the right side of space, objects approaching the right space are now approaching the left hand instead of the right hand. Here, we would like to demonstrate that the positions of nociceptive stimuli can be completely remapped according a spatial representation of the body. To this end we used a crossing hands procedure, that is, when the relative position of the hands in external space is manipulated according to the sagittal midline of the body. Indeed, crossing the hands over the body midline generates a mismatch between the somatotopic and spatiotopic representations, enabling to dissociate between these two types of reference frames. This procedure makes it then possible to test whether the ability to perceive the spatial position of a somatosensory stimulus on the body is only based on the hemispheric projection of the somatosensory receptive field, or also on the relative position of the stimulated limb in external space.

For tactile information, such dissociation has been shown in studies with patients with right hemisphere lesions. For example, Smania and Aglioti (1995) showed that the ability of patients with hemispatial neglect and/or tactile extinction to detect somatosensory stimuli applied to the left hand changed according to the location of the hand in external space. Whereas the perception of stimuli applied to the left hand was poor in an uncrossed posture, especially when the right hand was concurrently stimulated, the perception was improved when the left hand was crossed over the body midline and was positioned in the right side of space. These results demonstrate that the somatosensory deficits of these patients are not only linked to the anatomical projection of sensory inputs to a damaged hemisphere, but also to a defective computation of body-centered spatial coordinates. Moreover, they showed that the coding of the spatial position of the hands depends on their relative positions in external space, irrespective to their positions from the body midline (Aglioti, Smania, & Peru, 1999).

In healthy volunteers the existence of a spatiotopic reference frame has been demonstrated using tactile TOJ tasks and crossmodal congruency tasks. Studies using the TOJ task have frequently found that participants could correctly report the temporal order of two tactile stimuli when the hands were uncrossed, but often misreport the order when the hands were crossed over the body midline (Pagel, Heed, & Röder, 2009; Röder, Rösler, & Spence, 2004; Shore, Spry, & Spence, 2002; Yamamoto & Kitazawa, 2001). In these tasks, participants were probably confused due to a competition between a somatotopic reference frame and a remapping of the tactile stimuli according to spatiotopic coordinates

(Yamamoto & Kitazawa, 2001). In the crossmodal congruency task with tactile targets and visual distractors, it was shown that the interference of visual stimuli on tactile processing was space-based. In the crossed posture the discrimination of tactile stimuli applied to the left hand was more influenced by right- than left-sided visual stimuli, and vice versa (Holmes, Sanabria, Calvert, & Spence, 2006; Kennett, Eimer, Spence, & Driver, 2001; Kennett, Spence, & Driver, 2002; Spence, Pavani, & Driver, 2004; van Elk, Forget, & Blanke, 2013). This result was not observed in a split-brain patient showing that remapping somatosensory information according to space-based reference frames is not possible when the cortical hemispheres are disconnected (Spence, Shore, Gazzaniga, Soto-Faraco, & Kingstone, 2001).

In monkeys, the ability to remap tactile inputs according to a peripersonal frame of reference has been suggested to rely on the existence of bimodal visuotactile neurons that have been reported in the ventral premotor cortex and the ventral intraparietal sulcus of the monkey (Graziano, Yap, & Gross, 1994). Bimodal cells are cells that fire both for tactile stimuli and for visual stimuli, presented near the stimulated area. For instance, Graziano, Hu, and Gross (1997) showed that the visual receptive fields (RFs) of these bimodal cells are remapped when the monkey's posture changes, i.e., the visual RFs follow the hands in space as different postures are adapted.

For nociceptive stimuli, it has been shown that crossing the hands over the body midline affects the judgments concerning the temporal order of nociceptive stimuli applied to either hand (Sambo et al., 2013), and even the perception of their intensity (Gallace, Torta, Moseley, & Iannetti, 2011). The fact that crossing the hands affects the temporal sensitivity of participants suggests that nociceptive processing is influenced by the conflict generated by the crossing hands procedure between the somatotopic representation of the body, and a spatiotopic representation. These studies demonstrate the usefulness of the crossing hands procedure to investigate the remapping of nociceptive stimuli applied to the body in a space-based frame of reference.

In the present study we used the crossing hands procedure and investigated the contribution of posture to code the position of nociceptive stimuli applied to a specific body part relative to external stimuli occurring close to that body part. This was investigated in two TOJ experiments, during which participants had to decide which of two nociceptive stimuli, one applied to either hand at various SOAs, had been perceived to occur first while their hands were either in an uncrossed or a crossed posture. The occurrence of the nociceptive stimuli was cued by visual stimuli. In Experiment 1, these cues were presented

both in near and far space. In Experiment 2, the cues were only presented in near space. We hypothesized that, if the spatial coding of nociceptive stimuli is accounted only by the hemispheric projection of the sensory inputs, visual information on the left side of space would always prioritize stimuli presented to the left side of the body, and vice versa. The ability to report the perception of a nociceptive stimulus applied to one hand should not be affected by crossing the hands. Conversely, if nociceptive stimuli are mapped in a spatiotopic frame of reference, visual information in the left side of space would prioritize nociceptive stimuli presented to the left hand when hands are uncrossed, but to the right hand when hands are crossed (and vice versa for visual stimuli in the right side of space). The closer the visual stimulus to the body, the stronger should be this bias. In addition, the participants should be less accurate in reporting the temporal order of the nociceptive stimuli when the hands are crossed.

2 METHODS

2.1 EXPERIMENT 1

2.1.1 PARTICIPANTS

Twenty-two paid participants volunteered to take part in this experiment. One participant was excluded because of the use of antidepressant medication at the time of the experiment. The mean age of the 21 remaining participants (17 women; 19 right-handed) was 23 years (ranging from 19 to 38 years). All of the participants had normal to corrected-to-normal vision. History of neurological, psychiatric or chronic pain diseases, and usual intake of psychotropic drugs were considered as exclusion criteria. The experimental procedure was approved by the ethics committee of the faculty of psychology and educational sciences of the UGent (2014/46). All of the participants provided written informed consent prior to taking part in the study.

2.1.2 STIMULI AND APPARATUS

The nociceptive stimuli were delivered by means of intra-epidermal electrical stimulation (IES) (DS7 Stimulator, Digitimer Ltd, UK), with stainless steel concentric bipolar electrodes (Nihon Kohden, Japan; Inui, Tsuji, & Kakigi, 2006). The electrodes consisted of a needle cathode (length: 0.1 mm, \emptyset : 0.2 mm) surrounded by a cylindrical anode (\emptyset : 1.4 mm). By gently pressing the device against the participant's skin, the needle electrode was inserted into the epidermis of the dorsum of the hand in the sensory territory of the superficial branch of the radial nerve. Using intra-epidermal

stimulation at maximum twice the absolute threshold was shown to selectively activate the free nerve endings of the A δ fibers (Inui et al., 2006; Mouraux, Iannetti, & Plaghki, 2010; Mouraux, Marot, & Legrain, 2014). The detection threshold was determined with single-pulse stimuli (0.5 ms square wave pulse) using a staircase procedure (Churyukanov, Plaghki, Legrain, & Mouraux, 2012). The detection threshold was established separately for each hand. Next, the stimulus intensity was set at twice the detection threshold. If necessary, the intensity of the stimuli was adjusted so that the stimuli delivered to each hand were perceived as being equally intense. During the course of the experiment proper, the stimuli consisted of trains of four consecutive 0.5 ms square-wave pulses separated by a 5-ms inter-pulse interval. Using a set of pain words from the Dutch McGill Pain questionnaire (Vanderiet, Adriaensen, Carton, & Vertommen, 1987) the stimuli were described as pricking. After each experimental block, the participants were asked to estimate the intensity elicited by the nociceptive stimuli on a numerical graphic rating scale (10 cm) with the following labels selected from the Dutch version of the McGill pain questionnaire (Vanderiet et al., 1987) (0 = felt nothing, 2.5 = lightly intense, 5 = moderately intense, 7.5 = very intense, 10 = enormously intense). This scale was used in order to ensure that: (1) the stimuli were still perceived, and (2) the percept elicited by the IES delivered to each of the participant's hands was still equivalent. If one of these two criteria was not met, the stimulus intensities were modified accordingly (with a maximum increase of 0.10 mA). If this adaptation proved to be unsuccessful (i.e. one of the criteria was still not met), the electrodes were displaced and the procedure was restarted.

The visual stimuli were presented by means of four green light-emitting diodes (LEDs). The LEDs were illuminated for 20 ms, and these stimuli were perceived by participants as a green light that briefly flashed. In a practice phase, the visibility of each of the LEDs was tested by asking the participants to report on the location of the LED that was illuminated (e.g., 'left near', 'right far').

2.1.3 PROCEDURE

The participants sat on a chair in a dimly illuminated, sound-attenuated room. They rested their arms on the table in front of them. The distance between the participant's hands and their trunk, as well as the distance between the participant's index fingers was 40 cm. The participant's head was immobilized in a chin-rest positioned at 10 cm from the trunk, in order to prevent movements of the head. The height of the chin-rest was individually adapted. Two of the LED's were placed in near space, and two in far space. The LEDs in near space were positioned 40 cm from the trunk, in between thumb and

index finger. The distance between the two LEDs was approximately 40 cm. The LEDs in far space were situated 70 cm in front of the LEDs in near space. Participants were fixating on a red LED positioned equidistantly from the LEDs in far and near space, and equidistantly from the left and right LEDs (Figure 1). Responses were given by means of two foot pedals, one positioned under the toes, and one under the heel. Participants were instructed to keep the foot pedals depressed, and to either raise their heel or their toes very briefly to respond which hand was stimulated first. Half of the participants responded with their left foot, the other half with their right foot. The response mapping (toe = left hand, heel = right hand, or vice versa) was counterbalanced between participants. Participants were instructed to be as accurate as possible, speed was not important.

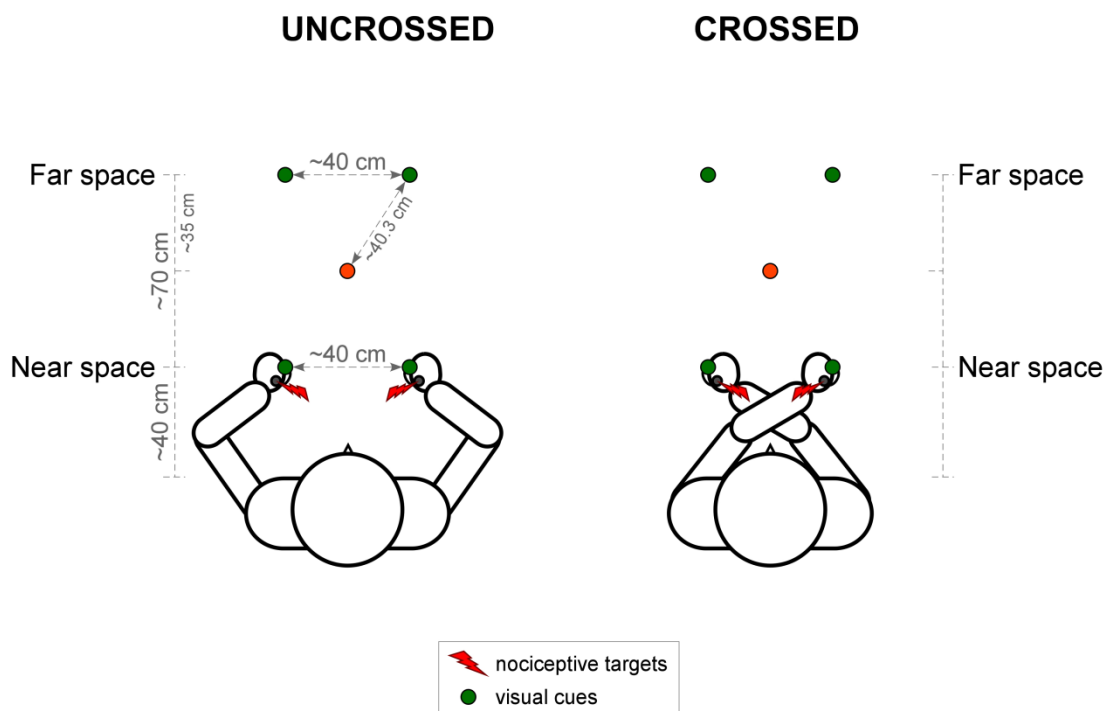


FIGURE 1. ILLUSTRATION OF THE EXPERIMENTAL SET-UP FOR EXPERIMENT 1. NOCICEPTIVE STIMULI, REPRESENTED BY THE RED LIGHTNING SYMBOLS, WERE APPLIED TO BOTH OF THE PARTICIPANT'S HANDS. VISUAL CUES, REPRESENTED BY THE GREEN CIRCLES, WERE PRESENTED AT FOUR DIFFERENT LOCATIONS IN EACH TRIAL: EITHER UNILATERALLY OR BILATERALLY, EITHER IN BETWEEN THUMB AND INDEX FINGER OF THE PARTICIPANT (IN NEAR SPACE) OR IN FRONT OF THE PARTICIPANT'S HANDS (IN FAR SPACE). PARTICIPANTS WERE FIXATING ON A RED LED (REPRESENTED BY THE RED CIRCLE) THAT WAS POSITIONED IN BETWEEN THE LEDS IN NEAR AND FAR SPACE. IN HALF OF THE BLOCKS PARTICIPANTS WERE ASKED TO CROSS THEIR HANDS OVER THE BODY MIDLINE (RIGHT SIDE OF THE FIGURE). IN EXPERIMENT 2, THE SET-UP WAS IDENTICAL, EXCEPT FOR THE FACT THAT THE LEDS WERE ONLY PRESENTED IN NEAR SPACE.

To get used to the stimulus response mapping, a first practice session contained 1 block of 20 trials, in which participants were presented with one IES target, either on the left or the right hand. Participants indicated, by means of the foot pedals, which hand was stimulated. In a second practice phase of 2 blocks (one with the uncrossed and one with the crossed posture) of 36 trials participants practiced the actual experiment with cues and nociceptive targets, but only using the three largest SOAs, to ensure correct task performance. The experiment did not proceed until participants had 80% correct performance on the largest SOAs in both blocks.

The actual experiment consisted of 8 blocks of 60 trials. Four blocks contained visual stimuli in near space only, and four blocks visual stimuli in far space only. The order of the blocks was randomized for the first 4 blocks and the reversed order was used for the last 4 blocks. In half of the blocks participants were asked to cross their hands, one arm over the other. The posture (crossed/uncrossed) of the arms was alternated over blocks and the order was counterbalanced. In half of the crossed hands blocks, participants had to cross their left arm over their right arm. In the other half they had to cross their right arm over their left arm. The order was again counterbalanced.

A trial started with the fixation LED being illuminated. This fixation LED stayed on during the entire trial. 500 ms after the onset of the fixation LED, the visual stimulus was presented either in near or far space. The visual stimulus consisted of either a single unilateral flash occurring in left space, a single unilateral flash occurring in right space, or two flashes resulting from the bilateral and simultaneous illumination of the LEDs on both sides. The visual stimulus was followed 80 ms after its onset by a pair of nociceptive stimuli, one applied to either hand. The first nociceptive stimulus could be applied either to the left or the right hand. Five possible SOAs were used between the two nociceptive stimuli for each order of stimulation (left hand first vs. right hand first): ± 200 , ± 90 , ± 55 , ± 30 , ± 10 ms (where positive values indicate that the participant's right hand was stimulated first, and negative values indicate that their left hand was stimulated first).

The trials were created combining 3 spatial locations of the visual stimuli (unilateral left, unilateral right or bilateral) x 2 orders for the nociceptive stimuli x 5 SOAs. Trials were randomly presented within each block of stimulation. The visual cues were spatially uninformative, and the location of any forthcoming nociceptive stimulus could thus not be predicted by the cue.

Participants were instructed to keep their gaze on the fixation LED throughout each block of trials and to indicate by means of the foot pedals, which hand was stimulated

first, irrespective of the side of space in which their hand was located. After the participants had made their response, the fixation LED was turned off. If participants did not respond within 10s, the fixation LED flickered 3 times before the experiment continued. After 1000 ms, the next trial started. The experiment took on average 75 minutes.

2.1.4 MEASURES

The procedure followed that reported in Spence, Shore, & Klein (2001) (see also Shore, Gray, Spry, & Spence, 2005; Van Damme, Gallace, Spence, Crombez, & Moseley, 2009). For each participant, and for each SOA for each of the 8 within-participant conditions (bilateral vs. unilateral cues x near vs. far space x uncrossed vs. crossed), the proportion of trials on which participants perceived the cued hand as being stimulated first, was calculated. A sigmoid function was fitted to these proportions (Figure 2). Subsequently, the proportion of *left/right hand first responses* (left hand when the cue was presented at the side of space in which the left hand was situated, and right hand first when the cue was presented at the side of space in which the right hand was situated) was converted into z-scores by means of a standardized cumulative normal distribution (probits). The best-fitting straight line was computed for each participant and each condition, and the derived slope and intercept values were used to compute the point of subjective simultaneity (PSS) and the just noticeable difference (JND). The PSS refers to the point at which participants report the two events (i.e., the nociceptive stimuli presented to the right and left hand) as occurring first equally often. This is equivalent to the SOA value corresponding to a proportion of *left/right hand first responses* of 0.5 (Spence et al., 2001). The PSS is computed as the opposite of the intercept divided by the slope from the best-fitting straight line. In the unilateral cue condition, the sign of the PSS for the conditions in which the cues were presented on the side of space where the right hand was positioned, was reversed and for each participant the final PSS value was calculated by taking the average of the PSS values for cues presented at the position of the left hand, and the reversed PSS value for cues presented at the position of the right hand. Hence, the PSS reflects how much time the stimulus at the *uncued hand* had to be presented before/after the *cued hand* in order to be perceived as having occurred at the same time. In the bilateral cue condition, there was no “cued” or “uncued” hand, as cues were always presented bilaterally. We decided to calculate the PSS from the amount of *left hand first responses*. The PSS for the bilateral cue trials thus reflects how much time the stimulus at the *right hand* has to be presented before/after the *left hand* stimulus in order to be perceived as presented at the same time. In sum, the PSS provides information

concerning biases in spatial attention resulting from the presentation of the visual cues. In order to control whether the side at which the visual cue was presented could have influenced the PSS values in unilateral cue trials, we did a separate analyses including *side of the visual stimulation* as a factor. These analyses showed that merging PSS values for cues presented on the left and the right side of space will not distort the results (see Appendix, section 6.2).

The JND was measured as $0.675/\text{slope}$ (Spence et al., 2001). This corresponds to the value achieved by subtracting the SOA at which the best fitted line crosses the 0.75 point from the SOA at which the same line crosses the 0.25 point, and dividing this by two and indicates the interval needed to achieve 75% correct performance, and, as such provides a standardized measure of the sensitivity of participant's temporal perception.

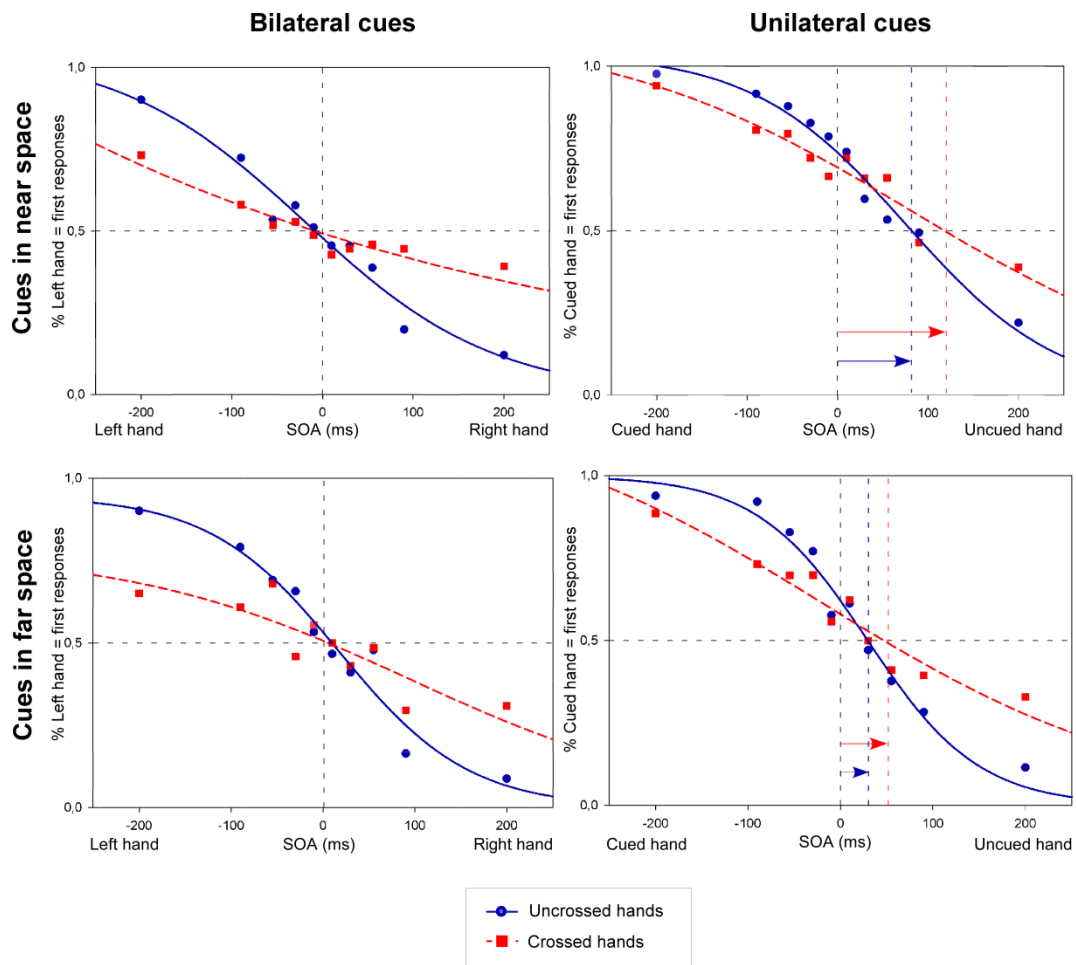


FIGURE 2. NOCICEPTIVE TEMPORAL ORDER JUDGMENTS (TOJ'S) IN EXPERIMENT 1. THE FIGURES ILLUSTRATE THE FITTED CURVES FROM CUMULATIVE DATA FROM 21 PARTICIPANTS. TRIALS WERE EITHER ASSOCIATED WITH BILATERAL CUES (LEFT SIDE OF THE FIGURE), OR WITH AN UNILATERAL CUE (RIGHT SIDE OF THE FIGURE), WITH CUES IN NEAR SPACE (UPPER PART FIGURE), OR WITH CUES IN FAR SPACE (LOWER PART FIGURE), AND WITH AN UNCROSSED (BLUE SOLID LINE) OR A CROSSED (RED DASHED LINE) POSTURE. DATA ARE PLOTTED AS THE MEAN PROPORTION OF *LEFT HAND FIRST RESPONSES* (ON THE Y-AXIS; LEFT SIDE OF FIGURE, BILATERAL CUES) OR *CUED HAND FIRST RESPONSES* (ON THE Y-AXIS; RIGHT SIDE OF FIGURE, UNILATERAL CUES), AS A FUNCTION OF THE STIMULUS ONSET ASYNCHRONIES (SOA) (ON THE X-AXIS). ON THE X-AXIS, FOR THE BILATERAL CUE CONDITIONS, THE NEGATIVE VALUES OF THE SOA'S INDICATE THAT THE LEFT HAND WAS STIMULATED FIRST, AND THE POSITIVE VALUES INDICATE THAT THE RIGHT HAND WAS STIMULATED FIRST. IN THE UNILATERAL CUE CONDITION, NEGATIVE VALUES INDICATE THAT THE CUED HAND WAS STIMULATED FIRST, WHILE POSITIVE VALUES INDICATE THAT THE UNCUED HAND WAS STIMULATED FIRST. THE BLUE (UNCROSSED HANDS) AND RED (CROSSED HANDS) VERTICAL DASHED LINES, AND THE LENGTH OF THE BLUE AND RED ARROW COINCIDE WITH THE PSS VALUES. COMPARED TO THE BILATERAL CUE CONDITIONS, THE CURVES IN THE UNILATERAL CUE CONDITIONS WERE SHIFTED TOWARD THE UNCUED SIDE BOTH FOR THE UNCROSSED AND THE CROSSED POSTURE. THIS INDICATES THAT THE NOCICEPTIVE STIMULUS ON THE UNCUED HAND HAD TO BE PRESENTED SEVERAL MILLISECONDS BEFORE THE STIMULUS ON THE CUED HAND TO HAVE AN EQUAL CHANCE TO BE PERCEIVED FIRST, REGARDLESS OF POSTURE. THE JND CHARACTERIZES THE SLOPE OF THE FUNCTIONS: THE STEEPER THE SLOPE, THE LOWER THE JND AND THE HIGHER THE TEMPORAL SENSITIVITY (AND VICE VERSA).

2.1.5 ANALYSES

Analyses were performed on the PSS and JND values. PSS values that exceeded twice the maximum SOA were excluded from the data, together with their corresponding JND values. Extremely large PSS values indicate that participants were not able to perform the task correctly even at large SOAs, where the task performance is expected to be nearly perfect. Therefore, the results in some conditions are missing for some participants. In order to test if this was influenced by the position of the hands, the difference in missing values between the uncrossed and the crossed posture condition was compared using a chi-squared test for equality of proportions.

To address the question of whether there was an attentional bias (due to the capture of attention by the visual cues), we tested whether the PSS differed significantly from 0, using one-sample t-tests.

Next, in order to compare the PSS across the different conditions, results were analyzed using the linear mixed effects models as implemented in the R package “Linear and Nonlinear Mixed Effects Models” (Pinheiro & Bates, 2000). Linear mixed effects models account for the correlations in within-subject data by estimating subject-specific deviations (or random effects) from each population-level factor (or fixed factor) of interest (see West, Welch, & Galecki, 2007 for an elaboration). We chose to analyze the data with linear mixed models because it is a more subject-specific model and it allows unbalanced data, unlike the classical general linear models which requires a completely balanced array of data (West et al., 2007).

The primary outcome variable was the Point of Subjective Simultaneity (PSS). The independent variables were the *laterality* (unilateral/bilateral), the *cue distance* (near/far) and the *posture* (uncrossed/crossed). These were manipulated within subjects. Each analysis required three steps. First, all relevant factors and interactions were entered in the model as fixed factors, and we assessed whether it was necessary to add a random effect for each of the fixed factors in the analysis: If a random effect significantly increased the fit of the model, it was included in the final model. By default, a random effect was added introducing adjustments to the intercept conditional on the *Subject* variable. In the second step, we searched for the most parsimonious model that fitted the data. To achieve this, we systematically restricted the full model, comparing the goodness of fit using likelihood-ratio tests. Finally, in the third step, we inspected the ANOVA table of the final model and tested specific hypotheses about possible main effects or interactions (for a similar approach see De Ruddere et al., 2011; Durnez & Van Damme,

2015; De Ruddere, Goubert, Stevens, Amanda, & Crombez, 2013; Verbruggen, Aron, Stevens, & Chambers, 2010). Kenward-Roger approximations to the degrees of freedom were used to adjust for small sample sizes (Kenward & Roger, 1997). When an interaction effect was significant, it was further investigated with follow-up contrast analyses, corrected for multiple testing according to the Holm-Bonferroni corrections (Holm, 1979). Standardized regression coefficients were reported as a measure of the effect size. The models are presented in the Appendix (section 6.1, Table 1 to 3).

The same method was used to assess the influence of the different experimental conditions on the JND. The models are presented in the Appendix (section 6.1, Table 7 to 9).

2.2 EXPERIMENT 2

2.2.1 PARTICIPANTS

Seventeen paid participants volunteered to take part in this experiment. The mean age of the participants (12 women; 12 right-handed) was 19 years (ranging from 18 to 22 years). All of the participants had normal to corrected-to-normal vision. History of neurological, psychiatric or chronic pain diseases, and usual intake of psychotropic drugs were considered as exclusion criteria. The experimental procedure was approved by the ethics committee of the faculty of psychology and educational sciences of the UGent (2014/46). All of the participants provided written informed consent prior to taking part in the study.

2.2.2 STIMULI AND APPARATUS

The experimental set-up was largely similar to the set-up of Experiment 1. As we were mostly interested in the effect of the posture (uncrossed/crossed) on the interaction between nociceptive and visual inputs in peripersonal space, the LEDs in Experiment 2 were only presented in near space. The distance between the participants' hands and their trunk, as well as the distance between their index fingers was 40 cm. The two LEDs were presented in between thumb and index finger. The same procedure was used to determine the detection threshold.

In order to reduce the number of rejected values from the dataset compared to Experiment 1, we used a larger range of SOAs between the two nociceptive targets: ± 600 , ± 400 , ± 250 , ± 100 , ± 70 , ± 50 , ± 30 , ± 15 (positive values indicate that the right hand was

stimulated first, negative values indicate that the left hand was stimulated first). Due to technical failure of the foot pedals, responses were given verbally.

2.2.3 PROCEDURE

The practice session contained 2 blocks (one uncrossed, one crossed) of 18 trials with nociceptive targets only with the three largest SOAs to ensure correct task performance (80% correct performance was required in both conditions (uncrossed/crossed) for the maximum SOA), and 2 blocks (one uncrossed, one crossed) of 18 trials with the cues and the targets (again only the three largest SOAs were used and 80% correct performance was required in order to proceed with the experiment). The experiment consisted of 4 blocks of 96 trials. In two blocks participants were asked to cross their hands, in the other two blocks hands were uncrossed. The order was alternated and counterbalanced across participants. In half of the crossed hands blocks, participants had to cross their left arm over their right arm, in the other half they had to cross their right arm over their left arm. The order was again counterbalanced.

A trial started with the fixation cross being illuminated. This fixation LED stayed on during the entire trial. 500 ms after the onset of the fixation LED, a single unilateral visual flash (either on the right or left side), or paired bilateral visual flashes were presented. The visual stimulus was followed 80 ms after its onset by a pair of nociceptive stimuli, one applied to either hand. Eight possible SOAs were used between the two nociceptive stimuli for each order of stimulation (left hand first vs. right hand first): ± 600 , ± 400 , ± 250 , ± 100 , ± 70 , ± 50 , ± 30 , ± 15 ms (positive values indicate that the right hand was stimulated first, negative values indicate that the left hand was stimulated first). Each block of trials was created by combining the 3 spatial locations of the visual stimuli (unilateral left, unilateral right or bilateral) \times 2 orders of the nociceptive stimuli \times 8 SOA's. Trials were presented randomly within each block of stimulation. The visual cues were not spatially informative and the location of any forthcoming nociceptive stimulus could thus not be predicted by the cue.

Participants were instructed to keep their gaze on the fixation LED and to indicate which hand was stimulated first in two blocks, and which hand was stimulated second in the other two blocks. By using both a "*Which came first?*" and a "*Which came second?*" task, we were able to control for response bias (that is, the tendency of participants to respond with the side on which the unilateral cue had been presented; see Cairney, 1975; Drew, 1896; Shore, Spence, & Klein, 2001; Spence, Shore, & Klein, 2001). The instruction was alternated between blocks of trials and the order of presentation was

counterbalanced across participants. Participants were explicitly instructed to tell which *hand* was stimulated first/second, irrespective of the side of space in which their hand was stimulated. Participants' responses were provided verbally and registered by the experimenter by pressing one of two keys on a keyboard. After a response was given, the fixation LED was turned off. After 1000 ms, the next trial started. The experiment took on average 60 minutes.

2.2.4 MEASURES

For each participant, and for each SOA of the 4 within-participant conditions (bilateral vs. unilateral cues x uncrossed vs. crossed posture), the proportion of trials on which participants perceived the cued hand as being stimulated first was calculated (see Figure 3). In order to increase the number of trials per condition, we merged the data over the variable *Task* (Which first? vs. Which second?), as this variable was not of primary interest, and previous studies with a similar paradigm had shown that the task participants have to perform, has no significant influence on the TOJ performance (De Paepe et al., 2014). PSS and JND values were calculated from these proportions identically to the first experiment. In order to control whether the side at which the visual cue was presented could have influenced the PSS values in unilateral cue trials, we did a separate analyses including *side of the visual stimulation* as a factor. These analyses showed that merging PSS values for cues presented on the left and the right side of space will not distort the results (see Appendix, section 6.2).

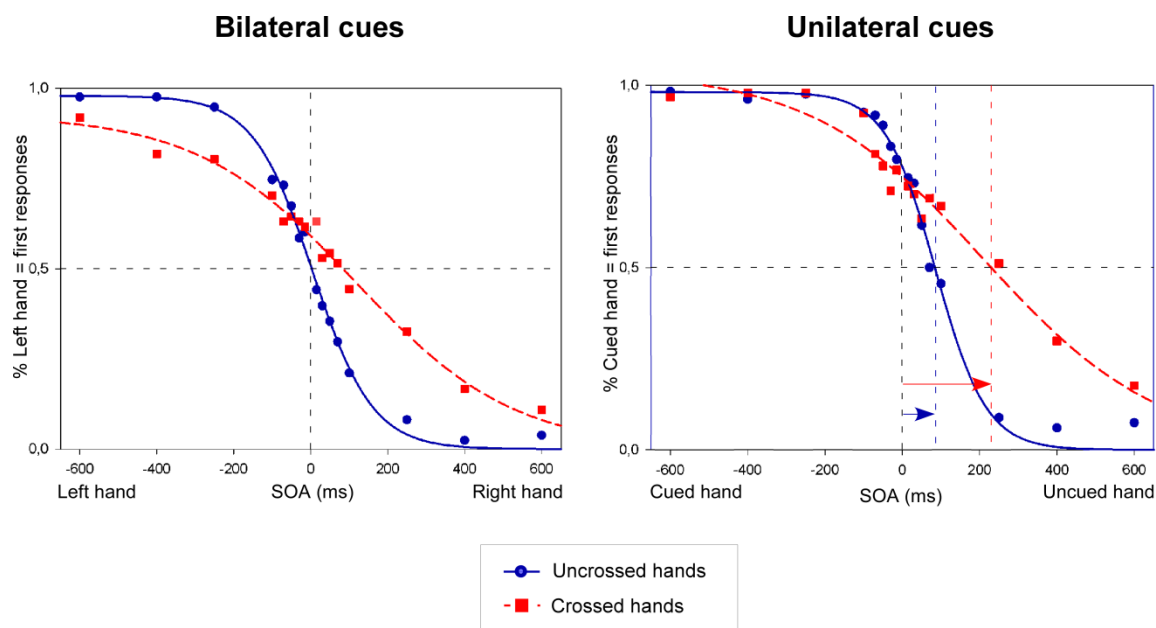


FIGURE 3. NOCICEPTIVE TEMPORAL ORDER JUDGMENTS (TOJ'S) IN EXPERIMENT 2. THE FIGURES ILLUSTRATE THE FITTED CURVES FROM CUMULATIVE DATA FROM 17 PARTICIPANTS. TRIALS WERE EITHER ASSOCIATED WITH BILATERAL CUES (LEFT SIDE OF THE FIGURE), OR WITH AN UNILATERAL CUE (RIGHT SIDE OF THE FIGURE), AND WITH AN UNCROSSED (BLUE SOLID LINE) OR A CROSSED (RED DASHED LINE) POSTURE. DATA ARE PLOTTED AS THE MEAN PROPORTION OF *LEFT HAND FIRST RESPONSES* (ON THE Y-AXIS; LEFT SIDE OF FIGURE, BILATERAL CUES) OR *CUED HAND FIRST RESPONSES* (ON THE Y-AXIS; RIGHT SIDE OF FIGURE, UNILATERAL CUES), AS A FUNCTION OF THE STIMULUS ONSET ASYNCHRONIES (SOA) (ON THE X-AXIS). ON THE X-AXIS, FOR THE BILATERAL CUE CONDITIONS, THE NEGATIVE VALUES OF THE SOAS INDICATE THAT THE LEFT HAND WAS STIMULATED FIRST, AND THE POSITIVE VALUES INDICATE THAT THE RIGHT HAND WAS STIMULATED FIRST. IN THE UNILATERAL CUE CONDITION, NEGATIVE VALUES INDICATE THAT THE CUED HAND WAS STIMULATED FIRST, WHILE POSITIVE VALUES INDICATE THAT THE UNCUED HAND WAS STIMULATED FIRST. THE VERTICAL DASHED LINES COINCIDE WITH THE PSS VALUES. AS IN EXPERIMENT 1, THE CURVES IN THE UNILATERAL CUE CONDITIONS WERE SHIFTED TOWARD THE UNCUED SIDE BOTH FOR THE UNCROSSED AND THE CROSSED POSTURE. THIS INDICATES THAT THE NOCICEPTIVE STIMULUS ON THE UNCUED HAND HAD TO BE PRESENTED SEVERAL MILLISECONDS BEFORE THE STIMULUS ON THE CUED HAND TO HAVE AN EQUAL CHANCE TO BE PERCEIVED FIRST. THIS EFFECT WAS EVEN STRONGER FOR THE CROSSED POSTURE.

2.2.5 ANALYSES

In this experiment PSS values that exceeded the maximum SOA (± 600 , instead of twice the maximum SOA) were excluded from the data, together with their corresponding JND values, and were considered as missing values. This was done, because taking twice the maximum SOA as cut-off would mean that participants could have PSS values as large as 1200, which we considered to be too extreme. The difference in missing values between the uncrossed and the crossed posture condition was compared using a chi-squared test for equality of proportions. We evaluated whether the PSS values were significantly different from 0 using one-sample t-tests. In order to compare the PSS across the different experimental conditions, results were analyzed using the linear mixed effects models as implemented in the R package “Linear and Nonlinear Mixed Effects Models” (Pinheiro & Bates, 2000). The first outcome variable

was the Point of Subjective Simultaneity (PSS). The independent variables were the *Laterality* (unilateral/bilateral), and the *Posture* (uncrossed/crossed). The same analyses approach as for the first experiment was used. The models are shown in the appendix (section 6.1, Table 4 to 6).

The same method was used to assess the influence of the different experimental conditions on the JND. The models are shown in the appendix (section 6.1, Table 10 to 12).

3 RESULTS

3.1 INTENSITY OF THE NOCICEPTIVE STIMULI

The mean current intensities used during Experiment 1 were 0.58 ± 0.20 mA and 0.58 ± 0.21 mA for the left and right hands respectively. During Experiment 2, the current intensities were 0.58 ± 0.23 mA and 0.55 ± 0.23 mA for the left and right hand respectively. The differences between the left and the right hand were not significant (Experiment 1: $t(20) = 0.08$, $p = 0.94$; Experiment 2: $t(16) = 1.0$, $p = 0.33$). The mean self-reported intensities (VAS) were, during Experiment 1, 3.13 ± 1.68 for the left hand and 3.36 ± 1.53 for the right hand ($t(20) = -2.37$, $p = 0.03$). During Experiment 2 the self-reported intensities were 4.07 ± 1.66 for the left hand, and 3.82 ± 1.40 for the right hand ($t(16) = 1.92$, $p = 0.07$). The analyses revealed that the self-reported intensities were significantly different for the left and the right hand in both experiments, but such a difference was marginal (0.23 for Experiment 1, and 0.25 for Experiment 2), and did not affect the results.

3.2 MISSING VALUES

In Experiment 1, 28 out of 168 (17%) of the values were excluded; 25 of these were from the crossed posture condition. A chi-squared test indicated that the proportion missing values was significantly larger for the crossed posture (30%) than for the uncrossed posture (4%) ($\chi^2(1, N = 168) = 18.9$; $p < 0.001$). In Experiment 2, 6 out of 68 (9%) of the values were excluded; all of these were from the crossed posture condition. A chi-squared test indicated that the proportion missing values was significantly larger for the crossed posture (18%) than for the uncrossed posture (0%) ($\chi^2(1, N = 68) = 6.58$; $p = 0.03$). These results show a larger number of missing values for the crossed hands condition in both experiments. In order to account for the large amount of missing values in the crossed posture condition,

two further analyses were conducted to check whether results remained the same when the participants who performed poorest were removed from the analyses. Removing these participants did not substantially change results (see Appendix, section 6.3).

3.3 PSS

Mean PSS values for Experiment 1 and Experiment 2 are displayed in Figure 4.

3.3.1 EXPERIMENT 1

In the unilateral cue conditions, the one-sample t-test revealed that for the uncrossed posture, all PSS values were significantly different from 0 (all $t > 2.0$, all $p < 0.05$), suggesting a significant bias in the temporal order judgment. For the crossed posture, the PSS values were significantly different from 0 when cues were presented near the participants ($t(9) = 2.36$, $p = 0.04$), but not when cues were presented far from the participants ($t(14) = 0.16$, $p = 0.88$). In the bilateral cue condition, none of the PSS values were significantly different from 0, neither for the uncrossed posture (all $t < 0.45$, all $p > 0.65$), nor for the crossed posture (all $t < 1.5$, all $p > 0.15$). This result indicates that the PSS is only biased by the presence of an unilateral visual cue, and never in the presence of bilateral cues.

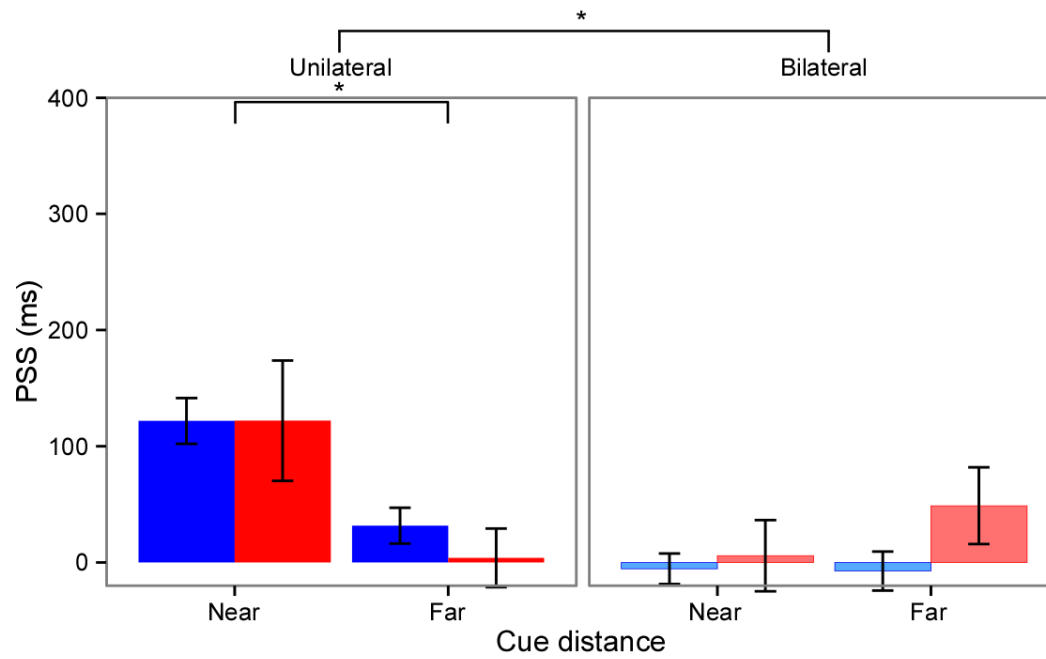
The linear mixed effects model that demonstrated the best fit with our data includes all fixed factors, the interaction effect between *laterality* and *cue distance*, and a random subject-based intercept. In this final model, we found a main effect of *laterality* ($F(1,122.76) = 24.06$; $p < 0.001$; $\beta = 0.57$), indicating that the PSS was more positive when cues were presented unilaterally than when they were presented bilaterally. Moreover, there was a significant interaction effect between *laterality* and *cue distance* ($F(1,119.24) = 12.38$; $p < 0.001$, $\beta = -1.24$). Post-hoc analyses show that there was no significant effect of *cue distance* in bilateral trials ($\chi^2(1, N = 21) = 0.63$, $p = 0.43$), however *cue distance* had a significant effect in unilateral trials ($\chi^2(1, N = 21) = 16.36$, $p < 0.001$): in these trials the PSS was more positive when cues were presented near, than when they were presented far. The main effect of *posture* was not significant ($F(1,123.70) = 0.47$, $p = 0.49$, $\beta = 0.05$), showing that the cued hand was prioritized, no matter whether the hands were uncrossed or crossed. The main effect of *cue distance* was not significant ($F(1,117.5) = 0.62$, $p = 0.43$, $\beta = 0.08$).

3.3.2 EXPERIMENT 2

The t-tests showed that the PSS values were significantly different from 0 when cues were presented unilaterally (all $t > 6.0$, all $p < 0.001$), whereas no bias was induced when cues were presented bilaterally (all $t < 2.0$, all $p > 0.10$).

The model that demonstrated the best fit with our data includes all fixed factors and a random subject-based intercept. In this model, there was a main effect of *laterality* ($F(1,45.48) = 22.09, p < 0.001, \beta = 0.51$), indicating that PSS values were larger when cues were presented unilaterally, than when they were presented bilaterally. Moreover, there was a main effect of *posture* ($F(1, 45.48) = 10.21, p = 0.002, \beta = 0.34$), indicating that PSS values were larger when hands were crossed than when hands were uncrossed. However, in both cases the PSS is positive, indicating an attentional bias towards the cued hand irrespective of posture.

A. Experiment 1



B. Experiment 2

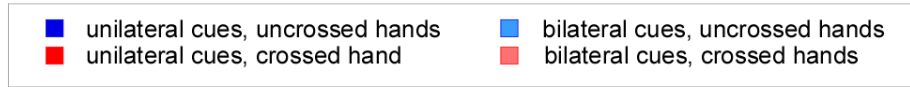
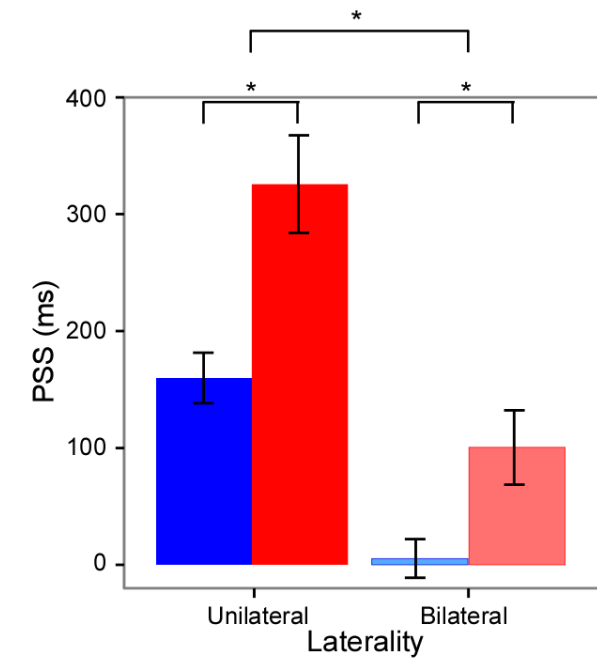


FIGURE 4. MEANS AND STANDARD ERRORS FOR THE POINT OF SUBJECTIVE SIMULTANEITY (PSS) FOR EXPERIMENT 1 (A) AND EXPERIMENT 2 (B). FOR EXPERIMENT 1, PSS VALUES WERE CALCULATED ACCORDING THE LATERALITY OF THE VISUAL CUES (LEFT GRAPHIC, UNILATERAL CUES; RIGHT GRAPHIC, BILATERAL CUES), DISTANCE OF THE CUES (LEFT PART OF THE GRAPHICS, NEAR; RIGHT PART OF THE GRAPHICS, FAR), AND POSTURE OF THE HANDS (BLUE BARS, UNCROSSED; RED BARS, CROSSED). FOR EXPERIMENT 2, PSS VALUES WERE CALCULATED ACCORDING THE LATERALITY OF THE VISUAL CUES (LEFT GRAPHIC, UNILATERAL CUES; RIGHT GRAPHIC, BILATERAL CUE) AND POSTURE OF THE HANDS (BLUE BARS, UNCROSSED; RED BARS, CROSSED). SIGNIFICANT EFFECTS ARE INDICATED WITH AN ASTERISK.

3.4 JND

Mean JND values for Experiments 1 and 2 are shown in Figure 5.

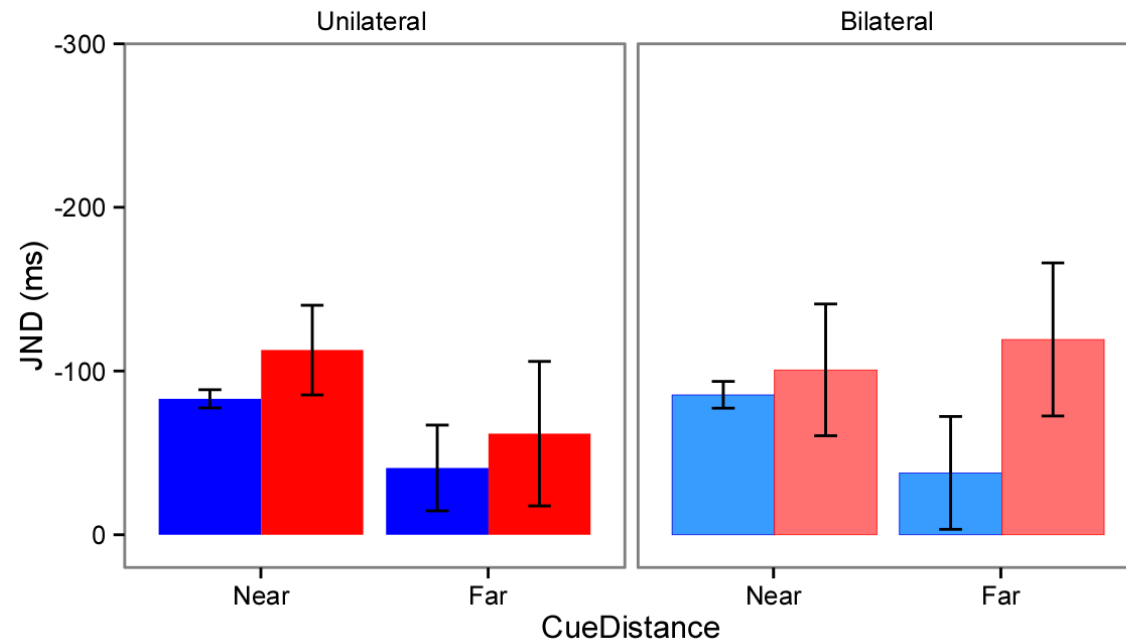
3.4.1 EXPERIMENT 1

The model with the best fit included all fixed factors, a random subject-based intercept, and a random effect for *cue distance* and *posture*. In this model, there were no significant effects present (see Appendix, section 6.1, Table 9).

3.4.2 EXPERIMENT 2

For Experiment 2, the model chosen included all fixed factors, a random subject-based intercept, and a random effect for *posture*. This model demonstrated a significant main effect of *posture* ($F(1,16.09) = 18.33, p < 0.001, \beta = -0.64$), showing that participants' temporal order judgments were less accurate when their hands were crossed, than when their hands were uncrossed.

A. Experiment 1



B. Experiment 2

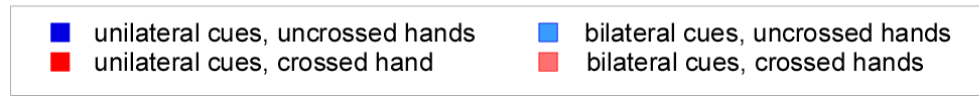
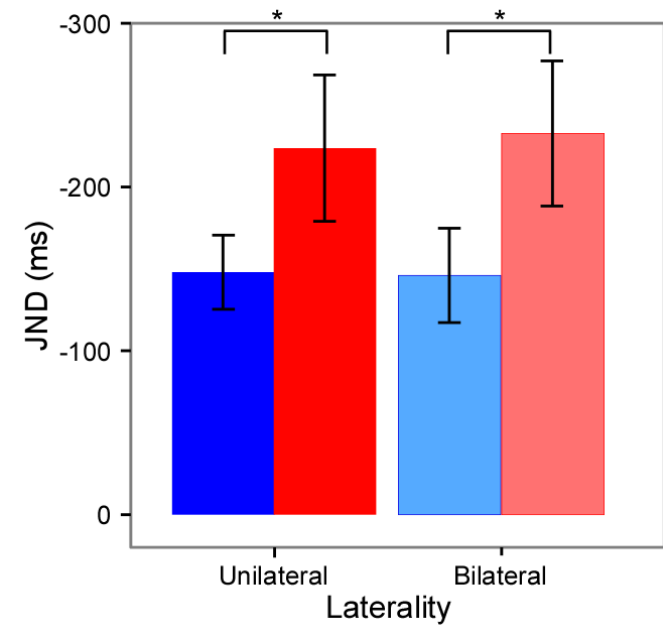


FIGURE 5. MEANS AND STANDARD ERRORS FOR THE JND FOR EXPERIMENT 1 (A) AND 2 (B). FOR EXPERIMENT 1 (A), JND VALUES WERE CALCULATED ACCORDING THE LATERALITY OF THE VISUAL CUES (LEFT GRAPHIC, UNILATERAL CUES; RIGHT GRAPHIC, BILATERAL CUES), DISTANCE OF THE CUES (LEFT PART OF THE GRAPHICS, NEAR; RIGHT PART OF THE GRAPHICS, FAR), AND POSTURE OF THE HANDS (BLUE BARS, UNCROSSED; RED BARS, CROSSED). THERE WERE NO SIGNIFICANT DIFFERENCES BETWEEN CONDITIONS. FOR EXPERIMENT 2 (B), JND VALUES WERE CALCULATED ACCORDING THE LATERALITY OF THE VISUAL CUES (LEFT GRAPHIC, UNILATERAL CUES; RIGHT GRAPHIC, BILATERAL CUES) AND POSTURE OF THE HANDS (BLUE BARS, UNCROSSED; RED BARS, CROSSED). SIGNIFICANT EFFECTS ARE INDICATED WITH AN ASTERISK.

4 DISCUSSION

This study investigated whether nociceptive stimuli are mapped according to a spatiotopic frame of reference, and more particularly a peripersonal frame of reference that takes into account both the influence of external sensory events near the body, and the relative position of the stimulated body part in external space. Two TOJ studies were conducted in which pairs of nociceptive stimuli were presented, one stimulus applied to either hand at various SOAs. The nociceptive stimuli were shortly preceded by visual cues, and the influence of these cues on the TOJ performance was assessed. The crucial manipulation in the present experiments was that participants' posture was changed across the experimental blocks. In some blocks participants' hands were uncrossed, whereas in other blocks participants were asked to cross their hands across the sagittal midline of the body. The results of both experiments demonstrated that the temporal order of nociceptive stimuli was not merely influenced by the position of the nociceptive stimuli on the body, but mostly by the position of the stimulated hand in external space. Indeed, PSS values were shifted towards the uncued side of space, and these shifts were influenced by the relative posture. In other words, a left visual cue prioritized the perception of nociceptive stimuli applied to the left hand in the uncrossed posture, but to the right hand in the crossed posture, and vice versa. In Experiment 1, we further showed that the influence of the cues was smaller when they were presented far in front of the participants' hand as compared to when they were presented at its close proximity (De Paepe et al., 2014). In addition, the temporal order judgments were less accurate in the crossed than in the uncrossed posture condition, as witnessed by the larger amount of errors and the larger JND in the former than in the latter condition.

The localization of nociceptive stimuli is an important function of the nociceptive system. It not only enables us to detect which part of the body is damaged, but also to detect the source of the damage in the external space. Therefore, a finely-tuned localization of noxious stimuli will help to react adequately against potentially threatening objects. In daily life, we are constantly moving, so that our limbs can be positioned in different locations, also at the opposite side of space. Therefore, a somatotopic frame of reference is insufficient to localize nociceptive stimuli, and the body space has to be remapped into a spatiotopic frame of reference, which takes into account the relative position of the body limbs in external space. Several studies have found evidence for the existence of a spatiotopic reference frame for the localization of both tactile (Pagel et al., 2009; Röder et al., 2004; Shore et al., 2002; Yamamoto & Kitazawa, 2001) and nociceptive stimuli (Gallace et al., 2011; Sambo et al., 2013) using the crossing hands procedure. In the two present studies we wanted to go one

step further by showing that nociceptive stimuli are mapped in a peripersonal frame of reference that also integrates the occurrence of external objects presented near the body. For tactile stimuli, several studies using a crossmodal congruency task performed with uncrossed and crossed posture, already showed that visual cues prioritize the tactile stimulation applied to the hand lying in the cued side of space (Holmes et al., 2006; Kennett et al., 2001, 2002; Spence et al., 2004; van Elk et al., 2013). This indicates that representations of visuotactile peripersonal space are updated when hands are crossed over the body midline. In the present studies we extended these findings to nociceptive stimuli. We showed that the influence of visual stimuli on nociceptive processing is space-based, i.e. the visual cues prioritized the processing of the nociceptive stimuli applied to the hand located in the cued side of space, irrespective of its posture. Moreover, in Experiment 1, we found that the influence of the visual stimuli is larger when they were presented near the hands of the participants as opposed to when they were presented far away. This is in accordance with previous findings showing that the processing of nociceptive stimuli is affected by visual cues presented in peripersonal space, but to a lesser extent by cues presented in extrapersonal space (De Paepe et al., 2014). Taken together, these results provide strong evidence for the existence of a peripersonal frame of reference for the localization of nociceptive stimuli. A peripersonal frame of reference allows for the construction of a stable perception of external space, which is necessary to react quickly and efficiently to stimuli in the environment. Peripersonal space can be seen as a kind of safety margin around the body that is scanned for potentially threatening stimuli and that enables us to detect, localize and react against these stimuli (Legrain, Iannetti, Plaghki, & Mouraux, 2011; Moseley, Gallace, & Iannetti, 2012).

It is interesting to note that, in Experiment 2, the PSS values were larger when the hands were crossed as compared to conditions during which the hands were uncrossed. This could suggest that the dissociation generated between somatotopic and spatiotopic frames of reference by the crossed posture facilitated the influence of visual stimuli on the spatial processing of nociceptive stimuli. However, such a hypothesis was not supported by the data from Experiment 1, and therefore needs further demonstration.

The JND gives an indication of the temporal sensitivity of participants' judgments. In previous studies a crossed hands deficit is consistently found both in studies using tactile (Pagel et al., 2009; Röder et al., 2004; Shore et al., 2002; Yamamoto & Kitazawa, 2001) and nociceptive stimuli (Sambo et al., 2013). These studies show larger JND values, and thus decreased temporal sensitivity when hands are crossed over the body midline. It is argued that the decreased performance resulting from crossing the hands can be explained by a

competition between a somatotopic and a spatiotopic frame of reference (Sambo et al., 2013; Yamamoto & Kitazawa, 2001). The right hand most commonly occupies the right side of space, and the left hand occupies the left side of space. When the posture is changed, a process of remapping is thus required to correct the position. This remapping process takes time, which explains why the ability to discriminate the order in which the hands are stimulated is impaired at shorter intervals: the position of the first stimulus is still being processed, while the second stimulus is presented (Sambo et al., 2013; Yamamoto & Kitazawa, 2001). Based on reversal errors at smaller intervals, Yamamoto and Kitazawa (2001) suggested that this remapping process takes around 300 ms to complete. However inter-subject variability in the time this remapping process takes might be present.

In the present study, we only found a significant difference in the JND between the different postures in Experiment 2, but not in Experiment 1. A possible explanation for this apparent discrepancy is the fact that, in Experiment 1, we had to exclude significantly more values in the crossed (30%) than in the uncrossed condition (3%). Doing this might have artificially reduced the difference in JND between the uncrossed and the crossed posture. However, keeping these values in the analyses made no sense, as the PSS values in these conditions were extreme (e.g., 1.19×10^{18}), indicating that participants were unable to perform the task. Indeed, the larger amount of excluded trials in the crossed hands condition indicates that the posture of the hands affected the ability of the participants to judge the temporal order of the nociceptive stimuli. For these participants the remapping process might have been incomplete even at the largest SOAs (+/- 200 ms), making it impossible for them to complete the task successfully when hands were crossed. This result is in line with the suggestion of Yamamoto et al. (Yamamoto & Kitazawa, 2001) that the remapping process takes around 300 ms. Moreover it is in line with a study of Azanon and Soto-Faraco (Azañón & Soto-Faraco, 2008), in which the time-course of the remapping process from a somatotopic to a spatiotopic frame of reference was investigated using a crossmodal cuing paradigm. Participants held their arms crossed over the body midline, and were instructed to judge the vertical position (up vs. down) of light flashes. These flashes were preceded by irrelevant tactile cues with varying cue target onset asynchronies (CTOA). They found that at short CTOAs the spatial cuing effect corresponded to somatotopic representations, demonstrated by the fact that touches to the left hand (placed in the right hemisphere) facilitated processing of left hemispace visual events and vice versa. This pattern reversed after 200 ms so that tactile cues facilitated the processing of targets presented at the same external location. In a subsequent study they showed that these crossmodal links are spatially specific, as they appear to be stronger in peripersonal space

than in extrapersonal space. This study reveals the time-course of the encoding of events in tactile space, from a somatotopic frame of reference, reflecting the neural organization in the primary somatosensory cortex (SI), to an external representation of space, enabling orienting behaviors. This remapping process would not start before 60 ms after stimulus application, and would be completed after 180 to 360 ms.

In Experiment 2, larger SOAs were used (up to 600 ms) to make the task easier. As expected, we had to exclude less values in the crossed hands condition (18%), indicating that for most participants, the remapping process had completed at the largest SOAs. Of interest, we now found that the JND was significantly higher when hands were crossed than when hands were uncrossed, indicating reduced temporal sensitivity when hands were crossed. Moreover, when we excluded the subjects who performed poorest in Experiment 1, a marginally significant effect of posture was also found, again demonstrating a reduced temporal sensitivity in the crossed posture condition. Therefore, we can conclude that our pattern of results is in line with the previous studies (Pagel et al., 2009; Röder et al., 2004; Sambo et al., 2013; Shore et al., 2002; Yamamoto & Kitazawa, 2001), showing that changing the posture affects the ability to process the spatial location of somatosensory stimuli, including nociceptive stimuli. It confirms our prediction according to which the spatial perception of nociceptive stimuli is made according to a spatiotopic mapping system.

The present study also points out the importance of spatial perception for the understanding of the pathophysiology and the treatment of chronic pain. Some chronic pain patients, more particularly patients with CRPS, show impairment in body representation and spatial perception (for a review, see Legrain, Bultitude, De Paepe, & Rossetti, 2012). These patients tend to ignore or have an altered mental representation of the affected limb, and movements are smaller and less frequent (Frettlöh, Hüppe, & Maier, 2006; Galer, Butler, & Jensen, 1995; Galer & Jensen, 1999; Lewis, Kersten, McCabe, McPherson, & Blake, 2007). Using a TOJ task, Moseley et al. (2009) found that CRPS patients prioritize the perception of tactile stimuli applied to the unaffected arm to the detriment of those presented to the affected arm. Interestingly, when participants were asked to cross their arms, results were reversed: the perception of tactile stimuli on the affected arm was prioritized over the perception of those on the unaffected arm. In addition, crossing the hands also affected their accuracy in reporting the temporal order of the tactile stimuli. These data suggest that the impairment in these patients is not linked to the affected limb itself, but rather to the side of space in which the limb normally resides. The presence of chronic pain and other CRPS-related symptoms can thus alter the ability to perceive the body, not only according to somatotopic but also according to spatiotopic frames of reference (Legrain, Bultitude, et al.,

2012). Furthermore, some studies showed that manipulating the spatial perception of these patients can alleviate pain (Bultitude & Rafal, 2010; Sumitani et al., 2007). These studies used prism adaptation to shift the visual field of CRPS patients towards the unaffected side, resulting in an after-effect towards the affected limb. They found that this relieved pain and autonomic dysfunction, and that it reduced their pathological perceptions of the body midline. These studies illustrate that some somatosensory deficits are not explained by somatotopic frames of reference but rather by space-based frames of reference. Moreover, they suggest that manipulating the spatial perception could be a potential rehabilitation technique for some chronic pain patients.

It has to be noted that based on the present results, we cannot be sure whether the crossmodal shifts in the PSS between vision and nociception result from exogenous shifts of spatial attention from one space (i.e. external proximal space) to another space (i.e. bodily space), or from intrinsic multisensory integration (Spence & Driver, 2004). In the former case, salient but spatially non-predictive visual cues could have attracted multisensory spatial attention to its location, leading to a faster processing of the forthcoming nociceptive target. Multisensory integration on the other hand occurs when two different-modality stimuli that are presented around the same time and place are integrated to form a unified perceptual object, instead of a collection of unrelated sensations. This would result from an additive sensory response from specialized neurons that respond to stimuli of both modalities (Stein & Meredith, 1993). Another mechanism relies on the existence of multimodal neurons with multiple receptive fields to code the location of sensory inputs from different modalities. The non-somatic (i.e., visual and auditory) receptive fields extend the region of the somatic (i.e., tactile) receptive field into the immediate adjacent space. Therefore, these neurons respond both to the stimuli applied to a specific area of the skin surface and to stimuli appearing in the space proximal to the stimulated body area (Graziano & Gross, 1994; Graziano et al., 1997). Further studies are needed to dissociate these different mechanisms in the spatial perception of nociceptive stimuli.

One could argue that the judgment bias induced by proximal visual stimuli on the processing of nociceptive stimuli does not fully support the hypothesis that nociceptive inputs can be remapped according to a spatiotopic frame of reference. Indeed, because the spatial position of visual stimuli is primarily coded by the cortical projections of the retinas, one should also evidence how visual inputs are remapped from retinotopic to spatiotopic frames of reference. More specifically, further studies are needed to understand how, during crossmodal interaction between somatosensory and visual inputs, visual stimuli are remapped according to their proximity to body parts into a body-centered representation of

external space. However, this does not preclude that previous and present data support the hypothesis according to which nociceptive mapping can be spatiotopic. First, our previous studies (De Paepe et al., 2014) showed that changing gaze fixation, and thus changing the position of the visual stimulus on the retina, does not change the results. Second, judgments' sensitivity, as indexed by JND, was affected by the posture of the hands, both with (present data) or without (Sambo et al., 2013) visual cues, suggesting that nociceptive mapping depends on the relative position of the body limb in external space (see also Aglioti et al., 1999; Azañón & Soto-Faraco, 2008; Pagel et al., 2009; Röder et al., 2004; Shore et al., 2002; Smania & Aglioti, 1995; Yamamoto & Kitazawa, 2001).

Finally, despite the procedure applied to match intensities of the nociceptive stimuli applied to left and right hands, the strict equivalence between the subjective perception of the intensities between the two hands could not always be achieved. Such differences were very marginal (0.23 to 0.25 cm on a rating scale of 10 cm) and could not have affected the results. Indeed, the results show that the PSS, and, therefore, the judgment biases, were not affected by the hand on which the nociceptive stimuli were perceived as the most intense (for instance, in the bilateral conditions, the PSS are never significantly different from 0), but only by the side of the visual cues.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest related to the present article.

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6 APPENDIX

6.1 LINEAR MIXED EFFECT MODELS

For the behavioral measures (PSS and JND), we started with a full model of the fixed effects. We then added the random effects that were necessary, based on Akaike's information criterion (AIC, Sakamoto, Ishiguro, & Kitagawa, 1986), and the likelihood-ratio test. Subsequently, we determined if interactions between the fixed effects should be included. As we were interested in all included variables, fixed effects were never removed from the model. At each step the most parsimonious model was selected, that, at the same time, performed best at predicting the dependent variables. When the fixed effects were determined, the final model was refitted with REML estimation and the relevant contrasts were calculated. For each behavioral measure, the three fitting steps are presented below. For each step, the AIC, the χ^2 for the relevant model comparisons, and the corresponding p-values are presented. The final table for each measure shows the Anova table, and the parameter estimates with their corresponding t-values.

Model	Test	Random	AIC	Df	χ^2	<i>p</i> -value
1	Initial fit	1	1700.2	10		
2	Random Laterality (1 vs. 2)	1 + Laterality	1701.9	12	$\chi^2(2) = 2.31$	0.31
3	Random Cue Distance (1 vs. 3)	1 + Cue Distance	1704	12	$\chi^2(2) = 0.0036$	0.998
4	Random Posture (1 vs. 4)	1 + Posture	1700.9	12	$\chi^2(2) = 3.30$	0.19

TABLE 1. STEP 1 EXPERIMENT 1 - PSS. DETERMINE RANDOM EFFECTS STRUCTURE, ALL MODELS HAVE 'SUBJECT' AS RANDOM INTERCEPT. DECISION: NO RANDOM EFFECTS ADDED, KEEP MODEL 1.

Model	Test	Fixed	AIC	Df	χ^2	<i>p</i> -value
1	Initial fit	Laterality*Posture* Cue Distance	1700.2	10		
2	Remove three-way interaction (1 vs. 2)	Laterality*Cue Distance + Laterality*Posture + Posture*Cue Distance	1699.4	9	$\chi^2(1) = 1.16$	0.28
3	Remove interaction with Posture (2 vs. 3)	Laterality*Cue Distance + Posture	1697.7	7	$\chi^2(2) = 2.30$	0.32
4	Remove interaction with Laterality (2 vs. 4)	Cue Distance*Posture + Laterality	1709.7	7	$\chi^2(2) = 14.35$	<0.001
5	Remove interaction with Cue Distance (2 vs. 5)	Laterality*Posture + Cue Distance	1707.7	7	$\chi^2(2) = 12.29$	0.002
6	Remove all interactions (3 vs. 6)	Laterality + Posture + Cue Distance	1708.0	6	$\chi^2(1) = 12.27$	<0.001

TABLE 2. STEP 2 EXPERIMENT 1 - PSS. DETERMINE FIXED EFFECTS - TRIM DOWN THE MODEL. DECISION: CHOOSE MODEL 3 WITH THE INTERACTION BETWEEN LATERALITY * CUE DISTANCE

Effects	F	Df1	Df2	<i>p</i>	β
Laterality	24.06	1	122.76	<0.001	0.57
Cue Distance	0.62	1	117.50	0.43	0.08
Posture	0.47	1	123.70	0.49	0.05
Laterality*Cue Distance	12.38	1	119.24	<0.001	-1.24

	<i>B</i>	SE(<i>B</i>)	<i>t</i>
Intercept	-5.612	18.13	-0.31
Laterality	123.143	25.027	4.92
Cue Distance	18.19	22.99	0.79
Posture	11.82	17.21	0.69
Laterality*Cue Distance	-120.43	34.17	-3.52

TABLE 3. STEP 3 EXPERIMENT 1 - PSS. TEST FINAL MODEL.

Model	Test	Random	AIC	Df	χ^2	<i>p</i> -value
1	Initial fit	1	808.01	6		
2	Random Laterality (1 vs. 2)	1 + Laterality	810.70	8	$\chi^2(2) = 1.32$	0.52
3	Random Posture (1 vs. 3)	1 + Posture	809.73	8	$\chi^2(2) = 2.28$	0.32

TABLE 4. STEP 1 EXPERIMENT 2 - PSS. DETERMINE RANDOM EFFECTS STRUCTURE, ALL MODELS HAVE 'SUBJECT' AS RANDOM INTERCEPT. DECISION: CHOOSE MODEL 1 WITHOUT ADDITIONAL RANDOM EFFECTS.

Model	Test	Fixed	AIC	Df	χ^2	<i>p</i> -value
1	Initial fit	Laterality*Posture	808.01	6		
2	Remove interaction (1 vs. 2)	Laterality + Posture	806.86	5	$\chi^2(1) = 0.85$	0.36

TABLE 5. STEP 2 EXPERIMENT 2 - PSS. DETERMINE FIXED EFFECTS - DETERMINE FIXED EFFECTS - TRIM DOWN THE MODEL. DECISION: CHOOSE MODEL 2 WITHOUT INTERACTION.

Effects	F	Df1	Df2	<i>p</i>	β
Laterality	22.09	1	45.48	<0.001	0.51
Posture	10.21	1	45.48	0.002	0.34

	<i>B</i>	SE(<i>B</i>)	<i>t</i>
Intercept	-10.14	32.83	-0.309
Laterality	185.60	39.34	4.718
Posture	126.17	39.34	3.207

TABLE 6. STEP 3 EXPERIMENT 2 - PSS. TEST FINAL MODEL.

Model	Test	Random	AIC	Df	χ^2	<i>p</i> -value
1	Initial fit	1	1786.4	10		
2	Random Laterality (1 vs. 2)	1 + Laterality	1790.4	12	$\chi^2(2) = 0$	1
3	Random Cue Distance (1 vs. 3)	1 + Cue Distance	1776.7	12	$\chi^2(2) = 13.72$	0.001
4	Random Cue Distance and Posture (3 vs. 4)	1 + Cue Distance + Posture	1767.3	15	$\chi^2(3) = 15.39$	0.002
5	Random Cue Distance, Posture and Laterality (4 vs. 5)	1 + Cue Distance + Posture + Laterality	1774.6	19	$\chi^2(4) = 0.69$	0.95

TABLE 7. STEP 1 EXPERIMENT 1 - JND. DETERMINE RANDOM EFFECTS STRUCTURE, ALL MODELS HAVE 'SUBJECT' AS RANDOM INTERCEPT. DECISION: CHOOSE MODEL 6 WITH CUE DISTANCE AND POSTURE AS RANDOM EFFECTS.

Model	Test	Fixed	AIC	Df	χ^2	<i>p</i> -value
1	Initial fit	Laterality*Posture* Cue Distance	1767.3	15		
2	Remove three-way interaction (1 vs. 2)	Laterality*Cue Distance + Laterality*Posture + Posture*Cue Distance	1766.6	14	$\chi^2(1) = 1.31$	0.25
3	Remove interaction with Posture (2 vs. 3)	Laterality*Cue Distance + Posture	1765.4	12	$\chi^2(2) = 2.78$	0.25
4	Remove interaction with Laterality (2 vs. 4)	Cue Distance*Posture + Laterality	1765.0	12	$\chi^2(2) = 2.31$	0.32
5	Remove interaction with Cue Distance (2 vs. 5)	Laterality*Posture + Cue Distance	1765.1	12	$\chi^2(2) = 2.41$	0.30
6	Remove all interactions (2 vs. 6)	Laterality + Posture + Cue Distance	1764.4	11	$\chi^2(3) = 3.72$	0.29

TABLE 8. STEP 2 EXPERIMENT 1 - JND. DETERMINE FIXED EFFECTS - TRIM DOWN THE MODEL. DECISION: CHOOSE MODEL 6 WITHOUT INTERACTIONS.

Effects	F	Df1	Df2	<i>p</i>	β
Laterality	0.73	1	85.10	0.40	0.11
Cue Distance	0.73	1	19.88	0.40	0.06
Posture	1.23	1	19.17	0.28	-0.13

	<i>B</i>	SE(B)	<i>t</i>
Intercept	-83.75	17.31	-4.84
Laterality	15.32	17.83	0.859
Cue Distance	28.67	33.51	0.856
Posture	-34.82	31.16	-1.12

TABLE 9. STEP 3 EXPERIMENT 1 - JND. TEST FINAL MODEL.

Model	Test	Random	AIC	Df	χ^2	<i>p</i> -value
1	Initial fit	1	692.00	6		
2	Random Laterality (1 vs. 2)	1 + Laterality	695.46	8	$\chi^2(2) = 0.54$	0.76
3	Random Posture (1 vs. 3)	1 + Posture	666.37	8	$\chi^2(2) = 29.63$	<0.001

TABLE 10. STEP 1 EXPERIMENT 2 - JND. DETERMINE RANDOM EFFECTS STRUCTURE, ALL MODELS HAVE 'SUBJECT' AS RANDOM INTERCEPT. DECISION: CHOOSE MODEL 3 WITH POSTURE AS RANDOM EFFECT.

Model	Test	Fixed	AIC	Df	χ^2	<i>p</i> -value
1	Initial fit	Laterality*Posture	666.37	8		
2	Remove interaction (1 vs. 2)	Laterality + Posture	665.35	7	$\chi^2(1) = 0.98$	0.32

TABLE 11. STEP 2 EXPERIMENT 2 - JND. DETERMINE FIXED EFFECTS - TRIM DOWN THE MODEL. DECISION: CHOOSE MODEL 2 WITHOUT INTERACTION.

Effects	F	Df1	Df2	<i>p</i>	β
Laterality	1.07	1	27.44	0.31	-0.06
Posture	18.33	1	16.09	<0.001	-0.64

	<i>B</i>	SE(B)	<i>t</i>
Intercept	-142.90	8.69	-16.44
Laterality	-8.19	7.90	1.037
Posture	-92.89	21.69	-4.28

TABLE 12. STEP 3 EXPERIMENT 2 - JND. TEST FINAL MODEL.

6.2 ANALYSES TO CONTROL FOR EFFECTS OF THE SIDE OF THE VISUAL STIMULATION.

To check whether an effect of the side at which the visual cue was presented existed, a separate analysis was performed on the unilateral cue trials. In Experiment 1, we looked at the PSS as a function of the *side of the visual cue*, the *posture*, and the *cue distance*. There was a main effect of *side* ($F(1,110.43) = 5.56, p = 0.02$), indicating that PSS values were overall higher when the left side was cued, than when the right side was cued. There was also a main effect of *cue distance* ($F(1,113.30) = 29.92, p < 0.001$), indicating that the PSS values were higher when cues were presented near the participants than when they were presented far away. The main effect of *posture* was not significant ($F(1,116.49) = 0, p = 0.99$). However, as there was no interaction effect involving the *side of the visual cue*, merging data for left and right cues will not distort results.

In Experiment 2, we looked at the PSS as a function of the *side of the visual cue*, and the *posture*. There was a main effect of *posture* ($F(1,42.62) = 10.77, p = 0.002$), indicating that PSS values were higher when hands were crossed than when they were uncrossed. The main effect of *side* was not significant ($F(1,36.80) = 0.33, p = 0.57$).

6.3 SENSITIVITY ANALYSES

In order to account for the large amount of missing values in the crossed posture condition, we conducted two further analyses to check whether results remained the same when the subjects who performed poorest would be removed from the analyses. In a first analysis, we excluded those subjects for whom more than 2 PSS values had to be excluded. By doing this, we ensured that every participant included in the analyses had at least 2 (out of 4) PSS values remaining in both the uncrossed and the crossed condition. In Experiment 1, 4 participants had to be excluded from the analyses. For the remaining 17 participants, 12 out of 136 (9%) of the values were excluded; all of these were from the crossed posture condition. A chi-squared test indicated that the proportion missing values was significantly larger for the crossed posture (18%) than for the uncrossed posture (0%) ($\chi^2(1, N = 136) = 11.06; p < 0.001$). In Experiment 2, maximum 1 PSS value per participant had to be excluded, so results for Experiment 2 remained the same as reported in section 3.3 and 3.4. For Experiment 1, results of the linear mixed effects model show identical effects as obtained with the original analyses: a main effect of *laterality* ($F(1,106.09) = 22.72; p < 0.001; \beta = 0.58$), and a significant interaction effect between *laterality* and *cue distance* ($F(1,104.93) = 13.59; p < 0.001, \beta = -1.37$). Post-hoc analyses show that there was no significant effect of *cue distance* in bilateral trials ($\chi^2(1, N = 17) = 1.34, p = 0.25$), however *cue distance* had a significant effect in unilateral trials ($\chi^2(1, N = 17) = 16.75, p < 0.001$). The main effect of *posture* was not significant ($F(1,105.47) = 0.26, p = 0.61, \beta = 0.04$), nor was the main effect of *cue distance* ($F(1,104.41) = 1.28, p = 0.26, \beta = 0.13$). For the JND there were still no significant effects present.

In a second analysis, we excluded all subjects who had on average no 80 percent correct on the trials with the largest SOA (analogous to De Paepe et al., 2014), as this is an indication that participants were not able to perform the task satisfactory. In Experiment 1, 11 participants had to be excluded. For the remaining 10 participants, only three PSS values had to be excluded (4%), and maximum 1 PSS value per participant; all of these were from the crossed posture condition. A Pearson chi square test indicated there was no significant difference in missing values between the uncrossed and the crossed posture condition ($\chi^2(N=80) = 2.37; p=0.12$). In Experiment 2 all participants had on average more than 80% correct, and results remain the same as reported in section 3.3 and 3.4.

For Experiment 1, results of the linear mixed effects model show identical effects as obtained with the original analyses: a main effect of *laterality* ($F(1,16.25) = 13.32; p = 0.002; \beta = 0.65$), and a significant interaction effect between *laterality* and *cue distance* ($F(1,54.81) = 5.91; p = 0.02, \beta = -0.96$). Post-hoc analyses show that there was no significant effect of *cue*

distance in bilateral trials ($\chi^2(1, N = 10) = 6.42, p = 0.79$), however *cue distance* had a significant effect in unilateral trials ($\chi^2(1, N = 10) = 89.74, p < 0.001$). The main effect of *posture* was not significant ($F(1,54.79) = 0.02, p = 0.88, \beta = 0.01$), nor was the main effect of *cue distance* ($F(1,54.68) = 0.07, p = 0.79, \beta = -0.03$). For the JND there was a marginally significant main effect of *posture* ($F(1,8.99) = 3.85, p = 0.08, \beta = -0.31$), indicating that participants' temporal order judgments were less accurate when their hands were crossed than when their hands were uncrossed. No other significant effects were present ($F < 1.5, p > 0.20$).

CHAPTER 3

REMAPPING NOCICEPTIVE STIMULI INTO A PERIPERSONAL REFERENCE FRAME IS SPATIALLY LOCKED TO THE STIMULATED LIMB.¹

ABSTRACT

The localization of harmful stimuli approaching our body is essential for survival. Here we investigated whether the mapping of nociceptive stimuli is based on a spatial representation that is anchored to the stimulated limb. In three experiments, we measured the effect of unilateral visual stimuli on the perceived temporal order of nociceptive stimuli, applied to each hand. Crucially, the position of the hands and the visual stimuli was manipulated, so that visual and nociceptive stimuli occurred in an adjacent or non-adjacent spatial position. Temporal order judgments of nociceptive stimuli were biased in favor of the stimulus applied to the hand most adjacent to the visual stimulus. This suggests that the ability to determine the position of a nociceptive stimulus on a specific body area is based on a spatial frame of reference that is spatially locked to that area and follows it during limb displacement.

¹ Based on: De Paepe, A.L., Crombez, G., Legrain, V. (in preparation). Remapping nociceptive stimuli into a peripersonal reference frame is spatially locked to the stimulated limb.

1 INTRODUCTION

Localizing somatosensory stimuli on the body is an important ability to adapt our behavior to external stimuli. This ability is highly relevant for touch to reach toward and manipulate objects, but it is even more crucial for nociception to defend the physical integrity of the body against potentially harmful objects (Haggard, Iannetti, & Longo, 2013; Legrain & Torta, 2015). Adequate localization requires the construction of a global representation of the space closely surrounding the body, which has been termed *peripersonal space*. Within this space the location of somatosensory stimuli, the location of visual stimuli occurring close to the body and information about body posture are integrated (Cardinali, Brozzoli, & Farne, 2009; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981; Spence & Driver, 2004). In animals such ability depends on neurons with multimodal receptive fields (RFs), mainly in the premotor and the intraparietal areas (Graziano & Gross, 1994; Graziano, Hu, & Gross, 1997). More specifically, these neurons were shown to be active in response to both tactile stimuli and to visual stimuli occurring close to the stimulated body parts. The visual RFs of such neurons are limited in size and are spatially locked to the tactile RFs, independently of the position of the visual inputs on the retina and the position of the stimulated limb in external space (Fogassi et al., 1996; Graziano et al., 1997).

Also in humans there is evidence for the use of peripersonal frames of reference for the localization of somatosensory stimuli, but most studies have focused on a frame of reference centered on the trunk, coding separate representations of the two hemispaces of the body. di Pellegrino, Ladavas & Farnè (1997) have shown that, in patients with right brain damage, the perception of a tactile stimulus applied to the hand contralateral to the lesion side is affected by the occurrence of a concomitant tactile stimulus applied to the opposite hand (unimodal extinction). Interestingly, extinction also occurs when a concomitant visual stimulation is applied to the opposite side, but only when the visual stimulus appears in the space near the opposite hand (crossmodal extinction). Crossmodal extinction is not observed when visual stimuli are presented far from the opposite hand or close to another body part (di Pellegrino et al., 1997).

Here we extended research in healthy volunteers by showing that those spatial areas of interplay between somatosensory and visual inputs are anchored to each limb, and follow the limb when it moves. We used temporal order judgment tasks with nociceptive stimuli: Participants had to judge which of two nociceptive stimuli, one applied on each hand, was perceived as first delivered. Before each pair, one visual stimulus was presented either in

the left or the right side of space. Crucially, the position of both the stimulated hand and the visual stimulus was manipulated so that the visual and the somatosensory stimuli occurred either at a close adjacent position or at a certain distance from each other, independently of their relative proximity from the body midline. Across blocks of stimulation, hands and visual lights were displaced according to the anteroposterior axis (i.e. in depth in front of the trunk, Experiment 1), the mediolateral axis (i.e. eccentricity relative to the body midline, Experiment 2), and the longitudinal axis (i.e. according to elevation positions, Experiment 3).

2 METHOD

2.1 PARTICIPANTS

Throughout the experiments, we always aimed at a sample size of 25 participants, so that we were sure to keep at least 20 participants for data-analysis. Depending on the availability of participants, and the cancellation of appointments, sample sizes may vary over experiments. In Experiment 1, 26 participants volunteered to take part in the study. Two male participants had to stop the experiment during the first block, because they were not able to feel the IES despite repeated displacement of the electrodes (see section 2.2.). The mean age of the remaining 24 participants (20 female, 22 right-handed) was 23 years (ranging from 19 to 47 years). In Experiment 2, 22 participants volunteered to take part in the study. The mean age of the participants (18 women, 20 right-handed) was 23 years (ranging from 18 to 29 years). In Experiment 3, 25 participants volunteered to take part in the study. One participant was excluded due to the use of antidepressant medication at the time of the experiment. Another participant was excluded due to technical failure. The mean age of the remaining 23 participants (15 women, 20 right-handed) was 22 years (ranging from 18 to 26 years). All participants had normal, or corrected-to-normal vision, did not report any neurological, psychiatric or chronic pain problems, and were not currently using any psychotropic drugs, which were exclusion criteria. The experimental procedure was approved by the local ethics committee. All of the participants provided written informed consent prior to taking part in the study.

2.2 STIMULI AND APPARATUS

The nociceptive stimuli were delivered by means of intra-epidermal electrical stimulation (IES) (DS7 Stimulator, Digitimer Ltd, UK), with stainless steel concentric bipolar electrodes (Nihon Kohden, Japan; Inui, Tsuji, & Kakigi, 2006). The electrodes consisted of a needle cathode (length: 0.1 mm, \emptyset : 0.2 mm) surrounded by a cylindrical anode (\emptyset : 1.4 mm). By gently pressing the device against the participant's skin, the needle electrode was inserted into the epidermis of the dorsum of the hand in the sensory territory of the superficial branch of the radial nerve. Using intra-epidermal stimulation at maximum twice the absolute threshold was shown to selectively activate the free nerve endings of the A δ fibers (Inui et al., 2006; Mouraux, Iannetti, & Plaghki, 2010; Mouraux, Marot, & Legrain, 2014). The detection threshold was determined with single-pulse stimuli (0.5 ms square wave pulse) using a staircase procedure (Churyukanov, Plaghki, Legrain, & Mouraux, 2012). The detection threshold was established separately for each hand. Next, the stimulus intensity was set at twice the detection threshold. If necessary, the intensity of the stimuli was adjusted so that the stimuli delivered to each hand were perceived as being equally intense. During the course of the experiment, the stimuli consisted of trains of four consecutive 0.5 ms square-wave pulses separated by a 5-ms inter-pulse interval. Using a set of pain words from the Dutch McGill Pain questionnaire (Vanderiet, Adriaensen, Carton, & Vertommen, 1987) the stimuli have been found to be best described as pricking. After each experimental block, the participants were asked to estimate the intensity elicited by the nociceptive stimuli on a numerical graphic rating scale (10 cm) with the following labels selected from the Dutch McGill Pain questionnaire (Vanderiet et al., 1987): 0 = felt nothing, 2.5 = lightly intense, 5 = moderately intense, 7.5 = very intense, 10 = enormously intense. This scale was used in order to ensure that: (1) the stimuli were still perceived, and (2) the percept elicited by the IES delivered to each of the participant's hands was still equivalent. If one of these criteria was not met, the stimulus intensities were modified accordingly (with a maximum increase in intensity of 0.10 mA). If this adaptation proved to be unsuccessful (i.e. one of the criteria was still not met), the electrodes were displaced and the procedure was restarted.

The visual stimuli were presented by means of four green light-emitting diodes (LEDs). The LEDs were illuminated for 20 ms. They were perceived by participants as a green light that briefly flashed. In a practice phase, the visibility of each of the LEDs was tested by asking the participants to report on the location of the LED that was illuminated (e.g., 'left near', 'right far').

The participants sat on a chair in a dimly illuminated, sound-attenuated room. The participant's head was immobilized in a chin-rest positioned at 10 cm from the trunk in order to prevent movements of the head. The height of the chin-rest was individually adjusted.

2.2.1 EXPERIMENT 1

In Experiment 1, 35 cm in front of the participants' trunk, on the line extending the body midline, a red fixation LED was attached to the table. Participants were asked to keep their gaze on this fixation LED throughout the experiment. Four green LEDs were positioned relative to the anteroposterior axis, in front of the participants. Two LEDs were positioned at a proximal position relative to the participants' body, and two LEDs were positioned at a distal position. The proximal LEDs were placed 20 cm from the line extending the midline of the body, 40 cm apart from each other. The LEDs far from the body were positioned 50 cm in front of the midline of the body, and 30 cm in front of the near LEDs. The position of the participants' hands was manipulated: in half of the blocks, participants were asked to lay their hands on the table in front of them so that the near LEDs were between their thumb and index finger. In the other half of the blocks, they were asked to lay their hands on the table in front of them so that the far LEDs were between their thumb and index finger. In both cases the hands were approximately 40 cm apart. In the blocks during which hands were next to the proximal LEDs, the hands were 20 cm in front of the participants' trunk, while in the blocks with hands next to distal LEDs, the hands were 50 cm in front of the trunk (Figure 1A).

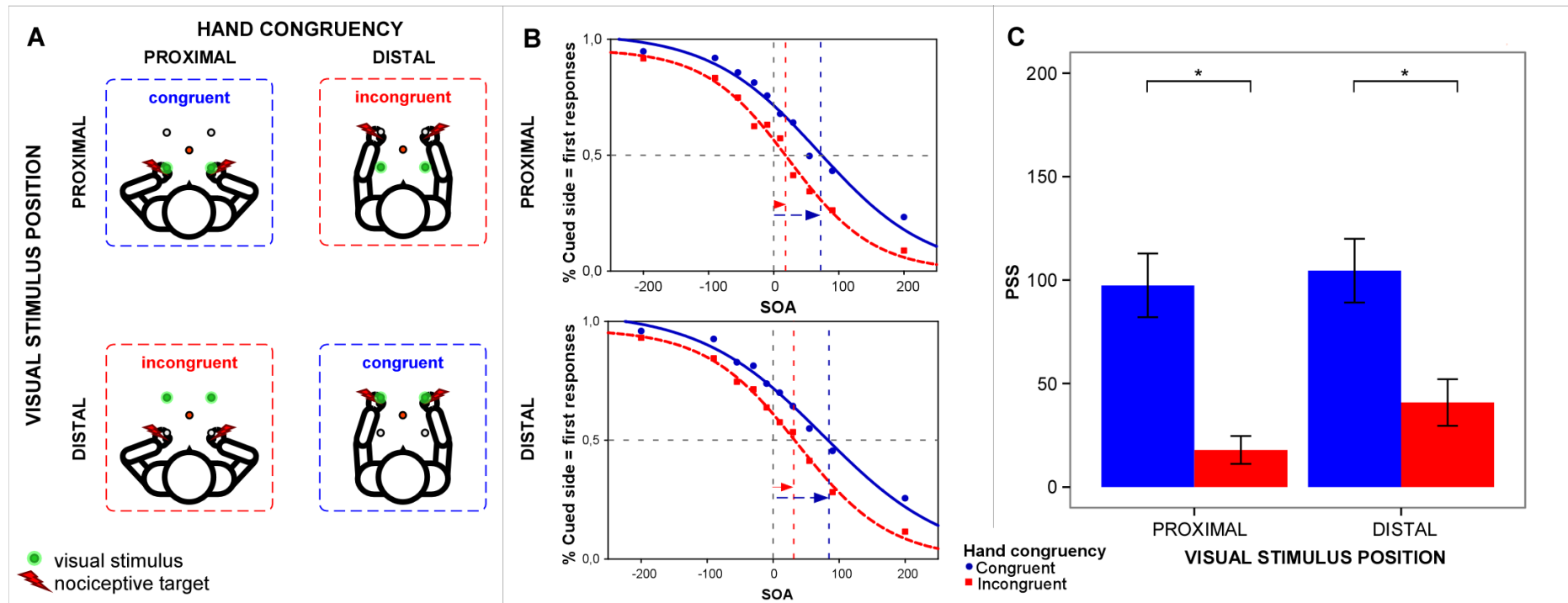


FIGURE 1. [A] EXPERIMENTAL SET-UP EXPERIMENT 1. VISUAL STIMULUS POSITION WAS MANIPULATED ACCORDING TO THE ANTEROPOSTERIOR AXIS, AND HANDS WERE POSITIONED AT A CONGRUENT OR INCONGRUENT POSITION. [B] NOCICEPTIVE TEMPORAL ORDER JUDGMENTS (TOJ'S) FOR EXPERIMENT 1. THE FIGURE ILLUSTRATES THE FITTED CURVES FROM CUMULATIVE DATA FROM 24 PARTICIPANTS. TRIALS WERE EITHER ASSOCIATED WITH VISUAL STIMULI AT A PROXIMAL POSITION (UPPER FIGURE) OR AT A DISTAL POSITION (LOWER FIGURE), AND WITH HANDS ON THE CONGRUENT POSITIONS (BLUE SOLID LINE) OR HANDS ON THE INCONGRUENT POSITIONS (RED DOTTED LINE). DATA ARE PLOTTED AS THE MEAN PROPORTION OF *CUED HAND FIRST RESPONSES* (ON THE Y-AXIS), AS A FUNCTION OF THE STIMULUS ONSET ASYNCHRONIES (SOA) (ON THE X-AXIS). ON THE X-AXIS, NEGATIVE VALUES INDICATE THAT THE CUED HAND WAS STIMULATED FIRST, WHILE POSITIVE VALUES INDICATE THAT THE UNCUED HAND WAS STIMULATED FIRST. THE VERTICAL DASHED LINES COINCIDE WITH THE PSS VALUES. ALL CURVES WERE SHIFTED TOWARD THE UNCUED SIDE, INDICATING THAT THE NOCICEPTIVE STIMULUS ON THE UNCUED HAND HAD TO BE PRESENTED SEVERAL MILLISECONDS BEFORE THE STIMULUS ON THE CUED HAND TO HAVE AN EQUAL CHANCE TO BE PERCEIVED FIRST. IMPORTANTLY, THIS BIAS WAS LARGER WHEN HAND POSITION WAS CONGRUENT TO THE VISUAL STIMULUS POSITION, IRRESPECTIVE OF THE DISTANCE OF THE VISUAL STIMULUS TO THE BODY AS A WHOLE. [C] MEANS AND STANDARD ERRORS FOR THE POINT OF SUBJECTIVE SIMULTANEITY (PSS) FOR EXPERIMENT 1. SIGNIFICANT DIFFERENCES ARE INDICATED WITH AN ASTERISK ($P < 0.05$).

2.2.2 EXPERIMENT 2

In Experiment 2, 40 cm in front of the participants' trunk, on the line extending the body midline, a red fixation LED was attached to the table. Participants were asked to keep their gaze on this fixation LED throughout the experiment. Twenty cm to the left and the right of fixation, two green LEDs were attached to the table (medial position relative to the mediolateral axis). Two other green LEDs were attached to the table at a horizontal distance of 50 cm to the left and right of the fixation LED (lateral position), and at a horizontal distance of 30 cm from the medial LEDs. The position of the participants' hands was manipulated: in half of the blocks they were asked to rest their arms on the table in front of them so that the medial LEDs were between the thumb and index finger of their hands. In the other half of the blocks they were asked to rest their arms on the table in front of them so that the lateral LEDs were between the thumb and index finger of their hands. In the former case the hands were 40 cm apart. In the latter case, the hands were 100 cm apart. In both cases the hands were positioned 40 cm in front of the trunk (Figure 2A).

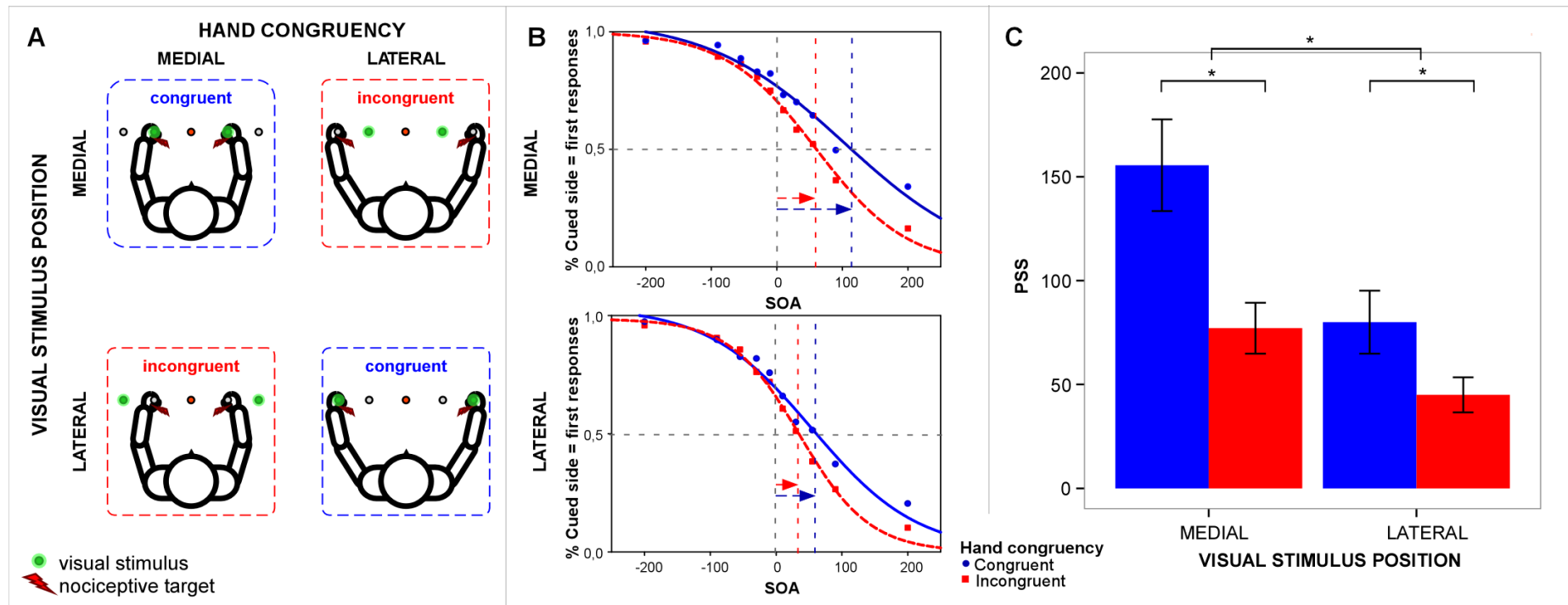


FIGURE 2. [A] EXPERIMENTAL SET-UP EXPERIMENT 2. VISUAL STIMULUS POSITION WAS MANIPULATED ACCORDING THE MEDIOLATERAL AXIS, AND HANDS WERE POSITIONED AT A CONGRUENT OR INCONGRUENT POSITION. [B] NOCICEPTIVE TEMPORAL ORDER JUDGMENTS (TOJ'S) FOR EXPERIMENT 2. THE FIGURE ILLUSTRATES THE FITTED CURVES FROM CUMULATIVE DATA FROM 22 PARTICIPANTS. TRIALS WERE EITHER ASSOCIATED WITH VISUAL STIMULI AT A MEDIAL (UPPER FIGURE) OR AT A LATERAL POSITION (LOWER FIGURE), AND WITH HANDS ON THE CONGRUENT (BLUE SOLID LINE) OR THE INCONGRUENT POSITIONS (RED DOTTED LINE). DATA ARE PLOTTED AS THE MEAN PROPORTION OF *CUED HAND FIRST RESPONSES* (ON THE Y-AXIS), AS A FUNCTION OF THE STIMULUS ONSET ASYNCHRONIES (SOA) (ON THE X-AXIS). ON THE X-AXIS, NEGATIVE VALUES INDICATE THAT THE CUED HAND WAS STIMULATED FIRST, WHILE POSITIVE VALUES INDICATE THAT THE UNCUED HAND WAS STIMULATED FIRST. THE VERTICAL DASHED LINES COINCIDE WITH THE PSS VALUES. ALL CURVES WERE SHIFTED TOWARD THE UNCUED SIDE, INDICATING THAT THE NOCICEPTIVE STIMULUS ON THE UNCUED HAND HAD TO BE PRESENTED SEVERAL MILLISECONDS BEFORE THE STIMULUS ON THE CUED HAND TO HAVE AN EQUAL CHANCE TO BE PERCEIVED FIRST. IMPORTANTLY, THIS BIAS WAS LARGER WHEN HAND POSITION WAS CONGRUENT TO THE VISUAL STIMULUS POSITION. MOREOVER, THE DIFFERENCE IN PSS VALUES BETWEEN THE CONGRUENT AND THE INCONGRUENT HAND POSITION WAS LARGER WHEN VISUAL STIMULI WERE PRESENTED MEDIAL AS OPPOSED TO LATERAL. [C] MEANS AND STANDARD ERRORS FOR THE POINT OF SUBJECTIVE SIMULTANEITY (PSS) FOR EXPERIMENT 2. SIGNIFICANT DIFFERENCES ARE INDICATED WITH AN ASTERISK ($P < 0.05$).

2.2.3 EXPERIMENT 3

In Experiment 3, participants were sitting in front of a black 50-cm-high curved screen that was positioned vertically at 40 cm from the participants' trunk and about 5 cm above the table (Figure 3A). Four green LEDs were attached to the screen. Two of the LEDs were positioned at the bottom of the screen, 40 cm apart from each other (low position relative to the longitudinal axis of the body). The two other LEDs were attached at the top of the screen, 50 cm above the low cues (high position). Participants stretched their hands beneath the screen so that the index finger of their left and right hand were positioned underneath the left and right (low) LEDs respectively. Participants were fixating on a red LED that was attached to the screen at a position equidistantly from the low and high LEDs (25 cm above or below the green LEDs), and equidistantly from the left and right LEDs (20 cm to the left or right of the green LEDs). Participants were sitting so that the red fixation LEDs was positioned on the line extending the midline of the participants' body (therefore left and right green LEDs were equidistant from the body midline).

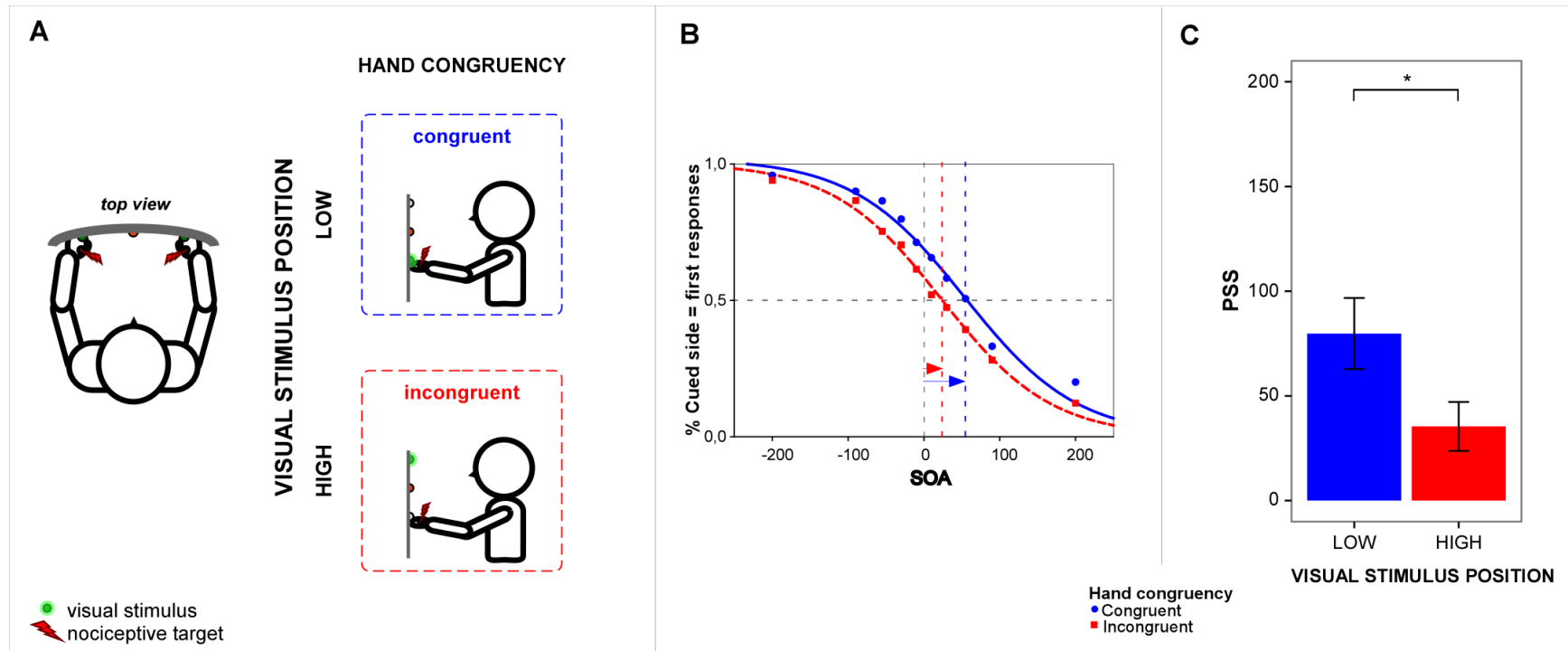


FIGURE 3. [A] EXPERIMENTAL SET-UP EXPERIMENT 3. VISUAL STIMULUS POSITION WAS MANIPULATED ACCORDING THE LONGITUDINAL AXIS, SO THAT THE VISUAL STIMULUS WAS EITHER AT A CONGRUENT OR INCONGRUENT POSITION WITH RESPECT TO THE HANDS. [B] NOCICEPTIVE TEMPORAL ORDER JUDGMENTS (TOJ'S) FOR EXPERIMENT 3. THE FIGURE ILLUSTRATES THE FITTED CURVES FROM CUMULATIVE DATA FROM 23 PARTICIPANTS. TRIALS WERE EITHER ASSOCIATED WITH VISUAL STIMULI AT A CONGRUENT (BLUE SOLID LINE) OR AN INCONGRUENT POSITION (DASHED RED LINE). DATA ARE PLOTTED AS THE MEAN PROPORTION OF *CUED HAND FIRST RESPONSES* (ON THE Y-AXIS), AS A FUNCTION OF THE STIMULUS ONSET ASYNCHRONIES (SOA) (ON THE X-AXIS). ON THE X-AXIS, NEGATIVE VALUES INDICATE THAT THE CUED HAND WAS STIMULATED FIRST, WHILE POSITIVE VALUES INDICATE THAT THE UNCUED HAND WAS STIMULATED FIRST. THE VERTICAL DASHED LINES COINCIDE WITH THE PSS VALUES. ALL CURVES WERE SHIFTED TOWARD THE UNCUED SIDE, INDICATING THAT THE NOCICEPTIVE STIMULUS ON THE UNCUED HAND HAD TO BE PRESENTED SEVERAL MILLISECONDS BEFORE THE STIMULUS ON THE CUED HAND TO HAVE AN EQUAL CHANCE TO BE PERCEIVED FIRST. IMPORTANTLY, THIS BIAS WAS LARGER WHEN VISUAL STIMULUS POSITION WAS CONGRUENT AS OPPOSED TO INCONGRUENT TO THE HANDS. AS THE DISTANCE OF THE VISUAL STIMULI TO THE BODY WAS KEPT CONSTANT, IT IS UNLIKELY THAT THIS INFLUENCED RESULTS. [C] MEANS AND STANDARD ERRORS FOR THE POINT OF SUBJECTIVE SIMULTANEITY (PSS) FOR EXPERIMENT 3. SIGNIFICANT DIFFERENCES ARE INDICATED WITH AN ASTERISK ($P < 0.05$).

2.3 PROCEDURE

To get used to the stimulus response mapping, a first practice session contained 1 block of 20 trials, in which participants were presented with one IES target, either on the left or the right hand. Participants indicated, by means of the foot pedals, which hand was stimulated. In a second practice phase of 2 blocks (one for each LED position) of 24 trials, participants practiced the actual experiment with cues and nociceptive targets, but only using the three largest SOAs, to ensure correct task performance. The experiment did not proceed until participants had 80% correct performance on the largest SOAs in both blocks.

In Experiment 1 and 2, the experiment consisted of 8 blocks of 60 trials. In Experiment 1, visual stimuli were presented using the proximal LEDs in four of the blocks. For two of these blocks, the hands were placed at a congruent position, i.e. next to the proximal LEDs. For the other two blocks, the position of the hands was incongruent, i.e. next to the distal LEDs (that were actually not used for visual stimulation during these blocks). Visual stimuli were presented using the distal LEDs during the four remaining blocks. The position of the hands was congruent (distal) during two blocks and incongruent (proximal) during the two other blocks. A similar combination was used for Experiment 2: the medial LEDs were used for visual stimulation in four blocks, with the hands at a congruent (medial) position during two blocks, and at an incongruent (lateral) position during the other two blocks. The lateral LEDs were used in the four remaining blocks, with the hands at a congruent (lateral) position during two blocks and at an incongruent (medial) position during the other two blocks. The order was randomized for the first four blocks, and the reversed order was used for the last four blocks.

In Experiment 3, the actual experiment consisted of 4 blocks of 120 trials. In two blocks visual stimuli were presented using the low LEDs. In the other two blocks they were presented using the high LEDs. Therefore the position of the visual stimulus was congruent with respect to hand position during the blocks with low visual stimulus position, and incongruent during the blocks with high visual stimulus position. The order of the blocks was alternated and counterbalanced across participants.

A trial started with the red fixation LED being illuminated. This fixation LED stayed on during the entire trial. 500 ms after the onset of the fixation LED, the visual stimulus was flashed during 20 ms, using the LED from either the left or the right side of space. Probability of occurrence was equivalent for left and right visual stimuli. The visual stimulus was followed 80 ms later by a pair of nociceptive stimuli, one applied to either hand. The first nociceptive stimulus could be applied either to the left or the right hand. Five possible

SOAs were used between the two nociceptive stimuli for each order of stimulation (left hand first vs. right hand first): ± 200 , ± 90 , ± 55 , ± 30 , ± 10 ms (where positive values indicate that the participant's right hand was stimulated first, and negative values indicate that their left hand was stimulated first). The trials were created combining 2 spatial locations of the visual stimuli x 2 orders for the nociceptive stimuli x 5 SOAs. Trials were randomly presented within each block of stimulation. The visual cues were spatially uninformative, and the location of any forthcoming nociceptive stimulus could thus not be predicted by the cue.

Participants were instructed to keep their gaze on the red fixation LED throughout each block of trials and to indicate which hand was stimulated first. Responses were given by two foot pedals, one positioned under the toes, and one under the heel. Participants were instructed to keep the foot pedals pressed down, and to either raise their heel or their toes briefly to respond which hand was stimulated first. Half of the participants responded with their left foot, the other half with their right foot. The response mapping (toe = left hand, heel = right hand, or vice versa) was counterbalanced between participants. Participants were instructed to be as accurate as possible. Speed was not important. To mask any noise produced by the foot pedals, participants wore headphones (WESC, Conga) through which white noise was presented (42.2 dB).

After the participants had made their response, the fixation LED was turned off. If participants did not respond within 10s, the fixation LED flickered 3 times before the experiment continued. After 1000 ms, the next trial started. The experiment took approximately 60 minutes.

2.4 MEASURES

The procedure followed was the same for the three experiments and is similar to the one reported in Spence, Shore, & Klein (2001) (see also De Paepe, Crombez, & Legrain, 2015; De Paepe, Crombez, Spence, & Legrain, 2014; Shore, Gray, Spry, & Spence, 2005; Van Damme, Gallace, Spence, Crombez, & Moseley, 2009). For each participant, and for each SOA for the two or four within-participant conditions (in Experiment 1: proximal vs. distal visual stimulus position x congruent vs. incongruent hand position; in Experiment 2: medial vs. lateral visual stimulus position x congruent vs. incongruent hand position; in Experiment 3: congruent vs. incongruent visual stimulus position), the proportion of trials on which participants perceived the cued hand as being stimulated first (i.e., the proportion of trials during which the nociceptive stimulus delivered ipsilaterally to the visual stimulus was

perceived as first delivered) was calculated. A sigmoid function was fitted to these proportions (see Figure 1B, Figure 2B and Figure 3B, for Experiment 1, 2 and 3 respectively). Subsequently, the proportion of *cued hand first responses* was converted into *z*-scores by means of a standardized cumulative normal distribution (probits). The best-fitting straight line was computed for each participant and each condition, and the derived slope and intercept values were used to compute the point of subjective simultaneity (PSS)¹. The PSS refers to the point at which participants report the two events (i.e., the nociceptive stimulus presented to the cued hand and the nociceptive stimulus to the uncued hand, that is, the hand contralateral to the visual stimulus) as occurring first equally often. This is equivalent to the SOA value corresponding to a proportion of *cued hand first responses* of 0.5 (Spence et al., 2001). The PSS is computed as the opposite of the intercept divided by the slope from the best-fitting straight line. The PSS reflects how much time the nociceptive stimulus at the uncued hand had to be presented before/after the cued hand in order to be perceived as having occurred at the same time. In sum, the PSS provides information concerning biases in spatial attention resulting from the presentation of the visual stimuli.

2.5 ANALYSES

PSS values that exceeded twice the maximum SOA were excluded from the data. Extremely large PSS values indicate that participants were not able to perform the task correctly, even at large SOAs, when the task performance is expected to be nearly perfect. As a consequence, results in some conditions are missing for some of the participants. In order to test if this was influenced by the position of the LEDs and/or the hands, the difference in missing values between the two (four) conditions was compared using a chi-squared test for equality of proportions.

To address the question of whether there was an attentional bias (due to the capture of attention by the visual cues), we tested whether the PSS differed significantly from 0, using one sample t-tests.

Next, in order to compare the PSS values across the different conditions, results were analyzed using the linear mixed effects models as implemented in the R package “Linear and Nonlinear Mixed Effects Models” (Pinheiro & Bates, 2000). Linear mixed effect models

¹ Another measure often used in TOJ tasks is the just noticeable difference (JND), which provides a standardized measure of the sensitivity of participants’ temporal perception. However, as we were interested in the attentional bias induced by the cues, which is reflected by the PSS, we did not take the JND into account here for the sake of parsimony. Data are available on request.

account for the correlations in within-subject data by estimating subject-specific deviations (or random effects) from each population-level factor (or fixed factor) of interest (see West, Welch, & Galecki, 2007 for an elaboration). We chose to analyze the data with linear mixed models because it is a more subject-specific model and it allows unbalanced data, unlike the classical general linear models which require a completely balanced array of data (West et al., 2007).

The outcome variable was the PSS. The independent variables were the visual stimulus position (Experiment 1: proximal vs. distal; Experiment 2: medial vs. lateral; Experiment 3: congruent vs. incongruent) and, only in Experiments 1 and 2, the congruency of the hand position relative to the visual stimuli (congruent vs. incongruent). These were manipulated within subjects. Each analysis required three steps. First, all relevant factors and interactions were entered in the model as fixed factors, and we assessed whether it was necessary to add a random effect for each of the fixed factors in the analysis: if a random effect significantly increased the fit of the model, it was included in the final model. By default, a random effect was added introducing adjustments to the intercept conditional on the *Subject* variable. In the second step, we searched for the most parsimonious model that fitted the data. To achieve this, we systematically restricted the full model, comparing the goodness of fit using likelihood-ratio tests. Finally, in the third step, we inspected the ANOVA table of the final model and tested specific hypotheses about possible main effects or interactions (for a similar approach see De Paepe et al., 2015; De Ruddere et al., 2011; Verbruggen, Aron, Stevens, & Chambers, 2010). Kenward-Roger approximations to the degrees of freedom were used to adjust for small sample sizes (Kenward & Roger, 1997). When an interaction effect was significant, it was further investigated with follow-up contrast analyses, corrected for multiple testing according to the Holm-Bonferroni corrections (Holm, 1979). Standardized regression coefficients were reported as a measure of the effect size.

3 RESULTS

3.1 INTENSITY OF THE NOCICEPTIVE STIMULI

The mean current intensities used during Experiment 1 were 0.66 ± 0.18 mA and 0.66 ± 0.21 for stimuli applied to the left and right hand respectively. In Experiment 2, the mean intensities were 0.58 ± 0.17 mA and 0.61 ± 0.13 mA. Finally in Experiment 3 the mean intensities were 0.56 ± 0.15 mA and 0.57 ± 0.22 mA. The mean current intensities were not significantly different between stimuli to the left and to the right hand (Experiment 1: $t(23) = -0.50$, $p = 0.62$; Experiment 2: $t(21) = -0.97$; $p = 0.34$; Experiment 3: $t(22) = -0.02$; $p = 0.98$).

The mean self-reported intensities were 3.70 ± 1.60 and 3.75 ± 1.69 for the left and right hand respectively in Experiment 1, 3.83 ± 1.92 and 3.78 ± 1.76 in Experiment 2, and 3.91 ± 1.72 and 3.80 ± 1.82 in Experiment 3. These self-reported intensities for left-hand and right-hand stimuli did not differ significantly from each other (Experiment 1: $t(23) = -0.50$, $p = 0.62$; Experiment 2: $t(21) = 0.36$; $p = 0.72$; Experiment 3: $t(22) = 0.89$; $p = 0.38$). This suggests that stimuli applied to left and right hands were perceived as equivalent.

3.2 MISSING VALUES

In Experiment 1, 4 out of 96 (0.04%) values were excluded; all of these were from a condition where hands were on the congruent position. However, a chi-squared test indicated that the proportion missing values was not significantly different between the congruent and the incongruent hand position conditions ($\chi^2(1, N = 96) = 2.35$; $p = 0.13$). In Experiment 2, no values were excluded. Finally, in Experiment 3, 3 out of 46 (0.07%) values were excluded; all of these were from the blocks with visual stimuli at the congruent position. However, a chi-squared test indicated that the proportion missing values was not significantly different between the visual stimuli at congruent and those at incongruent positions ($\chi^2(1, N = 46) = 1.43$; $p = 0.23$).

3.3 PSS

3.3.1 EXPERIMENT 1

In Experiment 1, the t-test revealed that the PSS values were significantly different from 0 in all 4 conditions (proximal visual stimuli, hands at congruent position: $t(21) = 6.33$; $p < 0.001$; proximal visual stimuli, hands at incongruent position: $t(23) = 2.67$, $p =$

0.01; distal visual stimuli, hands at congruent position: $t(21) = 6.79, p < 0.001$; distal visual stimuli, hands at incongruent position: $t(23) = 3.64, p = 0.001$). This indicates that the PSS was biased by the presence of lateralized visual stimuli. The linear mixed effects model that demonstrated the best fit with the data, included the fixed factors (*visual stimuli position* and *hand congruency*), a random subject-based intercept and a random effect for *hand congruency*. Adding the interaction effect between the fixed factors did not significantly improve the model. The interaction effect was therefore not included in the model. In this final model, there was a main effect of *hand congruency* ($F(1,21.01) = 34.15; p < 0.001; \beta = -0.55$), indicating that PSS values were more positive when the position was congruent to the position of the visual stimuli, as compared to trials when visual stimuli and hand positions were incongruent. The main effect of *visual stimulus position* was not significant ($F(1,45) = 3.05; p = 0.09; \beta = -0.11$). These results indicate that the relative position of the visual stimuli to the stimulated body part had an influence on nociceptive processing, rather than the distance of the visual stimuli to the body (Figure 1C).

3.3.2 EXPERIMENT 2

In Experiment 2, the t-test revealed that the PSS values were significantly different from 0 in all 4 conditions (medial visual stimuli, hands at congruent position: $t(21) = 7.05; p < 0.001$; medial visual stimuli, hands at incongruent position: $t(21) = 6.29, p < 0.001$; lateral visual stimuli, hands at congruent position: $t(21) = 5.28, p < 0.001$; lateral visual stimuli, hands at incongruent position: $t(21) = 5.33, p < 0.001$). This indicates that the PSS was biased by the presence of lateralized visual stimuli. The linear mixed effects model that demonstrated the best fit with the data, included the fixed factors (*visual stimulus position* and *hand congruency*) as well as their interaction, a random subject-based intercept, and a random effect for *visual stimulus position* and *hand congruency*. In this final model, there was a main effect of *visual stimulus position* ($F(1,34.68) = 35.71; p < 0.001; \beta = 0.46$), a main effect of *hand congruency* ($F(1,30.47) = 5.45; p = 0.03; \beta = -0.22$), and an interaction effect between these two factors ($F(1,21) = 10.92; p = 0.003; \beta = -0.60$). Follow-up t-tests indicated that PSS values were overall higher for visual stimuli at the medial position, and in particular when hands were at the congruent position. This is illustrated by significantly higher PSS values for visual stimuli at the medial than at the lateral position (all $t > -4$, all $p < 0.001$), and significantly higher PSS values when hands were positioned at a congruent than at an incongruent position, especially when visual stimuli were presented at the medial positions ($t(21) = -3.76; p < 0.001$), but also, although to a lesser extent, when visual stimuli were presented at the lateral positions

($t(21) = -1.89, p = 0.04$). These results suggest that the relative distance between the visual stimuli and the stimulated body part had an influence on nociceptive processing over and above the influence of the distance of the visual stimuli to the body (Figure 2C).

3.3.3 EXPERIMENT 3

In Experiment 3, the t-test revealed that the PSS values were significantly different from 0 both when the visual stimuli were presented at the congruent position ($t(19) = 4.70; p < 0.001$) and at the incongruent position ($t(22) = 3.04; p = 0.006$). This indicates that the PSS was biased by the presence of lateralized visual stimuli. The linear mixed effects model that demonstrated the best fit with the data, included the fixed factor (*visual stimulus position*), and a random subject-based intercept. In this final model, there was a significant effect of *visual stimulus position* ($F(1,20.29) = 10.65; p = 0.004; \beta = 0.36$), indicating that the PSS was more positive with visual stimuli at the congruent position than at the incongruent position (Figure 3C).

4 DISCUSSION

We investigated whether the peripersonal space is constructed around the body as a whole, or rather around the stimulated body-part. Three experiments were conducted in which we examined the ability to locate nociceptive stimuli by studying the perceived temporal order of two nociceptive stimuli, one to each hand. Before the first nociceptive stimulation, an unilateral visual stimulus was presented. Crucially, the relative position between the hands and the LEDs used to present the visual stimuli was manipulated. We found that the influence of the visual stimuli on nociceptive judgments was most efficient when the stimulated hand was positioned in proximity of the visual stimuli, independently of their distance to the body (i.e., from *whole body* references, such as the trunk). These results provide evidence for the use of peripersonal frames of reference centered around distinct body parts for the spatial perception of nociceptive stimuli.

In a previous study, we used similar TOJ tasks with nociceptive stimuli applied to each hand. Two pairs of LEDs were placed on the horizontal plane, one pair close to the stimulated hands, the second pair further away, according the anteroposterior axis. When an unilateral visual stimulus was presented, nociceptive order judgments were biased in favor of the nociceptive stimulus applied to the hand ipsilateral to the visual stimulus. Importantly this effect was largest when the visual stimulus appeared in close proximity of the stimulated hand, as opposed to when presented at the far position (De Paepe et al.,

2014). Moreover, in a subsequent series of experiments, participants were asked to perform the same task both in normal posture, and with hands crossed over the body midline (De Paepe et al., 2015). Results showed that visual stimuli prioritized the perception of nociceptive stimuli applied to the hand lying in the cued side of space, irrespective of posture, providing evidence for a space-based frame of reference, in which body posture is taken into account. However, in these studies either the position of the visual stimuli (De Paepe et al., 2014) or the position of the hands (De Paepe et al., 2015) was manipulated, leaving us unable to conclude whether this spatial frame of reference is spatially locked to the body, or to distinct body parts. In Experiment 1 of the present studies, the same results were replicated, but, in addition and crucially, experimental conditions were added during which participants were asked to displace their hands more distally, that is, close to the farthest visual stimuli. Results were reversed in the sense that nociceptive judgments were now mostly influenced by the distal visual stimuli (the ones closest to the hands), whereas the influence of the visual stimuli at the proximal position was attenuated. This suggests that the crucial feature for crossmodal influence on nociceptive processing is the proximity of the visual stimuli to the body part on which the nociceptive stimuli were applied, and less to the body as a whole. Results were extended in two more experiments using the other body planes and axes as a reference, so that the positions of the hands and the visual stimuli were manipulated in three-dimensional space. In Experiment 2 the position of the visual stimuli was manipulated according the mediolateral axis. Results were globally the same as in Experiment 1, although the effect of the relative distance between the stimulated hand and the visual stimulus was less pronounced when visual stimuli were presented in the lateral position. This could suggest that the overall distance from the body as a whole can also have an influence on nociceptive processing. Alternatively, this result could be explained by the fact that the lateral position was the most eccentric position relative to the fovea in the three experiments of the present studies. Therefore the relative distance between the hands and the visual stimuli could be more difficult to perceive when the mediolateral axis was manipulated. Results from Experiment 3 were limited by the fact that hand position was not manipulated due to the uncomfortable body posture when the hands were at the high position. However, it is worth to note that the two pairs of LEDs (low and high position) were at the same distance from the participants' trunk, therefore the distance of the LEDs to the body is unlikely to have played a major role in the results. In addition, the gaze was directed toward a fixation LED positioned equidistantly from each of the four experimental LEDs. Therefore visual acuity is also unlikely to explain the present results.

The results of the present experiments strongly suggest that the ability to locate a nociceptive stimulus on the skin surface uses mapping systems that extend the representation of the body space in external space (i.e., peripersonal representation) with a coordinate reference system centered on each body part and more specifically, in the present studies, on each hand. The distance to the body as a whole played a minor role, suggesting that these peri-hand space representations are locked to their referential limb and move with them in space. These results are in line with studies investigating the modular organization of the peripersonal space in monkeys (e.g., Fogassi et al., 1996; Graziano & Gross, 1993). In monkeys several brain areas encode a multisensory map of space centered around a specific body part, including the putamen, area 7b, and the ventral intraparietal cortex (Graziano & Gross, 1994, 1995). In these areas many neurons respond both to the somatosensory stimulation of a specific body-part and to visual stimuli that occur close to that body-part (Graziano & Gross, 1994, 1995; Graziano et al., 1997). Interestingly, the region of space within which visual stimuli are effective in exciting these bimodal neurons is modulated by the position of the arms in space (e.g., Fogassi et al., 1996; Graziano & Gross, 1994; Graziano et al., 1997). Graziano et al. (1997) recorded the activity of bimodal neurons while the arm position, the head position and the gaze direction were manipulated. They found that for most bimodal neurons with a tactile response on the arm, the visual receptive field moved when the arm was moved. Conversely, most bimodal cells with a tactile response on the face had a visual receptive field anchored to the head, moving as the head was rotated. The visual receptive fields did not move when gaze direction was manipulated. Furthermore, after training monkeys to retrieve distant objects with a rake, the visual receptive fields of the bimodal neurons was altered to include the entire length of the rake (Iriki, Tanaka, & Iwamura, 1996), indicating that the peripersonal space is constructed around the modified representation of the hand.

In humans similar changes in cross-modal visuo-tactile effects after tool-use are documented (Farnè, Serino, & Ladavas, 2007; Maravita, Spence, & Driver, 2003; Farnè & Ladavas, 2000). Moreover neuropsychological evidence in patients suffering from left tactile extinction following right hemisphere damage suggests that the visuotactile peripersonal space is represented in limb-centered coordinates. These patients typically can detect a single touch on the left or right hand in isolation, but when both hands are stimulated simultaneously, only the right touch can be reliably detected (e.g., di Pellegrino et al., 1997; Mattingley, Driver, Beschin, & Robertson, 1997). Interestingly, extinction also occurs when a visual stimulus is presented near the ipsilesional hand. When the visual stimulus remained at a constant distance from the body, but the relative distance to the hand was increased, the

visual stimulus extinguished the perception of the tactile stimulus applied to the opposite hand only to a lesser extent (di Pellegrino et al., 1997).

In the present paper we were able to extend the results mentioned above to nociceptive processing in healthy volunteers. The ability to localize nociceptive stimuli is important, because it enables us to detect which part of the body is damaged, and to react against potential physical threats. The existence of a peripersonal frame of reference for the localization of nociceptive stimuli implies that nociceptive inputs are integrated in a multisensory system that monitors the space immediately surrounding our body and detects any sensory information having a potential impact on our body. Therefore the coding of nociceptive information in a peripersonal frame of reference may constitute a safety margin around the body that protects it from potential physical threats and represents a mechanism for preserving homeostatic control over the body (Moseley, Gallace, & Iannetti, 2012). Here we were able to show that this peripersonal frame of reference operates in limb-centered coordinates. This implies that the mere proximity to the body as a whole might not be sufficient for an external stimulus to be integrated in the peripersonal space. Instead this stimulus must be near the body part that is currently stimulated. Crucially, we showed that these peri-hand representations are anchored to the limb they code and are displaced with it in space. This would allow to give priority to stimuli around that limb even when they are still distant from the body as a whole. These results highlights the importance of spatial perception, to understand the processing of pain. Moreover, it may shed light on the pathophysiology and treatment of chronic pain, as some pain conditions (e.g., complex regional pain syndrome) are associated with cognitive deficits altering the ability to represent and perceive the body and the surrounding space (for a review see, Legrain, Bultitude, De Paepe, & Rossetti, 2012; Legrain & Torta, 2015).

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest related to the present article.

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PART 2

**WHAT ARE THE NEURAL UNDERPINNINGS OF
CROSSMODAL INTERACTIONS BETWEEN VISION AND
NOCICEPTION?**

CHAPTER 4

CROSSMODAL SPATIAL ATTENTION BETWEEN VISION AND NOCICEPTION IN THE PERIPERSONAL SPACE: AN ERP STUDY.¹

ABSTRACT

Two experiments were conducted, in which we tested whether lateralized visual cue stimuli could orient attention towards one side of space, and prioritize the processing and response to nociceptive and tactile stimuli applied to the hand laying in the same side of space (congruent) as compared to the hand laying in the opposite side of space (incongruent). Importantly, we tested whether this effect only appeared when visual cue stimuli were presented near the participants' hands as opposed to far in front of the hands. The visual cue stimuli were completely unpredictable for the location of the forthcoming nociceptive stimulus. Behavioral responses to tactile stimuli (Experiment 1) or to double nociceptive stimulation (Experiment 2), and event related potentials (ERPs) to single (non-target) nociceptive stimuli were investigated. In Experiment 1, tactile stimuli were faster discriminated with shorter reaction times for congruent than for incongruent trials, but only when visual cue stimuli were presented near the participant's hands. ERP results for this experiment were inconclusive. In Experiment 2, we found no significant behavioral results, but ERPs were larger in amplitude when visual stimuli were presented near the participant's hands and congruent to the location of the nociceptive stimuli, as opposed to far from the participant's hands and incongruent. This enhancement only clearly affected the N140 component, suggesting that the location of visual stimuli influenced nociceptive processing through a modulation of electrophysiological responses compatible with neural activity in the secondary somatosensory and insular cortices.

¹ Based on: De Paepe, A.L., Crombez, G., & Legrain, V. (in preparation). Crossmodal spatial attention between vision and nociception in the peripersonal space : an ERP study.

1 INTRODUCTION

The ability to localize and react to stimuli that might have an impact on the physical integrity of the body is essential for survival. Nociceptive stimuli are stimuli that activate peripheral receptors characterized by high-thresholds, and, therefore they have the specific ability to code and transmit information about noxious sensory events, that is, sensory events having the possibility to afflict tissue damage (Belmonte & Viana, 2008). Nociception can therefore be interpreted as an archetype of threat detection (Legrain et al., 2012). Spatial perception is an essential part of nociceptive processing as it enables us to detect which part of the body is being damaged and to prepare appropriate motor actions to protect ourselves against the threat (Legrain et al., 2012). This localization partially depends on a direct relationship between the spatial organization of the skin receptors and the spatial organization of neurons in the cerebral cortex (Kenshalo & Isensee, 1983). Most studies investigating the ability to localize pain have focused on the description of the somatotopic organization of neuronal responses to nociceptive and painful stimuli in the primary (SI) and secondary (SII) somatosensory cortices and in the insula (Andersson et al., 1997; Baumgärtner et al., 2010; Bingel et al., 2004; Henderson, Gandevia, & Macefield, 2007). However, this only allows the identification of their position on the skin surface. It is also of primary importance to perceive the position of threatening objects in external space, in order to guide defensive responses towards the location of threat. Therefore the ability to localize, selectively attend and react to nociceptive stimuli critically depends on the coordination of the spatial properties of the different senses, that is, to link information from the body space (somatosensory information) with information in the outside world (e.g., visual or auditory information). Such a link is thought to be made by crossmodal orientation of spatial attention. Crossmodal spatial attention defines processes by which focusing attention on a stimulus of one sensory modality facilitates the processing of sensory inputs from other sensory modalities, if those stimuli are presented in the same spatial area.

For external visual, auditory and tactile stimuli, behavioral and electrophysiological studies have shown that involuntary shifts of spatial attention triggered by stimuli in one modality can affect processing of subsequently presented stimuli in a different modality, thereby reflecting crossmodal links in spatial attention between vision/audition and touch (Kennett, Eimer, Spence, & Driver, 2001; McDonald & Ward, 2000; Spence & Driver, 1997). Moreover, it has been shown that these crossmodal effects between somatosensory and non-somatic stimuli only occur when the external stimuli are presented in the proximal part of external space (i.e. near the body) (Làdavas, di Pellegrino, Farnè, & Zeloni, 1998;

Rizzolatti, Fadiga, Fogassi, & Gallese, 1997; Sambo & Forster, 2009; Spence, Pavani, & Driver, 2004). This suggests that these crossmodal links in spatial attention could rely on a peripersonal frame of reference, an egocentric reference frame in which information from the body space interacts with information from the external world, provided that the external stimuli appear in close proximity to the body or one of the body parts.

For nociceptive processing, studies investigating unimodal spatial attention have shown for example that focusing attention on the limb on which nociceptive stimuli were applied, could significantly increase the magnitude of event-related potentials (ERPs) elicited by these stimuli, compared to when attention was oriented to the opposite limb (Legrain, Guérit, Bruyer, & Plaghki, 2002). Less is known about crossmodal links between vision and nociception in the orientation of spatial attention (see Legrain et al., 2012). It has been shown that lateralized nociceptive¹ cues can orient attention selectively to one hemibody and modify processing of visual stimuli (Favril, Mouraux, Sambo, & Legrain, 2014). Moreover, other studies demonstrated that ERPs evoked by nociceptive stimuli are modulated by the act of viewing the stimulated hand (Longo, Betti, Aglioti, & Haggard, 2009; Torta, Legrain, & Mouraux, 2015). However, to our knowledge, there is no study that assessed the influence of the distance of external visual stimuli with respect to the body on nociceptive processing. Recently, we measured the effect of unilateral visual stimuli, presented near or far from the participants' hands on perceived temporal order of nociceptive stimuli, applied to each hand. We found that temporal order judgments (TOJs) of the nociceptive stimuli were biased by the visual stimuli, but only when they were presented in close proximity of the stimulated hand. Visual stimuli presented further away from the stimulated hand, had less effect on nociceptive processing (De Paepe, Crombez, & Legrain, 2015; De Paepe, Crombez, Spence, & Legrain, 2014; De Paepe et al., in preparation), providing evidence for a peripersonal frame of reference for the mapping of nociceptive stimuli. However, these studies do not provide insight in the neural processes underlying such links. Investigating the neural underpinnings of these crossmodal links in spatial attention could provide valuable information, for example as to whether these crossmodal links affect early sensory-perceptual processes, or rather later, post-perceptual processing stages.

¹ Note that a distinction has to be made between “nociceptive stimuli” and “painful stimuli”. Nociceptive stimulus refers to a stimulus that activates nociceptors, regardless of whether it elicits a perception of pain. The term painful stimulus on the other hand, refers to a stimulus eliciting a perception of pain, regardless of whether it activates nociceptors (Loeser & Treede, 2008).

Here we conducted two experiments, in which we tested crossmodal links in spatial attention between vision and nociception in the peripersonal space while recording both behavioral and electrophysiological measures. Analogously to previous results, we hypothesized that the presentation of lateralized visual cue stimuli shortly before the presentation of a nociceptive stimulus will improve the processing and the detection of this nociceptive stimulus, if the visual stimulus is presented at the same (congruent) as opposed to the opposite (incongruent) side of space. Moreover, the difference between congruent and incongruent trials should be larger when the visual stimuli were presented near the participants' hands, as opposed to far away. Participants received nociceptive stimuli to their left or their right hand. Sometimes, these nociceptive stimuli were replaced by tactile stimuli (Experiment 1), or two nociceptive stimuli in rapid succession of one another (Experiment 2). Each somatosensory stimulus, either nociceptive or tactile, was preceded by a visual stimulus either in the left or the right side of space, and either near the participants' hands, or far from the participants' hands. The position of the visual stimuli was completely unpredictable for the position of the subsequent nociceptive and tactile stimuli. Participants were asked to discriminate the position of the tactile stimuli (Experiment 1) or the double nociceptive stimuli (Experiment 2) (i.e. left or right hand), while ignoring both the visual and the single nociceptive stimulus. We expected that the magnitude of the event-related potentials (ERPs) to the single nociceptive stimuli would be enhanced, and that the behavioral responses to the tactile/double nociceptive stimuli would be faster when visual stimuli were presented at the same side of space as the stimulated hand. Importantly, this effect should be larger when visual cue stimuli were presented in peripersonal space, as opposed to in extrapersonal space.

2 METHODS

2.1 EXPERIMENT 1

2.1.1 PARTICIPANTS

Twenty-seven paid participants took part in this experiment. Two participants were excluded from the analyses because no reliable ERP components could be extracted from their data. Four additional participants were excluded from the analyses because they performed poorly on one of the aspects of the task (see section 2.1.4.1.). The mean age of the remaining 21 participants (16 females, 20 right-handed) was 22 years (ranging from 19 to 26 years). All of the participants had normal to corrected-to-normal vision, reported no neurological, psychiatric, or chronic pain problems and were not currently using psychotropic drugs, which were exclusion criteria. The experimental procedure was approved by local ethics committee. All of the participants provided informed consent prior to taking part in the study.

2.1.2 STIMULI AND APPARATUS

The nociceptive stimuli were delivered by means of intra-epidermal electrical stimulation (IES) (DS7 Stimulator, Digitimer Ltd, UK), with stainless steel concentric bipolar electrodes (Nihon Kohden, Japan; Inui, Tsuji, & Kakigi, 2006). The electrodes consisted of a needle cathode (length: 0.1 mm, \emptyset : 0.2 mm) surrounded by a cylindrical anode (\emptyset : 1.4 mm). By gently pressing the device against the participants' skin, the needle electrode was inserted into the epidermis of the dorsum of the hand. This is the sensory territory of the superficial radial nerve. The method relies on the fact that cutaneous nociceptive free nerve endings are located more superficially than encapsulated A β fiber mechanoreceptors. In order to guarantee the selectivity of the nociceptive stimulation, a very strict procedure was used to adjust individually the intensity of the stimulus at twice the *absolute detection threshold* to a single 0.5 ms square-wave pulse (Colon, Nozaradan, Legrain, & Mouraux, 2012; Mouraux, Iannetti, & Plaghki, 2010) (see Section 2.1.3.). It has been shown that this procedure enables the selective activation of capsaicin-sensitive A δ -fiber nociceptors without activating more deeply located low-threshold A β -fiber mechanoreceptors (Mouraux et al., 2010). Conversely, higher intensity of stimulation, such as intensity corresponding to the *pain threshold*, compromises the selectivity of IES because stronger currents also activate more deeply located A β fibers (de Tommaso et al., 2011; Legrain & Mouraux, 2013; Perchet et al., 2012). During the experiment, stimuli consisted of trains of three consecutive pulses of 0.5 ms separated by a 5 ms inter-pulse interval (Inui et al., 2006).

These stimuli were perceived as a pinprick sensation related to the activation of A δ nociceptors (Bromm, Jahnke, & Treede, 1984; Nahra & Plaghki, 2003).

In some trials these nociceptive stimuli were replaced by tactile stimuli. These stimuli were presented by means of two resonant-type actuators (C-2 TACTOR, Engineering Acoustics, Inc., Florida, <http://www.eaiinfo.com>), consisting of moving magnet linear actuators in a housing of 3.05 cm diameter and 0.79 cm high, with a skin contactor of 0.76 cm diameter. The tactile stimuli had a frequency of 300 Hz, and a duration of 16.5 ms. Prior to the start of the experiment, the perceived stimulus intensities at both stimulation locations were individually matched (Weinstein, 1968). This was done by means of a double random staircase procedure, based on the 'simple up-down method' of Levitt (1971). In a first phase, 24 stimuli presented on the left hand were judged relative to a reference stimulus (power = 0.21 Watt) on a 5-point Likert scale ranging from 1 ('no sensation') to 5 ('maximum intensity'). The intensity that elicited an averaged rating of 3 was used as the stimulus intensity for the left hand, and was the reference stimulus for the second phase. In the second phase 24 stimuli on the right hand were judged relative to the reference stimulus on the left hand on a 5-point Likert scale (1 = 'more than less strong', 2 = 'less strong', 3 = 'equally strong', 4 = 'stronger', 5 = 'much stronger'). The intensity that elicited an averaged rating of 3 was used as the intensity of the stimulus at the right hand.

The visual stimuli were presented by means of four green light-emitting diodes (LEDs). The LEDs were illuminated for 20 ms, and these stimuli were perceived by participants as a green light that briefly flashed.

The experimental set-up is illustrated in Figure 1. The participants sat on a chair in a dimly illuminated, sound-attenuated room, with their head position fixed in a chin rest. They rested their arms on the table in front of them. The participants placed their hands, palm downward on the table. The distance between the participants' hands and their trunk, as well as the distance between the participants' index fingers was 40 cm. Two of the LEDs were situated in near/peripersonal space, and two in far/extrapersonal space. The LEDs in near space were positioned in between thumb and index finger. The LEDs in far space were positioned 50 cm in front of the LEDs in near space. A red fixation LED was positioned in between the LEDs in near and far space (i.e. 25 cm in front of the LEDs in near space). This fixation LED stayed on during the whole experiment. In some trials (randomly between 1 to 2 trials per block, but never the first trial), this fixation LED flickered, and participants were instructed to verbally report this by saying 'yes'. This

was done in order to ensure that participants kept fixating on this point. Trials in which the fixation LED flickered were not considered in the analyses.

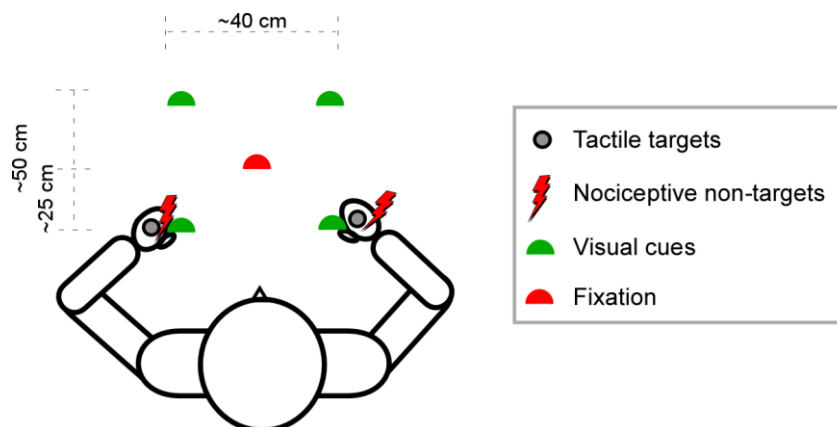


FIGURE 1. EXPERIMENTAL SET-UP OF EXPERIMENT 1. NOCICEPTIVE NON-TARGET STIMULI, REPRESENTED BY THE RED LIGHTNING SYMBOLS, OR TACTILE TARGET STIMULI, REPRESENTED BY THE GREY CIRCLES, WERE APPLIED TO ONE OF BOTH HANDS. VISUAL CUE STIMULI, REPRESENTED BY THE GREEN CIRCLES WERE PRESENTED AT ONE OF FOUR DIFFERENT LOCATIONS IN EACH TRIAL, EITHER LEFT OR RIGHT, AND EITHER NEAR OR FAR FROM THE PARTICIPANTS' HANDS. PARTICIPANTS WERE FIXATING ON A RED LED THAT WAS SITUATED EQUIDISTANTLY BETWEEN THE NEAR AND FAR VISUAL CUES.

2.1.3 PROCEDURE

After placement of the EEG electrodes, the detection threshold to IES was measured for each hand using the method of limits (Churyukanov, Plaghki, Legrain, & Mouraux, 2012). The electrode was placed on the hand dorsum and single-pulse stimuli were applied using a staircase procedure by increasing or decreasing the intensity of electrical current with steps of 0.10 mA. The intensity was set at twice the detection threshold. Intensities of the two electrodes were adapted in order to obtain an equivalent subjective intensity of perception between the two hands. After each experimental block, participants were asked to describe the percept elicited by IES in order to ensure that (1) the subjective intensity of perception was not habituating and disappearing and (2) the equivalence between the perceptions of IES from the two hands was still respected. If one of these two criteria was not met, stimulus intensity was adjusted (with a maximum increase of 0.10 mA). If the adaptation still proved to be unsuccessful, the electrodes were displaced, and the procedure was restarted.

The experiment started by illuminating the LEDs in near and far space one by one. Participants were asked to look at the fixation LED and to indicate where they saw a light

(e.g., left near, right far, ...). This was done to ensure that participants could see all the LEDs. Next, participants completed a practice phase of 24 trials, in which they had to achieve 90% correct performance in order to proceed with the experiment. All participants completed this practice phase successfully.

The experiment consisted of 8 blocks of 76 trials (see Figure 2). Each trial started with a visual stimulus, consisting of a LED being illuminated for 20 ms. After a random cue target onset asynchrony (CTOA) between 80 and 250 ms, a stimulus was presented either to the left or to the right hand, with equal probability. In 48 trials (24 congruent (12 left, 12 right), and 24 incongruent (12 left, 12 right)), the stimuli consisted of a nociceptive stimulus (*non-target*), and in 28 of the trials (14 congruent (7 left, 7 right), 14 incongruent (7 left, 7 right)) the stimulus consisted of a tactile stimulus (*target*). The order of the different types of trials was randomized with the restriction that none of the two first trials of each block contained a target tactile stimulus. The inter-trial interval, measured between the onsets of two consecutive nociceptive/tactile stimuli, varied randomly between 2500 and 3000 ms.

In four blocks the LEDs in near space were illuminated, in the other four blocks, the LEDs in far space were illuminated. The order of the blocks was randomized for the first 4 blocks, and the reversed order was used for the subsequent four blocks.

Participants were instructed to keep their gaze on the fixation point during the whole stimulation block. They were asked to respond as fast and as accurately as possible at which hand they received a tactile target. They did not have to respond to nociceptive non-targets. Responses were given by means of two foot pedals, one positioned beneath their toes and one beneath their heel. Participants were instructed to keep the foot pedals depressed during the experiment, and to lift either their toes or their heel to respond. Half of the participants responded with their left foot, the other half with their right foot. The response mapping (toe = left hand, heel = right hand, or vice versa) was counterbalanced between participants. Participants were informed that the visual cues were unpredictable for the position of the subsequent nociceptive and tactile stimuli. To mask any noise produced by either the foot pedals or the tactile stimuli, participants wore headphones (Sennheiser, HD201).

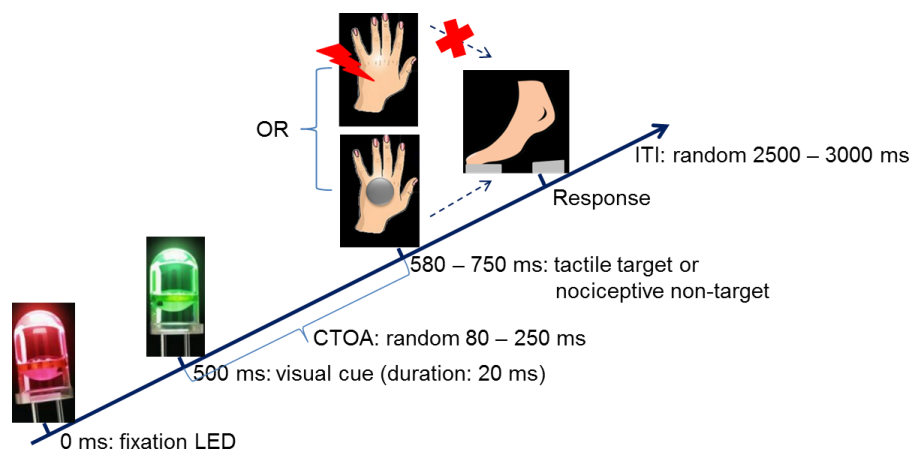


FIGURE 2. ILLUSTRATION OF THE EXPERIMENTAL PROCEDURE OF EXPERIMENT 1.

2.1.4 MEASURES

2.1.4.1 BEHAVIORAL TASK

For trials on which the fixation light flickered, a response was considered ‘correct’ when participants reported the flickering by saying ‘yes’. Any other response or no response was considered as ‘incorrect’. Four participants had less than 70% correct detections (corresponding to 3 or more incorrect responses) and were removed from further analyses. The remaining 21 participants detected on average $85 \pm 15\%$ of the trials.

For trials on which the fixation light did not flicker, a response was considered as ‘incorrect’ if no response was given to a tactile stimulus (missed response), if a response was given to a nociceptive stimulus (false alarm), and if participants reported to have felt a stimulation on the left hand, while the right hand was stimulated and vice versa. The percentage of correct responses was taken as a measure of response accuracy.

The mean reaction times (RTs) to the tactile stimuli were used as a measure of the response speed (excluding RTs to inaccurate responses). RTs lower than 150 ms or higher than 1500 ms were excluded from the analyses (1.1%).

2.1.4.2 EVENT-RELATED POTENTIALS

The electroencephalogram (EEG) was recorded using a 64-channel (pin-type) Biosemi Active Two system (<http://www.biosemi.com>) referenced to the CMS-DRL ground with an analog bandpass. Eye blinks and eye movements were monitored using an electro-oculogram (EOG) recorded from two pairs of electrodes placed at the upper-right and lower-left sides of the left eye (vertical EOG) and close to the lateral canthi of the left and right eyes (horizontal EOG). Signals were recorded, amplified and digitized using a 2024 Hz sampling rate.

Off-line analyses were carried out using LetsWave 5.0 (Université catholique de Louvain, Belgium). The continuous EEG recordings were band-pass filtered (0.3-30Hz) and segmented into 1500 ms epochs (-500 to 1000 ms relative to the onset of the nociceptive stimulus) for nociceptive ERPs. Artifacts produced by eye blinks and eye movements were corrected using independent component analyses (ICA) (Hyvärinen & Oja, 2000), and epochs with signal amplitude exceeding $\pm 100 \mu\text{V}$ were excluded. On average $8\% \pm 6\%$ of the total number of epochs had to be excluded. Signals were re-referenced to the mastoid electrodes (M1-M2) and baseline-corrected (from -500 to 0). Only ERP data in response to non-target nociceptive stimuli was analyzed to avoid contamination by decision – and movement-related processes. This data was used to test the effect of spatial attention on the early stages of nociceptive processing. In order to obtain a good signal-to-noise ratio of the ERPs to the nociceptive stimuli, the data obtained in response to left-and right-sided nociceptive stimuli were merged. Epochs were sorted and averaged according to the experimental conditions: *congruency* (congruent/incongruent) and *cue distance* (near/far).

The identification of ERP components was based on the latency and scalp topography of the obtained peaks. For the nociceptive ERPs, a negative component was isolated by re-referencing the temporal electrodes (T7 and T8) to Fz (Kunde & Treede, 1993). A negative component was isolated between 100 ms and 250 ms after stimulus onset (Favril et al., 2014; Legrain et al., 2002). This negative component was labeled according to its peak latency at temporal (T7/T8) electrodes, i.e. N140. Because we were only interested in the spatial location of nociceptive stimuli relative to the spatial location of the visual cues (i.e. their spatial congruency), lateralization of the ERP magnitude was only considered according to this spatial congruency irrespective of the true location of the nociceptive stimuli. Therefore, the magnitudes of ERP responses to right and left nociceptive stimuli over T7 and T8 were coded and merged according to their lateralization relative to the location of the eliciting nociceptive stimuli. More specifically,

the magnitude measured at T7 in response to right nociceptive stimuli and the magnitude at T8 in response to left nociceptive stimuli were pooled together and coded as contralateral responses. Similarly magnitudes at T7 for left stimuli and at T8 for right stimuli were pooled and coded as ipsilateral responses. Mean ERP amplitudes were measured for contralateral and ipsilateral temporal electrodes. Next, a positive component was identified between 250 and 450 ms after stimulus onset and measured at Cz, C3 and C4 (Favril et al., 2014; Legrain et al., 2002). This positive component was labeled according to its peak latency at Cz, i.e. P320. P320 magnitude was measured similarly to the procedure applied to lateral electrodes for N140: amplitudes at C3 in response to right nociceptive stimuli and at C4 in response to left stimuli were merged together and coded as contralateral central responses; amplitudes at C3 in response to left stimuli and at C4 in response to right stimuli were merged together and coded as ipsilateral central responses. At Cz, responses to left and right nociceptive stimuli were simply averaged together. Therefore, mean ERP amplitudes were measured for Cz, contralateral and ipsilateral central electrodes.

2.1.5 ANALYSES

2.1.5.1 INTENSITY OF THE NOCICEPTIVE AND TACTILE STIMULI

In order to ensure that the intensity of the IES delivered to each of the two hands was equivalent between the two hands, the intensities used during the experiment were compared by means of a paired-student t-test (left vs. right hand) both in terms of the self-reported intensity and in terms of the objective intensity. The same was done for the tactile stimulation.

2.1.5.2 PERFORMANCE ON THE BEHAVIORAL TASK

Accuracy and reaction times were compared using a 3-factor analysis of variance (ANOVA) for repeated measures with *cue distance* (near vs. far), *congruency* (congruent vs. incongruent) and *stimulated hand* (left vs. right hand) as within-subject factors. Effect sizes were calculated using Dunlap, Cortina, Vaslow, & Burke's (1996) formula. If an interaction proved to be significant, it was further investigated with follow-up t-tests.

2.1.5.3 NOCICEPTIVE ERPS

The amplitudes and latencies for the P320 and N140 component of the nociceptive ERPs were compared for the different experimental conditions by performing a 3-way repeated measures ANOVA with *cue distance* (cues in near vs. far space), *congruency* (congruent vs. incongruent), and *topography* (contralateral T vs. ipsilateral T for the

N140 and contralateral C vs. ipsilateral C vs. Cz for the P320) as within subject factors. Greenhouse-Geisser corrections were applied where necessary. Effect sizes were calculated using the formula of Dunlap et al. (1996). If an interaction proved to be significant, it was further investigated with follow-up t-tests.

2.2 EXPERIMENT 2

2.2.1 PARTICIPANTS

Twenty-five paid participants took part in this experiment. For one participant the experiment had to be terminated after the practice phase, because the building was evacuated due to fire alarm. Two participants were excluded from the analyses, because they performed poorly on one of the aspects of the task (see section 2.2.4.1.). The mean age of the remaining 22 participants (22 females, 20 right-handed) was 23 years (ranging from 19 to 29 years). All of the participants had normal to corrected-to-normal vision, reported no neurological, psychiatric, or chronic pain problems and were not currently using psychotropic drugs, which were exclusion criteria. The experimental procedure was approved by local ethics committee. All of the participants provided informed consent prior to taking part in the study.

2.2.2 STIMULI AND APPARATUS

The experimental set-up was exactly the same as in Experiment 1, except for the fact that no tactile stimuli were applied in Experiment 2.

2.2.3 PROCEDURE

The procedure was highly similar to Experiment 1, however, now the nociceptive non-target stimuli were sometimes replaced by two nociceptive stimuli, each consisting of trains of three consecutive pulses of 0.5 ms separated by a 5 ms inter-pulse interval. The inter-stimulus interval (ISI) between the two nociceptive stimuli was 500 ms (see Figure 3). This was done in order to make the nociceptive stimuli more task-relevant compared to Experiment 1, and as such to increase attention towards the nociceptive stimuli.

The experiment started by illuminating the LEDs in near and far space one by one. Participants were asked to look at the fixation LED and to indicate where they saw a light (e.g., left near, right far, ...). This was done to ensure that participants could see all the LEDs. Next, participants completed a practice phase of 24 trials, in which they had to

achieve 90% correct performance in order to proceed with the experiment. All participants completed this practice phase successfully.

The experiment consisted of 8 blocks of 76 trials. Each trial started with a visual stimulus, consisting of a LED being illuminated for 20 ms. After a random CTOA between 80 and 250 ms, a stimulus was presented either to the left or to the right hand, with equal probability. In 48 trials (24 congruent (12 left, 12 right), and 24 incongruent (12 left, 12 right)), the stimuli consisted of one nociceptive stimulus (*non-target*), and in 28 of the trials (14 congruent (7 left, 7 right), 14 incongruent (7 left, 7 right)) the stimulus consisted of two nociceptive stimuli (*target*). The order of the different types of trials was randomized with the restriction that none of the two first trials of each block contained a target nociceptive stimulus. The inter-trial interval, measured between the onsets of two consecutive nociceptive stimuli, varied randomly between 2500 and 3000 ms.

In four blocks the LEDs in near space were illuminated, in the other four blocks, the LEDs in far space were illuminated. The order of the blocks was randomized for the first 4 blocks, and the reversed order was used for the subsequent four blocks.

Participants were instructed to keep their gaze on the fixation point during the whole stimulation block. They were asked to respond as fast and accurately as possible at which hand they received two nociceptive stimuli. They did not have to respond when they only felt one nociceptive stimulus. Responses were given by means of two foot pedals, one positioned beneath their toes and one beneath their heel. Participants were instructed to keep the foot pedals depressed during the experiment, and to lift either their toes or their heel to respond. Half of the participants responded with their left foot, the other half with their right foot. The response mapping (toe = left hand, heel = right hand, or vice versa) was counterbalanced between participants. Participants were informed that the visual cues were unpredictable for the position of the subsequent nociceptive stimuli. To mask any noise produced by the foot pedals, participants wore headphones (Sennheiser, HD201).

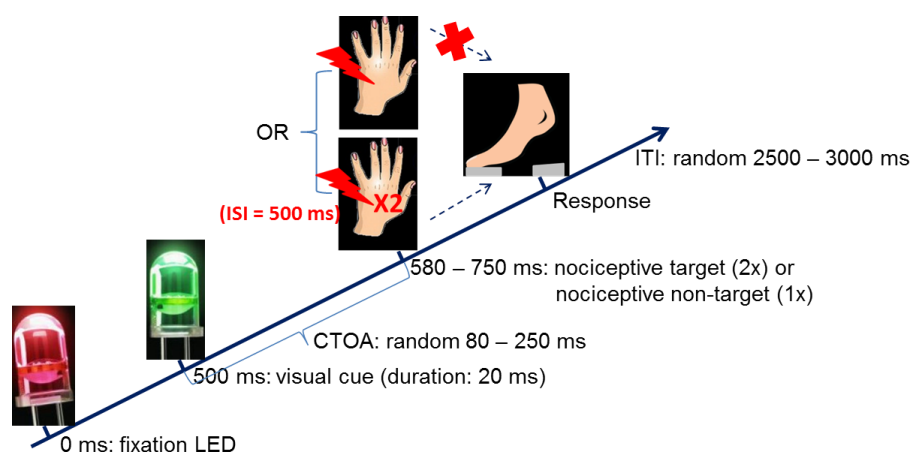


FIGURE 3. ILLUSTRATION OF THE EXPERIMENTAL PROCEDURE OF EXPERIMENT 2.

2.2.4 MEASURES

2.2.4.1 BEHAVIORAL TASK

For trials on which the fixation light flickered, a response was considered 'correct' when participants reported the flickering by saying 'yes'. Any other response or no response was considered as 'incorrect'. 2 participants had less than 70% correct detections (corresponding to 3 or more incorrect responses) and were removed from further analyses. The remaining 22 participants detected on average $96 \pm 5\%$ of the trials.

For trials on which the fixation light did not flicker, a response was considered as 'incorrect' if no response was given to a tactile stimulus (missed response), if a response was given to a single nociceptive stimulus (false alarm), and if participants reported to have felt a stimulation on the left hand, while the right hand was stimulated and vice versa. The percentage of correct responses was taken as a measure of response accuracy.

The mean RTs to the double nociceptive stimuli were used as a measure of the response speed (excluding RTs to inaccurate responses). RTs lower than 150 ms or higher than 1500 ms were excluded from the analyses (0.6%).

2.2.4.2 EVENT-RELATED POTENTIALS

EEG recording and off-line analyses were carried out analogously to Experiment 1.

The continuous EEG recordings were band-pass filtered (0.3-30Hz) and segmented into 1500 ms epochs (-500 to 1000 ms relative to the onset of the nociceptive stimulus) for nociceptive ERPs. Artifacts produced by eye blinks and eye movements were

corrected using independent component analyses (ICA) (Hyvarinen & Oja, 2000), and epochs with signal amplitude exceeding $\pm 80 \mu\text{V}$ were excluded. On average $5\% \pm 6\%$ of the total number of epochs had to be excluded. Signals were re-referenced to the mastoid electrodes (M1-M2) and baseline-corrected (from -500 to 0). Only ERP data in response to non-target nociceptive stimuli was analyzed. This data was used to test the effect of spatial attention on the early stages of nociceptive processing. Nociceptive target trials were excluded to avoid contamination by decision – and movement-related processes. In order to obtain a good signal-to-noise ratio of the ERPs to the nociceptive stimuli the data obtained in response to left- and right-sided nociceptive stimuli were merged. Epochs were sorted and averaged according to the experimental conditions: *congruency* (congruent/incongruent) and *cue distance* (near/far).

The identification of ERP components was based on the latency and scalp topography of the obtained peaks. A negative component was isolated between 100 ms and 250 ms after stimulus onset (Legrain et al., 2002; Favril et al., 2014), and was labeled N140, analogously to Experiment 1. Similarly to the procedure applied in Experiment 1, amplitudes at T7 in response to right nociceptive stimuli and at T8 in response to left stimuli were merged together and coded as contralateral temporal responses; amplitudes at T7 in response to left stimuli and at T8 in response to right stimuli were merged together and coded as ipsilateral temporal responses. Mean ERP amplitudes were measured for contralateral and ipsilateral temporal electrodes. Next, a positive component was identified between 250 and 450 ms after stimulus onset and measured at Cz, C3 and C4 (Favril et al., 2014; Legrain et al., 2002). For 2 participants this component could only be identified at Cz, and not at C3 and C4. As this component was found in the same time frame as in Experiment 1, it was also labeled P320. Again, amplitudes at C3 in response to right nociceptive stimuli and at C4 in response to left stimuli were merged together and coded as a contralateral central response; amplitudes at C3 in response to left stimuli and at C4 in response to right stimuli were merged together and coded as ipsilateral central responses. At Cz, responses to left and right nociceptive stimuli were simply averaged together. Therefore, P320 magnitude was measured at Cz, contralateral and ipsilateral central electrodes.

2.2.5 ANALYSES

2.2.5.1 INTENSITY OF THE NOCICEPTIVE STIMULI

In order to ensure that the intensity of the IES delivered to each of the two hands was equivalent between the two hands, the intensities used during the experiment were compared by means of a paired-student t-test (left vs. right hand) both in terms of the self-reported intensity and in terms of the objective intensity.

2.2.5.2 PERFORMANCE ON THE BEHAVIORAL TASK

Accuracy and reaction times were compared using a 3-factor analysis of variance (ANOVA) for repeated measures with *cue distance* (near vs. far), *congruency* (congruent vs. incongruent) and *stimulated hand* (left vs. right hand) as within-subject factors. Effect sizes were calculated using Dunlap, Cortina, Vaslow, & Burke's (1996) formula. If an interaction proved to be significant, it was further investigated with follow-up t-tests.

2.2.5.3 NOCICEPTIVE ERPs

The amplitudes and latencies for the P320 and N140 component of the nociceptive ERPs were compared for the different experimental conditions by performing a 3-way repeated measures ANOVA with *cue distance* (cues in near vs. far space), *congruency* (congruent vs. incongruent), and *topography* (contralateral T vs. ipsilateral T for the N140 and contralateral C vs. ipsilateral C vs. Cz for the P320) as within subject factors. Greenhouse-Geisser corrections were applied where necessary. Effect sizes were calculated using the formula of Dunlap et al. (1996). If an interaction proved to be significant, it was further investigated with follow-up t-tests. Participants for whom no reliable ERP component could be detected, were excluded from the analyses for that component.

3 RESULTS

3.1 EXPERIMENT 1

3.1.1 INTENSITY OF THE NOCICEPTIVE STIMULI

The mean current intensities used were 0.55 ± 0.23 for the left hand, and 0.60 ± 0.20 for the right hand. The intensity was not significantly different between the left and the right hand ($t(20) = -0.91$; $p = 0.37$). The mean self-reported intensities were 4.48 ± 1.34 for the left hand, and 4.49 ± 1.42 for the right hand, and were not significantly different ($t(20) = -0.10$; $p = 0.93$).

3.1.2 INTENSITY OF THE TACTILE STIMULI

The mean intensities were 0.24 ± 0.03 Watt for the left hand, and 0.25 ± 0.07 Watt for the right hand. The intensity was not significantly different for the left and the right hand ($t(20) = -0.83$, $p = 0.42$). The mean self-reported intensities were 3.48 ± 1.75 for the left hand and 3.48 ± 1.74 for the right hand, and were not significantly different ($t(20) = 0.02$, $p = 0.98$).

3.1.3 PERFORMANCE ON THE BEHAVIORAL TASK

Accuracies were overall high ($M = 0.98$; $SD = 0.02$). There was a main effect of *stimulated hand* ($F(1,20) = 5.74$; $p = 0.03$, $d = 0.60$, CI [0.06 to 1.15]) indicating that accuracy was significantly higher when the left hand ($M = 0.98$, $SD = 0.01$) was stimulated than when the right hand ($M = 0.97$, $SD = 0.02$) was stimulated. None of the other main or interaction effects were significant ($F < 2.6$, $p > 0.10$).

The RT data showed a main effect of *cue distance* ($F(1,20) = 11.95$; $p = 0.002$, $d = 0.16$, CI [0.01 to 0.31]). There was also a main effect of *stimulated hand* ($F(1,20) = 8.83$, $p = 0.008$, $d = 0.15$, CI [-0.03 to 0.34]), indicating that participants were overall faster when their left ($M = 716.04$, $SD = 119.91$) compared to their right ($M = 750.09$, $SD = 130.05$) hand was stimulated. Finally, there was a significant interaction effect between *cue distance* and *congruency* ($F(1,20) = 6.88$, $p = 0.02$, $d = 0.74$, CI [0.53 to 0.94]) (see Figure 4). The main effect of *congruency* was not significant ($F(1,20) = 2.49$, $p = 0.13$), nor were any of the interaction effects with the factor *stimulated hand* (all $F < 1.00$, all $p > 0.30$). Post-hoc t-tests showed that participants were significantly slower for incongruent than for congruent trials when cues were presented near the body ($t(20) = -2.80$, $p = 0.005$), however, when cues were presented far from the body, there was no significant difference between congruent and incongruent trials ($t(20) = 0.38$, $p = 0.65$). These

results show that visual cues influenced RTs only when they appeared in the peripersonal space, and not when they were presented in extrapersonal space.

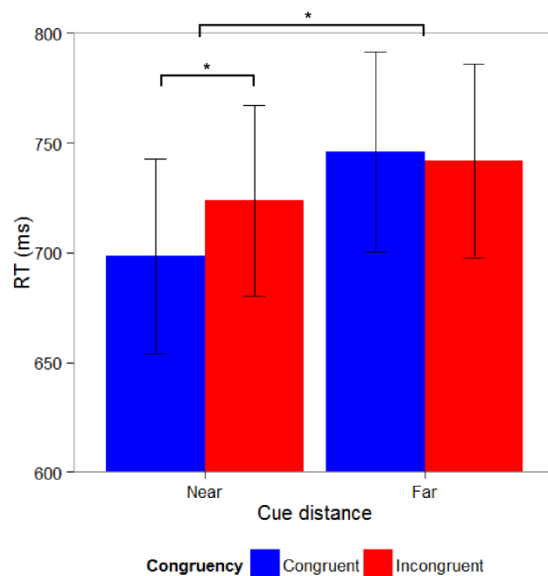


FIGURE 4. MEAN RT'S IN MS AND ASSOCIATED STANDARD ERRORS FOR EXPERIMENT 1. SIGNIFICANT RESULTS ARE INDICATED WITH AN ASTERISK ($P < 0.05$).

3.1.4 NOCICEPTIVE ERPs

3.1.4.1 LATENCY

N140. The latency of the N140 component was influenced by the *topography* ($F(1,20) = 11.54, p = 0.003, d = -0.12, CI [-0.21 \text{ to } -0.04]$), with shorter latencies for contralateral than for ipsilateral sites. Furthermore, latencies were influenced by the *cue distance* ($F(1,20) = 5.51, p = 0.03, d = -0.13, CI [-0.24 \text{ to } -0.03]$). Finally, the interaction effect between *cue distance* and *congruency* was also significant ($F(1,20) = 4.89, p = 0.04, d = -0.54, CI [-1.02 \text{ to } -0.05]$). None of the other main or interaction effects were significant (all $F < 2.5, p > 0.15$). The interaction effect between *cue distance* and *congruency* was further investigated for contralateral and ipsilateral sites separately.

For *contralateral* sites, there was only a marginally significant main effect of *cue distance* ($F(1,20) = 4.06; p = 0.06; d = -0.11; CI [-0.21 \text{ to } -0.004]$), with shorter latencies when visual stimuli were presented near, as opposed to far from the participants. Nor the

main effect of *congruency* ($F(1,20) = 2.43$; $p = 0.14$), nor the interaction effect between *congruency* and *cue distance* ($F(1,20) = 0.17$, $p = 0.69$) were significant.

At *ipsilateral* sites, there was a marginally significant main effect of *cue distance* ($F(1,20) = 4.17$; $p = 0.06$; $d = -0.14$; CI [-0.28 to -0.005]). The main effect of *congruency* ($F(1,20) = 0.84$; $p = 0.37$) was not significant. Finally, the interaction effect between *congruency* and *cue distance* was significant ($F(1,20) = 5.26$, $p = 0.03$, $d = -0.60$, CI [-1.13 to -0.06]). Follow-up t-tests show that latencies at ipsilateral sites were significantly shorter when cues were presented near as opposed to far from the participants for congruent ($t(20) = -2.82$, $p = 0.01$), but not for incongruent trials ($t(20) = -0.42$, $p = 0.68$). Moreover, the difference between congruent and incongruent trials was marginally significant when cues were presented near the participants ($t(20) = -1.90$, $p = 0.07$), but not when they were presented far ($t(20) = 0.66$, $p = 0.52$) from the participants.

P320. The latency of the P320 component was only affected by the *topography* ($F(1.28, 25.69) = 6.65$, $p = 0.01$, $d = 0.77$, CI [0.15 to 1.39]), with shorter latencies at Cz, than at contralateral and ipsilateral sites. None of the other main or interaction effects were significant (all $F < 3$, all $p > 0.09$).

3.1.4.2 AMPLITUDE

N140. Group level average waveforms and mean N140 amplitudes are shown in Figure 5. The repeated measures ANOVA revealed a main effect of *topography* ($F(1, 20) = 141.72$, $p < 0.001$, $d = -0.79$, CI [-0.94 to -0.63]), indicating that N140 amplitudes were higher contralateral to the nociceptive stimulation than ipsilateral. There was a marginally significant main effect of *congruency* ($F(1,20) = 3.37$, $p = 0.08$, $d = -0.20$, CI [-0.42 to 0.02]). The main effect of *cue distance* was also marginally significant ($F(1,20) = 3.56$, $p = 0.07$, $d = -0.17$, CI [-0.35 to 0.01]). Finally, the interaction effect between *congruency* and *cue distance* was marginally significant ($F(1,20) = 3.31$, $p = 0.08$, $d = -0.52$, CI [-1.12 to 0.08]). None of the other interaction effects reached significance (all $F < 2.5$, all $p > 0.15$). The interaction effect between *congruency* and *cue distance* was further investigated at contralateral and ipsilateral sites with a repeated measures ANOVA with *congruency* and *cue distance* as within subject factor.

At *contralateral* sites, there was only a marginally significant main effect of *cue distance* ($F(1,20) = 3.68$, $p = 0.07$, $d = -0.21$, CI [-0.41 to 0.005]), indicating that N140 amplitudes were higher when cues were presented near the participants, than when they were presented far. Nor the main effect of *congruency* ($F(1,20) = 0.35$, $p = 0.56$), nor the

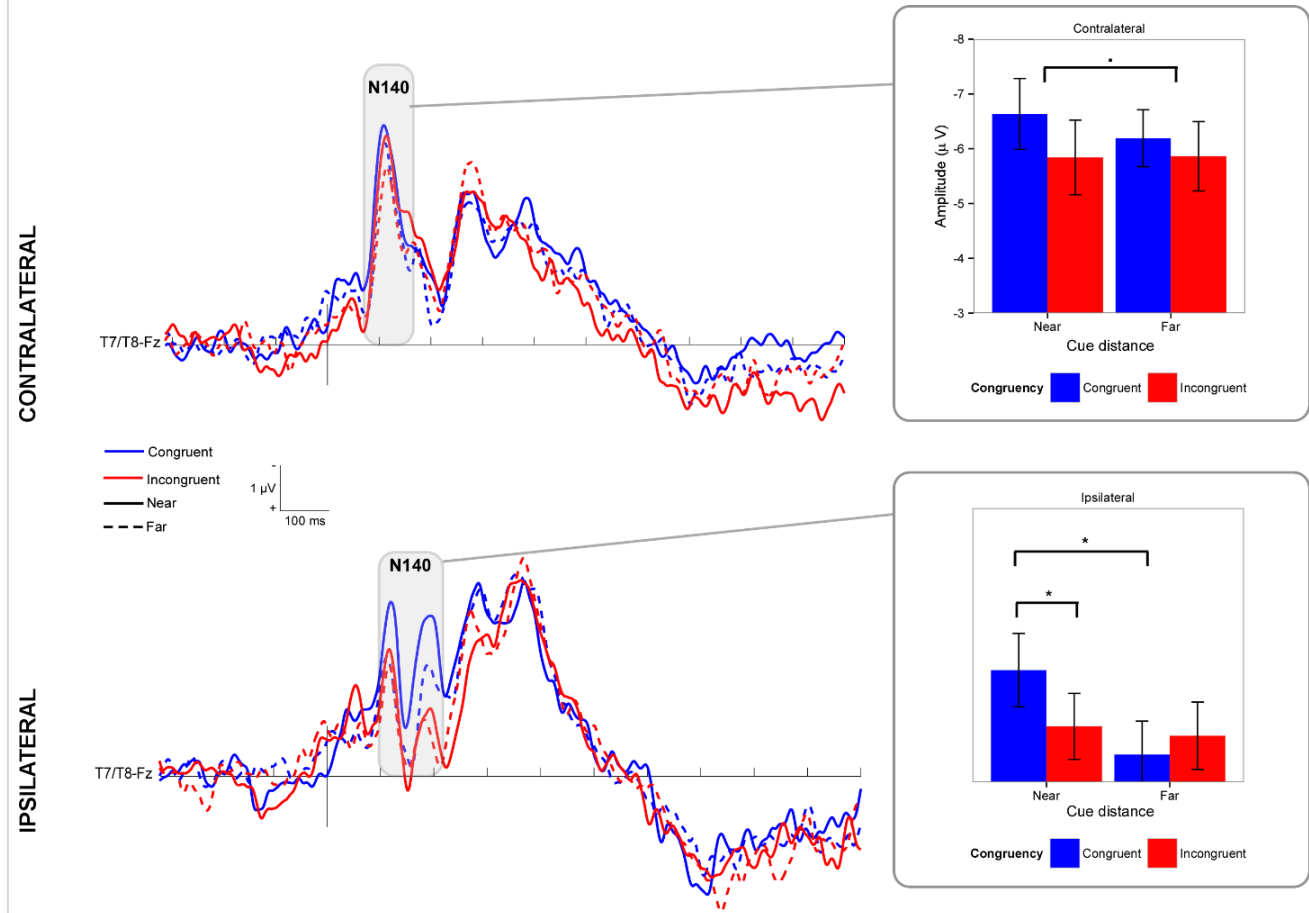
interaction effect between *congruency* and *cue distance* ($F(1,20) = 0.53, p = 0.48$) were significant.

At *ipsilateral* sites, there was a significant main effect of *congruency* ($F(1,20) = 5.07, p = 0.04, d = -0.31, CI [-0.53 \text{ to } -0.10]$). The main effect of *cue distance* was not significant ($F(1,20) = 1.52, p = 0.23$), but the interaction effect between *congruency* and *cue distance* was significant ($F(1,20) = 7.38, p = 0.01, d = -0.66, CI [-1.18 \text{ to } -0.13]$). Follow-up t-tests indicated that N140 amplitudes were significantly higher for congruent than for incongruent trials when cues were presented near the participant's hands ($t(20) = -3.41, p = 0.003$), but not when they were presented far from the participant's hands ($t(20) = -0.37, p = 0.71$). Moreover, N140 amplitudes were significantly higher when cues were presented near as opposed to far from the participants for congruent trials ($t(20) = -2.41, p = 0.03$), but not for incongruent trials ($t(20) = 1.09, p = 0.29$).

FIGURE 5. THE UPPER PART OF THE FIGURE DEPICTS THE N140 WAVEFORMS AND AMPLITUDES FOR CONTRALATERAL SITES, WHILE THE LOWER PART OF THE FIGURE DEPICTS THE N140 WAVEFORMS AND AMPLITUDES FOR IPSILATERAL SITES.

LEFT SIDE FIGURE: N140 WAVEFORMS AT TEMPORAL SITES (T7/T8), RE-REFERENCED TO FZ, IN RESPONSE TO NOCICEPTIVE STIMULI APPLIED TO THE HAND CONGRUENT (BLUE LINES) OR INCONGRUENT (RED LINE) TO THE SIDE OF THE VISUAL CUE. SOLID LINES REFLECT NOCICEPTIVE ERP'S FOR TRIALS ON WHICH THE VISUAL CUES WERE PRESENTED NEAR THE PARTICIPANTS. DASHED LINES REFLECT NOCICEPTIVE ERP'S FOR TRIALS ON WHICH THE VISUAL CUES WERE PRESENTED FAR FROM THE PARTICIPANTS.

RIGHT SIDE FIGURE: MEAN PEAK AMPLITUDE FOR THE N140 AT TEMPORAL SITES (T7/T8) INDUCED BY NOCICEPTIVE STIMULI APPLIED AT THE HAND CONGRUENT (BLUE BARS) OR INCONGRUENT (RED BARS) TO THE VISUAL CUES FOR TRIALS ON WHICH THE CUES WERE PRESENTED NEAR THE PARTICIPANTS (LEFT) OR FAR FROM THE PARTICIPANTS (RIGHT). SIGNIFICANT RESULTS ARE INDICATED WITH AN ASTERISK (* $P < 0.05$; $P = 0.07$). AT CONTRALATERAL SITES, THERE WAS ONLY A MARGINALLY SIGNIFICANT EFFECT OF CUE DISTANCE, INDICATING THAT N140 AMPLITUDES WERE MORE NEGATIVE WHEN VISUAL CUES WERE PRESENTED NEAR AS OPPOSED TO FAR FROM THE PARTICIPANTS. AT IPSILATERAL SITES, N140 AMPLITUDES WERE MORE NEGATIVE FOR CONGRUENT THAN FOR INCONGRUENT TRIALS, BUT ONLY WHEN CUES WERE PRESENTED NEAR THE PARTICIPANTS. MOREOVER, N140 AMPLITUDES WERE MORE NEGATIVE WHEN VISUAL CUES WERE PRESENTED NEAR AS OPPOSED TO FAR, BUT ONLY FOR CONGRUENT TRIALS.



P320. The repeated measures ANOVA revealed a main effect of *topography* ($F(1.13,22.66) = 8.66, p = 0.006, d = -0.75, CI [-1.23 \text{ to } -0.26]$), indicating that P320 amplitudes were highest at Cz, and somewhat higher contralateral than ipsilateral. There was also a main effect of *cue distance* ($F(1,20) = 17.55, p < 0.001, d = 0.31, CI [0.16 \text{ to } 0.46]$). The main effect of *congruency* was not significant ($F(1,20) = 1.14, p = 0.30$). Importantly, the interaction effect between *cue distance* and *congruency* was significant ($F(1,20) = 6.40, p = 0.02, d = 0.59, CI [0.10 \text{ to } 1.08]$). None of the other interaction effects reached significance ($F < 2, p > 0.20$). The interaction effect between *congruency* and *cue distance* was further investigated at Cz, as the P320 amplitude was maximal at this electrode site (see Figure 6).

At Cz, the repeated measures ANOVA with *congruency* and *cue distance* as within subject factor revealed a significant main effect of *cue distance* ($F(1,20) = 9.84, p = 0.005, d = 0.22, CI [0.08 \text{ to } 0.36]$). The main effect of *congruency* was not significant ($F(1,20) = 0.86, p = 0.37$). The interaction effect between *congruency* and *cue distance* ($F(1,20) = 5.85, p = 0.03, d = 0.61, CI [0.07 \text{ to } 1.15]$) was significant. Follow-up t-tests indicated that the difference between congruent and incongruent trials was not significantly different, nor when cues were presented near the participants ($t(20) = 0.71, p = 0.48$), nor when cues were presented far from the participants ($t(20) = -1.8, p = 0.09$). However, for congruent trials, P320 amplitudes were higher when cues were presented near as opposed to far from the participants ($t(20) = 3.72, p = 0.001$). This was not the case for incongruent trials ($t(20) = 1.23, p = 0.23$).

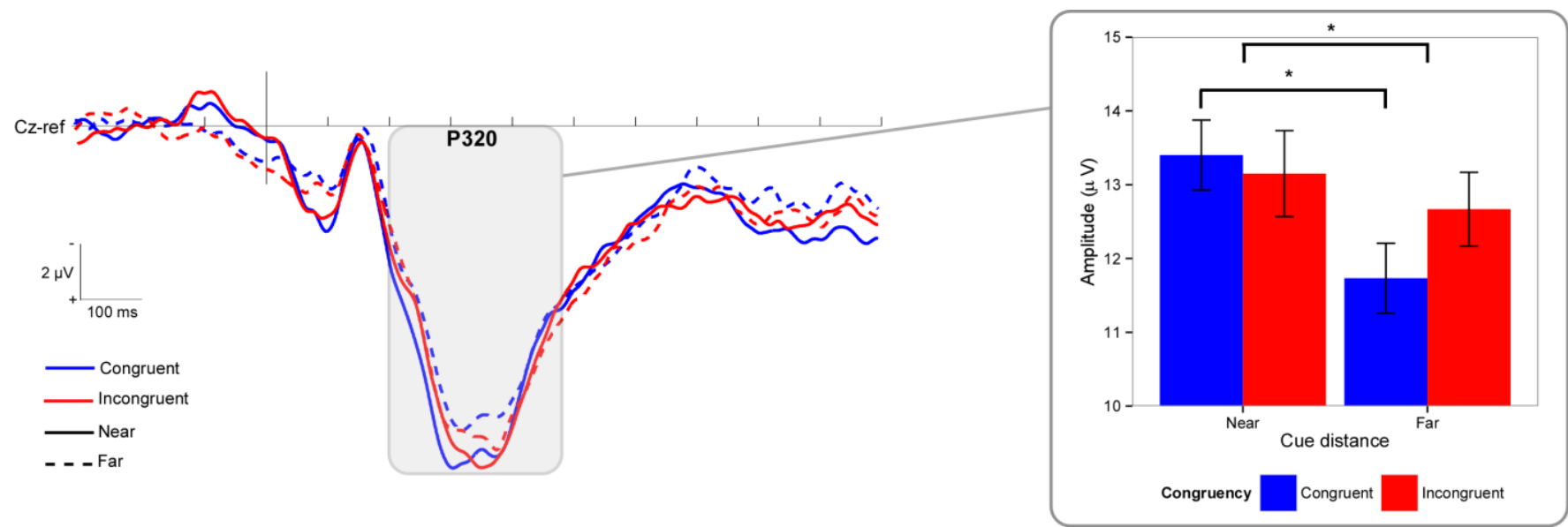


FIGURE 6. LEFT SIDE FIGURE: P320 WAVEFORMS AT CZ, RE-REFERENCED TO THE MASTOID ELECTRODES IN RESPONSE TO NOCICEPTIVE STIMULI APPLIED TO THE HAND CONGRUENT (BLUE LINES) OR INCONGRUENT (RED LINE) TO THE SIDE OF THE VISUAL CUE. SOLID LINES REFLECT NOCICEPTIVE ERPS FOR TRIALS ON WHICH THE VISUAL CUES WERE PRESENTED NEAR THE PARTICIPANTS. DASHED LINES REFLECT NOCICEPTIVE ERP'S FOR TRIALS ON WHICH THE VISUAL CUES WERE PRESENTED FAR FROM THE PARTICIPANTS.

RIGHT SIDE FIGURE: MEAN PEAK AMPLITUDE FOR THE P320 AT CZ INDUCED BY NOCICEPTIVE STIMULI APPLIED AT THE HAND CONGRUENT (BLUE BARS) OR INCONGRUENT (RED BARS) TO THE VISUAL CUES FOR TRIALS ON WHICH THE CUES WERE PRESENTED NEAR THE PARTICIPANTS (LEFT) OR FAR FROM THE PARTICIPANTS (RIGHT). SIGNIFICANT RESULTS ARE INDICATED WITH AN ASTERISK ($P < 0.05$). RESULTS SHOWED THAT THE P320 AMPLITUDES WERE SIGNIFICANTLY HIGHER WHEN CUES WERE PRESENTED NEAR AS OPPOSED TO FAR. HOWEVER, THIS DIFFERENCE WAS ONLY SIGNIFICANT WHEN CUES WERE PRESENTED CONGRUENTLY TO THE NOCICEPTIVE STIMULATION AND NOT WHEN THEY WERE PRESENTED INCONGRUENTLY.

3.2 EXPERIMENT 2

3.2.1 INTENSITY OF THE NOCICEPTIVE STIMULI

The mean current intensities used were 0.43 ± 0.07 for the left hand, and 0.43 ± 0.07 for the right hand. The intensity was not significantly different between the left and the right hand ($t(21) = -0.15$; $p = 0.89$). The mean self-reported intensities were 3.95 ± 1.95 for the left hand, and 3.90 ± 1.91 for the right hand, and were not significantly different ($t(21) = 0.41$; $p = 0.69$).

3.2.2 PERFORMANCE ON THE BEHAVIORAL TASK

Accuracies were overall high ($M = 0.94$; $SD = 0.24$). There was a marginally significant interaction effect between *stimulated hand* and *congruency* ($F(1,21) = 4.18$; $p = 0.054$, $d = 0.29$, CI [0.007 to 0.57]). Further investigation of this interaction effect with follow-up *t*-tests showed that accuracy was marginally significantly higher for congruent than for incongruent trials, but only when the left hand was stimulated ($t(21) = -1.37$; $p = 0.09$). When the right hand was stimulated, this difference was not significant ($t(21) = -0.78$; $p = 0.22$). None of the other main or interaction effects were significant ($F < 2$, $p > 0.15$).

For the RT data no significant main or interaction effects were found (all $F < 3.1$; all $p > 0.09$) (see Figure 7).

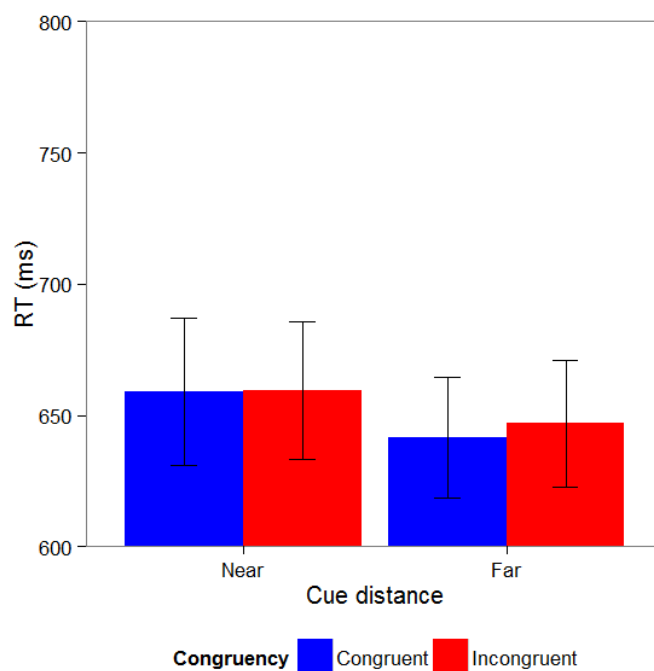


FIGURE 7. MEAN RT'S, MEASURED FROM THE ONSET OF THE SECOND NOCICEPTIVE STIMULUS, IN MS AND ASSOCIATED STANDARD ERRORS FOR EXPERIMENT 2.

3.2.3 NOCICEPTIVE ERPS

3.2.3.1 LATENCY

N140. The latency of the N140 component was not significantly influenced by any of the variables (all $F < 4.1$; all $p > 0.05$).

P320. The latency of the P320 component was influenced by the *topography* ($F(1,19)$, 24.78) = 5.61, $p = 0.02$, $d = 0.70$, CI [0.11, 1.29]), with shorter latencies at Cz than at contralateral or ipsilateral sites. There was also a main effect of *congruency* ($F(1,19)$ = 11.55, $p = 0.003$, $d = -0.54$, CI [-0.88, -0.21]), with shorter latencies for congruent than for incongruent trials. Finally, the latency was also influenced by the *cue distance* ($F(1,19)$ = 8.50; $p = 0.009$, $d = -0.55$, CI [-0.94, -0.15]) with shorter latencies when cues were presented near, as opposed to far. None of the interaction effects was significant (all $F < 2$; all $p > 0.15$).

3.2.3.2 AMPLITUDE

N140. Group level average waveforms and mean N140 amplitudes are shown in Figure 8. The N140 amplitude was influenced by *topography* ($F(1,19)$ = 16.73; $p = 0.001$; $d = -0.39$; CI [-0.58 to -0.21]). Moreover, there was a main effect of *congruency* ($F(1,19)$ = 27.63; $p < 0.001$; $d = -0.38$; CI [-0.53 to -0.24]), with more negative amplitudes for congruent, than for incongruent trials. The main effect of *cue distance* was also significant ($F(1,19)$ = 13.38; $p = 0.002$; $d = -0.49$; CI [-0.77 to -0.21]). Finally, the interaction effect between *topography* and *cue distance* was significant ($F(1,19)$ = 4.79; $p = 0.04$; $d = -0.61$; CI [-1.21 to -0.01]). To further investigate this interaction effect, a repeated measures ANOVA with *congruency* and *cue distance* as within subject factors was performed for each topography.

At contralateral sites, the N140 amplitudes were significantly influenced by the *congruency* ($F(1,19)$ = 11.54; $p = 0.003$; $d = -0.40$; CI [-0.64 to -0.16]), with more negative amplitudes for congruent, compared to incongruent trials. Moreover, the *cue distance* also significantly influenced N140 amplitudes ($F(1,19)$ = 16.07; $p = 0.001$; $d = -0.66$; CI [-1.02 to -0.31]), with more negative amplitudes when visual stimuli were presented near, as compared to far from the participants. The interaction effect was not significant ($F(1,19)$ = 0.47; $p = 0.50$).

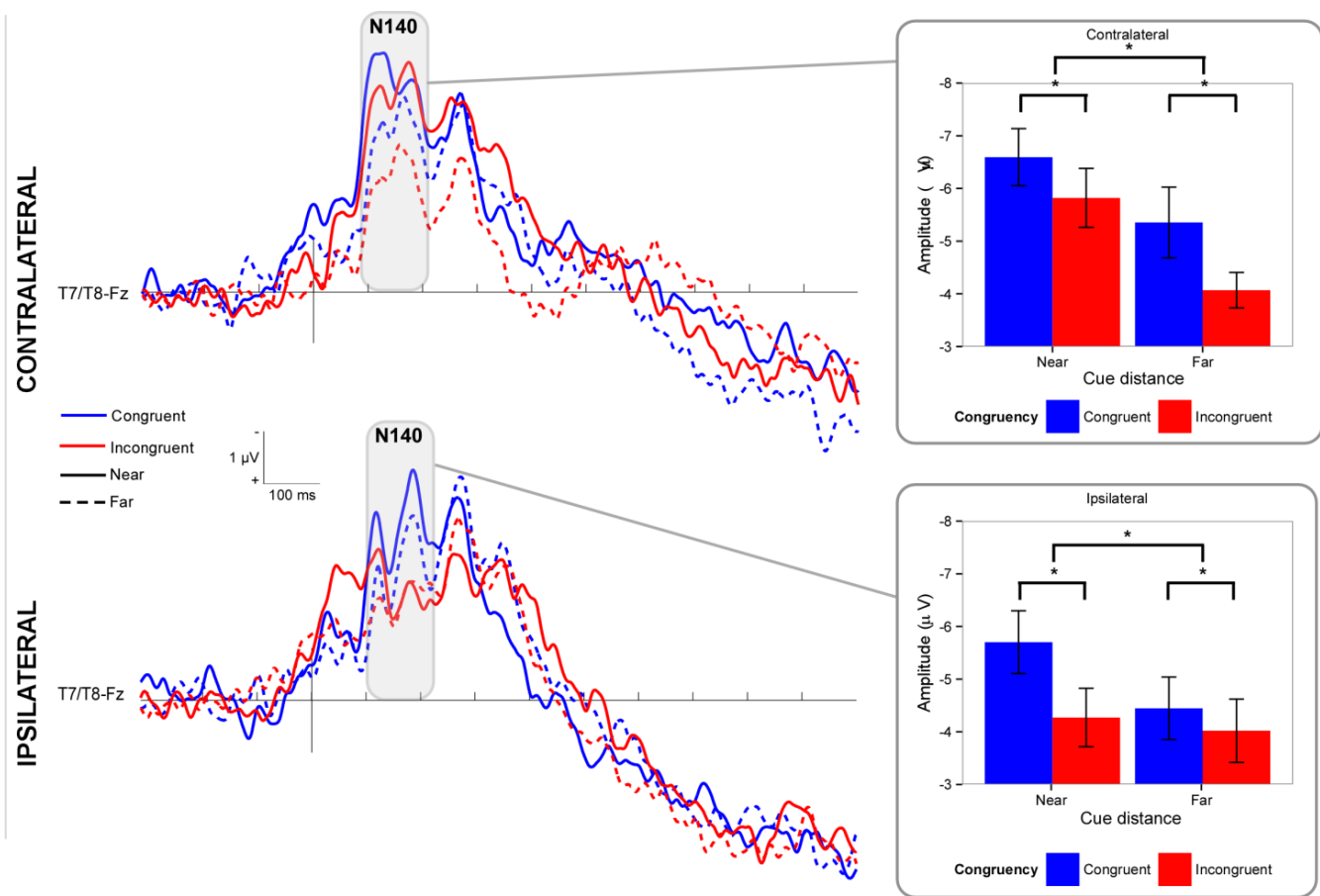
At ipsilateral sites, the same results were found. There was both a main effect of *congruency* ($F(1,19)$ = 12.24; $p = 0.002$; $d = -0.38$; CI [-0.59 to -0.16]), and a main effect of

cue distance ($F(1,19) = 5.29; p = 0.03; d = -0.30; CI [-0.56 \text{ to } -0.04]$), indicating that N140 amplitudes were more negative for congruent than for incongruent trials, and when visual stimuli were presented near as opposed to far from the participants. The interaction effect was not significant ($F(1,19) = 2.32; p = 0.15$).

FIGURE 8. THE UPPER PART OF THE FIGURE DEPICTS THE N140 WAVEFORMS AND AMPLITUDES FOR CONTRALATERAL SITES, WHILE THE LOWER PART OF THE FIGURE DEPICTS THE N140 WAVEFORMS AND AMPLITUDES FOR IPSILATERAL SITES.

LEFT SIDE FIGURE: N140 WAVEFORMS AT TEMPORAL SITES (T7/T8), RE-REFERENCED TO FZ, IN RESPONSE TO NOCICEPTIVE STIMULI APPLIED TO THE HAND CONGRUENT (BLUE LINES) OR INCONGRUENT (RED LINE) TO THE SIDE OF THE VISUAL CUE. SOLID LINES REFLECT NOCICEPTIVE ERP'S FOR TRIALS ON WHICH THE VISUAL CUES WERE PRESENTED NEAR THE PARTICIPANTS. DASHED LINES REFLECT NOCICEPTIVE ERP'S FOR TRIALS ON WHICH THE VISUAL CUES WERE PRESENTED FAR FROM THE PARTICIPANTS.

RIGHT SIDE FIGURE: MEAN PEAK AMPLITUDE FOR THE N140 AT TEMPORAL SITES (T7/T8) INDUCED BY NOCICEPTIVE STIMULI APPLIED AT THE HAND CONGRUENT (BLUE BARS) OR INCONGRUENT (RED BARS) TO THE VISUAL CUES FOR TRIALS ON WHICH THE CUES WERE PRESENTED NEAR THE PARTICIPANTS (LEFT) OR FAR FROM THE PARTICIPANTS (RIGHT). SIGNIFICANT RESULTS ARE INDICATED WITH AN ASTERISK (* $P < 0.05$). BOTH AT CONTRALATERAL AND IPSILATERAL SITES, N140 AMPLITUDES WERE MORE NEGATIVE FOR CONGRUENT THAN FOR INCONGRUENT TRIALS, AND WHEN VISUAL STIMULI WERE PRESENTED NEAR, AS OPPOSED TO FAR FROM THE PARTICIPANTS.



P320. Group level average waveforms and mean P320 amplitudes are shown in Figure 9. The P320 amplitude was significantly influenced by the *topography* ($F(1.40, 26.61) = 52.96$; $p < 0.001$; $d = -1.64$; CI [-2.10, -1.17]). There were also significant interaction effects between *topography* and *congruency* ($F(2,38) = 17.11$; $p < 0.001$; $d = -1.05$; CI [-1.68, -0.42]), between *topography* and *cue distance* ($F(1.24, 23.56) = 5.42$; $p = 0.02$; $d = 0.77$; CI [0.009, 1.53]), and between *topography*, *congruency* and *cue distance* ($F(2,38) = 7.25$; $p = 0.002$; $d = -0.87$; CI [-1.45, -0.29]). The three-way interaction was further investigated by looking at the P320 amplitude for each topography separately with a repeated measures ANOVA with *congruency* and *cue distance* as within subject factors.

For *contralateral* sites, the P320 amplitude was influenced by the *congruency* ($F(1,19) = 8.05$; $p = 0.01$; $d = 0.47$; CI [0.13, 0.81]), but not by the *cue distance* ($F(1,19) = 2.46$, $p = 0.13$). Moreover, there was a significant interaction effect between *congruency* and *cue distance* ($F(1,19) = 4.64$; $p = 0.04$; $d = 0.66$, CI [-0.004, 1.32]). Follow-up t-tests revealed that P320 amplitudes were significantly higher for congruent than for incongruent trials, when visual stimuli were presented near the participants ($t(19) = 3.01$; $p = 0.007$). When visual stimuli were presented far from the participants, this difference was not significant ($t(19) = 0.74$; $p = 0.47$). Moreover, for incongruent trials, P320 amplitudes were significantly higher when cues were presented far as opposed to near the participants ($t(19) = -2.73$; $p = 0.01$). This difference was not significant for congruent trials ($t(19) = -0.006$; $p > 0.99$).

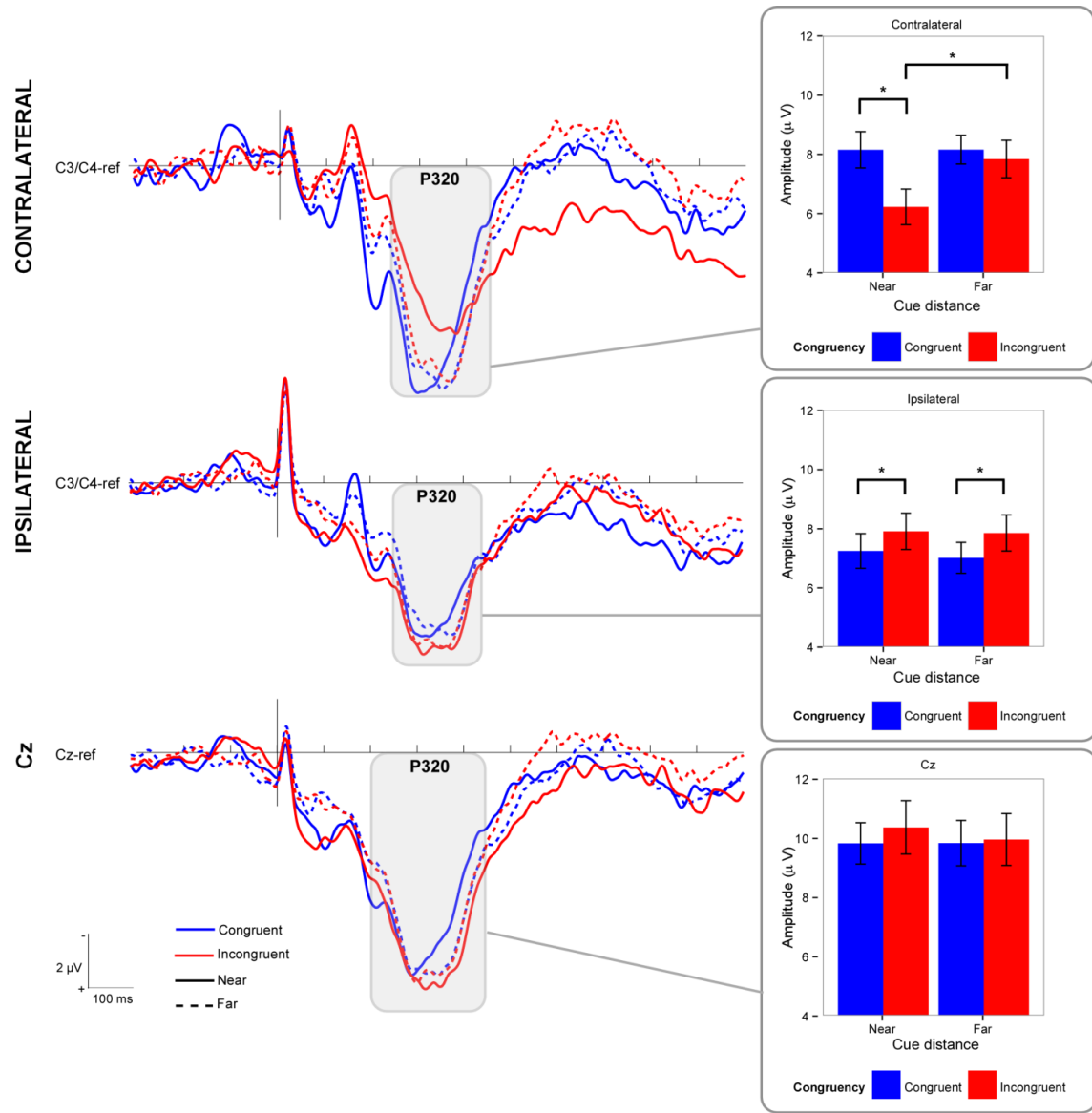
For *ipsilateral* sites, there was only a main effect of *congruency* ($F(1,119) = 5.14$; $p = 0.04$; $d = -0.30$; CI [-0.56, -0.04]), indicating that amplitudes were higher for incongruent, than for congruent trials. Nor the main effect of *cue distance* ($F(1,19) = 0.11$; $p = 0.74$), nor the interaction effect between *congruency* and *cue distance* ($F(1,19) = 0.10$; $p = 0.76$) were significant.

At Cz, there were no significant main or interaction effects (all $F < 1$; all $p > 0.4$).

FIGURE 9. THE P320 WAVEFORMS AND AMPLITUDES FOR CONTRALATERAL (UPPER FIGURE) AND IPSILATERAL SITES (MIDDLE FIGURE) AND AT CZ (LOWER FIGURE).

LEFT SIDE FIGURE: P320 WAVEFORMS AT CENTRAL SITES (C3/C4; CONTRALATERAL AND IPSILATERAL SITES) OR AT CZ, RE-REFERENCED TO THE MASTOID ELECTRODES, IN RESPONSE TO NOCICEPTIVE STIMULI APPLIED TO THE HAND CONGRUENT (BLUE LINES) OR INCONGRUENT (RED LINE) TO THE SIDE OF THE VISUAL CUE. SOLID LINES REFLECT NOCICEPTIVE ERP'S FOR TRIALS ON WHICH THE VISUAL CUES WERE PRESENTED NEAR THE PARTICIPANTS. DASHED LINES REFLECT NOCICEPTIVE ERP'S FOR TRIALS ON WHICH THE VISUAL CUES WERE PRESENTED FAR FROM THE PARTICIPANTS.

RIGHT SIDE FIGURE: MEAN PEAK AMPLITUDE FOR THE P320 AT CENTRAL SITES (C3/C4; CONTRALATERAL AND IPSILATERAL SITES) OR AT CZ INDUCED BY NOCICEPTIVE STIMULI APPLIED AT THE HAND CONGRUENT (BLUE BARS) OR INCONGRUENT (RED BARS) TO THE VISUAL CUES FOR TRIALS ON WHICH THE CUES WERE PRESENTED NEAR THE PARTICIPANTS (LEFT) OR FAR FROM THE PARTICIPANTS (RIGHT). SIGNIFICANT RESULTS ARE INDICATED WITH AN ASTERISK (* $P < 0.05$). AT CONTRALATERAL SITES, AMPLITUDES WERE HIGHER FOR CONGRUENT THAN FOR INCONGRUENT TRIALS, BUT ONLY WHEN VISUAL STIMULI WERE PRESENTED NEAR THE PARTICIPANTS. MOREOVER, FOR INCONGRUENT TRIALS, AMPLITUDES WERE HIGHER WHEN VISUAL STIMULI WERE PRESENTED FAR AS OPPOSED TO NEAR THE PARTICIPANTS. AT IPSILATERAL SITES, AMPLITUDES WERE HIGHER FOR INCONGRUENT THAN FOR CONGRUENT TRIALS. AT CZ, THE AMPLITUDES WERE NOT SIGNIFICANTLY INFLUENCED BY ANY OF THE VARIABLES.



4 DISCUSSION

Here we conducted two experiments, in which we investigated crossmodal links in spatial attention between vision and nociception in the peripersonal space. We tested whether lateralized visual cue stimuli could orient attention towards one side of space, and prioritize the processing and response to nociceptive and tactile stimuli applied to the hand laying in the same side of space (congruent) as compared to the hand laying in the opposite side of space (incongruent). Importantly, we tested whether this effect only appeared when visual cue stimuli were presented near the participants' hands (in peripersonal space) as opposed to far in front of the hands (in extrapersonal space). In Experiment 1, participants only had to react at which hand they felt a tactile stimulus, while ignoring both visual and nociceptive stimuli. Behavioral responses to the tactile stimuli, and ERPs to the nociceptive stimuli were investigated. In accordance with our hypothesis, participants responded more quickly to the tactile stimuli on congruent as opposed to incongruent trials, but only when visual cue stimuli were presented in peripersonal space. The ERPs to the nociceptive stimuli were inconclusive. Therefore, a second experiment was conducted in which the tactile stimuli were replaced by a double nociceptive stimulation. Participants only had to respond to these double nociceptive stimuli, while ignoring the single nociceptive and the visual stimuli. We now did not find the expected behavioral results in response to the double nociceptive stimuli, but we did find a more negative ERP signal around 140 ms when visual cue stimuli were presented near the participant's hands as opposed to far from the participant's hands. Both when visual stimuli were presented near and far, the ERP signal was more negative for congruent as opposed to incongruent trials. This shows that the magnitude of the N140 component in response to the non-target nociceptive stimuli was modulated both by the distance of the visual cue stimuli to the body, and by the congruency of the visual cues with respect to the stimulated hand. We did not find clear results for the later positive component of the nociceptive ERPs (i.e. the P320).

4.1 BEHAVIORAL RESPONSES TO THE TARGET STIMULI

Cuing paradigms have been extensively used to explore mechanisms of spatial attention. Posner (1978) has shown that people can focus their attention covertly (i.e. without head or eye movement) on a particular location, and so enhance the processing of stimuli occurring there. At least two different attentional mechanisms can be involved in this effect: stimulus-driven *exogenous* attention and expectancy-directed *endogenous* attention (Posner & Cohen, 1984). Typically, the former is elicited automatically by the presentation of spatially

uninformative peripheral cues, which precede target onset with short intervals (often less than 200 ms; Klein, 2000), as was the case in the present experiment, while the latter is effective at longer time intervals and is investigated using symbolic central cues (e.g., an arrow) or lateralized cues that are predictive of the location of the forthcoming target. The use of an exogenous, as opposed to an endogenous cuing task was motivated by the fact that the use of endogenous cues cannot exclude the possibility that participants may simply use the cue as an instruction to shift their attention strategically to the probable target side, *within the expected target modality*. This would lead to a unimodal shift in attention, as if a central arrow cue pointing to one side, or a purely verbal instruction to focus attention on a particular location, was given (Spence, Nicholls, Gillespie, & Driver, 1998). This possibility is excluded by using exogenous cues.

The phenomenon of exogenous cuing has been demonstrated in different sensory modalities, such as vision (Klein, Brennan, & Gilani, 1992), audition (Spence & Driver, 1994) and touch (Bradshaw, Howard, Pierson, Phillips, & Bradshaw, 1992). More recent studies have found that directing spatial attention to stimuli appearing in one sensory modality affects responses to targets appearing in other modalities (Spence & Driver, 1997; Spence, McDonald, & Driver, 2004), suggesting crossmodal interactions in spatial attention. In the first experiment we found, in accordance with these studies, that RTs were shorter when the tactile stimulus was presented at the hand laying in the same side of space as the visual cue stimulus (congruent), as compared to when the tactile stimulus was presented at the hand laying in the opposite side of space (incongruent). Importantly, we were able to show that this congruency effect was stronger when visual cues were presented near the participants' hands (in peripersonal space), as opposed to far in front of the hands (in extrapersonal space). These findings confirm that tactile processing is influenced by visual stimuli, but only when the visual stimuli are presented near the stimulated body part. This is consistent with the mapping of tactile stimuli in a peripersonal frame of reference, namely a global representation of the body and the space nearby, in which information from different senses can interact with each other (Rizzolatti et al., 1997).

Conversely, in Experiment 2, we failed to replicate these results with nociceptive stimuli. Not only did we not find a difference between the influence of visual stimuli presented in near and far space, but we also failed to find a congruency effect altogether. This is incompatible with previous studies showing that nociceptive processing is influenced by visual stimuli appearing near the participants' hands (De Paepe et al., 2015, 2014, in preparation). The deviation of our results from previous studies is most probably due to the nature of the nociceptive targets used. In this experiment participants only had to react

when they received two nociceptive stimuli (with ISI of 500 ms), while ignoring single nociceptive stimulations. A considerably large ISI was necessary in order for participants to be able to discriminate between a single or a double nociceptive stimulation. The fact that participants had to wait for a second stimulation, with a large interval between the first and the second one, could have abolished any effect of the visual cues on nociceptive processing. Indeed, attention might have already been oriented towards the stimulated hand at the time the second stimulation was applied, masking any effects of the visual cues on spatial attention.

4.2 ERPs ELICITED BY THE NOCICEPTIVE NON-TARGET STIMULI

In the present studies, nociceptive ERPs were elicited by IES (Inui, Tran, Hoshiyama, & Kakigi, 2002), a method that allows the specific and selective activation of skin nociceptors (that is, in absence of concomitant activation of mechanoreceptors associated to large fibers conveying information about touch), provided that the intensity of electrical current is not higher than twice the absolute detection threshold (Colon et al., 2012; Legrain & Mouraux, 2013; Mouraux, Marot, & Legrain, 2014). Nociceptive IES induced mainly a negative ERP component (N140) followed by a positive component (P320), occurring approximately 140 and 320 ms after stimulus onset. This is in accordance with previous studies using this type of stimulation (Favril et al., 2014). The N140 component was found at temporal regions, and was maximally over the contralateral site. The P320 component on the other hand was maximal at the vertex. The latency and topography of the P320 component of the present studies are highly similar to that of the P2 found in response to laser stimulation of heat-sensitive skin nociceptors (Kakigi, Shibasaki, & Ikeda, 1989; Kunde & Treede, 1993; Miyazaki et al., 1994; Spiegel, Hansen, & Treede, 1996; Treede, Kief, Hölzer, & Bromm, 1988; Valeriani, Rambaud, & Mauguiere, 1996; Xu et al., 1995). This P2 is thought to be mainly generated in the anterior cingulate gyrus (ACG) (Bromm & Lorenz, 1998; Frot, Rambaud, Guénot, & Mauguère, 1999; Lenz, Rios, Zirh, et al., 1998). The N140 component may correspond to the lateralized generators of the negative components of nociceptive laser-evoked potentials (LEPs), and could therefore be generated in bilateral operculum (secondary somatosensory (SII)/insular areas and possibly also primary somatosensory areas (SI)) (Bromm & Lorenz, 1998; Frot et al., 1999; K Inui & Kakigi, 2012; Lenz, Rios, Chau, et al., 1998; Valentini et al., 2012). The N140 was found predominantly contralateral to the stimulation in the present study, which contrasts with the negative N2 component of the nociceptive laser-evoked potentials, which has a symmetrical distribution (the lateralized N1 component is often masked in the ascending slope of the N2). However, previous studies

have shown that when the spatial location constitutes a relevant feature of the task, as was the case in the present study, the N2 component of laser-evoked potentials can exhibit a lateralized topography contralateral to the stimulation site (Bentley et al., 2004; Legrain, Bruyer, Guérit, & Plaghki, 2003; Legrain et al., 2002). Legrain et al. (2002) have shown that laser-evoked negativities are modulated by spatial attention. They suggested that gain control mechanisms could be involved in such an attentional modulation. The *sensory gain control hypothesis* states that the flow of information is efferently gated in cortical areas, in such way that the processing of attended stimuli is facilitated compared to unattended stimuli (Hillyard, Mangun, Woldorff, & Luck, 1995). In this sense, N2 could originate from bilateral activations, but following the gain control hypothesis, spatial attention may operate by increasing the activity of contralateral areas generating N2. This would result in a greater response in contralateral areas, relative to ipsilateral areas. Similarly, the scalp topography of the P320, despite its maximum at the scalp vertex, was also greater over the contralateral than over the ipsilateral hemisphere. This suggests that in the present studies, the contralateral sources of nociceptive ERPs were the dominant contributors to the scalp recorded waveforms, because of the relevance of space for the task.

N140 component. Previous studies have shown that directing attention to a specific body location can modulate neural activity evoked by the nociceptive stimuli in brain regions generating the N1 and N2 components. This leads to larger N1 and N2 amplitudes for attended as compared to unattended body locations (Legrain et al., 2002). Similarly, in the present studies we expected that the N140 amplitudes to the nociceptive stimuli would be larger when visual stimuli were presented at the same side of space (congruent trials), as opposed to the opposite side of space (incongruent trials). Moreover, we expected that this congruency effect would be larger when visual stimuli were presented near the participants' hands, as opposed to when they were presented far in front of the hands. In Experiment 1, we found these expected results at ipsilateral sites. However, at contralateral sites, where N140 amplitudes were highest, the amplitude was only influenced by the cue distance, with more negative N140 when cues were presented near as opposed to far from the participants' hands. Moreover, both at ipsilateral and contralateral sites, similar effects were also found for the latency of the N140 component. Therefore, the possibility that the modulation of the amplitude of the ERP components by spatial attention was related to overlap with new components cannot be excluded. So, although it seems as though the visual cue stimuli had some effect on subsequent nociceptive processing, results of the first experiment were inconclusive and a second experiment was conducted.

In Experiment 2, the target stimuli now consisted of two identical nociceptive stimuli instead of a tactile stimulus, in an attempt to make the nociceptive stimuli more task relevant, and increase attention towards them. ERPs were still recorded for the single (non-target) nociceptive stimuli. N140 amplitudes were again more negative at contralateral than at ipsilateral sites. At both sites, N140 amplitudes were influenced both by the congruency of the visual cues with respect to the nociceptive stimuli, and the distance of the visual cues to the participants' hands, with more negative N140 amplitudes for congruent than for incongruent trials, and when cues were presented near as opposed to far from the participants' hands. There was no latency difference between conditions, suggesting that the modulation of the N140 by spatial attention was related to an amplitude enhancement of the N140. The congruency effect provides evidence for crossmodal effects of spatial attention between visual and nociceptive stimuli. Although a congruency effect was present both when cues were presented near and far from the participants' hands, the more negative N140 amplitudes when cues were presented near the participants indicate that nociceptive processing was mostly influenced under this condition. This demonstrates that these crossmodal effects could rely on the existence of a peripersonal frame of reference, integrating the space of the body and the proximal part of the external space (Làdavas et al., 1998; Rizzolatti et al., 1997; Spence et al., 2004). Moreover, the modulation of the N140 component of nociceptive ERPs confirms that crossmodal attention can affect sensory processing of nociceptive inputs, and is compatible with the hypothesis of a crossmodal modulation of unimodal processing (Eimer & Driver, 2001; Favril et al., 2014; Macaluso & Driver, 2001; Macaluso, Frith, & Driver, 2005). For visual processing it has already been shown that the amplitude of the visual N1 component, generated in extrastriate cortex, in ventral occipitotemporal and occipitoparietal areas (Clark, Fan, & Hillyard, 1994; Clark & Hillyard, 1996; Gomez Gonzalez, Clark, Fan, Luck, & Hillyard, 1994), can be modulated by the location of nociceptive cues (Favril et al., 2014). Here, we showed the reverse, namely that the N140 component of nociceptive processing, which is supposed to be generated mainly in bilateral SII and insular areas (Bromm & Lorenz, 1998; Frot et al., 1999; Lenz, Rios, Chau, et al., 1998), can be modulated by the location of visual cues. This shows, in accordance with the sensory gain control hypothesis (Hillyard et al., 1995), that selective attention can amplify neural activity in processing attending inputs.

P320 component. In Experiment 1, we found that P320 amplitudes were highest at Cz, compared to contralateral and ipsilateral trials, which seems to correspond to the laser-evoked P2. As the different experimental conditions had no differential effect on the P320 amplitude depending on the topography, only the amplitudes at Cz were further analyzed

and reported. The congruency of the visual cues had no significant effect on the P320 amplitude, nor when they were presented near the participants' hands, nor when they were presented far in front of the participants. However, P320 amplitudes were significantly higher when visual cue stimuli were presented in peripersonal as opposed to extrapersonal space. This difference only reached significance for congruent trials. There was no latency difference between conditions, suggesting that the modulations of the P320 were related to an amplitude enhancement of the P320. Despite the fact that the laser P2 is also influenced by the level of attention given to the eliciting stimuli, including spatial attention (see Legrain et al., 2002 for a review), it has been shown to overlap with a P3a-like component (Legrain et al., 2002, 2003, 2005, 2009). The P3a component, which is thought to reflect an orienting response (Halgren & Marinkovic, 1995), i.e. an involuntary switch of attention towards unexpected deviant events interfering with ongoing processing (Escera, Alho, Winkler, & Naatanen, 1998; Knight, 1996). Accordingly, larger P2 amplitude has been found in response to rare laser stimuli mismatching the preceding stimuli according two or more physical features, as compared to more frequent regular stimuli, irrespective of whether they were attended or not (Legrain et al., 2002; Legrain, Perchet, García-Larrea, & García-Larrea, 2009). It is important to note that in the present experiments, every visual stimulus condition associated with the nociceptive stimuli (congruent vs. incongruent and near vs. far) was equally probable. Therefore, novelty or probability of the stimuli could not have driven any modulations of the P320 amplitudes observed. The lower dependency of the P2 on the direction of spatial attention could be one of the reasons why the P320 amplitude in the present experiment was not modulated by the congruency of the visual stimuli with respect to the nociceptive stimuli.

In Experiment 2, P320 amplitudes were highest at Cz compared to contralateral and ipsilateral sites, however in this experiment the different experimental conditions had differential effects depending on the topography. Therefore, we now investigated the effects of the visual cue stimuli on nociceptive processing at each of the three sites. At contralateral sites, we found the expected interaction effect: P320 amplitude was significantly higher for congruent than for incongruent trials, but only when the visual stimuli were presented in peripersonal space, and not when they were presented in extrapersonal space. This could reflect increased attention towards the hand congruent to the visual stimuli, especially when these stimuli were presented near the stimulated hand. However, P320 amplitudes were not overall lower when visual cues were presented far from the participants' hands. Moreover, as both the congruency between the visual and nociceptive stimuli and the cue distance had a significant effect on the latency of this component, we cannot be sure

whether the modulations of the P320 were related to an amplitude enhancement of the P320, or to overlap with new components. Furthermore, this effect was not found at Cz or at ipsilateral sites.

At Cz, no significant modulations of the P320 amplitude were found. At ipsilateral sites, P320 amplitudes were higher for incongruent than for congruent trials, exactly the reverse of what was found at contralateral sites. Moreover, at ipsilateral sites, this effect was not dependent on the cue distance. The enhancement of P320 amplitude for incongruent trials could reflect an attentional switch from the actual focus of attention (the side of the visual stimulation) to the other side of space, i.e. towards the nociceptive stimuli (Legrain et al., 2002, 2009). Nevertheless, it remains unclear why opposite results were found for contralateral and ipsilateral sites, and why no significant effects were found at Cz, where the highest P320 amplitudes were found.

Taken together in the two experiments reported here, we found some modulations of the P320 evoked by nociceptive stimuli, but these modulations were not consistent across experiments, and across topographies (Cz, contralateral or ipsilateral sites). As argued above, this P320 most probably corresponds to the P2 elicited by laser stimuli. The P2 has been mostly investigated for endogenous cuing paradigms, and has been shown to be less affected by the direction of spatial attention, and more so by the novelty or probability of the stimuli (Legrain et al., 2003, 2002). In the present studies, an exogenous cuing paradigm was used, and the probability of the nociceptive stimulation was constant across the experimental conditions. It remains unclear what the positive component identified in the present experiments reflects. Further studies are needed to investigate the involvement of the P2 evoked by nociceptive stimuli in exogenous cuing paradigms.

4.3 CROSSMODAL LINKS IN SPATIAL ATTENTION IN THE PERIPERSONAL SPACE

Across the two experiments conducted here, we found some evidence for crossmodal links in spatial attention between visual and tactile information (Experiment 1, behavioral results), and between visual and nociceptive information (Experiment 2, modulation of the N140 component). Importantly, these crossmodal effects depended on the distance of the visual cue stimuli to the body, providing evidence that the crossmodal effects of spatial attention observed here rely on peripersonal frames of reference. The peripersonal space constitutes a multisensory-motor interface between the body and the environment, in which information from the body surface (somatosensory information) is integrated with stimuli in the external world (e.g., visual or auditory information) to construct one coherent

representation of the space immediately surrounding the body (Rizzolatti et al., 1997). For touch, it has been shown that this relies on bimodal neurons in the premotor and parietal cortices of monkeys (Duhamel, Colby, & Goldberg, 1998; Graziano & Gross, 1994; Graziano, Hu, & Gross, 1997; Graziano, Yap, & Gross, 1994; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981). These neurons fire both for tactile and visual stimuli, and their visual receptive field (RF) extends from the approximate region of the tactile RF into the immediate adjacent space. Similarly, Dong et al. (1994) found neurons responding both to nociceptive and visual stimuli presented in vicinity of the somatosensory RF. In humans, it has been hypothesized that frontal and parietal areas play an important role in nociceptive processing and pain perception both in healthy individuals (Legrain, Iannetti, Plaghki, & Mouraux, 2011) and in chronic pain patients (Maihöfner & Peltz, 2011; Maihofner et al., 2007). Nociceptive inputs activate a large array of cortical areas such as mainly operculo-insular and cingulate areas, but also frontal and parietal areas (Tracey & Mantyh, 2007). Recently, it was argued that these brain areas are not specifically involved in nociceptive processing and pain perception. Instead, these areas could reflect the activity of a salience detection network, involved in the detection, localization and reaction to sensory events that are meaningful for the integrity of the body (Legrain et al., 2011). In accordance with this view, it was found that viewing a noxious stimulus applied to the hand activated mid-cingulate and parietal areas extending from the superior parietal gyrus to the parietal operculum, even in the absence of concomitant nociceptive input (Lloyd, Morrison, & Roberts, 2006). This visually-induced noxious illusion was obtained by applying the noxious stimulus to a fake rubber hand, experienced by the subject as belonging to his own body. Cortical responses faded when this illusion was disrupted, showing that the effect only appeared when the noxious stimulus was perceived as occurring close to the body. By using peripersonal frames of reference to code the spatial location of nociceptive stimuli, the brain can form an integrated representation of the part of the body in pain and the location of the external object causing that pain. This would serve to facilitate the processing of physical threat and to select and prepare the most appropriate motor response (Graziano & Cooke, 2006). In accordance with this view, several studies have provided evidence in humans for the influence of vision and proprioception on pain processing and perception (Longo et al., 2009; Longo, Iannetti, Mancini, Driver, & Haggard, 2012; Mancini, Longo, Kammers, & Haggard, 2011; Moseley, Parsons, & Spence, 2008; Sambo, Forster, Williams, & Iannetti, 2012; Sambo, Liang, Cruccu, & Iannetti, 2012). Recently, we found that these interactions between vision and nociception primarily occur when visual stimuli were presented within the peripersonal space, and to a lesser extent when they were presented in the extrapersonal space (De Paepe et al., 2015, 2014, in preparation).

In the present study, we were especially interested in the electrophysiological correlates of the crossmodal effects of spatial attention between vision and nociception in the peripersonal space. We found that the N140 component was modulated by the position of the visual stimuli, with higher N140 amplitudes when visual stimuli were presented in peripersonal space and congruent to the nociceptive stimulation as opposed to in extrapersonal space and incongruent to the nociceptive stimulation. Due to the similarities to the lateralized negativities found in responses to laser stimulation, the present N140 could be hypothesized to originate mainly from bilateral SII/insular areas (Bromm & Lorenz, 1998; Frot et al., 1999; Inui & Kakigi, 2012; Lenz, Rios, Chau, et al., 1998). The fact that activity in these brain areas can be modulated by visual stimuli appearing near the stimulated body part, indicates that crossmodal attention can affect sensory processing of nociceptive inputs. This is in accordance with the view that crossmodal links in spatial attention operate via a feedback mechanism from multimodal structures to unimodal areas (Eimer & Driver, 2001; Kennett et al., 2001; Macaluso & Driver, 2001; Macaluso, Frith, & Driver, 2000; Macaluso et al., 2005; McDonald & Ward, 2000).

However, it is important to note some limitations of the studies reported here. In the first experiment, we found the expected behavioral results, but the electrophysiological results were inconclusive. Conversely, in the second experiment we did not find any behavioral results, and while the N140 component was modulated both by the distance and the congruency of the visual cue stimuli with respect to the nociceptive stimuli, we did not find the expected interaction effect between cue distance and congruency. The difficulty to find reliable results might be related to the use of IES. An important limitation of IES is, that it is selective for nociceptors only when very low current intensities are used (Legrain & Mouraux, 2013; Mouraux et al., 2010). However, at these intensities the stimulus generates a very weak percept, and the signal-to-noise ratio of the elicited potentials is very low. We tried to circumvent this by increasing the strength of the nociceptive afferent volley through temporal summation, i.e. by using trains of three IES delivered using a 5 ms inter-stimulus interval. It has been shown that this increases the magnitude of the elicited potentials, while the latency remains unaffected, indicating that using trains of IES does not affect the type of activated fibers (Mouraux et al., 2014). Nevertheless, the signal-to-noise ratio still remained quite low, making it difficult to find reliable ERP components. Therefore, it would be interesting to replicate these studies with another kind of nociceptive stimulation, like laser stimulation, for which nociceptive ERPs have been extensively studied in attentional tasks, and to see whether similar results can be found. Furthermore, most studies investigating nociceptive ERPs have used endogenous cuing tasks with a long cue-to-target interval to

avoid temporal overlap of activities elicited by the cues and the targets. Here we chose to use an exogenous cuing task to disentangle the direct stimulus-driven capture of attention by visual stimuli from a strategic shift of attention to the most probable target side. The drawback of using an exogenous cuing task is that the attentional manipulation of the cued side is confounded to some extent with variations in stimulation (i.e. with the side of the cue). We tried to control for this by using a short visual cue (20 ms) and by randomly jittering the CTOAs across a considerably wide range (80 to 250 ms). Consequently, we expect that during averaging any possible overlapping responses cancelled each other out. However, we cannot completely exclude the possibility that some ERP changes are due to the summing of a nociceptive response, together with an entirely separate visual response to a closely preceding light on the same versus the opposite side in near or far space. Finally, as most studies have focused on investigating components of endogenous attention, little is known about the expected modulation of nociceptive ERP components due to exogenous attention. As argued above, the lack of consistent modulations of the nociceptive ERPs, and more specifically for the P320 component, could be due to the mere fact that this component is less affected by exogenous attention. Further research investigating modulations of nociceptive ERPs by exogenous attention are needed to confirm these findings.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest related to the present article.

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PART 3

**HOW DO DYNAMICAL VISUAL STIMULI INFLUENCE
SOMATOSOSENSORY PROCESSING?**

CHAPTER 5

WHAT'S COMING NEAR?

THE INFLUENCE OF DYNAMICAL VISUAL STIMULI ON NOCICEPTIVE PROCESSING.¹

ABSTRACT

Objects approaching us may pose a threat, and signal the need to initiate defensive behavior. Detecting these objects early is crucial to either avoid the object, or prepare for contact most efficiently. This requires the construction of a coherent representation of our body, and the space closely surrounding our body, i.e. the peripersonal space. This study, with 27 healthy volunteers, investigated how the processing of nociceptive stimuli applied to the hand is influenced by dynamical visual stimuli either approaching or receding from the hand. On each trial a visual stimulus was either approaching or receding the participant's left or right hand. At different temporal delays from the onset of the visual stimulus, a nociceptive stimulus was applied either at the same or the opposite hand, so that it was presented when the visual stimulus was perceived at varying distances from the hand. Participants were asked to respond as fast as possible at which side they perceived a nociceptive stimulus. We found that reaction times were fastest when the visual stimulus appeared near the stimulated hand. Moreover, investigating the influence of the visual stimuli along the continuous spatial range (from near to far) showed that approaching lights had a stronger spatially dependent effect on nociceptive processing, compared to receding lights. These results suggest that the coding of nociceptive information in a peripersonal frame of reference may constitute a safety margin around the body that is designed to protect it from potential physical threat.

¹ Based on: De Paepe, A.L., Crombez, G., & Legrain, V. (under review). What's coming near? The influence of dynamical visual stimuli on nociceptive processing. *PLoS one*.

1 INTRODUCTION

Localizing potentially harmful objects approaching our body is essential to adequately defend ourselves (Legrain et al., 2012; Mancini, Longo, Iannetti, & Haggard, 2011). This ability requires the construction of a coherent representation of our body, and the space closely surrounding our body, i.e. the peripersonal space. The peripersonal space serves as a multisensory motor interface between our body and the environment (Graziano & Cooke, 2006; Rizzolatti, Fadiga, Fogassi, & Gallese, 1997), in which information from the body surface (e.g., tactile or nociceptive stimuli) is integrated with information from the external world (e.g., visual or auditory stimuli). This enables us to interact with the world: we can reach and grasp objects, and we can also avoid objects or defend ourselves against threatening objects intruding our peripersonal space. In monkeys this ability has been found to rely on bimodal visuotactile neurons in the ventral premotor cortex and the ventral intraparietal sulcus, which fire both for tactile stimuli and for visual stimuli presented near the stimulated area (Graziano et al., 1994). Similarly, Dong et al. (1994) found neurons in area 7b of the inferior parietal lobe of monkeys, that respond to nociceptive stimuli and to dynamical visual stimuli moving towards the receptive fields of these neurons. Dong et al. (1994) suggested that this area provides visuo-somatic information about potentially noxious stimuli, and that it directs motor adjustments so that body exposure and contact with the threatening stimuli is minimized. In humans, a similar system has been proposed for tactile and visual stimuli (for a review, see Spence & Driver, 2004), and more recently also for nociceptive and visual stimuli (De Paepe, Crombez, & Legrain, 2015; De Paepe et al., 2014; Sambo, Forster, Williams, & Iannetti, 2012; Sambo & Iannetti, 2013; Sambo, Liang, Cruccu, & Iannetti, 2012). However, unlike animal studies, most of the behavioral research in humans has used external (e.g., visual) stimuli at only two fixed locations (i.e. one position near the participants, and one far from the participants), instead of dynamical stimuli. There are several reasons why it could be more interesting to study the influence of *dynamical* stimuli on nociceptive (and tactile) processing. First, it would increase the ecological validity of the studies, as in real life objects are continuously moving around in the environment. Second, it would make research in humans more comparable to the animal studies mentioned above investigating multisensory integration within the peripersonal space (Dong et al., 1994; Graziano et al., 1994). Third, the neural systems representing the peripersonal space show a preference for moving stimuli over static stimuli, both in monkeys and in humans. In monkeys, visual and tactile responses of some of the bimodal neurons in the premotor cortex are directionally specific (Duhamel, Colby, & Goldberg, 1998; Fogassi et al., 1996; Graziano et al., 1997). Moreover, the firing rates of some of these

neurons change dynamically with stimulus velocity (Fogassi et al., 1996). Also in humans there is some evidence that approaching visual, auditory and tactile stimuli evoke increased neural activity within the intraparietal sulcus and the ventral premotor cortex (Bremmer et al., 2001; Makin, Holmes, & Zohary, 2007). Because of the relevance of moving objects to the peripersonal space system, Canzoneri, Magosso, & Serino (2012) developed a paradigm that enables to investigate the influence of dynamical *auditory* stimuli on *tactile* processing. In this task, Canzoneri et al. (2012) measured reaction times (RTs) to a tactile stimulus applied to the right index finger while dynamical sounds, which gave the impression of either approaching or receding from the subject's hand, were presented. Tactile stimulation was delivered at different temporal delays from the onset of the sound, such that it occurred when the sound source was perceived at varying distances from the body. Participants were asked to respond as fast as possible, trying to ignore the sound. They found that an auditory stimulus speeded up the processing of a tactile stimulus applied to the hand when the sound was administered within a limited distance from the hand. Moreover, results suggested that approaching sounds had a stronger spatially-dependent effect on tactile processing compared to receding sounds.

The ability to quickly localize stimuli on the body and in external space seems especially relevant in the context of pain. Indeed, potentially harmful objects approaching our body have to be quickly localized so that an appropriate defensive response can be prepared. In this study, we adapted the paradigm of Canzoneri et al. (2012) to investigate the influence of dynamical *visual* stimuli on *nociceptive* processing. A visual stimulus was either approaching or receding the participant's left or right hand. At different temporal delays from the onset of the visual stimulus, a nociceptive stimulus was applied either at the same or the opposite hand, so that it was presented when the visual stimulus was perceived at varying distances from the hand. Participants were asked to respond as fast as possible at which side they perceived a nociceptive stimulus. We expected that RTs to nociceptive stimuli would progressively decrease as a function of the perceived approach of the visual stimulus. Conversely, we expected RTs to increase as a function of the perceived recession of the visual stimulus. Moreover, we expected that this effect would be larger when visual stimuli were approaching/receding at the side of space in which the stimulated hand resided as opposed to when they were approaching/receding at the opposite side of space. The best fitting curves of the RTs as a function of the perceived position of the visual stimuli in space were studied in order to compare the influence of approaching versus receding visual stimuli on nociceptive processing.

2 METHODS

2.1 PARTICIPANTS

30 paid participants volunteered to take part. Three participants (2 males, 1 female) were excluded because they failed to feel the stimulation despite repeated displacement of the electrodes (see section 2.2.). The final sample consisted of 27 participants (26 females, all right handed) with a mean age of 21 years (ranging from 18 to 26 years). All of the participants had normal or corrected-to-normal vision. Recent neurological, psychiatric or chronic pain diseases and usual intake of psychotropic drugs were considered as exclusion criteria. The experimental procedure was approved by the ethics committee of the faculty of psychology and educational sciences of Ghent University (2014/46). All of the participants provided written informed consent prior to taking part in the study.

2.2 STIMULI AND APPARATUS

The nociceptive stimuli were delivered by means of intra-epidermal electrical stimulation (IES) (DS7 Stimulator, Digitimer Ltd, UK), with stainless steel concentric bipolar electrodes (Nihon Kohden, Japan; Inui et al., 2006). The electrodes consisted of a needle cathode (length: 0.1 mm, \emptyset : 1.4 mm). By gently pressing the device against the participant's skin, the needle electrode was inserted into the epidermis of the dorsum of the hand in the sensory territory of the superficial branch of the radial nerve. Using intra-epidermal stimulation at maximum twice the absolute threshold was shown to selectively activate the free nerve endings of the A δ fibers (Inui et al., 2006; Mouraux et al., 2010, 2014). The detection threshold was determined with single-pulse stimuli (0.5 ms square wave pulse) using a staircase procedure (Churyukanov et al., 2012). The detection threshold was established separately for each hand. Next, the stimulus intensity was set at twice the detection threshold. If necessary, the intensity of the stimuli was adjusted so that the stimuli delivered to each hand were perceived as being equally intense. During the course of the experiment, the stimuli consisted of trains of four consecutive 0.5 ms square-wave pulses separated by a 5-ms inter-pulse interval. Using a set of pain words from the Dutch McGill Pain questionnaire (Vanderiet et al., 1987) the stimuli were described as pricking. After each experimental block, the participants were asked to estimate the intensity elicited by the nociceptive stimuli on a numeric graphic rating scale (10 cm) with the following labels selected from the Dutch version of the McGill pain questionnaire (Vanderiet et al., 1987): 0 = felt nothing, 2.5 = lightly intense, 5 = moderately intense, 7.5 = very intense, 10 = enormously intense). This scale was used to ensure that: (1) the stimuli were still perceived,

and (2) the percept elicited by the IES delivered to each of the participant's hands was still equivalent. If one of these two criteria was not met, the stimulus intensities were modified (with a maximum intensity of 0.50 mA). If this adaptation proved to be unsuccessful (i.e. if one of the criteria was still not met), the electrodes were displaced and the procedure was restarted.

The visual stimuli were presented by means of fourteen green light-emitting diodes (LEDs), and a red LED for fixation.

The participants sat on a chair in a dimly illuminated, sound-attenuated room, with their head position fixed in a chin rest. The height of the chin rest was individually adapted. Participants rested their arms on the table in front of them, and placed their hands, palm downward on the table. The distance between the participants' hands and their trunk, as well as the distance between the participants' index fingers was 40 cm. In total 14 LEDs were positioned at different distances from the hands. 7 LEDs were positioned in the left side of space, and 7 LEDs in the right side of space. At both sides, the first LED was positioned in between thumb and index finger, the next six LEDs were positioned on a straight line one in front of the other with 12 cm in between successive LEDs, so that the last LED was 72 cm in front of the first LED. On each trial, the LEDs on one side were successively illuminated, creating the illusion of a light coming closer towards the participant (if the first LED illuminated was the LED at a distance of 72 cm from the participants), or going further away from the participant (if the first LED illuminated was the LED in between thumb and index finger). Each LED was illuminated for 280 ms, and each offset was immediately followed by the illumination of the next LED,, so that the total dynamical visual stimulus had a duration of 1960 ms. A red fixation LED was positioned in between the LEDs in left and right space, 36 cm in front of the first LEDs. This fixation LED was illuminated at the beginning of each trial, and was turned off for 1s at the end of each trial.

2.3 PROCEDURE

The experiment started by illuminating the LEDs one by one. Participants were asked to look at the fixation LED and to indicate verbally at which side of space a light was illuminated (i.e. "left" or "right"). This was done to ensure that participants could see all the LEDs. Next, participants completed a practice phase of 14 trials, in which they had to achieve 90% correct performance in order to proceed with the experiment.

Each trial started with the illumination of the fixation LED for 1s. Thereafter the dynamical visual stimulus started. At different temporal delays after the onset of the visual stimulus, a nociceptive stimulus could be presented: T1, a nociceptive stimulus was administered 170 ms from light onset; T2, 450 ms from light onset; T3, 730 ms from light onset; T4, 1010 ms from light onset; T5, 1290 ms from light onset; T6, 1570 ms from light onset; T7, 1850 ms from light onset. This was true both for the approaching and the receding light. That way, the light was perceived at different locations with respect to the body at the moment the nociceptive stimuli were presented. For example, when the light was approaching it appeared close at high temporal delays. Conversely, when the light was receding, it appeared close at low temporal delays (see Figure 1).

The experiment consisted of 8 blocks of 56 trials each. The trials were created by crossing the moving direction of the visual stimulus (approaching vs. receding) with the congruency of the visual and nociceptive stimulus (congruent vs. incongruent), the side at which the visual stimulus was presented (left/right side of space) and the 7 different temporal delays (T1 - T7). 1/8 of the trials (i.e. 7 trials) per block were randomly assigned as catch trials, in which no nociceptive stimulus was presented.

Participants were instructed to keep their gaze on the fixation LED during the whole block. They were asked to respond as fast and accurately as possible. Responses were given by means of two foot pedals, one positioned beneath the toes, and one beneath their heel. Participants were instructed to keep the foot pedals depressed during the experiment, and to lift either their toes or their heel to respond. Half of the participants responded with their left foot, the other half with their right foot. The response mapping (toe = left hand, heel = right hand, or vice versa) was counterbalanced between participants. Participants were informed that the visual stimulus was unpredictable of the delivery of the subsequent nociceptive target. To mask any noise produced by the foot pedals, participants wore headphones (Sennheiser, HD201). The experiment took on average 60 minutes to complete.

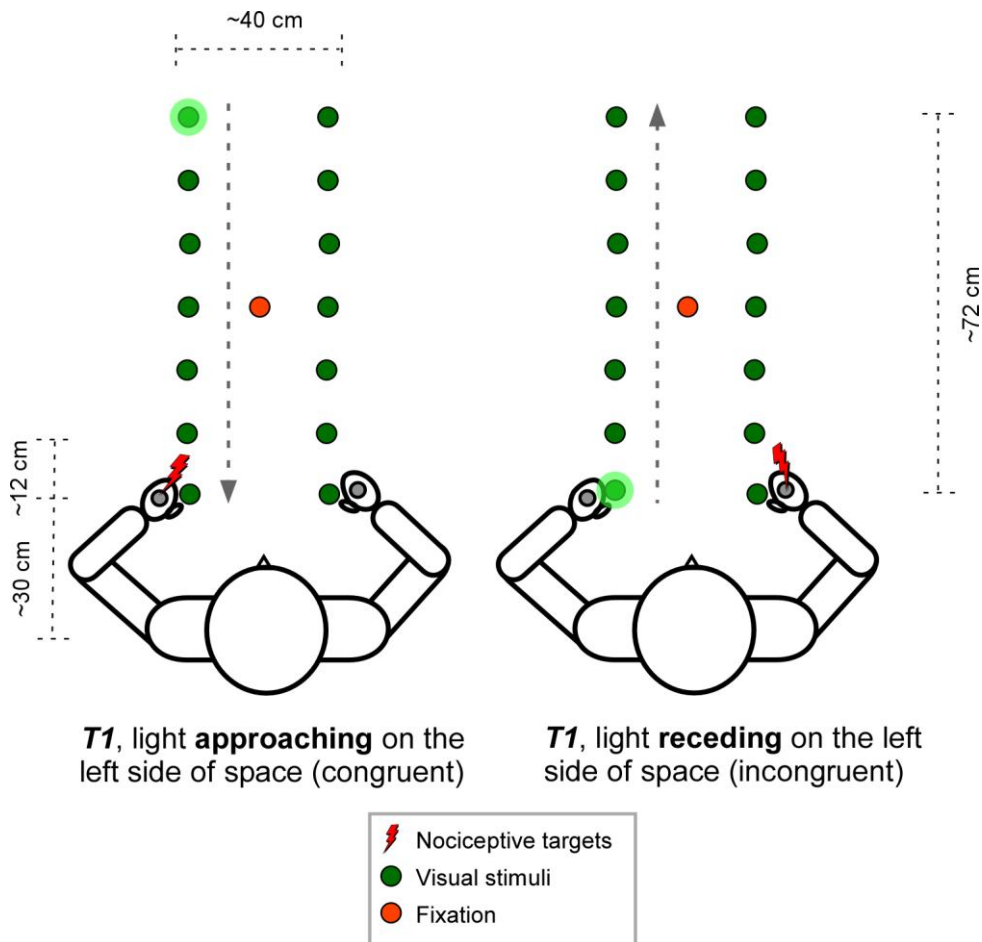


FIGURE 1. EXPERIMENTAL SET-UP. AT THE LEFT SIDE OF THE FIGURE, A LIGHT IS APPROACHING THE PARTICIPANT AT THE LEFT SIDE OF SPACE. AT T1 (170 MS FROM LIGHT ONSET) THE PARTICIPANT GETS A NOCICEPTIVE STIMULATION TO THE LEFT HAND (CONGRUENT TO THE SIDE OF SPACE WHERE THE LIGHT IS PRESENTED). AT THAT TIME, THE LIGHT IS AT 72 CM FROM THE PARTICIPANTS HAND. AT THE RIGHT SIDE OF THE FIGURE, A SIMILAR SITUATION IS DEPICTED, HOWEVER NOW THE LIGHT IS RECEDING FROM THE PARTICIPANTS HAND, SO THAT THE LIGHT IS IN BETWEEN THE THUMB AND THE INDEX FINGER AT THE TIME OF STIMULATION. MOREOVER, NOW THE RIGHT HAND IS STIMULATED (INCONGRUENT TO THE SIDE OF SPACE WHERE THE LIGHT IS PRESENTED). THE DASHED ARROW INDICATES THE MOVING DIRECTION OF THE LIGHTS.

2.4 MEASURES

Because participants were highly accurate in performing the task (see section 3.3.), performance was only analyzed in terms of the reaction time (RT). Only RTs from correct trials were considered for analysis. RTs exceeding three times the median absolute deviation (MAD) (Leys, Ley, Klein, Bernard, & Licata, 2013) were considered outliers and were trimmed from the analyses (4% of trials on average over all conditions). Mean RTs were calculated for every temporal delay, for congruent and incongruent trials, and for approaching and receding visual stimuli, creating 28 different conditions.

After the experiment participants were asked to indicate how threatening they thought the visual lights were both when the light was approaching, and when the light was receding,

on a scale from 0 (not at all) to 10 (extremely). The perceived threat score was compared for approaching and receding visual stimuli.

2.5 ANALYSES

Results were analyzed using linear mixed effects models as implemented in the package “Linear and Nonlinear Mixed Effects Models (Pinheiro & Bates, 2000). Linear mixed effects models account for the correlations in within-subject data by estimating subject-specific deviations (or random effects) from each population-level factor (or fixed factor) of interest (see West et al., 2007, for an elaboration). The outcome variable of interest was the RT. The independent variables were the *visual stimulus direction* (approaching vs. receding lights), the *congruency* of the nociceptive target (congruent vs. incongruent to the visual stimulus), and the *temporal delay* (T1 to T7). These were manipulated within subjects. Each analysis required three steps. First, all relevant factors and interactions were entered in the model as fixed factors, and we assessed whether it was necessary to add a random effect for each of the fixed factors in the analysis: If a random effect significantly increased the fit of the model, it was included in the final model. By default, a random effect was added introducing adjustments to the intercept conditional on the *Subject* variable. In the second step, we searched for the most parsimonious model that fitted the data. To achieve this, we systematically restricted the full model, comparing the goodness of fit using likelihood ratio tests. Finally, in the third step, we inspected the ANOVA table of the final model and tested specific hypotheses about possible main effects or interactions. Kenward-Roger approximations to the degrees of freedom were used to adjust for small sample sizes (Kenward & Roger, 1997). When an interaction effect was significant, it was further investigated with follow-up contrast analyses.

3 RESULTS

3.1 INTENSITY OF THE NOCICEPTIVE STIMULATION

The mean current intensities used during the experiment were not significantly different for the left ($M = 0.43$ mA, $SD = 0.05$) and the right ($M = 0.43$ mA, $SD = 0.07$) hand, $t(26) = 0.42$, $p = 0.68$. However, the mean self-reported intensities (numeric graphic rating scale) were significantly lower for the left ($M = 2.63$, $SD = 1.50$) than for the right ($M = 3.72$, $SD = 1.77$) hand, $t(26) = -3.54$, $p = 0.002$. To check whether this difference in self-reported intensities had an effect on task performance, the *side of the nociceptive stimulus* was added to the model as additional variable. However, nor the main effect of *side* ($F(1,1455) = 1.91$; $p = 0.17$), nor the interaction effect of *side* with any of the other variables (all $F < 1.6$; $p > 0.20$) were significant. For the sake of parsimony and to increase power, this variable was left out of further analyses.

In a number of trials participants didn't feel anything, despite the fact that a stimulation to one of both hands was applied. On average 1% ($\pm 3\%$) of the stimuli was not felt. Two participants did not feel respectively 7% and 12% of the stimuli. However, these participants still had more than 80% correct responses in total, and were thus kept in the analyses (see section 3.3.).

3.2 PERCEIVED THREAT VALUE VISUAL STIMULI

Mean perceived threat scores were overall low, but significantly higher when the lights were approaching ($M = 1.78$, $SD = 2.47$) the participants, than when they were receding ($M = 0.81$, $SD = 1.44$), $t(26) = 3.22$, $p = 0.003$.

3.3 ACCURACY

All participants had on average more than 80% correct task performance, and we decided to keep all participants in the analyses. Mean accuracy was 96% ($\pm 4\%$). Accuracies were not further analyzed.

3.4 REACTION TIMES

The relationship between the RTs to the nociceptive targets, the different *temporal delays* at which the nociceptive stimuli were administered (from T1 to T7), the *visual stimulus direction* (approaching vs. receding) and the *congruency* of the nociceptive stimulation (congruent vs. incongruent to the visual cue) are represented in Figure 2.

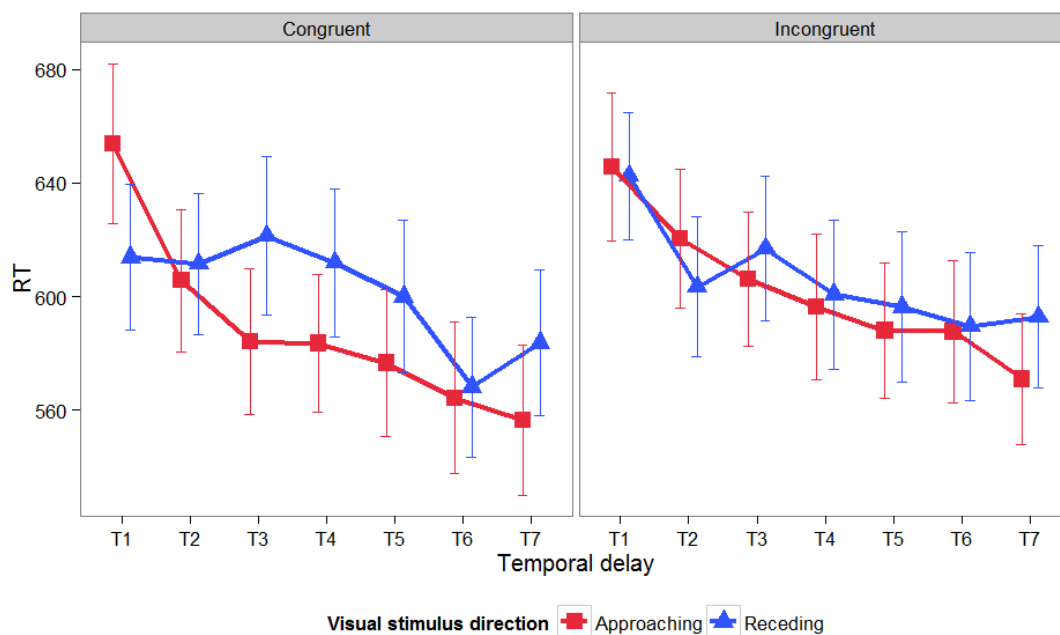


FIGURE 2. MEAN RT'S TO THE NOCICEPTIVE TARGETS AND THEIR ASSOCIATED STANDARD ERRORS IN FUNCTION OF THE DIFFERENT TEMPORAL DELAYS AT WHICH THE NOCICEPTIVE STIMULI WERE ADMINISTERED (FROM T1 TO T7), THE DIRECTION OF THE VISUAL STIMULUS (APPROACHING VS. RECEDING) AND THE CONGRUENCY OF THE NOCICEPTIVE STIMULATION (CONGRUENT VS. INCONGRUENT TO THE VISUAL CUE).

The linear mixed effects model that demonstrated the best fit with the data, included all fixed factors together with their two- and three-way interactions, a random subject-based intercept, and a random effect for *temporal delay*. The parameter estimates of the fixed effects together with their 95% confidence interval (CI) are shown in Table 1. In this final model, there was a significant main effect of *visual stimulus direction* ($F(1,546) = 17.20$; $p < 0.001$), a significant main effect of *temporal delay* ($F(6,172.61) = 13.71$; $p < 0.001$), a significant interaction effect between *visual stimulus direction* and *congruency* ($F(1,546) = 7.25$; $p = 0.007$), a significant interaction between *visual stimulus direction* and *temporal delay* ($F(6,546) = 6.89$; $p < 0.001$), and finally a significant three-way interaction between *visual stimulus direction*, *congruency*, and *temporal delay* ($F(6,546) = 2.14$; $p = 0.04$). The

main effect of *congruency* ($F(1,546) = 0.95; p = 0.33$), and the interaction effect between *congruency* and *temporal delay* ($F(6,546) = 1.33; p = 0.24$) did not reach significance.

	Parameter estimate	95% CI
Intercept	661.10	[631.03 to 691.17]
Visual stimulus direction	-44.30	[-65.24 to -23.36]
Congruency	-10.41	[-31.35 to 10.53]
Temporal delay (T2)	-48.99	[-70.84 to -27.14]
Temporal delay (T3)	-74.51	[-97.09 to -51.94]
Temporal delay (T4)	-74.00	[-97.54 to -50.46]
Temporal delay (T5)	-85.26	[-109.83 to -60.68]
Temporal delay (T6)	-96.57	[-120.49 to -72.65]
Temporal delay (T7)	-100.51	[-125.04 to -75.97]
Visual stimulus direction x Congruency	40.68	[11.06 to 70.29]
Visual stimulus direction x Temporal delay (T2)	43.61	[13.99 to 73.22]
Visual stimulus direction x Temporal delay (T3)	82.79	[53.18 to 112.40]
Visual stimulus direction x Temporal delay (T4)	71.24	[41.63 to 100.85]
Visual stimulus direction x Temporal delay (T5)	72.40	[42.78 to 102.01]
Visual stimulus direction x Temporal delay (T6)	50.85	[21.24 to 80.46]
Visual stimulus direction x Temporal delay (T7)	69.64	[40.03 to 99.25]
Congruency x Temporal delay (T2)	22.43	[-7.19 to 52.04]
Congruency x Temporal delay (T3)	33.22	[-3.61 to 62.84]
Congruency x Temporal delay (T4)	18.60	[-11.02 to 48.21]
Congruency x Temporal delay (T5)	24.62	[-4.99 to 54.23]
Congruency x Temporal delay (T6)	38.83	[9.22 to 68.44]
Congruency x Temporal delay (T7)	21.60	[-8.01 to 51.21]
Visual stimulus direction x Congruency x TD (T2)	-56.99	[-98.86 to -15.11]
Visual stimulus direction x Congruency x TD (T3)	-67.53	[-109.40 to -25.65]
Visual stimulus direction x Congruency x TD (T4)	-52.29	[-94.17 to -10.41]
Visual stimulus direction x Congruency x TD (T5)	-57.48	[-99.36 to -15.61]
Visual stimulus direction x Congruency x TD (T6)	-52.01	[-93.89 to -10.13]
Visual stimulus direction x Congruency x TD (T7)	-40.26	[-82.14 to 1.62]

TABLE 1. PARAMETER ESTIMATES (IN MS) AND ASSOCIATED 95% CONFIDENCE INTERVALS (CI) FOR THE FIXED EFFECTS OF THE FITTED MODEL PREDICTING RT'S IN FUNCTION OF VISUAL STIMULUS DIRECTION, CONGRUENCY AND TEMPORAL DELAY (TD).

To further investigate the three-way interaction, two separate linear mixed effects models were fitted for congruent and incongruent trials with *visual stimulus direction* and *temporal delay* as independent variables and RT as dependent variable.

For *congruent* trials, the model that demonstrated the best fit with the data included the fixed factors and their interaction, and a random subject-based intercept. In this model, there was a main effect of *visual stimulus direction* ($F(1,338) = 14.14; p < 0.001$), a main effect of *temporal delay* ($F(6,338) = 17.37; p < 0.001$), and an interaction effect between *visual stimulus direction* and *temporal delay* ($F(6,338) = 5.67; p < 0.001$). Follow-up tests indicated that at T1, RTs were significantly slower for approaching than for receding visual stimuli ($\chi^2(1) = 14.14, p < 0.001$). This effect reversed at T3, T4, T5 and T7, where reaction times were significantly slower for receding than for approaching visual stimuli (T3: $\chi^2(1) = 10.67, p = 0.001$; T4: $\chi^2(1) = 5.23, p = 0.02$; T5: $\chi^2(1) = 5.69, p = 0.02$; T7: $\chi^2(1) = 4.63, p = 0.03$). At T2 and T6 reaction times did not differ significantly between approaching versus receding visual stimuli (T2: $\chi^2(1) = 0.004, p = 0.95$; T6: $\chi^2(1) = 0.31, p = 0.58$).

For *incongruent* trials, a similar model was fitted with all fixed factors, and their interaction, and a random subject-based intercept. In this model there was only a main effect of *temporal delay* ($F(6,338) = 10.60; p < 0.001$). The main effect of *visual stimulus direction* ($F(1,338) = 0.10; p = 0.75$) and the interaction effect between *temporal delay* and *visual stimulus direction* ($F(1,338) = 1.67; p = 0.13$) were not significant.

Because there was no significant interaction between *temporal delay* and *visual stimulus direction* for incongruent trials, further analyses focused on congruent trials. Pairwise comparisons between the different temporal delays for approaching visual stimuli showed that reaction times at T1 were significantly slower than at any other temporal delay (all $|t| > 1.5$; all $p < 0.05$). Furthermore, reaction times at T2 were significantly slower than reaction times at T6 and T7 (all $|t| > 1.5$; all $p < 0.05$). No other comparisons were significant (all $|t| < 1.5$; all $p > 0.1$). For receding visual stimuli, reaction times at T6 were significantly faster than at T1 and T3 (all $|t| > 1.5$; all $p < 0.05$). No other comparisons were significant (all $|t| < 1.65$; all $p > 0.05$).

Finally, we evaluated whether the model for congruent trials could be further simplified by considering *temporal delay* as a continuous variable instead of a factor, so that T1 corresponds to 170 ms, T2 to 450 ms, T3 to 730 ms, T4 to 1010 ms, T5 to 1290 ms, T6 to 1570 ms and T7 to 1850 ms. The nature of the relationship between the independent variable *temporal delay* and the dependent variable RT was investigated by fitting models with RT as dependent variable and *temporal delay* as independent variable separately for

approaching and receding visual stimuli. At each time the restricted models (with *temporal delay* as continuous variable) were compared with the full model (with *temporal delay* as categorical variable). For approaching visual stimuli a linear relationship was first considered, assuming a constant decrease/increase of RT as a function of temporal delay. This model fitted significantly worse than the model with *temporal delay* as a categorical predictor ($\chi^2(5) = 16.64, p = 0.005$). Next, a quadratic relationship was considered by adding the square of the independent variable *temporal delay* to the model. This model did not fit the data significantly worse than the full model ($\chi^2(4) = 5.53, p = 0.24$). For approaching visual stimuli it thus seems that the relationship between the RT and *temporal delay* could be adequately described by assuming a quadratic model. For receding visual stimuli, the same strategy was applied. Again, the linear model fitted significantly poorer than the model with the categorical predictor ($\chi^2(5) = 12.98, p = 0.02$), however now also the quadratic model fitted the data significantly worse ($\chi^2(4) = 9.93, p = 0.04$). A square root model was fitted by adding the square root of *temporal delay* to the model. This model fitted the data only marginally significantly worse than the model with the categorical predictor ($\chi^2(4) = 9.38; p = 0.052$). The fitted curves are shown in Figure 3. Taken together these results indicate that when the visual stimuli were approaching the participants, reaction times steeply decreased at small temporal delays, and remained more constant at higher temporal delays. For receding visual stimuli, reaction times remained rather stable (and even increased a bit) at small temporal delays, and only decreased at the higher temporal delays.

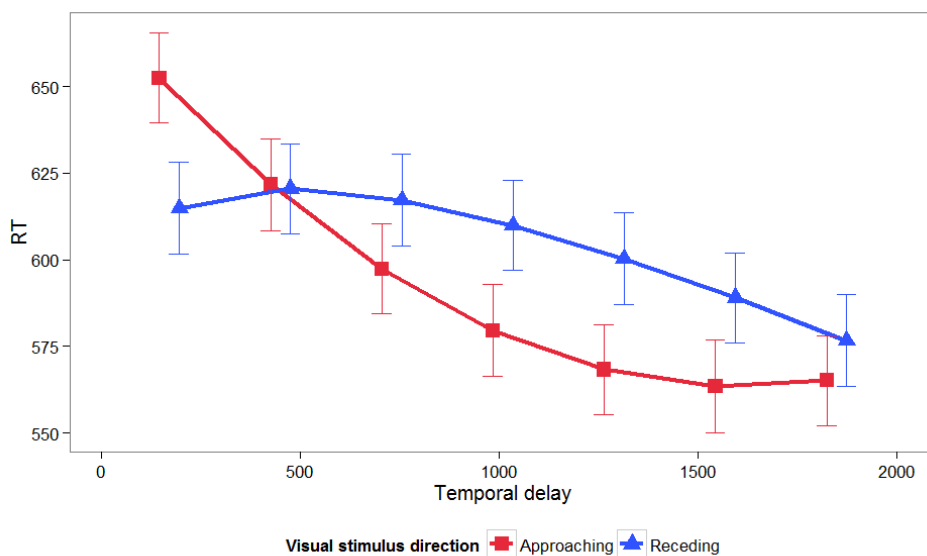


FIGURE 3. PREDICTED VALUES FOR THE RELATIONSHIP BETWEEN TEMPORAL DELAY AND REACTION TIME (RT) FOR CONGRUENT TRIALS AND THEIR ASSOCIATED STANDARD ERRORS. FOR APPROACHING VISUAL STIMULI A QUADRATIC MODEL FITTED THE DATA BEST. FOR RECEDING VISUAL STIMULI, A SQUARE ROOT MODEL WAS USED TO DESCRIBE THE DATA.

4 DISCUSSION

This study investigated the influence of dynamical visual stimuli on nociceptive processing. Results showed that visual stimuli presented near the stimulated hand influenced nociceptive processing more than visual stimuli presented far from the hand, providing evidence for a body-part centered peripersonal frame of reference for the processing of nociceptive stimuli. Moreover, by using dynamical visual stimuli we were able to investigate the influence of visual stimuli along a continuous spatial range (from near to far space) both for approaching and receding stimuli.

To adequately defend ourselves against potential threats we need to be able to construct a coherent representation of our body and the space closely surrounding our body (i.e. the peripersonal space). Within this space the location of somatosensory stimuli, the location of visual stimuli close to the body and information about body posture are integrated (Cardinali, Brozzoli, & Farnè, 2009; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981; Spence & Driver, 2004). In monkeys this ability depends on neurons with multimodal receptive fields (RFs), found mainly in the premotor and intraparietal areas (Graziano & Gross, 1994; Graziano et al., 1997). These neurons are activated in response to both tactile stimuli and to visual stimuli occurring close to the stimulated body parts. In humans, the use of a peripersonal frame of reference for the localization of somatosensory stimuli has been demonstrated in neuropsychological studies with patients suffering from crossmodal extinction after a right hemisphere stroke. These patients can feel a tactile stimulation to their left hand in isolation, but when the right hand is concurrently stimulated (unimodal extinction) or when a right visual stimulus was presented near the right hand (crossmodal extinction) patients fail to report the left hand stimulation. However, when the right visual stimulus was presented far from the patients' hand, the degree of extinction was reduced (di Pellegrino, Làdavas, & Farnè, 1997; Làdavas, di Pellegrino, Farnè, & Zeloni, 1998). These results are in agreement with the electrophysiological findings from monkeys suggesting that the representation of peripersonal space is body-part centered (Graziano et al., 1997). Behavioral studies with healthy volunteers using a crossmodal congruency task (Holmes et al., 2006; Sambo & Forster, 2009; Spence, Pavani, & Driver, 2000; Spence et al., 2004; for a review see Spence & Driver, 2004) found similar results. Recently, we extended these results to nociceptive stimuli using temporal order judgment (TOJ) tasks. In these tasks participants received two nociceptive stimulations, one to each hand, with different stimulus onset asynchronies (SOA's) between both hands. Slightly before the first nociceptive stimulation a visual cue stimulus was presented either in the left or the right

side of space, and either near or far from the participants' hand. We found that visual stimuli presented near the stimulated hand facilitated processing of the nociceptive stimuli applied to that hand. Conversely, visual stimuli presented far from the hand only influenced nociceptive processing to a lesser extent (De Paepe et al., 2015, 2014). In the current study we were able to replicate these findings showing that when the visual stimuli were presented at the side of space of the stimulated hand, reaction times were faster for receding visual stimuli at low temporal delays, and conversely they were faster for approaching visual stimuli at high temporal delays. This indicates that nociceptive processing was facilitated whenever a visual stimulus was presented near the stimulated hand. This was not the case when the visual stimuli were presented at the opposite side of space of the stimulated hand, indicating that it is the proximity to the stimulated body part and not so much to the body as a whole that is important. Taken together these results confirm previous findings with a different paradigm, and provide evidence for a peripersonal frame of reference centered on the stimulated body-part for the localization of nociceptive stimuli.

An important new aspect of the present study was the use of dynamical visual stimuli instead of static stimuli at two fixed positions (one near, one far) used in most previous studies. The use of moving stimuli is more ecologically valid and more comparable to animal studies investigating multimodal integration in the peripersonal space (Dong et al., 1994; Graziano et al., 1994). Furthermore studies in both humans and monkeys (Bremmer et al., 2001; Duhamel et al., 1998; Fogassi et al., 1996; Graziano et al., 1997; Makin et al., 2007) have shown that the neural systems representing the peripersonal space show a preference for moving stimuli. By using dynamical visual stimuli, we were able to investigate multisensory integration along a continuum between near and far space. This was done by searching the best fitting function for the relationship between the RTs and the temporal delay at which the nociceptive stimuli were presented. This was only investigated for congruent trials, because the visual stimulus direction (approaching versus receding) did not significantly affect incongruent trials, indicating that the distance of the visual stimuli to the body had no significant influence on RTs for these trials. For approaching trials a quadratic function adequately described the data, indicating that RTs did not decrease linearly as a function of the approaching light. Instead, the RTs dropped strongly in the beginning (T1 and T2), and decreased more slowly at higher temporal delays. This is also shown by the fact that RTs at low temporal delays (T1 and T2) were significantly higher than reaction times to nociceptive stimuli presented at higher temporal delays. For receding trials, a square root function fitted the

data well, indicating that reaction times did not increase/decrease linearly with the receding light. For these trials reaction times remained stable (and slightly increased) at low temporal delays, and then slowly decreased at higher temporal delays. It is surprising that despite the fact that the lights receded from the hand, reaction times nevertheless decreased at higher temporal delays (when the light was far away from the hand). Previous studies using a similar paradigm (Canzoneri et al., 2012; Teneggi, Canzoneri, di Pellegrino, & Serino, 2013) also did not find the expected increase in RTs when stimuli were receding. However, in these studies RTs did not decrease at high temporal delays, but remained stable. It is important to note that there are some differences between these studies and the present study. First, these studies used auditory stimuli and tactile targets. Next, Canzoneri et al. (2012) also used 'unimodal' stimuli, i.e. tactile stimuli could occur during a silence period, preceding or following sound administration. Furthermore, in the present study both the left and the right hand could be stimulated and the lights were approaching/receding at the same or the opposite side of space. The previous studies only stimulated the right hand (Canzoneri et al., 2012) or cheek (Teneggi et al., 2013). Lastly, and most importantly, Canzoneri et al. (2012) and Teneggi et al. (2013) had more catch trials (respectively 40% and ~33% out of the total amount of trials, compared to 12.5% in the present study). These catch trials should ensure that the expectation to receive a nociceptive stimulation to one of the hands does not increase with higher temporal delays. In the present study, catch trials were presented in 1/8 of the trials in each block. It could be that this was not sufficient to avoid the fact that participants expected to get a stimulation, and that this expectation increased as the trial proceeded. This could also be the reason why for incongruent trials RTs decreased with increasing temporal delay, equally for approaching and receding visual stimuli. We chose to decrease the amount of catch trials to limit the amount of trials (and therefore the duration of the experiment) to ensure that participants could remain concentrated until the very end. These differences can be the cause of the decrease in RTs for receding stimuli. However despite this general effect of temporal delay, we were able to find a differential effect of visual stimulus direction (approaching vs. receding) on RTs for congruent trials, indicating that over and above the general decrease in reaction times with time, the distance of the lights to the hand significantly influenced RTs.

In accordance with the results of Canzoneri et al. (2012) in the context of touch, our results suggest that the approaching lights had a stronger spatially dependent effect on nociceptive processing, compared to the receding lights. Indeed, the quadratic function

describing the relationship between RTs and the temporal delay at which nociceptive stimuli were delivered, showed a steep decrease immediately after the onset of the visual stimuli. Conversely, for the receding lights no such steep increase/decrease was present. In fact, reaction times remained stable and only decreased in the end, which is, as argued above, probably due to an increasing expectation of receiving a stimulation. These results are in agreement with studies in primates and humans showing adaptive avoidance responses to both real and simulated approaching stimuli (Schiff, Caviness, & Gibson, 1962; Schiff, 1965; Tinbergen, 1951). For example, a rapidly expanding shadow elicits fear responses in rhesus monkeys (Schiff et al., 1962) and human infants (Ball & Tronick, 1971), but rapidly contracting shadows do not. Similarly, in the present study, participants rated the approaching stimuli as more threatening than the receding stimuli, albeit that the overall level of fear was low. Furthermore, bimodal neurons in the ventral premotor cortex and the posterior parietal cortex of monkeys respond preferentially to approaching visual stimuli (Bremmer, Duhamel, Ben Hamed, & Graf, 2002; Colby, Duhamel, & Goldberg, 1993; Duhamel, Bremmer, Benhamed, & Graf, 1997). At a behavioral level, humans process tactile stimuli applied to the cheek more rapidly when an object approached the cheek or the region closely surrounding the cheek, but not when this object was receding from the cheek (Kandula, Hofman, & Dijkerman, 2014). These results can be explained by the fact that objects approaching us may pose a threat, and signal the need to initiate defensive behavior. Detecting these objects early is therefore crucial to either avoid the object, or prepare for contact most efficiently. Cooke and Graziano (2004, 2006) found that when the monkeys' brain regions that respond to approaching or nearby objects are stimulated, the animal executes defensive movements like withdrawing or blocking. In humans, it was argued that the peripersonal frame of reference may constitute a safety margin around the body that is designed to protect it from potential physical threat and that represents a mechanism for preserving homeostatic control over the body (Legrain & Torta, 2015; Moseley, Gallace, & Iannetti, 2012).

This study has some limitations. First, the use of dynamical visual stimuli increased the ecological validity of this study. However, one could question the generalizability of a standardized experimental situation to real life. Indeed, it could be interesting to investigate the effect of real life objects (e.g., a syringe or a needle) approaching (or receding) from participants, as has been done in some animal studies (e.g., Dong et al., 1994) and recently also in humans (Van der Biest, Legrain, De Paepe, & Crombez, 2015). On the other hand, the use of standardized visual stimuli enabled us to investigate the

influence of visual stimuli on nociceptive processing along a spatial continuum from near to far space, which would have been much more difficult to investigate in less standardized situations. Second, despite the procedure used to match the intensities of the nociceptive stimuli applied to both hands, the strict equivalence in subjective perception of the intensities between the two hands could not always be achieved. However, these differences were rather marginal (a difference of 1.09 cm on a rating scale of 10 cm), and analyses showed that the side of stimulation did not affect the RTs. Finally, as mentioned above, we found a general effect of the temporal delay at which nociceptive stimuli were applied, which is most likely due to an increasing expectation to receive a nociceptive stimulus with time. Future studies could possibly avoid this by adding more trials without nociceptive stimulation (i.e. catch trials).

In conclusion, the present study provides evidence for the mapping of nociceptive stimuli in a peripersonal frame of reference. This guarantees a swift and efficient localization of threatening objects by integrating nociceptive information with visual information presented near the stimulated body part, enabling the preparation of a defensive motor response towards the location of threat. Moreover, by using dynamical visual stimuli we were able to investigate the relationship between nociceptive processing and the position of visual stimuli along a spatial continuum from near to far space. For approaching visual stimuli this relationship is best described by a quadratic function, meaning that reaction times sharply decrease quickly after the onset of the visual stimulus. Conversely, for receding stimuli, no such sharp increase or decrease was found. This indicates that people are sensitive to the direction of visual stimuli, with approaching objects influencing nociceptive processing more profoundly than receding objects.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest related to the present article.

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CHAPTER 6

CAN FAR BECOME NEAR? THE EFFECT OF APPROACHING VISUAL STIMULI ON TACTILE PROCESSING IN FIBROMYALGIA PATIENTS AND CONTROLS.¹

ABSTRACT

Within the space closely surrounding us (i.e. the peripersonal space), stimuli on the body surface are integrated with stimuli in the external world. This enables us to interact with the world, and to defend ourselves against potentially threatening objects approaching our body. It has been shown that attention towards stimuli approaching us can differ depending on, for example, the level of anxiety. The present study investigated whether fibromyalgia (FM) patients have a heightened attention to stimuli entering the peripersonal space compared to healthy control participants. This was done by investigating the differential influence of dynamical visual stimuli approaching the body on tactile processing for control participants versus FM patients. For control participants we found, in accordance with previous research, that visual stimuli presented near as opposed to far from the body influenced tactile processing more. For FM patients this difference was less clear, possibly indicating that FM patients have more attention for potentially threatening stimuli at further distance. The curves describing the reaction times along the continuous spatial range (from near to far) indicated that FM patients have a heightened attention for stimuli entering the peripersonal space compared to controls. However, as this difference was only found when curve-fitting the data, we argue that our results should be interpreted with caution, and need further corroboration and replication.

¹ Based on: 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.

1 INTRODUCTION

The peripersonal space is the space immediately surrounding our body in which we can interact with the external world (Graziano & Cooke, 2006; Rizzolatti, Fadiga, Fogassi, & Gallese, 1997). This interaction is only possible when stimuli on the body space are integrated with stimuli occurring in the external world. Indeed, it has been shown that external stimuli (e.g., visual stimuli) occurring within the peripersonal space, are integrated with somatosensory stimuli on the body space, whereas stimuli occurring beyond the peripersonal space (i.e. in extrapersonal space) are not (or to a lesser extent) (for nociceptive stimuli: De Paepe, Crombez, & Legrain, 2015; De Paepe, Crombez, Spence, & Legrain, 2014; for tactile stimuli: see Spence & Driver, 2004, for a review).

Besides the possibility to interact with the world, this ability also provides us with a protective mechanism, allowing us to, for example, brush away an insect before it can sting us. In this sense, the peripersonal space can be considered a 'safety margin' around our body, which we are scanning for potentially threatening objects approaching our body and which allows for the swift preparation of defensive reactions against intruders (Legrain & Torta, 2015; Legrain, 2011; Moseley, Gallace, & Spence, 2012). Evidence in favor of this view has been provided by cortical stimulation studies. When the brain areas associated with multisensory processing in monkeys are electrically stimulated, defensive arm movements and withdrawing of the arm and the head are observed (Graziano & Cooke, 2006). In humans, it has been shown that three-dimensional visual distractors rapidly approaching participants' hands modulated corticospinal excitability over the primary motor cortex (Makin, Holmes, Brozzoli, Rossetti, & Farnè, 2009).

It has been argued that the boundaries of the peripersonal space are not fixed. This has been demonstrated by the fact that the peripersonal space can be 'extended' through tool-use (Bassolino, Serino, Ubaldi, & Làdavas, 2010; Farnè, Serino, & Làdavas, 2007; Maravita & Iriki, 2004; Serino, Bassolino, Farnè, & Làdavas, 2007). For example, Farnè & Làdavas (2000) used a crossmodal paradigm, used to reveal visuo-tactile interaction, in patients with tactile extinction. These patients can detect tactile stimulation to their left hand in isolation, but when the right hand is concurrently stimulated (unimodal extinction) or when a right visual stimulus is presented near the right hand (crossmodal extinction) patients fail to report the left hand stimulation. Farnè & Làdavas (2000) assessed crossmodal visual-tactile extinction by presenting visual stimuli far from the patients' ipsilesional hand (~30 cm), near the distal edge of a rake that was held in their hand. The study revealed that following the use of the rake to retrieve distant objects, crossmodal extinction was more severe as opposed to when

the rake was not used. This effect only lasted for a few minutes after tool-use. This shows that the use of a tool can increase the spatial extent of the representation of the peri-hand space to incorporate a tool. Other studies showed that the peripersonal space can be modulated by social interactions with others (Teneggi, Canzoneri, di Pellegrino, & Serino, 2013), or by anxiety (Taffou & Viaud-Delmon, 2014). Taffou & Viaud-Delmon (2014) investigated the extent of the peripersonal space in the presence of threatening (dog growling) and non-threatening (sheep bleating) auditory stimuli looming from the rear hemifield in non-fearful and dog-fearful individuals. They found that the peripersonal space of dog-fearful individuals was enlarged when a threatening sound as opposed to a non-threatening sound approached them. This effect was not found in non-fearful individuals. The authors argued that this enlargement of the peripersonal space in the presence of feared elements would be adaptive as it provides more time to prepare for a defensive response, and as such it fits with the proposed protective function of the peripersonal space.

In the present study, we investigated whether attention to stimuli approaching the body can be different for fibromyalgia patients compared to healthy control participants. Fibromyalgia is characterized by chronic widespread pain and tenderness in muscles and joints. Studies have indicated that FM patients demonstrate an exaggerated response to experimentally induced noxious stimuli, compared to other groups (Granges, Gibson, Littlejohn, & Helme, 1993; Granges & Littlejohn, 1993; Lautenschlager, Seglias, Bruckle, & Muller, 1991; Scudds, Rollman, Harth, & McCain, 1987; Tunks, Crook, Norman, & Kalaher, 1988). Interestingly, some studies suggest that patients with chronic pain not only have an over-responsiveness to painful stimuli, but also to stimuli in other modalities (e.g., sound) (Crombez, Van Damme, & Eccleston, 2005; McDermid, Rollman, & McCain, 1996). For example, Hollins et al. (2009) exposed FM patients, patients with temporomandibular disorders (TMD) and control participants to a set of pressure stimuli and a set of auditory stimuli and asked to rate the intensity, as well as the unpleasantness of each stimulus. FM patients rated the intensity and the unpleasantness of the stimuli significantly higher than the two other groups in both modalities, although the effect was stronger for the cutaneous stimuli. The origin of FM is still unknown, but the pattern of complaints and perceptual amplification associated with FM suggests dysfunctions in central processes (Wall, 1993). One hypothesis is that patients with FM are characterized by 'hypervigilance', referring to 'a habit to attend to somatic distress signals' (Chapman, 1978). It is proposed that this results from a cognitive process in which FM patients are concerned about, and therefore closely monitor, those sensations that could accompany or warn impending pain, leading to an increase of response to all stimuli of that type (Hollins et al., 2009). It has to be noted that

hypervigilance is only one mechanism that may account for the research findings demonstrating hypersensitivity in FM patients, such as the study of Hollins et al. (2009). Other processes such as central sensitization (e.g., Arendt-Nielsen & Henriksson, 2007; Staud, Robinson, & Price, 2007) have also been suggested to account for lowered pain threshold and tolerance levels in FM patients. To talk about 'hypervigilance' one should demonstrate the involvement of attentional processes, like vigilance and scanning towards those sensations that could accompany or warn impending pain (Crombez et al., 2005; Damme et al., 2009).

Here we want to investigate whether FM patients have a heightened attention for stimuli entering the peripersonal space or whether they scan a larger share of the external space for potentially salient and threatening information. To investigate this hypothesis, we studied the influence of dynamical visual stimuli on tactile processing in healthy control participants and FM patients. A visual stimulus was either approaching or receding the participant's left or right hand. At different temporal delays from the onset of the visual stimulus, a tactile stimulus was applied either at the same or the opposite hand, so that it was presented when the visual stimulus was perceived at varying distances from the hand. Participants were asked to respond as fast as possible at which side they perceived a tactile stimulus. We expected that RTs to tactile stimuli would progressively decrease as a function of the perceived approach of the visual stimulus. Conversely, we expected RTs to increase as a function of the perceived recession of the visual stimulus. This effect should be more pronounced when the light was presented at the same as opposed to the opposite side of the tactile stimulation. The best fitting curves of the RTs as a function of the perceived position of the visual stimuli in space were studied in order to compare the influence of approaching visual stimuli on tactile processing between FM patients and healthy controls.

2 METHODS

2.1 PARTICIPANTS

Forty patients with FM and a control group of forty-one participants matched for age, sex and level of education were recruited. FM patients were recruited via the Multidisciplinary Pain Clinic of Ghent University Hospital. Inclusion criteria were a diagnosis of FM (Wolfe et al., 2010), an age between 18 and 65 years, normal or corrected-to-normal eyesight (e.g., lenses, glasses), normal or corrected-to-normal hearing (e.g., hearing aid), and Dutch speaking. Exclusion criteria were suffering from neurological problems (e.g., epilepsy) and insensitivity on the hands. Potential participants were informed about the possibility of participating by means of a poster in the waiting room, information given by the physician and information letters. When they agreed to participate, they received a phone call from the researcher providing details about the study. 2 patients were excluded from the sample, because they performed poorly on the task (see section 3.3.). The remaining 38 patients reported pain complaints for, on average, 15 years ($SD = 12$ years). Pain was reported on an average of 171 days ($SD = 26$) over the last 6 months. 63% of them were not working because of the pain and received a monthly allowance. On average, the FM group reported being unable to perform daily activities (work, household) on 87 days ($SD = 72$) over the last 6 months.

The control participants were recruited via advertisement in local newspapers (e.g., Zone09), social media (Twitter, Facebook) and flyers distributed around the university campus, the local library, etc. Inclusion criteria were an age between 18 and 65 years, normal or corrected-to-normal eyesight (e.g., lenses, glasses), normal or corrected-to-normal hearing (e.g., hearing aid), and Dutch speaking. Exclusion criteria were suffering from pain of a severe intensity, meeting the criteria of FM according to the questionnaire of Wolfe et al. (2010), suffering from neurological problems and insensitivity on the hands. Pain of a severe intensity was operationalized as a grade score on the Von Korff scale (Von Korff, Ormel, Keefe, & Dworkin, 1992) greater than or equal to three, indicating the experience of pain that is at least moderately disabling. Three control participants were excluded because of this exclusion criterion. One other participant was excluded because he/she fulfilled the criteria for FM as described in Wolfe et al. (2010).

The final sample consisted of 38 patients and 37 control participants. Demographics and scores on the Von Korff scale (Von Korff et al., 1992) and the FM questionnaire (Wolfe et al., 2010) for both groups can be found in Table 1.

The experiment lasted approximately 1.5 hours and was part of a larger protocol that had been approved by the Ethical Committee of the Ghent University Hospital (see <http://hdl.handle.net/1854/LU-7032736>). At the end of the experiment, the participants received 25 euros as reimbursement for their expenses.

	Patients (N = 38)	Controls (N = 37)	t/χ^2	P
Age	44.76 (9.14)	45.38 (10.25)	-0.27	.78
Sex (% female)	92%	89%	0.19	.70
Education level			5.34	0.25
Primary school (< 12 years)	3%	0%		
Lower secondary school (< 15 years)	21%	5%		
Higher secondary school (< 18 years)	39%	54%		
High school	34%	38%		
University	3%	3%		
Handedness (% right handed)	87%	92%	0.50	.70
% unmarried/divorced/widow	39%	54%	1.07	.30
% having children	79%	59%	2.49	.11
Unemployment	74%	24%	16.35	<.001***
% participants reporting poor state of health	15%	0%	6.35	.02*
FM questionnaire (Wolfe et al., 2010) :				
<i>Widespread Pain Index (WPI)</i>	10.45 (4.18)	1.38 (1.46)	12.62	<.001***
<i>Severity Symptom scale (SS)</i>	7.61 (2.19)	2.89 (1.81)	10.18	<.001***
Grade score (Von Korff et al., 1992)	3.24 (1.13)	0.11 (0.31)	15.59	<.001***

TABLE 1. DEMOGRAPHICS AND PAIN SCORES FOR 38 PATIENTS AND 37 CONTROL PARTICIPANTS. * $P < 0.05$, *** $P < 0.001$

2.2 STIMULI AND APPARATUS

Vibrotactile stimuli were presented by means of two resonant-type actuators (C-2 TACTOR, Engineering Acoustics, Inc., Florida, <http://www.eaiinfo.com>), consisting of moving magnet linear actuators in a housing of 3.05 cm diameter and 0.79 cm high, with a skin contactor of 0.76 cm diameter. The tactile stimuli had a frequency of 300 Hz, and a duration of 10 ms. The intensity of the tactile stimuli was determined for each participant individually by means of a random staircase procedure. Twenty tactile stimuli were presented to one of the hands (i.e. the 'reference hand', for half of the participants this was the left hand, for the other half the right hand) (the intensity started between 0 and 0.27 Watt) and self-reports were collected on a 11-point Likert scale (0 = 'not intense at all' to 10 = 'very intense'). The intensity that elicited an average rating of 7 was selected as the intensity of the tactile stimulation for the reference hand during the experiment. The perceived stimulus intensity of the other hand was matched (Weinstein, 1968). This was done by means of a double random staircase procedure, based on the 'simple up-down method' of Levitt (1971). Twenty-four stimuli on this hand were judged relative to the stimulus on the reference hand on a 5-point Likert scale (1 = 'more than less strong', 2 = 'less strong', 3 = 'equally strong', 4 = 'stronger', 5 = 'much stronger'). The intensity that elicited an averaged rating of 3 was used as the intensity of the stimulus on the other hand.

The visual stimuli were presented by means of fourteen green light-emitting diodes (LEDs). One red LED was used for fixation.

The participants sat on a chair in a dimly illuminated, sound-attenuated room, with their head position fixed in a chin rest. The height of the chin rest was individually adapted. Participants rested their arms on the table in front of them, and placed their hands, palm downward on the table. The distance between the participants' hands and their trunk, as well as the distance between the participants' index fingers was 40 cm. In total 14 LEDs were positioned at different distances from the hands. Seven LEDs were positioned in the left side of space, and 7 LEDs in the right side of space. At both sides, the first LED was positioned in between thumb and index finger, the next six LEDs were positioned on a straight line, one in front of the other with 12 cm in between successive LEDs, so that the last LED was 72 cm in front of the first LED. On each trial, the LEDs on one side were successively illuminated, creating the illusion of a light coming closer towards the participant (the last LED, at 72 cm distance, was first illuminated), or going further away from the participant (the first LED, in between thumb and index finger, was first illuminated). Each LED was illuminated for 280 ms, and each offset was immediately followed by the illumination of the next LED, so that the total dynamical visual stimulus had

a duration of 1960 ms. A red fixation LED was positioned in between the LEDs in left and right space, 36 cm in front of the first LEDs. This fixation LED was illuminated at the beginning of each trial, and was turned off for 1s after a response was given.

2.3 PROCEDURE

The experiment started by illuminating the LEDs one by one. Participants were asked to look at the fixation LED and to indicate verbally at which side of space a light was illuminated (i.e. “left” or “right”). This was done to ensure that participants could see all the LEDs. Next, participants completed a practice phase of 14 trials, in which they had to achieve 90% correct performance in order to proceed with the experiment. All participants reached this criterion.

The procedure is based on a study of Canzoneri, Magosso, & Serino (2012). Each trial started with the illumination of the fixation LED for 1s. Thereafter the dynamical visual stimulus started. At different temporal delays after the onset of the first visual stimulus, a tactile stimulus could be presented: T1, a tactile stimulus was administered 170 ms from first light onset; T2, 450 ms from first light onset; T3, 730 ms from first light onset; T4, 1010 ms from first light onset; T5, 1290 ms from first light onset; T6, 1570 ms from first light onset; T7, 1850 ms from first light onset. This was true both for the approaching and the receding light. In this way, the light was perceived at different locations with respect to the body at the moment the tactile stimulation occurred. For example, when the light was approaching it appeared close at high temporal delays. Conversely, when the light was receding, it appeared close at low temporal delays (see Figure 1).

The experiment consisted of 8 blocks of 56 trials each. The trials were created by crossing the moving direction of visual stimulus (approaching vs. receding) with the congruency of the visual and tactile stimulus (congruent vs. incongruent), the side at which the visual stimulus was presented (left/right side of space) and the 7 different temporal delays (T1 - T7). 1/8 of the trials (i.e. 7 trials) per block were randomly assigned as catch trials, in which no tactile stimulus was presented.

Participants were instructed to keep their gaze on the fixation LED during the whole block. They were asked to respond as fast and accurately as possible. Responses were given by means of two foot pedals, one positioned beneath the toes, and one beneath their heel. Participants were instructed to keep the foot pedals depressed during the experiment, and to lift either their toes or their heel to respond. Half of the participants responded with their

left foot, the other half with their right foot. The response mapping (toe = left hand, heel = right hand, or vice versa) was counterbalanced between participants. Participants were informed that the visual stimulus was unpredictable for the position of the subsequent tactile target. To mask any noise produced by either the foot pedals or the tactile stimuli, participants wore headphones (Sennheiser, HD201). The experiment took on average 75 minutes to complete.

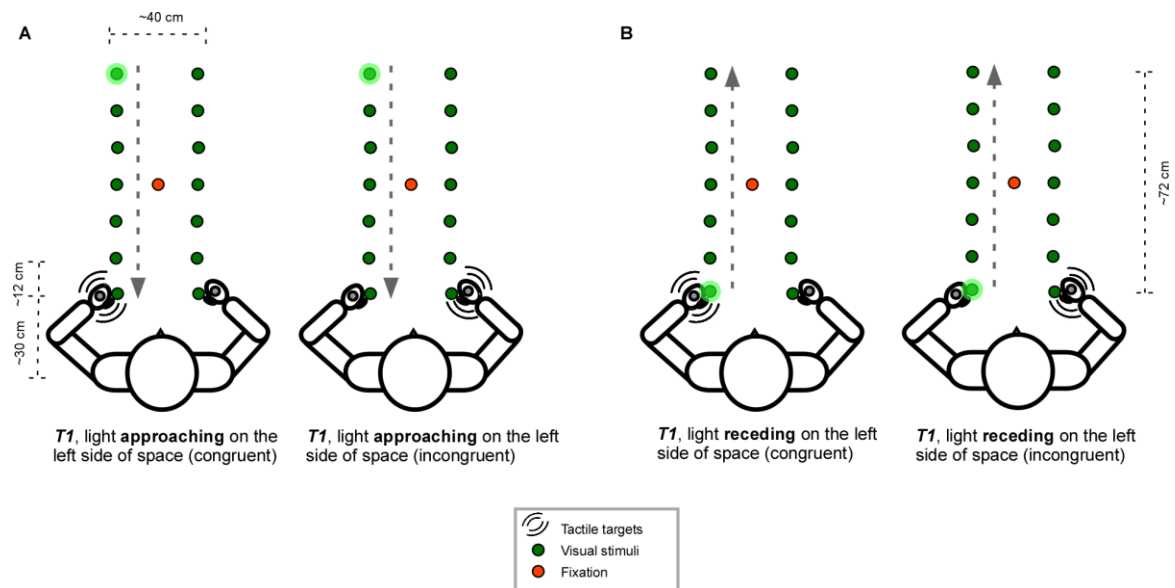


FIGURE 1. EXPERIMENTAL SET-UP. [A] A LIGHT IS *APPROACHING* THE PARTICIPANT AT THE LEFT SIDE OF SPACE. AT T1 (170 MS FROM FIRST LIGHT ONSET) THE PARTICIPANT GETS A TACTILE STIMULUS APPLIED TO THE LEFT HAND (LEFT FIGURE, CONGRUENT TO THE SIDE OF SPACE WHERE THE LIGHT IS PRESENTED) OR TO THE RIGHT HAND (RIGHT FIGURE, INCONGRUENT TO THE SIDE OF SPACE WHERE THE LIGHT IS PRESENTED). AT THAT TIME, THE LIGHT IS AT 72 CM FROM THE PARTICIPANT'S HAND. [B] A LIGHT IS *RECEDING* FROM THE PARTICIPANT'S HAND, SO THAT THE LIGHT IS NOW IN BETWEEN THE THUMB AND THE INDEX FINGER AT THE TIME OF STIMULATION. AT T1 (170 MS FROM FIRST LIGHT ONSET) THE PARTICIPANT GETS A TACTILE STIMULUS APPLIED TO THE LEFT HAND (LEFT FIGURE, CONGRUENT TO THE SIDE OF SPACE WHERE THE LIGHT IS PRESENTED) OR TO THE RIGHT HAND (RIGHT FIGURE, INCONGRUENT TO THE SIDE OF SPACE WHERE THE LIGHT IS PRESENTED).

2.4 MEASURES

Because participants were very accurate in performing the task (see section 3.3.), performance was only analyzed in terms of the reaction time (RT). Only RTs from correct trials were considered in the analyses. Inspection of quantile-quantile plots suggested that the data was not normally distributed and that an Inverse-Gaussian transformation was optimal both for the data of control participants and of FM patients (Ratcliff, 1993). After transforming the data, RTs exceeding three times the median absolute deviation (MAD) (Leys, Ley, Klein, Bernard, & Licata, 2013) were considered outliers and were trimmed from

the analyses separately for FM patients and control data (respectively 0.8 and 1.4% of trials on average over all conditions). The inversely transformed RTs were multiplied by -1000 so that coefficients would have the same sign as for models with untransformed RTs, at the same time avoiding very small values and a too restricted range for the dependent variable. Mean RTs were calculated for every temporal delay, for congruent and incongruent trials, and for approaching and receding visual stimuli, creating 28 different conditions for each group (control vs. patient).

Between each block participants were asked to rate the intensity of the stimulation for the left and the right hand on a 10-point numerical rating scale (going from 0 = felt nothing, over 5 = fairly intense, to 9 = very intense). The equivalence of the average intensity for the left compared to the right hand for both groups was assessed using paired samples t-tests. Moreover, the equivalence of the self-reported intensity ratings was compared between both groups using one-sample t-tests.

After the experiment participants were asked to indicate how threatening they thought the visual lights were both when the light was approaching, and when the light was receding, on a scale from 0 (not at all) to 10 (extremely). The perceived threat score was compared for approaching and receding visual stimuli for both groups using Wilcoxon signed rank test for paired samples. Moreover, the perceived threat scores were compared for both groups using Wilcoxon signed rank test for unpaired samples.

2.5 ANALYSES

Based on previous research we expected the lights approaching the stimulated hand to have a stronger spatially dependent effect on tactile processing than either receding lights or lights approaching the non-stimulated hand (Canzoneri et al., 2012; De Paepe, Crombez, & Legrain, under review; Teneggi et al., 2013). If this is true, it would be especially interesting to compare control and patient data for the trials in which the lights were approaching the stimulated hand. To check this, we first analyzed control and patient data separately and checked whether approaching and receding lights differentially affected reaction times for both groups (**Step 1**: effect of visual stimulus direction). Next, to increase power and for the sake of parsimony, we only compared control and patient data for trials in which the lights were approaching participants' stimulated hand (**Step 2**: effect of group).

Results were analyzed using linear mixed effects models as implemented in the package "Linear and Nonlinear Mixed Effects Models" (Pinheiro & Bates, 2000). Linear mixed effects

models account for the correlations in within-subject data by estimating subject-specific deviations (or random effects) from each population-level factor (or fixed factor) of interest (see West, Welch, & Galecki, 2007, for an elaboration). The outcome variable of interest was the RT. During **Step 1** the independent variables were the *visual stimulus direction* (approaching versus receding lights), the *congruency* (congruent vs. incongruent), and the *temporal delay* (T1 to T7). These were manipulated within subjects. During **Step 2** the independent variables were *group* (control vs. patient) and *temporal delay* (T1 to T7), which were respectively between - and within-subjects variables. Each analysis required three steps. First, all relevant factors and interactions were entered in the model as fixed factors, and we assessed whether it was necessary to add a random effect for each of the fixed (within subject) factors in the analysis: If a random effect significantly increased the fit of the model, it was included in the final model. By default, a random effect was added introducing adjustments to the intercept conditional on the *Subject* variable. In the second step, we searched for the most parsimonious model that fitted the data. To achieve this, we systematically restricted the full model, comparing the goodness of fit using likelihood ratio tests. Finally, in the third step, we inspected the ANOVA table of the final model and tested specific hypotheses about possible main effects or interactions. Kenward-Roger approximations to the degrees of freedom were used to adjust for small sample sizes (Kenward & Roger, 1997). When an interaction effect was significant, it was further investigated with follow-up contrast analyses.

3 RESULTS

3.1 INTENSITY OF THE TACTILE STIMULATION

The mean intensities were not significantly different between the left and the right hand nor for the control participants (left hand: 0.53 ± 0.07 Watt, right hand: 0.50 ± 0.07 Watt; $t(36) = 1.80, p = 0.08$), nor for the FM patients (left hand: 0.51 ± 0.09 Watt, right hand: 0.48 ± 0.08 Watt; $t(37) = 1.94, p = 0.06$). There was no significant difference in intensities between control participants and FM patients (left hand: $t(67.70) = 1.10, p = 0.27$; right hand: $t(72.40) = 1.44, p = 0.15$).

The average self-reported intensities did not differ significantly for the left and the right hand, nor for the control participants (left hand: 3.08 ± 1.71 ; right hand: 3.28 ± 1.74 ; $t(36) = -1.97, p = 0.06$), nor for the FM patients (left hand: 3.45 ± 1.38 ; right hand: 3.62 ± 1.48 ; $t(37) = -1.31, p = 0.20$). There was no significant difference in self-reported intensities between

controls and FM patients (left hand: $t(69.07) = -1.05, p = 0.30$; right hand: $t(70.63) = -0.91, p = 0.36$).¹

3.2 PERCEIVED THREAT VALUE VISUAL STIMULI

Mean perceived threat scores were overall low, and were not significantly different when the lights were approaching (control participants: $M = 0.51, SD = 1.33$; FM patients: $M = 1.05, SD = 2.20$), compared to when they were receding (control participants: $M = 0.41, SD = 1.09$; FM patients: $M = 1.02, SD = 2.22$) from the participants (control participants: $Z = 3, p = 0.37$; FM patients: $Z = 8.5, p = 0.89$). Moreover, there was no significant difference in perceived threat scores between healthy controls and FM patients (Approaching: $Z = 639, p = 0.36$; Receding: $Z = 635.5, p = 0.33$).

3.3 ACCURACY

All control participants had more than 80% correct task performance. Mean accuracy for this group was 97% ($\pm 3\%$). Two FM patients had less than 80% correct (79.91% and 50.22%) and were excluded from further analyses. Mean accuracies for the remaining patients was 97% ($\pm 2\%$). Accuracies were not further analyzed.

¹ To control whether the side of the stimulation had an influence on the task performance, the *side of the tactile stimulus* was added to the model as additional variable. For control participants, there was a significant interaction effect between *congruency* and *side of stimulation* ($F(1,2004) = 6.59; p = 0.01$), showing that participants were significantly faster to respond on congruent as opposed to incongruent trials when their right hand was stimulated ($\chi^2(1) = 23.39; p < 0.001$), but not when their left hand was stimulated ($\chi^2(1) = 1.46; p = 0.23$). Nor the main effect of *side of stimulation* ($F(1,2004) = 0.21; p = 0.65$), nor any of its interactions with other variables were significant (all $F < 1; p > 0.45$). For FM patients, there was a marginally significant main effect of the *side of stimulation* ($F(1,1998) = 2.82; p = 0.09$), indicating that patients responded faster when the right hand was stimulated than when the left hand was stimulated. However, none of the interaction effects between *side of stimulation* and any of the other variables were significant, indicating that this did not influence the effect of the lights on somatosensory processing (all $F < 0.6; p > 0.70$). Therefore, the side of stimulation was left out of any further analyses.

3.4 REACTION TIMES

3.4.1 EFFECT OF VISUAL STIMULUS DIRECTION

3.4.1.1 CONTROL PARTICIPANTS

For control participants, the relationship between the RTs and the tactile targets, the different *temporal delays* at which the tactile stimuli were administered (from T1 to T7), the *direction* of the visual stimulus (approaching vs. receding) and the *congruency* of the tactile stimulation (congruent vs. incongruent to the visual stimuli) are represented in Figure 2.

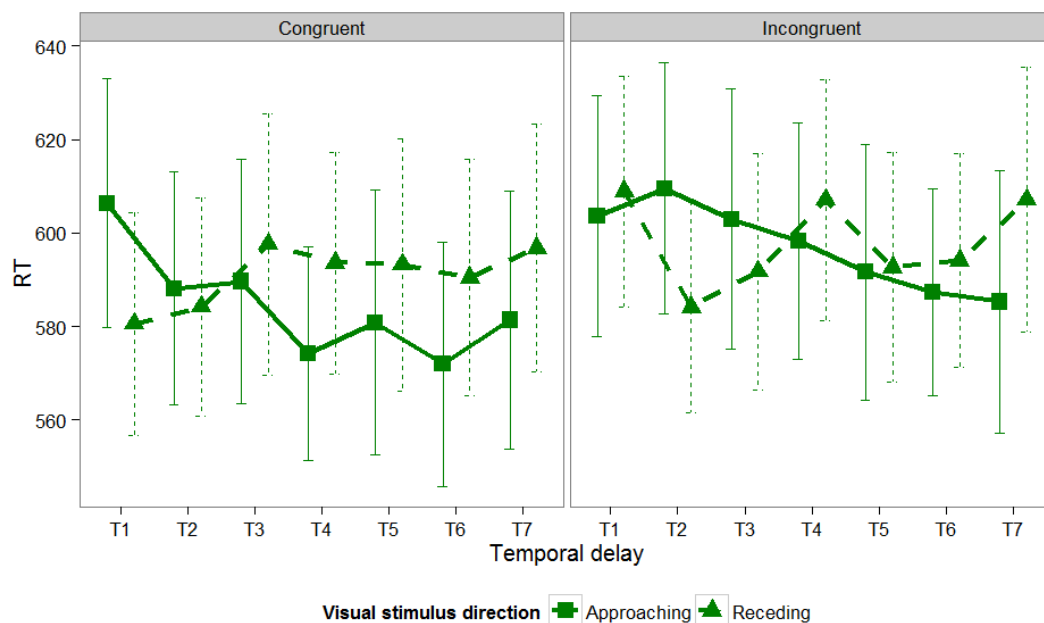


FIGURE 2. MEAN RT'S TO THE TACTILE TARGETS AND THEIR ASSOCIATED STANDARD ERRORS IN FUNCTION OF THE DIFFERENT TEMPORAL DELAYS AT WHICH THE TACTILE STIMULI WERE ADMINISTERED (FROM T1 TO T7), THE DIRECTION OF THE VISUAL STIMULUS (APPROACHING VS. RECEDING) AND THE CONGRUENCY OF THE TACTILE STIMULATION (CONGRUENT VS. INCONGRUENT TO THE VISUAL STIMULUS) FOR CONTROL PARTICIPANTS. THE LEFT SIDE OF THE FIGURE REPRESENTS THE CONGRUENT TRIALS, WHILE THE RIGHT SIDE REPRESENTS THE INCONGRUENT TRIALS. THE SOLID AND DASHED GREEN LINES DEPICT THE RT'S IN FUNCTION OF THE TEMPORAL DELAYS FOR THE APPROACHING AND RECEDING LIGHTS RESPECTIVELY.

The linear mixed effects model that demonstrated the best fit with the data, included all fixed factors together with their two- and three-way interactions, and a random subject-based intercept. The parameter estimates of the fixed effects together with their 95% confidence interval (CI) are shown in the Appendix (Table 1). In this final model,

there was a significant main effect of *visual stimulus direction* ($F(1,972) = 5.67$; $p = 0.02$) and *temporal delay* ($F(6,972) = 3.89$; $p < 0.001$). Moreover, there was a significant interaction effect between *visual stimulus direction* and *congruency* ($F(1,972) = 5.12$; $p = 0.02$) and between *visual stimulus direction* and *temporal delay* ($F(6,972) = 3.41$; $p = 0.002$). Finally, the three-way interaction between *visual stimulus direction*, *congruency* and *temporal delay* was marginally significant ($F(6,972) = 1.88$; $p = 0.08$). The main effect of *congruency* ($F(1,972) = 0.02$; $p = 0.90$) and the interaction effect between *congruency* and *temporal delay* ($F(6,972) = 1.25$; $p = 0.28$) were not significant. To further investigate the three-way interaction and the two-way interactions, two separate linear mixed effect models were fitted for congruent and incongruent trials with *visual stimulus direction* and *temporal delay* as independent variables and RT as dependent variable.

For *congruent* trials, the model that demonstrated the best fit with the data included all fixed effect factors and their interaction, and a random subject-based intercept. In this model there was a significant main effect of *visual stimulus direction* ($F(1,468) = 5.19$; $p = 0.02$), a significant main effect of *temporal delay* ($F(6,468) = 3.56$; $p = 0.002$) and a significant interaction effect between *visual stimulus direction* and *temporal delay* ($F(6,468) = 3.12$; $p = 0.005$). Follow-up tests indicated that RTs at T1 were significantly faster for trials with receding visual stimuli than for those with approaching visual stimuli ($\chi^2(1) = 5.19$; $p = 0.02$). At T2 and T3 there was no significant difference in RTs between trials with approaching and receding visual stimuli (all $\chi^2 < 0.75$; all $p > 0.35$). Finally, from T4 to T7 the effect was reversed and RTs were now significantly faster for trials with approaching stimuli than for receding stimuli (T4: $\chi^2(1) = 4.43$; $p = 0.04$; T5: $\chi^2(1) = 4.13$; $p = 0.04$; T6: $\chi^2(1) = 5.78$; $p = 0.02$; T7: $\chi^2(1) = 4.11$; $p = 0.04$). Pairwise comparisons between the different temporal delays only revealed a marginally significant difference between T1 and T6 ($t(36) = -1.54$; $p = 0.07$) for approaching visual stimuli, indicating that, when lights were approaching, RTs were significantly slower at T1 than at T6. No other comparisons were significant nor for approaching, nor for receding visual stimuli (all $|t| < 1.35$; all $p > 0.10$).

For *incongruent* trials, a similar model was fitted to the data, that included all fixed effect factors and their interaction, and a random subject-based intercept. There was a significant main effect of *temporal delay* ($F(6,468) = 3.59$; $p = 0.002$), and a significant interaction effect between *visual stimulus direction* and *temporal delay* ($F(6,468) = 2.66$; $p = 0.01$). The main effect of *visual stimulus direction* did not reach significance ($F(1,468) = 0.75$; $p = 0.39$). Follow-up tests indicated that at T2, RTs for trials with receding visual stimuli were significantly faster than for those with approaching visual stimuli ($\chi^2(1) =$

5.45; $p = 0.02$). Conversely, at T7, RTs were significantly faster for trials with approaching visual stimuli than for trials with receding visual stimuli ($\chi^2(1) = 9.70$; $p = 0.002$). At the remaining temporal delays there was no significant difference between RTs for approaching versus receding stimuli trials (all $\chi^2 < 0.75$; all $p > 0.35$). Pairwise comparisons between the different temporal delays revealed a marginally significant difference between T2 and T7 ($t(36) = -1.42$; $p = 0.08$) for approaching visual stimuli. No other comparisons were significant, nor for approaching, nor for receding visual stimuli (all $|t| < 1.02$; $p > 0.16$).

3.4.1.2 FM PATIENTS

For FM patients, the relationship between the RTs and the tactile targets, the different temporal delays at which the tactile stimuli were administered (from T1 to T7), the direction of the visual stimulus (approaching vs. receding) and the congruency of the tactile stimulation (congruent vs. incongruent to the visual stimulus) are represented in Figure 3.

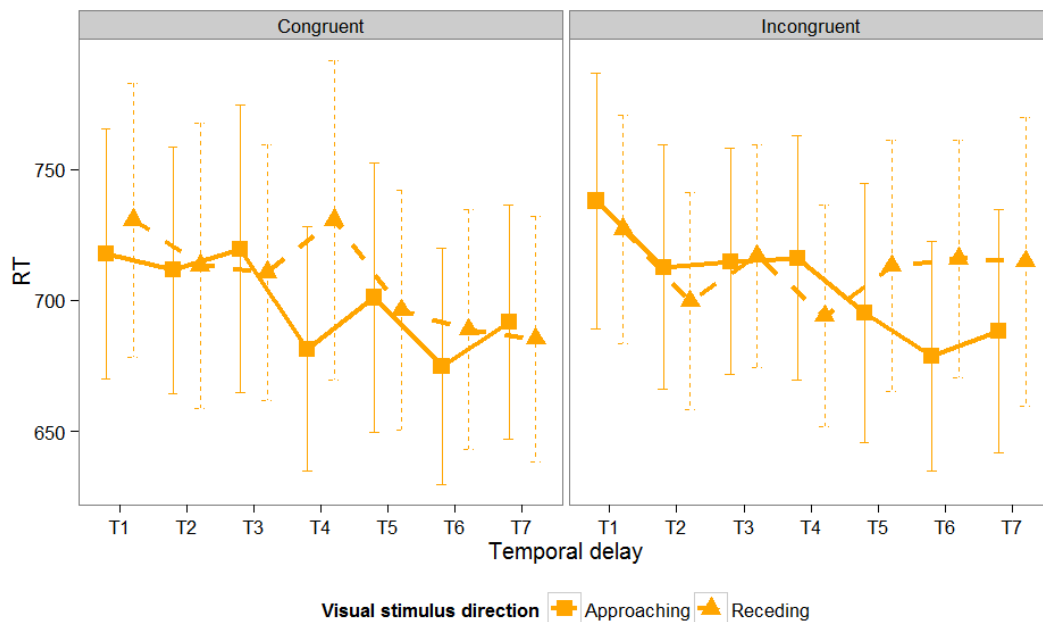


FIGURE 3. MEAN RT'S TO THE TACTILE TARGETS AND THEIR ASSOCIATED STANDARD ERRORS IN FUNCTION OF THE DIFFERENT TEMPORAL DELAYS AT WHICH THE TACTILE STIMULI WERE ADMINISTERED (FROM T1 TO T7), THE DIRECTION OF THE VISUAL STIMULUS (APPROACHING VS. RECEDING) AND THE CONGRUENCY OF THE TACTILE STIMULATION (CONGRUENT VS. INCONGRUENT TO THE VISUAL STIMULUS) FOR FM PATIENTS. THE LEFT SIDE OF THE FIGURE REPRESENTS THE CONGRUENT TRIALS, WHILE THE RIGHT SIDE REPRESENTS THE INCONGRUENT TRIALS. THE SOLID AND DASHED ORANGE LINES DEPICT THE RT'S IN FUNCTION OF THE TEMPORAL DELAYS FOR THE APPROACHING AND RECEDING LIGHTS RESPECTIVELY.

The linear mixed effects model that demonstrated the best fit with the data, included all fixed factors together with their two- and three-way interactions, a random subject-based intercept, and a random effect for *congruency* and *temporal delay*. The parameter estimates of the fixed effects together with their 95% confidence interval (CI) are shown in the Appendix (Table 2). In this final model, there was a significant main effect of *temporal delay* ($F(6,255.28) = 4.50$; $p < 0.001$), a significant interaction between *visual stimulus direction* and *temporal delay* ($F(6,740) = 2.70$; $p = 0.01$), and a significant three-way interaction between *visual stimulus direction*, *congruency* and *temporal delay* ($F(6,740) = 2.33$; $p = 0.03$). The main effects of *visual stimulus direction* ($F(1,740) = 0.26$; $p = 0.61$) and *congruency* ($F(1,568.41) = 1.45$; $p = 0.23$) as well as the interaction effects of *visual stimulus direction* with *congruency* ($F(1,740) = 0.62$; $p = 0.43$) and of *congruency* with *temporal delay* ($F(6,740) = 1.25$; $p = 0.28$) did not reach significance. To further investigate the three-way interaction, two separate linear mixed effects models were fitted for congruent and incongruent trials with *visual stimulus direction* and *temporal delay* as independent variables and RT as dependent variable.

For *congruent* trials, the model that demonstrated the best fit with the data included the fixed factors and their interaction, and a random subject-based intercept. In this model there was a significant main effect of *temporal delay* ($F(6,481) = 5.79$; $p < 0.001$) and a significant interaction effect between *visual stimulus direction* and *temporal delay* ($F(6,481) = 2.26$; $p = 0.04$). The main effect of *visual stimulus direction* was not significant ($F(1,481) = 0.22$; $p = 0.64$). Follow-up tests indicated that RTs did not differ significantly between trials with approaching and receding visual stimuli from T1 to T3 (all $\chi^2 < 1.20$; all $p > 0.25$). At T4 and T6 RTs were (marginally) significantly faster for trials with approaching than for those with receding visual stimuli (T4: $\chi^2(1) = 9.75$; $p = 0.002$; T6: $\chi^2(1) = 3.34$, $p = 0.07$). At T5 and T7 RTs were not significantly different for trials with approaching and receding visual stimuli (all $\chi^2 < 0.30$; all $p > 0.50$). Pairwise comparisons between the different temporal delays showed that there were no significant differences in RTs between the temporal delays nor for approaching, nor for receding visual stimuli (all $|t| < 0.93$; all $p > 0.14$).

For *incongruent* trials, a similar model was fitted with all fixed factors, and their interaction, and a random subject-based intercept. In this model there was only a main effect of *temporal delay* ($F(6,481) = 5.64$; $p < 0.001$). The main effect of *visual stimulus direction* ($F(1,481) = 0.31$; $p = 0.58$) and the interaction effect between *temporal delay* and *visual stimulus direction* ($F(6,481) = 1.57$; $p = 0.15$) were not significant, indicating that RTs in this condition were less affected by the position of the visual stimuli in space.

3.4.2 EFFECT OF GROUP

The present study, as well as previous studies (Canzoneri et al., 2012; De Paepe et al., under review; Teneggi et al., 2013) suggest that stimuli approaching the stimulated hand have a larger spatially dependent effect on somatosensory processing compared to receding stimuli, or stimuli approaching the opposite side. Therefore, to assess potential differences in the spatially dependent effect of visual stimuli on somatosensory processing between FM patients and control participants we only used the congruent trials with approaching visual stimuli.

The model that demonstrated the best fit with the data included a main effect of *temporal delay*, a main effect of *group*, and a random subject-based intercept. Adding the interaction effect between *temporal delay* and *group* did not significantly increase the fit of the model. Therefore the interaction effect was not included in the model. In the final model, there was a significant main effect of *temporal delay* ($F(6,444) = 8.91; p < 0.001$), and a significant main effect of *group* ($F(1,73) = 8.53; p = 0.005$), indicating that FM patients responded significantly slower than the control participants.

Finally, to assess whether the curves describing the relationship between the RTs and the *temporal delay* were different between FM patients and healthy controls, we simplified the model for both groups by considering *temporal delay* as a continuous variable instead of a factor, so that T1 corresponds to 170 ms, T2 to 450 ms, T3 to 730 ms, T4 to 1010 ms, T5 to 1290 ms, T6 to 1570 ms and T7 to 1850 ms. The nature of the relationship between the independent variable *temporal delay* and the dependent variable RT was investigated by fitting models with RT (on the original scale) as dependent variable and *temporal delay* as independent variable separately for FM patients and control participants². At each time the restricted models (with *temporal*

² It should be noted that previous studies investigating modulations of the peripersonal space fitted a sigmoid function of the following form to their data: $y = \frac{y_{min} + y_{max} \cdot e^{(x-x_c)/b}}{1 + e^{(x-x_c)/b}}$, where x represents the independent variable (temporal delay), y the dependent variable (i.e., RT), y_{min} and y_{max} the lower and upper saturation levels of the sigmoid, x_c the value of the abscissa at the central point of the sigmoid (i.e., the value of x at which $y = (y_{min} + y_{max})/2$) and b establishes the slope of the sigmoid at the central point (Teneggi et al., 2013; Taffou et al., 2014). For the sake of comparability we tried to fit this sigmoid function to our data. Values of the parameters y_{min} and y_{max} were set a priori to the minimum and maximum values for each participant, and the estimated parameters were the central position of the sigmoid (x_c) and the slope of the sigmoid at the central point. A sigmoid function could only be fitted for 21 out of 37 control participants (56%), and for 23 out of 38 FM patients (61%). For these participants the parameter x_c was compared for control participants and FM patients as a measure of the distance, at which the visual stimuli started affecting

Continued on next page...

delay as continuous variable) were compared with the full model (with *temporal delay* as categorical variable). For the control participants a linear relationship was considered assuming a constant increase/decrease of RTs as a function of temporal delay. This model did not fit the data significantly worse than the model with temporal delay as a categorical variable ($\chi^2(5) = 5.51, p = 0.36$). For control participants the relationship between the RTs and *temporal delay* could thus be adequately described by assuming a linear model. For FM patients the same strategy was applied. First, a linear relationship was considered, assuming a constant increase/decrease of RTs as a function of the temporal delay. This model fitted the data significantly worse than the model with *temporal delay* as a categorical predictor ($\chi^2(5) = 12.05; p = 0.03$). Next, a quadratic relationship was considered by adding the square of the independent variable *temporal delay* to the model. This model did not fit the data significantly worse than the full model ($\chi^2(4) = 8.41, p = 0.08$). For FM patients the relationship between the RTs and *temporal delay* could be adequately described by assuming a quadratic model. The predicted values of these models, centered around the group means, together with their fitted curves are shown in Figure 4.

tactile RTs. Results showed that this parameter was not significantly different for FM patients ($M = 789.09, SD = 331.03$) as compared to healthy control participants ($M = 808.70; SD = 305.91$) ($t(41.99) = 0.20; p = 0.80$). Since a sigmoid function could only be fitted to less than 60% of the data, this approach seems less appropriate for the present study.

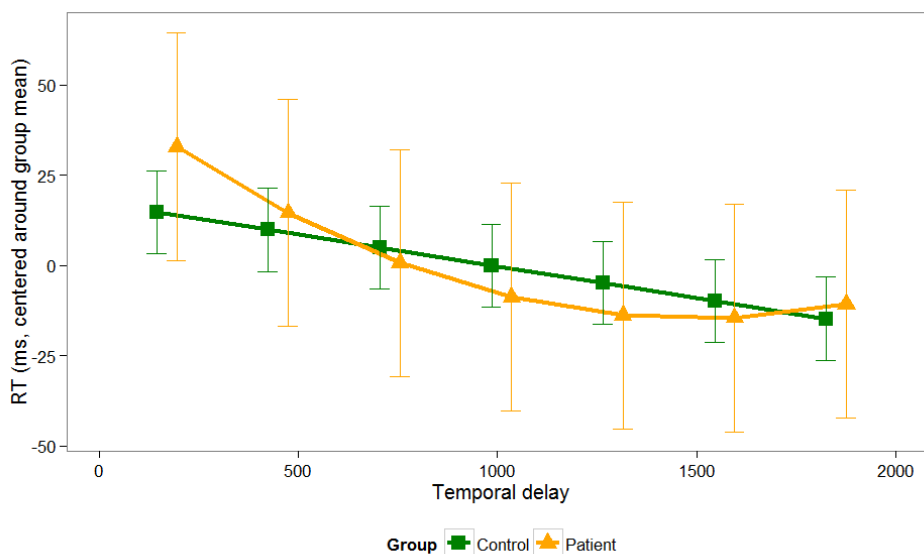


FIGURE 4. PREDICTED VALUES AND STANDARD ERRORS FOR THE RELATIONSHIP BETWEEN RT'S TO THE TACTILE TARGETS IN FUNCTION OF THE DIFFERENT TEMPORAL DELAYS AT WHICH THE TACTILE STIMULI WERE ADMINISTERED (FROM T1 TO T7), AND THE GROUP TO WHICH PARTICIPANTS BELONG (FM PATIENT VS. CONTROL). TO EASILY COMPARE THE CURVES FOR BOTH GROUPS, THE PREDICTED VALUES ARE CENTERED AROUND THE GROUP MEAN. FOR CONTROL PARTICIPANTS, A LINEAR MODEL ADEQUATELY FITTED THE DATA (GREEN CURVE), WHEREAS FOR FM PATIENTS A QUADRATIC MODEL FITTED THE DATA BEST (ORANGE CURVE).

4 DISCUSSION

In the present study, we investigated whether attention towards stimuli approaching the participant's body differed for FM patients compared to healthy control participants. To this end, the differential influence of dynamical visual stimuli on tactile processing was studied for control participants and FM patients. For control participants, we found that visual stimuli presented near the stimulated hand influenced tactile processing more than visual stimuli presented far from the hand. For FM patients this difference was less clear. The influence of the approaching visual stimuli on tactile processing along a continuous spatial range (from near to far) was compared for controls and FM patients. Although there were no significant differences in RTs between both groups, the curves describing the RTs along the spatial range were different for FM patients compared to healthy control participants. However, as this difference was only found when curve-fitting the data, our results should be interpreted with caution, and need further corroboration and replication.

The ability to interact with the world closely surrounding us depends on the integration of somatosensory stimuli on the body space, external stimuli presented near the body, and information about body posture (Cardinali, Brozzoli, & Farnè, 2009; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981; Spence & Driver, 2004). For visuo-tactile integration it has been

demonstrated in monkeys that this ability relies on neurons with multimodal receptive fields (RFs), found mainly in the premotor and intraparietal areas (Graziano, Hu, & Gross, 1997; Graziano, Yap, & Gross, 1994). These neurons are activated in response to both tactile stimuli and to visual stimuli occurring close to the stimulated body parts. Graziano & Cooke (2006) argued that one of the main functions of these cortical areas is to maintain a margin of safety around the body and to coordinate defensive actions. In humans, the use of a peripersonal frame of reference for the localization of somatosensory stimuli has been demonstrated both in neuropsychological studies with patients suffering from crossmodal extinction consecutive to right hemisphere damages (di Pellegrino, Làdavas, & Farnè, 1997; Làdavas, di Pellegrino, Farnè, & Zeleni, 1998) and in healthy participants using crossmodal congruency tasks (Holmes, Sanabria, Calvert, & Spence, 2006; Sambo & Forster, 2009; Spence, Pavani, & Driver, 2000, 2004). Neuroimaging studies provide support for the role of the frontal cortex (Lloyd, Shore, Spence, & Calvert, 2003) and the parietal cortex (Makin, Holmes, & Zohary, 2007) in the multisensory representation of the body. This fronto-parietal network might in turn boost the activity of unisensory areas, facilitating the processing of sensory inputs from each modality (Kennett, Eimer, Spence, & Driver, 2001; Macaluso, Frith, & Driver, 2000; Taylor-Clarke, Kennett, & Haggard, 2002). Overall, these studies show that the crossmodal influence of visual stimuli on tactile processing is more pronounced when visual stimuli are presented near the stimulated body limb as opposed to far from that limb. Recently, these results were extended to the crossmodal interaction between visual stimuli and stimuli specifically activating nociceptive skin receptors (De Paepe et al., 2015, 2014, in preparation).

The studies mentioned so far have investigated multimodal integration in the peripersonal space using static stimuli at two fixed positions (near vs. far). Some studies have also demonstrated this phenomenon with moving stimuli (e.g., Canzoneri et al., 2012; Van der Biest, Legrain, De Paepe, & Crombez, 2015; De Paepe et al., under review). The use of moving stimuli is more ecologically valid and more comparable to animal studies investigating multimodal integration in the peripersonal space (Dong, Chudler, Sugiyama, Roberts, & Hayashi, 1994; Duhamel, Colby, & Goldberg, 1998; Graziano et al., 1997). Furthermore studies in both humans and monkeys (Graziano et al., 1997; Makin et al., 2007) have shown that the neural systems representing the peripersonal space show a preference for moving stimuli. The use of moving stimuli also enables the investigation of the influence of external stimuli along a continuous spatial range (from near to far). For example, Canzoneri et al., (2012) measured reaction times (RTs) to a tactile stimulus applied to the right index finger while dynamical sounds, which gave the impression of either approaching

or receding from the subject's hand, were presented. Tactile stimuli were delivered at different temporal delays from the onset of the sound, such that it occurred when the sound source was perceived at varying distances from the body. Participants were asked to respond as fast as possible, trying to ignore the sound. They found that an auditory stimulus speeded up the processing of a tactile stimulus applied to the hand when the sound was administered within a limited distance from the hand. Moreover, results suggested that approaching sounds had a stronger spatially-dependent effect on tactile processing compared to receding sounds. Recently, we adapted this paradigm to investigate the influence of dynamical visual stimuli on nociceptive processing in healthy volunteers (De Paepe et al., under review). In this study, a visual stimulus was either approaching or receding the participant's left or right hand on each trial. At different temporal delays from the onset of the visual stimulus, a nociceptive stimulus was applied either at the same or the opposite hand, so that it was presented when the visual stimulus was perceived at varying distances from the hand. Participants were asked to respond as fast as possible at which side they perceived a nociceptive stimulus. We found similar results as Canzoneri et al. (2012): RTs were fastest when the visual stimulus appeared near the stimulated hand and approaching lights had a stronger spatially dependent effect on nociceptive processing, compared to receding lights.

In the present study we were able to replicate these results in *healthy, community dwelling* participants using the same paradigm with tactile stimuli instead of nociceptive stimuli. Results showed that at low temporal delays, RTs were faster for receding visual stimuli, whereas at high temporal delays, RTs were faster for approaching visual stimuli. This indicates that the visual stimuli had the largest impact on tactile processing when they were presented near the participants' hand. In contrast with the previous study (De Paepe et al., under review) we found that the effect of the temporal delay on RTs was dependent on the visual stimulus direction both for congruent and incongruent visual stimuli. However, further investigation of these interactions showed that for congruent visual stimuli there was a clear pattern going from faster RTs for receding visual stimuli trials at low temporal delays, over no difference at intermediate delays, to faster RTs for approaching visual stimuli at high temporal delays. Conversely, for incongruent trials there was only a significant difference between approaching and receding trials at T2 and T7, probably indicating that the effect of the visual stimuli was less robust when visual stimuli were approaching or receding the opposite (non-stimulated) hand. Our results are in line with studies in monkeys and humans, suggesting that the representation of peripersonal space is

body-part centered (De Paepe et al., under review; di Pellegrino et al., 1997; Graziano et al., 1997).

Next, we were interested whether a similar response pattern could be found in *FM patients*. In accordance with the previous study (De Paepe et al., under review), we found that the direction of the visual stimuli only influenced the relationship between the temporal delay and the RTs for congruent trials and not for incongruent trials. Further investigation of the congruent trials showed that RTs were faster for approaching versus receding visual stimulus trials at some of the high temporal delays (T4 and T6). At low temporal delays there was no significant difference. This may indicate that FM patients already had faster RTs for approaching stimuli at low temporal delays, causing the difference between receding and approaching trials to disappear. This would be in agreement with the idea that FM patients have altered reactions to stimuli at further distance from the body compared to healthy control participants. However, it should be noted that there was a large variability in RTs between patients: The variance of the random intercept explained 32% of the total variance for the FM data, compared to only 5% for the data of the control participants. This huge amount of variance between patients may have created a lot of noise, masking significant differences within the data. Therefore, caution is warranted in interpreting our results, and we feel yet unable to draw strong inferences. Further research may try to reduce the variability amongst patients, by categorizing patients into more similar groups based on age, onset of FM, amount of pain, or individual difference variables such as anxiety and catastrophizing that may be considered to play an important role.

Paradigms similar to the one of Canzoneri et al. (2012) have also been used to demonstrate modulations of the peripersonal space (Taffou & Viaud-Delmon, 2014; Teneggi et al., 2013), comparing the influence of approaching stimuli on tactile processing across different experimental conditions. In the present study, we compared the influence of the visual stimuli, approaching the stimulated hand of the participants, on tactile processing between control participants and FM patients. The comparison between both groups was only made for trials in which the visual stimulus was approaching the hand that received the tactile stimulus, because results of the present and previous studies indicated that stimuli approaching the stimulated hand have a larger spatially dependent effect on somatosensory processing than receding stimuli or stimuli approaching the opposite hand (Canzoneri et al., 2012; De Paepe et al., under review; Teneggi et al., 2013). Moreover, previous research investigating modulations of the peripersonal space across different conditions or groups also focused exclusively on approaching stimuli. Therefore, to increase the power of the

model and for the sake of parsimony, we only considered these trials. Results showed that RTs decreased with increasing temporal delays, but this decrease was not significantly different for FM patients compared to control participants. Additionally, we found that FM patients responded slower than control participants. This is in accordance with previous studies (Correa, Miró, Martínez, Sánchez, & Lupiáñez, 2011; del Paso, Montoro, & Duschek, 2015) and was suggested to be associated with a reduced capacity to maintain the level of activation necessary to perform the task (Correa et al., 2011; Miró et al., 2011), as shown by studies demonstrating impairments in the speed of processing (Cote & Moldofsky, 1997), in sustained attention (Dick, Eccleston, & Crombez, 2002; Dick, Verrier, Harker, & Rashiq, 2008) and in the alerting system (Miró et al., 2011) in FM patients. The fact that we did not find any differences between FM patients and healthy controls can be attributed to a number of factors. First, the cognitive deficits identified in FM patients, mentioned above, may make it difficult to find significant results in a cognitive demanding task such as the present study. Moreover, this may also explain the large inter-individual variability in RTs found in this study. Second, the large inter-individual variability in the FM group may have masked an effect in this group, making it difficult to find any differences between groups. Third, it should be noted that not all studies found evidence for perceptual amplification in modalities other than pain in FM patients (Carrillo-de-la-Peña, Triñanes, González-Villar, Gómez-Perretta, & García-Larrea, 2014; Lorenz, 1998; Van Damme et al., 2015) and the studies that did find differences used auditory instead of visual stimuli (Dohrenbusch, Sodhi, Lamprecht, & Genth, 1997; Hollins et al., 2009; McDermid et al., 1996).

Finally, we assessed differences in the spatially-dependent effect of the visual stimuli on tactile processing by fitting curves to the RTs at the different temporal delays for both groups. For control participants a linear function adequately described the data, indicating that RTs showed a constant decrease with increasing temporal delays. This is in contrast with the previous study in which a quadratic function (De Paepe et al., under review) described the data best. However, in the previous study nociceptive targets were used instead of tactile targets. A possible explanation could be that in the context of nociceptive stimuli the visual stimuli approaching the participants are experienced as more threatening than in the context of tactile stimuli. Indeed, although the perceived threat value of the approaching lights was low in both studies, it was significantly higher in the previous study ($M = 1.78$, $SD = 2.47$) (De Paepe et al., under review), than in the present study ($M = 0.51$, $SD = 1.33$), $t(36.90) = 2.42$; $p = 0.02$. Previous studies have shown that the spatially-dependent effect of external stimuli on nociceptive and tactile processing is stronger for approaching than for receding stimuli (Ball & Tronick, 1971; Bremmer, Duhamel, Ben Hamed, & Graf,

2002; Canzoneri et al., 2012; Colby, Duhamel, & Goldberg, 1993; De Paepe et al., under review; Duhamel, Bremmer, Benhamed, & Graf, 1997; Kandula, Hofman, & Dijkerman, 2014; Schiff, Caviness, & Gibson, 1962; Schiff, 1965; Tinbergen, 1951). It could be that this is especially true in a threatening context, in which it is crucial to quickly prepare an appropriate defensive response. This is consistent with research showing that individuals underestimate the time a visual stimulus approaching them will collide with them when the stimulus is threatening (snakes, spiders, angry faces) compared to when it is non-threatening (butterflies, rabbits, neutral faces) (Brendel, DeLucia, Hecht, Stacy, & Larsen, 2012; Vagnoni, Lourenco, & Longo, 2012). Although an intriguing hypothesis, future studies need to address this issue directly, by comparing the spatially-dependent effect of visual stimuli on nociceptive and tactile processing, preferably within the same participants. Conversely, for FM patients we found that a quadratic function best described the data. RTs showed a steep decrease at low temporal delays, to stabilize at higher temporal delays. The perceived threat value of the approaching stimuli for the patients was comparable to that of the previous study (De Paepe et al., under review) ($M = 1.05$, $SD = 2.20$; $t(52.05) = 1.22$, $p = 0.23$) and was somewhat higher (although not significantly) than the perceived threat value for the control group. This could explain why in agreement with the previous study, a quadratic function fitted the data best for FM patients, while a linear function fitted the data best for the healthy control participants. The fact that FM patients showed a quicker decline in RTs at high temporal delays seems compatible with the hypothesis that FM patients would have a heightened attention for stimuli entering the peripersonal space. The difference between FM patients and healthy control participants, could result from the fact that FM patients are 'hypervigilant' for sensory information. The mechanisms of hypervigilance or still not completely understood. Although different theories exist (e.g., Chapman, 1978; Hollins et al., 2009; McDermid et al., 1996; Rollman & Lautenbacher, 1993), the 'attentional gain control theory' of Hollins et al. (2009) seems most compatible with the present results. Hollins et al. (2009) proposed that "*hypervigilance begins as a cognitive process, in which an individual is concerned about, and therefore closely monitors, particular types of sensations – especially those that, while not necessarily unpleasant in themselves, accompany or warn impending pain. (...) Sustained direction of this affect-charged attention to a particular kind of stimulation, produces, over time, an increase in the perceptual gain for all stimuli of that type*" (Hollins et al., 2009, p 221). Because of this heightened attention for stimuli signaling potential threat to the body, FM patients may show a stronger spatially dependent effect of the approaching lights on tactile reaction times than control participants.

It should be noted that based on the present study we cannot be sure whether any differences observed between controls and FM patients are due to a modulation of the peripersonal space (i.e. whether the same system is now used to perceive stimuli both at near and far positions) or rather to a more extreme reaction to stimuli in the extrapersonal space. In the latter view, two distinct systems would still be distinguishable to perceive stimuli at a proximal versus farther positions, but stimuli at farther positions are now perceived equally threatening or relevant as proximal stimuli. This contrast is difficult to make and depends on the conceptualization of the peripersonal space. Here we defined peripersonal space as ‘the space in which stimuli on the body space are integrated with stimuli occurring in the external world’. In some of the previous studies this integration seems to be best described by a sigmoid function (Canzoneri et al., 2012; Taffou & Viaud-Delmon, 2014; Teneggi et al., 2013), and the abscissa at the inflection point of the sigmoidal curve is taken as the boundary of the peripersonal space. This boundary between peripersonal and extrapersonal space seems rather arbitrary, and in the present study sigmoid functions did not fit our data adequately. We argue that a strict boundary between the peripersonal and extrapersonal space is unlikely to exist, and that some multimodal integration will probably also occur in what we call the ‘extrapersonal’ space (see e.g., De Paepe et al., 2015, 2014; Rizzolatti et al., 1981). Therefore, ‘a modulation of the peripersonal space’ should be seen as a difference in attention towards stimuli approaching the body, rather than the extension or reduction of a strict boundary between peripersonal and extrapersonal space.

This study has some limitations. First of all, the high inter-individual variability in the patient data posed a great challenge for analyzing and interpreting the data. As mentioned above, this could be due to attentional and information processing problems in FM patients (Correa et al., 2011; Miró et al., 2011) and may always be a problem when using RT as dependent variable. Future studies should focus on paradigms using different measures (such as accuracy) (e.g., temporal order judgment tasks). Second, the present study was not designed to explain the underlying mechanisms of possible modulations of the peripersonal space due to FM. One possibility is that FM patients appraise bodily sensations as dangerous, and are therefore more likely to continuously scan the body and the space closely surrounding it for threatening sensations (Chapman, 1978; Crombez, Eccleston, Van den Broeck, Goubert, & Van Houdenhove, 2004). This could lead to the perceptual amplification and possibly also to a modulation of the peripersonal space compared to healthy control participants. In this respect it could be interesting to take psychological variables such as catastrophizing about pain or body vigilance into account. Apart from adding these variables

to the model as covariates, another possibility would be to categorize the participants into several subgroups based on these variables. As mentioned above, this could have the additional advantage of reducing inter-individual variability. It is possible that only a particular subgroup of patients showed the effect. Unfortunately, our study lacked statistical power for such an approach. Third, in the present study we investigated the influence of visual stimuli on tactile processing. Previous studies showing evidence for perceptual amplification have largely used auditory stimuli (Dohrenbusch et al., 1997; Hollins et al., 2009; McDermid et al., 1996). It could be that FM patients do not show perceptual amplification for visual stimuli, or that perceptual amplification is much weaker for visual stimuli. Moreover, studies showing modulations of the peripersonal space have used auditory stimuli in a detection task, in which participants have to respond as quickly as possible when they felt something (Taffou & Viaud-Delmon, 2014; Teneggi et al., 2013). In the present study we used a localization task, in which participants have to respond as quickly as possible which hand was stimulated. To be able to compare our results with those of previous studies, it could be interesting to adapt the paradigm, using auditory stimuli in a detection task instead of visual stimuli in a localization task.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest related to the present article.

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6 APPENDIX

	Parameter estimate	95% CI
Intercept	-1.75	[-1.83 to -1.67]
Visual stimulus direction	-0.07	[-0.12 to -0.01]
Congruency	0.004	[-0.05 to 0.06]
Temporal delay (T2)	-0.05	[-0.10 to 0.004]
Temporal delay (T3)	-0.06	[-0.11 to -0.004]
Temporal delay (T4)	-0.09	[-0.14 to -0.04]
Temporal delay (T5)	-0.10	[-0.16 to -0.05]
Temporal delay (T6)	-0.11	[-0.17 to -0.06]
Temporal delay (T7)	-0.09	[-0.14 to -0.03]
Visual stimulus direction x Congruency	0.09	[0.01 to 0.17]
Visual stimulus direction x Temporal delay (T2)	0.05	[-0.03 to 0.13]
Visual stimulus direction x Temporal delay (T3)	0.09	[0.01 to 0.17]
Visual stimulus direction x Temporal delay (T4)	0.13	[0.05 to 0.20]
Visual stimulus direction x Temporal delay (T5)	0.13	[0.05 to 0.20]
Visual stimulus direction x Temporal delay (T6)	0.14	[0.06 to 0.21]
Visual stimulus direction x Temporal delay (T7)	0.13	[0.05 to 0.20]
Congruency x Temporal delay (T2)	0.07	[-0.007 to 0.15]
Congruency x Temporal delay (T3)	0.03	[-0.04 to 0.11]
Congruency x Temporal delay (T4)	0.07	[-0.009 to 0.15]
Congruency x Temporal delay (T5)	0.05	[-0.03 to 0.13]
Congruency x Temporal delay (T6)	0.07	[-0.008 to 0.15]
Congruency x Temporal delay (T7)	0.0009	[-0.08 to 0.08]
Visual stimulus direction x Congruency x Temporal delay (T2)	-0.13	[-0.24 to -0.02]
Visual stimulus direction x Congruency x Temporal delay (T3)	-0.13	[-0.24 to -0.02]
Visual stimulus direction x Congruency x Temporal delay (T4)	-0.14	[-0.25 to -0.03]
Visual stimulus direction x Congruency x Temporal delay (T5)	-0.13	[-0.24 to -0.02]
Visual stimulus direction x Congruency x Temporal delay (T6)	-0.15	[-0.25 to -0.04]
Visual stimulus direction x Congruency x Temporal delay (T7)	-0.07	[-0.18 to 0.04]

TABLE 1. PARAMETER ESTIMATES AND ASSOCIATED 95% CONFIDENCE INTERVALS (CI) FOR THE FIXED EFFECTS OF THE FITTED MODEL PREDICTING THE INVERSE TRANSFORMED RT'S IN FUNCTION OF THE VISUAL STIMULUS DIRECTION, CONGRUENCY AND TEMPORAL DELAY FOR CONTROL PARTICIPANTS.

	Parameter estimate	95% CI
Intercept	-1.55	[-1.66 to -1.44]
Visual stimulus direction	-0.01	[-0.07 to 0.04]
Congruency	0.03	[-0.02 to 0.09]
Temporal delay (T2)	-0.04	[-0.09 to 0.02]
Temporal delay (T3)	-0.02	[-0.08 to 0.04]
Temporal delay (T4)	-0.11	[-0.18 to -0.05]
Temporal delay (T5)	-0.09	[-0.16 to -0.03]
Temporal delay (T6)	-0.13	[-0.19 to -0.06]
Temporal delay (T7)	-0.09	[-0.15 to -0.02]
Visual stimulus direction x Congruency	0.03	[-0.04 to 0.10]
Visual stimulus direction x Temporal delay (T2)	-0.006	[-0.08 to 0.07]
Visual stimulus direction x Temporal delay (T3)	-0.02	[-0.09 to 0.05]
Visual stimulus direction x Temporal delay (T4)	0.10	[0.03 to 0.18]
Visual stimulus direction x Temporal delay (T5)	0.03	[-0.04 to 0.10]
Visual stimulus direction x Temporal delay (T6)	0.07	[-0.007 to 0.14]
Visual stimulus direction x Temporal delay (T7)	0.02	[-0.05 to 0.10]
Congruency x Temporal delay (T2)	-0.005	[-0.08 to 0.07]
Congruency x Temporal delay (T3)	-0.002	[-0.08 to 0.07]
Congruency x Temporal delay (T4)	0.06	[-0.01 to 0.14]
Congruency x Temporal delay (T5)	-0.02	[-0.09 to 0.05]
Congruency x Temporal delay (T6)	0.01	[-0.06 to 0.08]
Congruency x Temporal delay (T7)	-0.02	[-0.10 to 0.05]
Visual stimulus direction x Congruency x Temporal delay (T2)	-0.02	[-0.13 to 0.08]
Visual stimulus direction x Congruency x Temporal delay (T3)	-0.002	[-0.105 to 0.102]
Visual stimulus direction x Congruency x Temporal delay (T4)	-0.15	[-0.25 to -0.05]
Visual stimulus direction x Congruency x Temporal delay (T5)	0.02	[-0.09 to 0.12]
Visual stimulus direction x Congruency x Temporal delay (T6)	-0.03	[-0.13 to 0.08]
Visual stimulus direction x Congruency x Temporal delay (T7)	-0.003	[-0.106 to 0.100]

TABLE 2. PARAMETER ESTIMATES AND ASSOCIATED 95% CONFIDENCE INTERVALS (CI) FOR THE FIXED EFFECTS OF THE FITTED MODEL PREDICTING THE INVERSE TRANSFORMED RT'S IN FUNCTION OF VISUAL STIMULUS DIRECTION, CONGRUENCY AND TEMPORAL DELAY FOR FM PATIENTS.

GENERAL DISCUSSION

*“Space is not an ether in which all things float (...).
The points in space mark, in our vicinity, the varying
range of our aims and our gestures.”*

(Maurice Merleau-Ponty)

PREFACE

The ability to localize nociceptive stimuli is essential for an organism to make a swift and appropriate response to bodily threat (Legrain, Mancini, et al., 2012; Mancini, Longo, Iannetti, & Haggard, 2011). Therefore, nociceptive processing involves spatial localization in order to detect which part of the body is potentially being damaged, and to focus attention towards protecting the threatened body part (Legrain, Mancini, et al., 2012). This localization partially depends on a direct relationship between the spatial organization of skin receptors and the spatial organization of neurons in the cortex. However, this somatotopic representation of the body space only allows identification of the position of objects on the body space and is insufficient to localize the source of threat in external space, in order to guide defensive motor responses towards the location of threat. Physical threats represent complex objects that also provide information to our other senses. The peripersonal frame of reference is of particular importance in this respect, because it codes both the position of somatosensory stimuli on the body surface and the position of stimuli in external space (e.g., visual stimuli), when they are close to the body (Holmes & Spence, 2004; Maravita, Spence, & Driver, 2003). It therefore allows an individual to coordinate the map of the body and the map of external close space into an integrated multisensory representation of space (Cardinali, Brozzoli, & Farnè, 2009; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981; Spence & Driver, 2004).

Despite the importance of spatial perception and more specifically the peripersonal frame of reference for nociceptive processing, studies directly investigating this issue are scarce. In this PhD thesis, we investigated how spatial mapping can influence nociceptive processing. First, we aimed to investigate whether nociceptive stimuli are indeed mapped in a peripersonal frame of reference. Second, we investigated the neural correlates underlying crossmodal interactions between vision and nociception in the peripersonal space with event-related potentials (ERPs). Third, we investigated the influence of moving visual stimuli, either approaching or receding from the body, on nociceptive processing in healthy volunteers. Finally, we assessed whether chronic pain, and more specifically fibromyalgia, can alter spatial perception. This was investigated by looking at the differential influence of moving visual stimuli on tactile processing for fibromyalgia patients compared to healthy controls.

In this general discussion, main research findings will be highlighted, interpreted and integrated. Next, theoretical and clinical implications of the studies conducted will be discussed. Finally, some limitations and avenues for future research will be proposed.

1 MAIN FINDINGS

1.1 PART 1

In this part we investigated whether nociceptive stimuli are mapped in a peripersonal frame of reference in healthy volunteers.

In **Chapter 1**, we tested whether nociceptive processing is influenced by visual stimuli occurring near the body. Two experiments were conducted in which participants performed temporal order judgments (TOJs) on pairs of nociceptive stimuli, one presented on each hand. Briefly before the first nociceptive stimulus, an unilateral stimulus or bilateral visual stimuli were presented either near the participants (i.e. in peripersonal space) or far in front of the participants (i.e. in extrapersonal space). Results showed that the perception of the nociceptive stimuli was biased in favor of the stimulus delivered on the hand adjacent to the unilateral visual stimulus, especially when the visual stimulus was presented in peripersonal space, and less so when presented in extrapersonal space. This suggests that a peripersonal frame of reference is used to map the position of nociceptive stimuli in multisensory space.

In **Chapter 2**, we investigated whether the position of the stimulated body part in external space is taken into account when processing nociceptive information. Two TOJ experiments were conducted, during which participants had to decide which of two nociceptive stimuli, one applied to either hand, had been presented first while their hands were either uncrossed or crossed over the body midline. The occurrence of the nociceptive stimuli was cued by uninformative visual cues that appeared either near or far from the body. We found that unilateral visual stimuli prioritized the perception of nociceptive stimuli applied to the hand laying in the cued side of space, irrespective of posture. Moreover, the influence of the visual stimuli was smaller when they were presented far in front of participants' hands as compared to when they were presented in close proximity. Finally, participants' temporal sensitivity was reduced by changing posture. These findings are compatible with the existence of a spatiotopic, and more particularly a peripersonal frame of reference for the localization of nociceptive stimuli, in which the posture of the body limbs with respect to each other and with respect to objects appearing near the body is taken into account.

In **Chapter 3**, we investigated whether the mapping of nociceptive stimuli is based on a spatial representation that is anchored to the stimulated limb or rather to the body trunk. In three TOJ experiments the effect of unilateral visual stimuli on the perceived temporal

order of pairs of nociceptive stimuli, one applied to each hand, was assessed. Crucially, the position of the hands and the visual stimuli was manipulated, so that visual and nociceptive stimuli occurred in an adjacent or non-adjacent spatial position. TOJs of nociceptive stimuli were biased in favor of the stimulus applied to the hand most adjacent to the visual stimulus, irrespective of the distance to the body. This suggests that the ability to determine the position of a nociceptive stimulus on a specific body area is based on a spatial frame of reference that is spatially locked to that area and follows it during limb displacement.

1.2 PART 2

In the second part, we aimed to investigate the neural correlates underlying crossmodal interactions between vision and nociception in the peripersonal space with ERPs.

In **Chapter 4**, two experiments were conducted in which an exogenous crossmodal cuing paradigm, with visual cue stimuli and tactile or nociceptive target stimuli, was used. Visual stimuli were either presented at the same side of space as the stimulated hand (congruent), or at the opposite side of space (incongruent), and either near the participants' hands or far in front of the hands. Behavioral responses to tactile stimuli (Experiment 1) or to double nociceptive stimulation (Experiment 2), and ERPs to single (non-target) nociceptive stimuli were investigated. In Experiment 1, we found that tactile stimuli were discriminated faster, with shorter reaction times, for congruent than for incongruent trials, but only when visual cue stimuli were presented near as opposed to far from the participant's hands. ERP results for this experiment were inconclusive. In Experiment 2, we found no significant behavioral results, but ERPs were larger in amplitude when visual stimuli were presented near the participant's hands and congruent to the location of the nociceptive stimuli, as opposed to far from the participant's hands and incongruent. This enhancement only clearly affected the N140 component, suggesting that the location of visual stimuli influenced nociceptive processing through a modulation of electrophysiological responses compatible with neural activity in the secondary somatosensory and insular cortices.

1.3 PART 3

In the third part, we were interested in the influence of moving visual stimuli on somatosensory processing.

In **Chapter 5**, we investigated, in healthy volunteers, how the processing of nociceptive stimuli is influenced by dynamical visual stimuli, either approaching or receding from the hand. On each trial a visual stimulus was either approaching or receding the participant's left or right hand. At different temporal delays from the onset of the visual stimulus, a nociceptive stimulus was applied either at the same or at the opposite hand, so that it was presented when the visual stimulus was perceived at varying distances from the hand. Participants were asked to respond as fast as possible at which side they perceived a nociceptive stimulus. We found that reaction times were fastest when the visual stimulus appeared near the stimulated hand. Moreover, investigating the influence of the visual stimuli along the continuous spatial range (from near to far) showed that approaching lights had a stronger spatially dependent effect on nociceptive processing, compared to receding lights. These results suggest that the coding of nociceptive information in a peripersonal frame of reference may constitute a safety margin around the body that is designed to protect it from potential physical threat.

In **Chapter 6**, we investigated the differential influence of dynamical visual stimuli on tactile processing for fibromyalgia (FM) patients compared to healthy control participants. For control participants we found, in accordance with previous research, that visual stimuli presented near as opposed to far from the body influenced tactile processing more. For FM patients this difference was less clear, possibly indicating that FM patients had more attention for potentially threatening stimuli at further distance. The curves describing the reaction times along the continuous spatial range (from near to far) indicated that FM patients had a heightened attention for stimuli entering the peripersonal space compared to controls. However, as this difference was only found when curve-fitting the data, these results should be interpreted with caution, and need further corroboration and replication.

2 THEORETICAL IMPLICATIONS

2.1 NOCICEPTIVE STIMULI ARE MAPPED IN A PERIPERSONAL FRAME OF REFERENCE

The aim of the first part of this PhD thesis was to investigate whether nociceptive stimuli are integrated with visual stimuli occurring near the body in a multisensory representation of the body and the proximal part of external space, known as the peripersonal space. Regarding touch, there is ample evidence showing that tactile processing is influenced by visual or auditory stimuli appearing near the body (Làdavas, di Pellegrino, Farnè, & Zeloni, 1998; Rizzolatti, Fadiga, Fogassi, & Gallese, 1997; Sambo & Forster, 2009; Spence & Driver, 2004). Moreover, these multisensory interactions have been shown to occur across changes in posture and limb position (Kennett, Eimer, Spence, & Driver, 2001; Shore, Spry, & Spence, 2002; Smania & Aglioti, 1995; Yamamoto & Kitazawa, 2001). Although well established for touch, the use of a peripersonal frame of reference for localizing nociceptive stimuli has remained largely unexplored. Most studies focused upon the somatotopic organization of the neuronal responses to nociceptive and painful stimuli (Andersson et al., 1997; Baumgärtner et al., 2010; Bingel et al., 2004; Henderson, Gandevia, & Macefield, 2007). Only recently, studies have started exploring the ability to localize pain according to non-somatotopic frames of reference. Several studies have found evidence for a spatiotopic frame of reference for the mapping of nociceptive stimuli (Gallace, Torta, Moseley, & Iannetti, 2011; Sambo et al., 2013), and for the influence of vision on nociception (Favril, Mouraux, Sambo, & Legrain, 2014; Longo, Betti, Aglioti, & Haggard, 2009; Longo, Iannetti, Mancini, Driver, & Haggard, 2012; Mancini, Longo, Kammers, & Haggard, 2011; Sambo, Forster, Williams, & Iannetti, 2012a; Sambo & Iannetti, 2013; Sambo, Liang, Cruccu, & Iannetti, 2012b; Van Ryckeghem et al., 2011). However, none of these studies can draw strong conclusions as to whether the spatial perception of nociceptive stimuli is coordinated with that of proximal visual stimuli into a peripersonal frame of reference. Indeed, in some of these experiments, the manipulation of vision was limited to the visual observation of the body (Longo et al., 2009, 2012; Mancini et al., 2011). In other experiments, visual stimuli were either not presented beyond the personal space (Sambo, Forster, et al., 2012; Sambo & Iannetti, 2013; Sambo et al., 2012a, 2012b), or the distance of the visual stimuli with respect to the body was not manipulated (Favril et al., 2014; Van Ryckeghem et al., 2011). Despite the lack of studies investigating this issue, the ability to quickly localize stimuli on the body and in external space seems especially relevant in the context of pain. Indeed, the peripersonal space is a multisensory motor-interface enabling interaction with the world,

and may serve the efficient localization and initiation of defensive actions against potentially harmful objects approaching our body (Graziano & Cooke, 2006).

In the first three chapters of this PhD dissertation, we investigated whether nociceptive stimuli are mapped in a peripersonal frame of reference. This was done by manipulating the distance of the visual cue stimuli relative to the body. Throughout all the experiments, we found that external visual stimuli presented near the body influenced the processing of nociceptive stimuli. Conversely, the influence of the visual stimuli on nociceptive processing was attenuated when they were presented far in front of the body. This suggests an automatic coordination between nociceptive and proximal visual inputs in a peripersonal frame of reference. These results are in accordance with previous studies investigating visuo-tactile interactions in the peripersonal space (Spence & Driver, 2004). Moreover, results are consistent with the identification of neurons that respond both to nociceptive stimuli and to visual stimuli presented in the vicinity of the somatosensory receptive field (RF) in area 7b, in the inferior parietal lobe of monkeys (Dong, Chudler, Sugiyama, Roberts, & Hayashi, 1994). This strongly indicates the construction of a multimodal map of the body extended in the nearby space for nociception.

It remains unclear whether these crossmodal interactions between vision and nociception observed in the experiments, result from exogenous shifts of spatial attention from one space (i.e. external proximal space) to another space (i.e. bodily space), or from intrinsic multisensory integration (Spence & Driver, 2004). In the former case, salient but spatially non-predictive visual cues could have attracted multisensory spatial attention towards its location, leading to a faster processing of the forthcoming nociceptive target. Multisensory integration on the other hand occurs when two different-modality stimuli that are presented around the same time and place are integrated to form a unified perceptual object, instead of a collection of unrelated sensations. This would result from an additive sensory response from specialized neurons that respond to stimuli of both modalities (Stein & Meredith, 1993). Another mechanism relies on the existence of multimodal neurons with multiple receptive fields to code the location of sensory inputs from different modalities, as identified in monkeys (Dong et al., 1994; Graziano, Hu, & Gross, 1997). The non-somatic (i.e., visual and auditory) receptive fields extend the region of the somatic (i.e., tactile or nociceptive) receptive field into the immediate adjacent space. Therefore, these neurons respond both to the stimuli applied to a specific area of the skin surface and to stimuli appearing in the space proximal to the stimulated body area (Dong et al., 1994; Graziano et al., 1997). One could argue that a distinction between mechanisms of spatial attention or multisensory integration could be made based upon the *relative timing* of events in the two

sensory modalities (Spence, McDonald, & Driver, 2004). One might expect maximal multisensory integration when stimuli in different modalities arise simultaneous or near-simultaneous, as was argued by Bolignini et al. (2005). However, the relative timing between crossmodal stimulations might not be decisive for the distinction between spatial attention or multisensory integration for at least two reasons. First, multisensory interactions found at the single-cell level, which are often taken as the prototypical example of neural multisensory integration, can arise between stimuli in different modalities with inter-stimulus intervals as long as 600 ms (King & Palmer, 1985; Meredith, Nemitz, & Stein, 1987). Second, 'simultaneity' between stimuli in different modalities not only has to be considered in the external world, but also for the arrival times of sensory input from each modality at various multimodal integration sites in the brain (e.g., Spence & Squire, 2003). These arrival times will differ between brain areas and will depend upon the particular stimuli used. 'Simultaneity' between different senses might thus be a complex matter, and cannot provide conclusive evidence in favor of one of the proposed accounts. Some authors have argued that the distinction between the different mechanisms may be rather 'semantic', at least when stimulus-driven exogenous mechanisms are considered (Macaluso, Frith, & Driver, 2001). In multimodal brain areas there may be considerable overlap between the mechanisms for stimulus-driven crossmodal spatial attention and that for stimulus-driven (exogenous) crossmodal spatial attention. Disentangling these mechanisms might therefore prove to be difficult.

In Chapter 1 and 3, we were mostly interested in examining the prioritization of a nociceptive stimulus applied to one of the hands with respect to the nociceptive stimulus applied to the other hand, following the presentation of lateralized visual cue stimuli, presented either near or far from the body (or body part). Therefore, in these chapters we focused on examining the point of subjective simultaneity (PSS) as primary outcome measure. Nevertheless in TOJ tasks another parameter, namely the just noticeable difference (JND) can also be investigated. Interestingly, in Chapter 1, we also observed effects on the JND. More specifically, the JND was larger when visual cues were presented in near space as opposed to far space, indicating lower discriminating performance in this condition. This was true both when cues were presented unilaterally and bilaterally. This pattern of results could suggest that participants were more distracted by the occurrence of proximal visual stimuli, regardless of their laterality relative to the somatosensory targets, resulting in poorer task performance. However, we did not consistently find this result over experiments, making interpretation of it difficult. Some other studies, interested primarily in the PSS, also reported to have found unexpected differences in JND values (Van Damme,

Gallace, Spence, Crombez, & Moseley, 2009; Vanden Bulcke, Van Damme, Durnez, & Crombez, 2013). Further studies are needed to reveal the mechanisms underlying this modulation of the JND.

In Chapter 2, we manipulated the posture of the hands, to dissociate effects resulting from a crossmodal displacement of spatial attention on the somatotopic representation of the skin surface, from effects resulting from a remapping of the position of nociceptive stimuli according to external spatial coordinates (i.e. a spatiotopic frame of reference). We found evidence that the position of nociceptive stimuli are mapped in a frame of reference that takes into account the position of the limbs in external space. First, this was shown by a lower temporal sensitivity (as indexed by the JND) when hands were crossed, compared to when they were uncrossed. This is in accordance with previous studies showing that crossing the hands over the body midline affects the ability to judge the temporal order of nociceptive stimuli applied to the hands (Sambo et al., 2013), and even the perception of their intensity (Gallace et al., 2011). Second, we also investigated crossmodal interactions between visual and nociceptive stimuli under different postures (as indexed by the PSS). By doing this, we were able to additionally illustrate the mapping of nociceptive stimuli in a peripersonal frame of reference, that not only takes into account the position of the limbs in external space, but also integrates the occurrence of external objects presented near the body.

It is interesting to note that two different accounts have been proposed for the mapping of somatosensory stimuli in an external frame of reference. One account postulates that somatosensory stimuli are initially mapped in a somatotopic or anatomical coordinate system, and are subsequently remapped into an external, spatiotopic reference frame. This remapping would take longer when the anatomical and external coordinates are in conflict, as is the case when hands are crossed (Yamamoto & Kitazawa, 2001). Alternatively, Gallace et al. (2011) proposed that somatosensory stimuli, rather than being converted from one frame of reference to another, are always mapped in a somatosensory *and* in a spatiotopic representation. The strength of the activation of each map would depend on a number of parameters, like the availability of proprioceptive and visual information and the immediate relevance of the task. Extensive connections are present between the two maps (Gallace & Spence, 2008, 2010). Because, in everyday life the right and left hand manipulate objects and are exposed to somatosensory stimuli that are most often present in the right or left side of space respectively, it is likely that the connections between these regions that are often simultaneously activated (e.g., the left hand area in the somatotopic map and the left side area of the spatiotopic map) display increased synaptic strength (Figure 1, left panel).

In uncrossed posture, the match between the two reference frames makes the processing of the sensory stimuli highly effective, whereas in crossed posture, these privileged synaptic connections are not engaged, making the correct localization of somatosensory stimuli less efficient (Figure 1, right panel). Evidence for this latter account comes from studies showing both serial and parallel processing in the human somatosensory system (Knecht, Kunesch, & Schnitzler, 1996). For example, after ischemic injury to one entire somatosensory area, patients can be completely unaware of tactile stimuli delivered to the contralateral body site, whereas they are still able to point correctly to where they occurred (Paillard, 1999; Volpe, LeDoux, & Gazzaniga, 1979). This suggests that spatial information regarding tactile stimuli can be processed and integrated with motor commands, without primary somatosensory cortex involvement, possibly via direct connections between the lateral posterior thalamic nuclei and the posterior parietal cortex (Gallace & Spence, 2010).

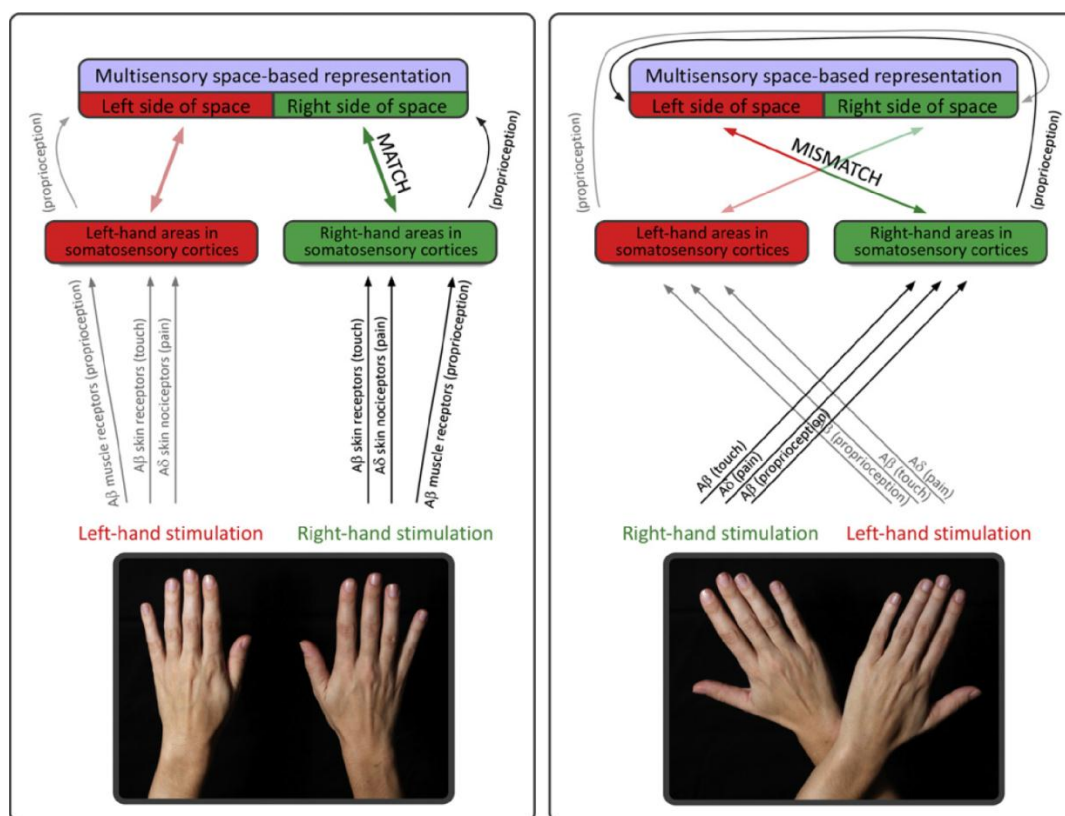


FIGURE 1. A NEUROCOGNITIVE MODEL PROPOSED BY GALLACE ET AL. (2011) TO EXPLAIN THE REDUCTION IN PERCEIVED INTENSITY OF SOMATOSENSORY STIMULI AFTER CROSSING THE HANDS. TACTILE, NOCICEPTIVE AND PROPRIOCEPTIVE INFORMATION ARISING FROM ONE OF BOTH HANDS (E.G., RIGHT HAND), REACHES THE CORRESPONDING AREA IN THE SOMATOSENSORY CORTICES. WHEN HANDS ARE UNCROSSED (LEFT PANEL), THESE INPUTS ACTIVATE MULTISENSORY AREAS MAPPING THE CORRESPONDING SIDE OF EXTERNAL SPACE (E.G., RIGHT SIDE OF SPACE). CONVERSELY, WHEN HANDS ARE CROSSED (RIGHT PANEL), THE INPUTS ACTIVATE THE MULTISENSORY AREAS MAPPING THE NON-CORRESPONDING SIDE OF EXTERNAL SPACE (E.G., LEFT SIDE OF SPACE), RESULTING IN A MISMATCH BETWEEN SOMATOSENSORY AND SPACE-BASED REPRESENTATIONS. FROM GALLACE ET AL. (2011).

Interestingly, congenitally blind people do not show spatial remapping effects (Röder, Rösler, & Spence, 2004), nor do children younger than 5^{1/2} years (Pagel, Heed, & Röder, 2009). This suggests that this remapping is not innate, but is acquired during ontogeny by developmental vision. This is also consistent with animal research showing that, although the multisensory neurons in monkeys, responding both to tactile and visual stimuli, exist in the superior colliculus already immediately after birth, their capability to integrate sensory input based on spatial features only develops during the first months of life (Wallace & Stein, 2001; for a review, see Wallace, 2004). Furthermore, when cats were reared in the dark, they were unable to integrate multisensory information, even for auditory-somatosensory stimuli (Wallace, 2004a, 2004b).

In Chapter 3, we manipulated both the position of the hands and the position of the visual stimuli, so that visual and nociceptive stimuli occurred on adjacent or non-adjacent spatial positions. We hereby provided the, to our knowledge, first direct evidence in humans that the position of nociceptive stimuli is based on a spatial frame of reference that is spatially locked to a specific body part and that follows it during limb displacement. This would allow to give priority to stimuli around the limb even when they are still distant from the body trunk. This is in accordance with studies in monkeys, in which several brain areas have been shown to encode a multisensory map of space, centered around a specific body part, including the putamen, area 7b, and the ventral intraparietal cortex (Graziano & Gross, 1995; Graziano et al., 1997; Graziano, Yap, & Gross, 1994). The region of space within which visual stimuli are effective in exciting these bimodal neurons is modulated by the position of the arms in space (e.g., Duhamel, Colby, & Goldberg, 1998; Fogassi et al., 1996; Graziano & Gross, 1994, 1998; Graziano et al., 1997). Graziano et al. (1997) recorded the activity of bimodal neurons while the arm position, the head position and the gaze direction were manipulated. They found that for most bimodal neurons with a tactile response on the arm, the visual receptive field moved when the arm was moved. Conversely, most bimodal cells with a tactile response on the face had a visual receptive field anchored to the head, moving as the head was rotated. The visual receptive fields did not move when gaze direction was manipulated. As a consequence, these neurons will continue to respond to visual objects presented near the somatosensory receptive fields to which they are anchored, even if the gaze is shifted. In humans, a limb-centered frame of reference was already suggested from neuropsychological evidence in patients suffering from left tactile extinction following right-hemisphere damage. These patients typically can detect a single touch on the left or right hand in isolation, but when both hands are stimulated simultaneously, only the right touch can be reliably detected (unimodal extinction) (e.g., di Pellegrino, Làdavas, & Farnè, 1997;

Mattingley, Driver, Beschin, & Robertson, 1997). Interestingly, extinction also occurred when a visual stimulus is presented near the ipsilesional hand (crossmodal extinction). When the visual stimulus remained at a constant distance from the body, but the relative distance to the hand was increased, the visual stimulus extinguished the perception of the tactile stimulus applied to the opposite hand only to a lesser extent (di Pellegrino et al., 1997). Other studies have found that after use of a rake to retrieve distant, otherwise non-reachable objects, the peri-hand multisensory area can be extended to include the distal part of the rake (Farnè & Làdavas, 2000; Farnè, Serino, & Làdavas, 2007; Maravita et al., 2003). These studies already suggest that the peripersonal frame of reference is limb-centered. By also manipulating the position of the hands in space in the experiments of Chapter 3, we stayed closer to the experiments conducted in monkeys, and we were able to show that the mere proximity to the body trunk might be insufficient for an external stimulus to be integrated in the peripersonal space. Instead, peri-hand representations are anchored to the limb they code *and* are displaced with it in space.

Taken together, the results of the experiments conducted in the first three chapters of this dissertation indicate that the localization of nociceptive stimuli depends on their mapping in limb-centered peripersonal frames of reference, in which the space of the body is integrated with the proximal part of external space. This multisensory system enables us to form an integrated representation of the part of the body in pain and the location of the external object causing that pain with respect to the body part. It is proposed that the ultimate aim of this system would be to facilitate the processing of physical threat and to select and prepare the most appropriate response (Graziano & Cooke, 2006). Therefore, the coding of nociceptive information in a peripersonal frame of reference may constitute a safety margin around the body that is designed to protect it from potential physical threat and represents a mechanism for preserving homeostatic control over the body (Legrain & Torta, 2015; Legrain, 2011; Moseley, Gallace, & Iannetti, 2012).

2.2 THE ELECTROPHYSIOLOGICAL CORRELATES OF CROSSMODAL SPATIAL ATTENTION BETWEEN VISION AND NOCICEPTION

While results of Chapter 1 to 3 demonstrated crossmodal interactions between vision and nociception, they do not provide any direct insight in the neural processes underlying these links, and therefore several questions regarding the presence of these crossmodal links remained unaddressed due to an exclusive focus on behavioral measures. One of the issues raised for example is whether the attentional prioritization of nociceptive stimuli, when visual stimuli are presented near the participant's hands, results from effects of crossmodal attention on perceptual processes or from attentional modulation at later, post-perceptual processing stages.

In Chapter 4, we used event-related potentials (ERP) to get further insight into the neural basis of the crossmodal interactions between vision and nociception. Two crossmodal congruency experiments were conducted and we found mixed results. For the first experiment, in which behavioral responses to tactile targets and ERPs to single nociceptive stimuli were investigated, we found, in accordance with previous studies investigating crossmodal visuo-tactile spatial attention in the peripersonal space (for a review, see Spence & Driver, 2004), that tactile discriminations were faster for congruent (i.e. visual cue and tactile target presented in the same side of space) than for incongruent trials (i.e. visual cue and tactile target presented in the opposite side of space), but only when visual cue stimuli were presented near the participant's hands, and not when they were presented far in front of the hands. However, ERP results for this experiment were inconclusive. We hypothesized that this might be due to the fact that in this experiment nociceptive stimuli were completely irrelevant. Therefore, in Experiment 2, we replaced the tactile targets by double nociceptive stimulations in order to increase attention towards the nociceptive stimuli. We now found a more negative ERP component around 140 ms when visual cue stimuli were presented near the stimulated hand, and congruent to the location of the nociceptive stimuli, as opposed to far from the stimulated hand and incongruent to the location of the nociceptive stimuli. Although a congruency effect was present both when cues were presented near and far from the participant's hands, the more negative N140 amplitude when cues were presented near the participant's hands indicate that nociceptive processing was most influenced under this condition. This demonstrates that, in accordance with the results found in Chapter 1 to 3, the crossmodal interactions between vision and nociception could rely on the existence of peripersonal frames of reference, integrating the space near the body and the proximal part of the external space (Làdavas et al., 1998; Rizzolatti et al., 1997; Spence et al., 2004). Previous studies have already shown that the magnitude of ERPs

evoked by nociceptive stimuli are modulated by the act of viewing the stimulated hand (Longo, Betti, Aglioti, & Haggard, 2009; Torta, Legrain, & Mouraux, 2015), and that viewing a noxious stimulus applied to a rubber hand activated mid-cingulate and parietal areas extending from the superior parietal gyrus to the parietal operculum, even in the absence of concomitant nociceptive input (Lloyd, Morrison, & Roberts, 2006). Here, we provided more direct evidence for the mapping of nociceptive stimuli in a peripersonal frame of reference, by showing differential effects when visual cues were presented near as opposed to far from the participant's hands.

The negative component identified in Chapter 4 may correspond to the lateralized generators of the negative components of nociceptive laser-evoked potentials (LEPs). Previous studies have shown that directing attention towards a specific body location can modulate neural activity evoked by nociceptive stimuli in brain regions generating N1 and N2 components, leading to larger N1 and N2 amplitudes for attended as compared to unattended body locations (Legrain, Guérit, Bruyer, & Plaghki, 2002). This is in accordance with the results found in the second experiment of Chapter 4. These negative components are thought to originate from bilateral operculum (secondary somatosensory (SII)/insular areas and possibly also primary somatosensory areas (SI)) (Bromm & Lorenz, 1998; Frot et al., 1999; Inui & Kakigi, 2012; Lenz, Rios, Chau, et al., 1998; Valentini et al., 2012). The fact that these brain areas can be modulated by visual stimuli appearing near the stimulated body part, indicates that crossmodal spatial attention can affect sensory processing of nociceptive inputs. These multisensory interactions might be obtained via three different pathways. First, these multisensory interactions might result from *feed-forward* convergence from sensory-specific areas to associative regions. Second, because early ERP components can be modulated by the location of cues in a different modality, it has been hypothesized that these crossmodal links in spatial attention are likely to operate via a *feedback* mechanism from multimodal cortical areas (e.g., parietal cortex) to unimodal areas (Eimer, Cockburn, Smedley, & Driver, 2001; Kennett, Eimer, Spence, & Driver, 2001; Macaluso & Driver, 2001; Macaluso, Frith, & Driver, 2000, 2005; McDonald & Ward, 2000). However, direct confirmation for such back-projections remains to be obtained. This might require lesion studies, showing for instance that a particular crossmodal spatial influence on 'unimodal' structures is lost when a critical multimodal structure gets destroyed, or perhaps even when such a structure is only transiently disrupted with transcranial magnetic stimulation in humans (Pascual-Leone, Walsh, & Rothwell, 2000). Finally, Liang et al. (2013) also demonstrated the existence of a third pathway, namely they found that sensory information can reach multimodal areas without being first processed in primary and

secondary-specific areas. This *direct thalamocortical* transmission of multimodal salient information would be parallel to the processing of finer stimulus attributes, which are transmitted in a modality-specific fashion from the thalamus to the relevant primary sensory areas. This direct pathway would enable the fast detection of salient events and the associated preparation of appropriate (defensive) behavior.

The results of Chapter 4 are compatible with the view that at least some of the brain areas activated by nociceptive stimuli, may reflect a '*salience detection system*', a brain network devoted to the processing of sensory information that signals potential danger in the proximal space and that prompts appropriate action (Legrain, Iannetti, Plaghki, & Mouraux, 2011). This salience detection system would represent mechanisms by which attentional systems are informed about changes in the representation of the body. Indeed, in non-human primates frontal and parietal areas have been shown to respond to multimodal threats occurring in the space proximal to the body, and to participate to defensive behaviors (Cooke & Graziano, 2004). These frontal and posterior parietal areas have also frequently been reported to be activated in response to nociceptive stimuli (Ingvar, 1999; Peyron, Laurent, & García-Larrea, 2000; Porro, 2003; Treede, Kenshalo, Gracely, & Jones, 1999). These cortical areas are involved in cognitive functions such as attention, selectively biasing the cortical processing of incoming sensory inputs according to their salience and relevance (Corbetta & Shulman, 2002; Yantis, 2008). Importantly, specific parieto-frontal networks have also been shown to be involved in coordinating perception and action. These areas would map sensory information according to specific representation frames to execute particular actions. For example, sensory information would be mapped in retinal space for saccades, in peripersonal space for grasping and in extrapersonal space for reaching (Colby & Goldberg, 1999; Rizzolatti et al., 1997). In monkeys, interactions between perceptual processing and motor output were suggested between the ventral parts of the intraparietal (VIP) and premotor (F4) areas. Stimulation of neurons within these areas has been shown to produce defensive behaviors, such as eye blinks or arm withdrawals (Cooke & Graziano, 2004). As mentioned before, neurons in these areas have multimodal RFs, meaning that they can be activated by somatosensory stimuli as well as by visual stimuli appearing in proximity of their somatosensory RF (Dong et al., 1994; Duhamel et al., 1998; Graziano & Gross, 1998). The activity of these neurons is likely to contribute to the construction of a multimodal map of the body and external close space in order to guide defensive actions against threat (Graziano et al., 1997). Also in humans fMRI studies have provided some evidence that these frontal and parietal brain regions are involved in coordinate transformations between different sensory systems (Bremmer et al., 2001).

Other evidence comes from patients with damage in the parietal or frontal lobe who display deficits in spatial perception across different modalities (e.g., neglect) (Làdavas, 2002). Liu et al. (2011) described neglect patients for whom detection of painful thermal stimuli applied to the contralesional hand was often mislocalized to the unaffected, ipsilesional side, and the submodality of the stimulus (hot or cold) was often misidentified. These studies indicate that nociceptive processing is indeed dependent upon spatial attention and that deficits in spatial attention could influence the perception of pain.

Some critical remarks have to be discussed with regard to Chapter 4. First, we did not find clear results for the later positive component of the nociceptive ERPs (i.e. P320). The P320 component found in these experiments most probably corresponds to the P2 elicited by laser stimuli. The P2 has been mostly investigated for endogenous cuing paradigms and has been shown to be less affected by the voluntarily-controlled direction of spatial attention, and more so by the novelty or the probability of the stimuli (Legrain et al., 2002; Legrain, Guérit, Bruyer, & Plaghki, 2003). In the present studies, an exogenous cuing paradigm was used, and the probability of the nociceptive stimulation was constant across the experimental conditions. It remains unclear what the positive component identified in the present experiments reflects. Further studies are needed to investigate the involvement of the P2 evoked by nociceptive stimuli in exogenous cuing paradigms.

Second, we also did not find evidence for crossmodal interactions between vision and nociception in the behavioral results, in contrast with the results found in Chapter 1 to 3. We argue that this lack in behavioral results could be due to the nature of the nociceptive targets used. Participants only had to react when they received two nociceptive stimuli (with ISI of 500 ms), while ignoring single nociceptive stimulations. A considerably large ISI was necessary in order for participants to be able to discriminate between a single or a double nociceptive stimulation. The fact that participants had to wait for a second stimulation, with a large interval between the first and the second one, could have abolished any effect of the visual cues on nociceptive processing. Indeed, attention might have already been oriented towards the stimulated hand at the time the second stimulation was applied, masking any effects of the visual cues on spatial attention.

Third, the difficulty to find reliable ERP results might be related to the use of intra-epidermal stimulation (IES). An important limitation of IES is, that it is selective for nociceptors only when very low current intensities are used (Legrain & Mouraux, 2013; Mouraux, Iannetti, & Plaghki, 2010). However, at these intensities the stimulus generates a very weak percept, and the signal-to-noise ratio of the elicited potentials is very low. We

tried to circumvent this by increasing the strength of the nociceptive afferent volley through temporal summation, i.e. by using trains of three IES delivered using a 5 ms inter-stimulus interval. It has been shown that this increases the magnitude of the elicited potentials, while the latency remains unaffected, indicating that using trains of IES does not affect the type of activated fibers (Mouraux, Marot, & Legrain, 2014). Nevertheless, the signal-to-noise ratio still remained quite low, making it difficult to find reliable ERP components. Therefore, it would be interesting to replicate these studies with another kind of nociceptive stimulation, like laser stimulation, for which nociceptive ERPs have been extensively studied in attentional tasks, and to see whether similar results can be found.

Finally, the mixed results found in Chapter 4, may be due to the use of an exogenous cuing task. Most studies investigating nociceptive ERPs have used endogenous cuing tasks with a long cue-to-target interval to avoid temporal overlap of activities elicited by the cues and the targets. Here we chose to use an exogenous cuing task to disentangle the direct stimulus-driven capture of attention by visual stimuli from a strategic shift of attention to the most probable target side. The drawback of using an exogenous cuing task is that the attentional manipulation of the cued side is confounded to some extent with variations in stimulation (i.e. with the side of the cue). We tried to control for this by using a short visual cue (20 ms) and by randomly jittering the CTOAs across a considerably wide range (80 to 250 ms). Consequently, we expect that during averaging any possible overlapping responses cancelled each other out. However, we cannot completely exclude the possibility that some ERP changes are due to the summing of a nociceptive response, together with an entirely separate visual response to a closely preceding light on the same versus the opposite side in near or far space. Finally, as most studies have focused on investigating components of endogenous attention, little is known about the expected modulation of nociceptive ERP components due to exogenous attention. As argued above, the lack of consistent modulations of the nociceptive ERPs, and more specifically for the P320 component, could be due to the mere fact that this component is less affected by exogenous attention. Further research investigating modulations of nociceptive ERPs by exogenous attention are needed to confirm these findings.

2.3 MOTION IN THE PERIPERSONAL SPACE: ASSESSING THE INFLUENCE OF DYNAMICAL VISUAL STIMULI ON SOMATOSENSORY PROCESSING ACROSS A SPATIAL CONTINUUM

In the third part of this PhD dissertation we investigated the influence of dynamical visual stimuli on somatosensory processing. The use of dynamical or moving visual stimuli, either approaching or receding from the participants, is more attractive compared to using static external stimuli at two fixed locations (i.e. one position near the participants, and one position far away from the participants), as we used in the previous chapters, for several reasons. First, it is more ecologically valid as external objects in real life are continuously moving in the environment. Second it is more comparable to animal studies investigating multimodal integration in the peripersonal space (Dong et al., 1994; Graziano et al., 1997). Third, studies in both humans and monkeys have shown that the neural systems representing the peripersonal space show a preference for moving stimuli (Bremmer et al., 2001; Duhamel et al., 1998; Fogassi et al., 1996; Graziano et al., 1997; Makin, Holmes, & Zohary, 2007). Finally, by using dynamical visual stimuli, we were able to investigate multisensory interactions along a spatial continuum between near and far space. Despite these advantages of moving over static stimuli, only few studies have investigated the influence of moving stimuli on somatosensory processing.

In Chapter 5, we were able to show that visual stimuli presented near the stimulated hand influenced nociceptive processing more than visual stimuli presented far from the hand. This is in accordance with the results reported in Chapter 1 to 3, and provides evidence for a body-part centered peripersonal frame of reference for the localization of nociceptive stimuli. Moreover, for approaching visual stimuli the relationship between the reaction times to the nociceptive stimuli and the position of the visual stimuli was best described by a quadratic function, indicating that reaction times sharply decreased quickly after the onset of the visual stimulus. Conversely, for receding stimuli, no such sharp increase or decrease was found. This indicates that people are sensitive to the direction of visual stimuli, with approaching objects influencing nociceptive processing more profoundly than receding objects. This is in accordance with animals studies, showing that bimodal neurons preferentially respond to visual objects when they are approaching the body, compared to when they are moving away from the body (Duhamel, Bremmer, Benhamed, & Graf, 1997; Duhamel et al., 1998; Graziano et al., 1997). Moreover, these results are compatible with studies in humans investigating the influence of moving auditory or visual stimuli on tactile processing (Canzoneri, Magosso, & Serino, 2012; Kandula, Hofman, & Dijkerman, 2014). These results can be explained by the fact that objects approaching us

may pose a threat, and signal the need to initiate defensive behavior. Detecting these objects early is therefore crucial to either avoid the objects, or prepare for contact most efficiently.

An interesting question is whether the peripersonal space representation codes space visually or rather action related (Rizzolatti et al., 1997). In the former case, it would code the location of objects relative to a specific body part by using a Cartesian or some other geometrical coordinate system (visual space). Conversely, in the latter case, it would code for a potential action, a motor schema, directed towards a particular spatial location (motor space). In case of the visual hypothesis, we would expect the spatial map not to take time into account, and therefore the spatial map would be static. In contrast, in motor space, the spatial map may have dynamical properties, because time is inherent to movement. The fact that approaching and receding stimuli differentially influence somatosensory processing indicates that the spatial map may also encode dynamical properties, and it could therefore suggest that the peripersonal space maps the stimulus position in motor terms. This is in accordance with studies in monkeys, in which it has been shown that the receptive field (RF) of bimodal neurons can increase in depth when the speed of an approaching stimulus increases (Fogassi et al., 1996). Moreover, both studies in primates and humans have shown that participants execute adaptive avoidance responses to both real and simulated approaching stimuli (Schiff, Caviness, & Gibson, 1962; Schiff, 1965; Tinbergen, 1951). This points out the importance of motor areas and motor-to-sensory pathways for the construction of space perception. The peripersonal space representation would then basically have a motor function: spatial locations of multisensory stimuli are encoded in relationship to body parts to generate appropriate motor responses (goal-directed, defensive, or avoidance movements) (Graziano & Cooke, 2006; Ladavas & Farnè, 2004; Rizzolatti et al., 1997). As mentioned before, the neural basis for this interplay between sensory and motor areas would be the fronto-parietal connections. These would enable a visuomotor coupling between visual stimuli and movements directed towards them (Rizzolatti et al., 1997).

An additional advantage of the use of dynamical visual stimuli is the fact that it allows to compare the influence of visual stimuli on somatosensory processing along a spatial continuum between different experimental conditions or groups. We were interested to investigate whether chronic pain can alter spatial perception to some extent. Therefore, in Chapter 6, we compared the influence of visual stimuli approaching the participant's body on tactile processing between fibromyalgia (FM) patients and healthy control participants. We chose to investigate FM patients, because these patients demonstrate an exaggerated response not only to noxious stimuli, but also to stimuli in other modalities (e.g., sound)

(Crombez, Van Damme, & Eccleston, 2005; McDermid, Rollman, & McCain, 1996). We wanted to investigate whether this over-responsiveness of FM patients could be associated with a heightened attention for stimuli entering the peripersonal space or whether FM patients scan a larger share of the external space for potentially salient and threatening information.

In line with the results of Chapter 1 to 4, we found for control participants that visual stimuli presented near as opposed to far from the body influenced tactile processing more. For FM patients, this difference was less clear, possibly indicating that FM patients have altered reactions to stimuli at further distance from the body, compared to healthy control participants. Furthermore, when curve fitting the data, we found that a linearly decreasing function adequately described the data for control participants, while a quadratic function, with a sharper decrease at small temporal delays, best described the data for FM patients. The fact that a linear function best described the data for control participants is in contrast with the results of Chapter 5, where a quadratic function best described the data. However, in Chapter 6 participants received tactile stimulation, while in Chapter 5 they received nociceptive stimulation. It could be that the strong spatially dependent effect of external stimuli on nociceptive stimuli is especially strong in a threatening context, in which it is crucial to quickly prepare an appropriate defensive response. This is consistent with research showing that individuals underestimate the time a visual stimulus approaching them will collide with them when the stimulus is threatening (snakes, spiders, angry faces) compared to when it is non-threatening (butterflies, rabbits, neutral faces) (Brendel, DeLucia, Hecht, Stacy, & Larsen, 2012; Vagnoni, Lourenco, & Longo, 2012). Also relevant in this context is the study by Lloyd et al. (2006), who found an increased activation in posterior parietal areas when a threatening object (a sharp probe) was seen approaching the hand, compared to a non-threatening object (a blunt probe). Although an intriguing hypothesis, future studies need to address this issue directly, by comparing the spatially-dependent effect of visual stimuli on nociceptive and tactile processing, preferably within the same participants.

The fact that a quadratic, instead of a linear function, best fitted the data for the FM patients, seems compatible with the hypothesis that FM patients would have a heightened attention for stimuli entering the peripersonal space, compared to healthy control participants. As argued in Chapter 6, this difference between FM patients and control participants could result from the fact that FM patients are 'hypervigilant' for sensory information. Indeed, it has been shown that FM patients not only have an over-responsiveness to painful stimuli, but also to stimuli in other modalities (e.g., sound)

(Crombez et al., 2005; McDermid et al., 1996). The mechanisms of hypervigilance or still not completely understood. Although different theories exist (e.g., Chapman, 1978; Hollins et al., 2009; McDermid et al., 1996; Rollman & Lautenbacher, 1993), the 'attentional gain control theory' of Hollins et al. (2009) seems most compatible with the present results. In this perspective hypervigilance would result from a cognitive process in which FM patients are concerned about, and therefore closely monitor, those sensations that could accompany or warn impending pain, leading to an increase of response to all stimuli of that type (Hollins et al., 2009). This theory could explain why FM patients show a heightened attention for stimuli signaling potential threat to the body, leading to a stronger spatially dependent effect of the approaching lights on tactile reaction times than control participants.

In Chapter 1 to 5, the focus lied exclusively on bottom-up attentional mechanisms, namely mechanisms that allow the detection and selection of sensory information based on the physical properties defining its salience. However the results in Chapter 6 indicate that the selection of sensory information can also be determined by its relevance relative to cognitive goals (top-down) (Corbetta & Shulman, 2002; Egeth & Yantis, 1997). Decisions about which information is relevant are stored in working memory to guide attention, and are driven by ongoing cognitive goals, but also by motivation and personality traits, such as catastrophizing, i.e. a tendency to consider any experience of pain as awful and unbearable (Legrain et al., 2009). It has been shown that the task performance of subjects with strong catastrophizing traits is more disrupted by the occurrence of novel electrocutaneous stimuli (Crombez, Eccleston, Baeyens, & Eelen, 1998). This suggests that in these subjects bodily sensations have acquired a stronger attentional weight, facilitating perception of body-related information. Moreover, the magnitude of responses to nociceptive stimuli in cingulate, insular, prefrontal and posterior parietal cortices has been shown to be related to catastrophizing in healthy volunteers (Seminowicz & Davis, 2006) and in fibromyalgia patients (Gracely et al., 2004). Therefore, it can be hypothesized that catastrophizing might play an important role in the heightened attention towards stimuli entering the peripersonal space found in FM patients in Chapter 6. However, the present study was not designed to explain the underlying mechanisms of possible modulations of the peripersonal space due to FM. Future studies could take psychological variables such as catastrophizing about pain or body vigilance into account to further investigate this. Moreover, it could be interesting to also include other pain patients, such as patients with rheumatoid arthritis, who also experience whole body pain, but do not show this pattern of over-responsiveness.

Three critical remarks should be made regarding the two chapters discussed in this section. First, it has to be noted that in Chapter 5, we also found a decrease in reaction times

in function of the temporal delay when visual stimuli were receding from the participants' body, instead of the expected increase in reaction times. This is not in accordance with previous studies using a similar paradigm. In these studies the expected increase in reaction times was also not found, but reaction times did not significantly decrease, but rather remained stable (Canzoneri et al., 2012; Teneggi, Canzoneri, di Pellegrino, & Serino, 2013). Our study differed in several aspects from the study of Canzoneri et al. (2012). According to us the most probable explanation for the discrepancy in results is the fact that we used less catch trials (i.e. trials in which no nociceptive stimulation was applied). These catch trials should ensure that the expectation to receive a nociceptive stimulation to one of the hands does not increase with higher temporal delays. Possibly, the amount of catch trials used in our experiment was insufficient to avoid the fact that participants expected to get a stimulation, and that this expectation increased as the trial proceeded. We chose to decrease the amount of catch trials to limit the amount of trials (and thereby the duration of the experiment) to ensure that participants could remain concentrated until the very end. However, we cannot rule out the possibility that other differences between our experiment and that of Canzoneri et al. (2012) caused this surprising result, such as the fact that we did not use unimodal trials (i.e. trials in which the nociceptive stimulus occurs during a silence period, preceding or following the presentation of the visual stimuli), the fact that participants had to perform a discrimination task (left hand or right hand) instead of a more simple detection task, or the mere fact of using nociceptive and visual stimuli instead of tactile and auditory stimuli. Indeed, in Chapter 6, we used the exact same experiment (with the same amount of catch trials), except for the fact that the target stimuli were tactile instead of nociceptive. Now, we did not find this decrease in reaction times in function of the temporal delay for the receding stimuli. For fibromyalgia patients this is not surprising, as we also did not find any decrease in reaction times for approaching stimuli. For control participants, we did find some evidence for a decrease in reaction times with increasing temporal delay when stimuli were approaching, but not when stimuli were receding, in contrast with the results of Chapter 5. This could indicate that the use of nociceptive instead of tactile stimuli could also have influenced the results. To be sure which of the factors caused the discrepancy in results, future studies could try to first replicate the results of Canzoneri et al. (2012) with nociceptive instead of tactile stimulation, and progressively deviate more from the original paradigm (e.g., in a second step use visual instead of auditory dynamical stimuli, etc.).

Second, in Chapter 6 there was a huge amount of variance in the patient data, which may have created a lot of noise, possibly masking significant differences within the patient data.

Therefore, no strong conclusions can be drawn from this experiment. Future studies should try to reduce this variance by categorizing patients into more similar groups based on age, onset of FM, amount of pain, or individual difference variables such as anxiety and catastrophizing that may be considered to play an important role. Alternatively, other kinds of experiments could be conducted in which reaction times are not the primary outcome, as it has been argued that reaction time data are less suitable to study attentional prioritization in chronic pain populations (Van Damme, Crombez, & Notebaert, 2008).

Finally, we want to stress the fact that based on the present study we cannot be sure whether any differences observed between controls and FM patients are due to a modulation of the peripersonal space (i.e. whether the same system is now used to perceive stimuli both at near and far positions) or rather to a more extreme reaction to stimuli in the extrapersonal space. In the latter view, two distinct systems would still be distinguishable to perceive stimuli at a proximal versus farther positions, but stimuli at farther positions are now perceived as equally threatening or relevant as proximal stimuli. This contrast is difficult to make and depends on the conceptualization of the peripersonal space. Here we defined peripersonal space as ‘the space in which stimuli on the body space are integrated with stimuli occurring in the external world’. In some of the previous studies this integration seems to be best described by a sigmoid function (Canzoneri et al., 2012; Taffou & Viaud-Delmon, 2014; Teneggi et al., 2013), and the abscissa at the inflection point of the sigmoidal curve is taken as the boundary of the peripersonal space. This boundary between peripersonal and extrapersonal space seems rather arbitrary, and in both the data of Chapter 5 and 6 sigmoid functions did not fit our data adequately. We argue that a strict boundary between the peripersonal and extrapersonal space is unlikely to exist, and that some multimodal integration will probably also occur in what we call the ‘extrapersonal’ space (see e.g., De Paepe, Crombez, & Legrain, 2015; De Paepe, Crombez, Spence, & Legrain, 2014; Rizzolatti et al., 1981). Therefore, we claim that in these experiments any ‘modulation of the peripersonal space’ should be seen as a difference in attention towards stimuli approaching the body, rather than the extension or reduction of a strict boundary between peripersonal and extrapersonal space.

3 CLINICAL IMPLICATIONS

In this dissertation, we have investigated the influence of spatial perception on the processing of nociceptive stimuli. Results first of all emphasize the non-specific, but inherent role of cognitive functions for nociception. As pointed out in the general introduction, at least three distinct cognitive processes can be involved in the processing of nociceptive stimuli: selective attention, spatial perception and action selection. Here, we convincingly showed that spatial perception plays an important role in the processing of nociceptive information. Indeed, we showed that nociceptive stimuli are remapped in a peripersonal frame of reference, in which they interact with stimuli from other modalities to form one coherent and multisensory perception of the proximal space. This enables us to quickly localize threatening objects on our body space, and to initiate appropriate motor actions directed towards the threatened body part.

Second, the relevance of spatial perception for pain becomes more apparent when studying neuropsychological assessments of patients with chronic pain, and more specifically patients with complex regional pain syndrome (CRPS) (Legrain, Bultitude, De Paepe, & Rossetti, 2012; Moseley, Gallace, & Spence, 2012). CRPS is a chronic pain disorder, characterized by unilateral sensory, autonomous, vasomotor and motor/trophic dysfunctions. CRPS patients also show a “neglect-like” symptomatology, i.e. they suffer from unilateral cognitive deficits leading to impaired perception and utilization of the affected limb (Förderreuther, Sailer, & Straube, 2004; Galer & Jensen, 1999; Moseley, 2004). Moseley et al. (2009) found, using a TOJ task with two tactile stimuli applied sequentially one to each hand, that CRPS patients tended to neglect stimuli applied to their affected hand, when hands were in normal posture. However, when hands were crossed over the body midline, the reverse pattern was observed: the perception of the stimuli applied to the unaffected hand tended to be extinguished. This suggests that the deficits in spatial perception observed in CRPS are not related to the pathological limb, but rather to the space where the pathological limb normally resides. Moseley et al. (2012) also showed significant changes in limb temperature when limbs were crossed over the body midline. Finally, by misaligning vision and proprioception with prismatic goggles, Moseley et al. (2013) were able to show that these effects are dependent on the perceived location of the hands, rather than their actual location. These results suggest that CRPS-related symptoms can alter, not only somatotopic representations, but also spatiotopic representations of the body space (Moseley et al., 2009).

By integrating insights about the role of spatial perception for pain with insights from neuropsychology, interesting rehabilitation techniques, aimed at alleviating pain, have been developed (Sumitani et al., 2007). Sumitani et al. (2007) showed in CRPS patients a displacement of the body midline estimation towards the affected side of the body (however, see Kolb, Lang, Seifert, & Maihöfner, 2012; Reinersmann et al., 2012). Subsequently, prismatic adaptation was used to modify patient's visual experience. Prismatic adaptation is a non-invasive technique in which participants perform a visuo-motor pointing task while wearing prism goggles inducing a lateral displacement of the visual field and a mismatch between the felt position of the pointing hand. After this adaptation procedure, the displacement of the body representation was significantly reduced. Importantly, after two weeks of prismatic adaptation, pain and associated CRPS symptoms such as edema, discoloration and motor impairment, were significantly reduced. Bultitude and Rafal (2010) reproduced these results in one patient showing that the benefits of the procedure were dependent of the use of the pathological hand during the prism adaptation. However, it should be noted that there is still no agreement as to whether CRPS patients really display neglect-like symptoms, and if they do, what it is that they neglect, their affected limb (Moseley et al., 2009) or rather their unaffected limb (Sumitani et al., 2007) (for a review, see Torta, Legrain, Rossetti, & Mouraux, 2015). Nevertheless, these studies underline the importance of understanding the mechanisms underlying the integration of nociceptive information in the multisensory representation of the bodily space for the rehabilitation of chronic pain patients.

A recent study has investigated the reverse association, namely the influence of deficits in spatial attention on the pain experience (Liu et al., 2011). This study tested extinction for thermal pain sensations in patients with unilateral hemi-neglect. As mentioned before, extinction is the phenomenon that contralesional stimuli can be detected in isolation, but not when both sides are stimulated simultaneously. The authors found that a proportion of subjects demonstrated extinction for thermal pain stimuli. Moreover, for those who did not show extinction, thermal stimuli applied to the contralesional (affected) side were often mislocalized to the ipsilesional (unaffected) side, and the submodality of the stimulus was often misidentified. This shows that apart from the fact that chronic pain can influence spatial perception, deficits in spatial perception can also influence the experience of pain, providing further evidence for the importance of spatial perception for the processing of nociceptive stimuli.

Finally, results of Chapter 6 indicate that other chronic pain patients, such as fibromyalgia patients, might also show alterations in their spatial perception, compared to

healthy controls, having a heightened attention for stimuli entering the peripersonal space, and possibly also an increased attention towards external stimuli at a further distance. Moreover, this indicates the relevance of top-down attentional influences on somatosensory processing, indicating that e.g., personality traits, such as catastrophizing might play an important role in nociceptive processing (Legrain et al., 2011). However, further studies are needed to replicate results, and to unravel which variables may underlie these alterations.

4 CHALLENGES FOR FUTURE RESEARCH

In this dissertation we were able to answer some of the questions regarding the mapping of nociceptive stimuli in a peripersonal frame of reference, but many questions still remain unanswered. Here we discuss some limitations of the experiments presented in this dissertation and some recommendations for future research.

Throughout the first three chapters, we used TOJ tasks to investigate crossmodal interactions between visual and nociceptive stimuli in the peripersonal space. The use of a TOJ task was motivated by the fact that TOJ responses are typically unspeeded and thus enable the investigation of the genuinely perceptual component of information processing, relatively unbiased by any response-related effects. However, the use of a TOJ task also had some drawbacks. First, the TOJ task, at least as it was used in the present experiments, proved to be quite difficult, as shown by the high amount of participants who were not able to perform the task at the required level, especially in Chapter 2 when participants had to perform the task with their hands crossed. We have argued that this could be attributed (1) to the low intensity of the nociceptive stimuli, which was needed to guarantee the selectivity for nociceptor activation (Mouraux et al., 2010), and (2) to jitter in input transmission due to the variability of the conduction velocity of A δ fibers (Adriaensen, Gybels, Handwerker, & Van Hees, 1983). In Chapter 2 and 3, we tried to address this issue by using linear mixed effect models to analyze the data (Pinheiro & Bates, 2000), which allowed us to only exclude excessively high PSS values, without having to exclude the participants altogether. This was possible, because linear mixed models allows unbalanced data, unlike the classical general linear models, which require a completely balanced array of data (West, Welch, & Galecki, 2007). Although we agree that even excluding only some values is still far from ideal, we like to stress the fact that sensitivity analyses were performed, and results did not substantially change when the worst performing participants were included or excluded from the analyses. Moreover, the loss of data did not prevent the observation of significant crossmodal shifts of the TOJ of nociceptive stimuli.

A second drawback of the TOJ task used in our experiments is that the precision of the PSS values is very much dependent on the total number of observations per condition. For example, an accidental judgment error or erroneous button press has a more severe influence on the PSS when only 5 observations per SOA are used (20% shift of the respective data point), compared to when you have 40 observations per SOA (2.5% shift of this data point). Although we tried to have as much observations per SOA as possible, the total number of trials is limited by the attention span of the participants. Moreover, the use of a within-subject design increases the number of conditions, and thus the number of PSS values that had to be calculated. Nevertheless, we still consider the use of a within-subject design to be preferred over a design in which all variables are manipulated between subjects, as this would be very inefficient in terms of power and the amount of participants needed.

For these reasons, a crossmodal congruency task was used from Chapter 4 onwards. Especially in Chapter 5 and 6, in which we aimed at investigating the influence of visual stimuli presented at more than 2 distances from the body, there would have been a rapid increase in the amount of trials needed to achieve reliable PSS values. Of course the use of a crossmodal congruency task comes with its own drawbacks. More particularly, the fact that reaction times are the primary outcome of this task proved to be unfortunate when working with chronic pain patients (Chapter 6). Indeed, as mentioned before, it has been argued in previous studies that reaction time data are less suitable to study attentional prioritization in chronic pain populations (Van Damme et al., 2008). We found a high inter-individual variability in reaction times in chronic pain patients, making it difficult to draw strong conclusions based on this experiment. Therefore, future research should use different paradigms to further investigate the impact of chronic pain on spatial perception. One possibility would be to use reachability estimates to investigate differences in the size of reachable space between healthy control participants and fibromyalgia patients. Reachability estimates were found to correlate with actual action possibilities, depending on the environmental context, the emotional state, postural constraints and even the presence of mental or neurological illness (for a review, see Delevoeye-Turrell, Bartolo, & Coello, 2010). Moreover, it has been shown that reachability judgments were influenced by object's characteristics, such as their level of danger (Coello, Bourgeois, & Iachini, 2012). Another possibility would be to compare the 'estimated time remaining until collision occurs with an approaching object' (time-to-collision, TTC) between healthy controls and fibromyalgia patients. This TTC has for example been shown to be reduced for threatening as compared to neutral pictures (Brendel et al., 2012).

Throughout all experiments conducted, we tried to control for response bias, that is any tendency of participants to respond with the side on which the unilateral cue had been presented (Cairney, 1975; Drew, 1896; Shore, Spence, & Klein, 2001; Spence, Shore, & Klein, 2001). This was done either by manipulating the task participants had to perform (in some of the TOJ experiments, *'which hand was stimulated first'* versus *'which hand was stimulated second'*), or by letting participants answer with two foot pedals, one positioned under the toes, one under the heel, and ask them to keep both pedals depressed during the experiment and either lift their heel or their toes to respond (both in some of the TOJ experiments, as well as in the crossmodal congruency experiments). However, ideally the response dimensions should be orthogonal to the coding dimensions of the position of the visual cue stimuli (Spence & Driver, 1994, 1997; Spence, Nicholls, Gillespie, & Driver, 1998). This was not the case in our experiments, as participants still made left/right judgments. An alternative would be to present nociceptive stimuli at two locations on each hand, one above the other, and to ask participants to make elevation judgments. However, for practical reasons this was not feasible in the experiments presented in this dissertation. It has been shown that the response mapping can have an influence on the reference frame used (i.e. somatotopic versus external) (Alberto Gallace, Soto-Faraco, Dalton, Kreukniet, & Spence, 2008), with e.g., a reduced crossed-hands deficit if the response code is orthogonal to the left-right dimension (Roberts & Humphreys, 2008). Therefore, we have to keep in mind that any effects observed might also partly be a consequence of the particular task used, and might not generalize to other tasks with e.g., different response dimensions.

One question arising from the results of Chapter 5 and 6, is whether visual stimuli approaching the participant's body could have a differential influence on somatosensory processing, depending on whether tactile or nociceptive stimuli are applied. It could be that the application of nociceptive stimuli creates a threatening context, in which it is crucial to quickly prepare an appropriate response. Therefore, the spatially dependent effect of external stimuli could be stronger for nociceptive compared to tactile stimuli. Indeed, it has been proposed that the network involved in the construction of the peripersonal space, discriminates the motivational relevance of objects in that space (whether noxious or innocuous) and elaborates the motivational-affective sensorimotor representation of the stimulus in terms of appropriate motor responses (Lloyd et al., 2006). Future studies could directly address this question by comparing the spatially-dependent effect of visual stimuli on nociceptive and tactile processing, within the same participants.

In Chapter 1 to 5, IES was used. An important limitation of IES is that it is selective for nociceptors only when very low current intensities are used (Legrain & Mouraux, 2013;

Mouraux et al., 2010). However, at these intensities the stimulus generates a very weak percept. Although we increased the strength of the nociceptive stimuli through temporal summations, i.e. by using trains of three (or four) IES with inter-stimulus intervals of 5 ms, the sensation remained quite subtle, at least for some participants. As outlined in the general introduction, nociception should be dissociated from pain. The stimuli used in the experiments were nociceptive (they were described as pricking and slightly unpleasant), but were not necessarily experienced as painful. In this respect, it is important to note that the aim of this PhD dissertation was to investigate the influence of spatial perception on nociceptive processing, and more specifically, the crossmodal interactions between vision and nociception in the peripersonal space. We suggested that the interaction of external visual stimuli and nociceptive stimuli may serve the localization and initiation of defensive actions against potentially harmful objects approaching our body. Nociceptive stimuli can be defined as stimuli that activate peripheral receptors characterized by high-thresholds, and therefore they have the specific ability to code and transmit information about noxious sensory events, that is, sensory events having the possibility to afflict tissue damage (Belmonte & Viana, 2008). Nociception can therefore be interpreted as an archetype of threat detection (Legrain, Mancini, et al., 2012), and the induction of pain was not deemed necessary for our research question.

Throughout all chapters of this dissertation, we assessed the influence of visual stimuli presented either near or far from the body on nociceptive (or tactile) processing. One could argue that any differential influence of near and far visual stimuli could be attributable to differences in the retinotopic representation of the visual stimuli presented near versus far from the body. Indeed, because the spatial position of visual stimuli is primarily coded by the cortical projections of the retinas, one should also evidence how visual inputs are remapped from retinotopic to spatiotopic frames of reference. Further studies are needed to understand how, during crossmodal interactions between somatosensory and visual inputs, visual stimuli are remapped according to their proximity to the body part into a body-centered representation of external space. However, we believe that this does not preclude that our data supports the hypothesis according to which nociceptive stimuli are mapped in a peripersonal frame of reference. First, in Chapter 1, we showed that changing gaze fixation, and thus changing the position of the visual stimulus on the retina, did not change results. Second, in Chapter 3, the influence of the visual stimuli on nociceptive processing was largest when hands were proximal to the visual stimuli, independently of the distance of the visual stimuli to the body. Moreover, in the third experiment of Chapter 3, the position of the visual stimuli was manipulated according to the longitudinal axis (i.e. according to elevation

positions), and the two pairs of LEDs (low and high position) were at the same distance from the participants' trunk. In addition, the gaze was directed toward a fixation LED positioned equidistantly from each of the four experimental LEDs. Therefore visual acuity is unlikely to explain the results found in this experiment. Finally, it has been shown that there is no strict scaling relationship between retinal image size and the importance of its perception. For example, Murray, Boyaci, & Kersten (2006) found that the V1 cortical response to visual stimuli does not merely depend on the retinal size of the stimuli, but it already integrates other contractual information such as the perception of deepness.

All of our experiments were conducted in an experimental setting, and artificial lights (i.e. light emitting diodes, LEDs) were used as external visual stimuli. Although this has the advantage of creating a highly standardized situation in which most variables are under control, one could question the ecological validity of these experiments. In Chapter 5 and 6, we used dynamical visual stimuli, which already closer resemble a natural environment, in which objects are constantly moving. However, we could still further increase the ecological validity by investigating the effect of real life objects (e.g., a syringe or a needle) approaching or receding from participants, as has been done in some animal studies (Dong et al., 1994) and recently also in humans (Van der Biest, Legrain, De Paepe, & Crombez, 2015). This has the additional advantage that one could compare the influence of threatening versus non-threatening objects approaching or receding from the body on somatosensory processing.

Finally, participants of most of our experiments were healthy undergraduate students (Chapter 1 to 5). Student samples are rather specific and homogenous, and may therefore not be representative for the general population. This may limit the generalizability of the findings of these studies to the general population. In Chapter 6, we conducted one experiment with fibromyalgia patients and healthy participants from the general population. For the healthy participants, results were comparable for those found in the student population, albeit with tactile instead of nociceptive stimulation.

5 CONCLUSION

In this PhD dissertation, we investigated how spatial mapping can influence nociceptive processing. More specifically, we investigated the mapping of nociceptive stimuli in a peripersonal frame of reference, which is thought to be a multisensory motor interface between our body and the environment, enabling the localization and initiation of defensive actions against potentially harmful objects approaching our body. First, we showed that nociceptive stimuli are indeed mapped in a peripersonal frame of reference. More specifically, we found that nociceptive processing is multimodal (i.e. it is influenced by the occurrence of visual stimuli occurring in close proximity to the body), spatiotopic (i.e. it depends on the position of the stimulated body part in external space), and limb-centered (i.e. peripersonal space is spatially locked to the stimulated body part and moves with it in space). Second, we investigated the neural correlates underlying the crossmodal interactions between vision and nociception in the peripersonal space with event-related potentials (ERPs). We found some evidence for a modulation of nociceptive ERPs (more specifically of the N140), suggesting that the visual stimuli, presented near the stimulated body part, can influence the early sensory-perceptual processing of nociceptive stimuli in the secondary somatosensory and insular cortices. However, results in these experiments were mixed and further replication is needed to draw definite conclusions. Third, we investigated crossmodal interactions between vision and nociception under more ecologically valid conditions by testing the effect of moving visual stimuli, either approaching or receding from the body on nociceptive processing in healthy volunteers. We again found evidence for crossmodal interactions between vision and nociception in the peripersonal space. Moreover, we found that approaching visual stimuli had a stronger spatially dependent effect on nociceptive processing, compared to receding nociceptive stimuli. Finally, we investigated the differential influence of moving visual stimuli on tactile processing for fibromyalgia (FM) patients compared to control participants. Results were difficult to interpret, due to a high inter-individual variability in reaction times for the FM patients. Nevertheless, we found some preliminary evidence that FM patients have a heightened attention for visual stimuli approaching the body, compared to healthy control participants. However, these results have to be replicated with paradigms not relying on reactions times as primary outcome. Moreover, further studies have to investigate the underlying mechanisms of this increased attention for approaching stimuli in FM patients.

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NEDERLANDSTALIGE SAMENVATTING

*“De meest fundamentele ideeën van de wetenschap
zijn in wezen eenvoudig
en kunnen in de regel worden uitgedrukt
in een taal die voor iedereen begrijpelijk is.”*

(Albert Einstein)

1 INLEIDING

Iedereen ervaart tijdens zijn of haar leven op regelmatige basis pijn. Het is een onaangenaam gevoel dat vaak, maar niet altijd, veroorzaakt wordt door intense, schadelijke stimuli. Pijn is adaptief, in de zin dat het een individu motiveert om zich terug te trekken uit gevaarlijke situaties, zich te verdedigen tegen bedreigingen, en om gelijkaardige situaties in de toekomst te vermijden (Chapman, Tuckett, & Song, 2008; Dawkins, 1995; Eccleston & Crombez, 1999). Onderzoek rond pijn heeft zich gedurende vele jaren voornamelijk gefocust op het identificeren van de unieke aspecten van pijn. Hierbij werden de invloed van aandachts- en motivationele factoren van pijn, op een organisme dat in interactie treedt met zijn natuurlijke omgeving, grotendeels verwaarloosd (Eccleston & Crombez, 1999). Pijn is meer dan een *“onaangename sensorische en emotionele ervaring veroorzaakt door feitelijk of mogelijke weefselbeschadiging of beschreven in termen van een dergelijke beschadiging”* (IASP, 1994, p 210). Vanuit een cognitief perspectief kan pijn gezien worden als *“een waarschuwingssignaal dat ons in staat stelt een stimulus die een potentiële bedreiging voor de fysieke integriteit van het lichaam vormt te detecteren, te lokaliseren en ertegen te reageren”* (Legrain & Torta, 2015). Deze definitie wijst op het belang van minstens drie cognitieve processen in het verwerken van nociceptieve stimuli: (1) de selectieve aandacht, het detecteren en het richten van de aandacht naar saliënte of relevante stimuli in de omgeving om de verwerking ervan prioriteit te geven, (2) de spatiale perceptie, het lokaliseren van stimuli op de ruimte van het lichaam en in de externe ruimte, (3) het selecteren en voorbereiden van de meest geschikte (verdedigende) motorische respons. Deze processen zijn niet specifiek voor nociceptie. Binnen dit perspectief ligt de nadruk dan ook niet langer op de kwaliteit van de sensatie uitgelokt door schadelijke stimuli, maar op de actie uitgelokt door het optreden van potentiële bedreigingen. Om te begrijpen hoe een levend organisme zich aanpast aan betekenisvolle veranderingen in de omgeving, en hoe het zich verdedigt tegen potentieel schadelijke stimuli, is het dus van belang te onderzoeken hoe selectieve aandacht, spatiale perceptie, en het selecteren van een gepaste reactie betrokken zijn in het verwerken van nociceptieve inputs (Legrain & Torta, 2015). In deze doctoraatsthesis lag de focus op de invloed van één van deze cognitieve processen, namelijk de *spatiale perceptie*, in het verwerken van nociceptieve stimuli.

De lokalisatie van een nociceptieve stimulus op het lichaam is essentieel als een organisme een snelle en aangepaste respons wil geven op lichaamsbedreigingen (Legrain, Mancini, et al., 2012; Mancini, Longo, Iannetti, & Haggard, 2011). Het stellen van een verdedigende respons, zoals het wegvegen van een wesp, lijkt een eenvoudige actie, maar toch stelt het een grote uitdaging voor de hersenen. De mogelijkheid om nociceptieve

stimuli te lokaliseren op het lichaam is gedeeltelijk afhankelijk van een directe relatie tussen de spatiale organisatie van de receptoren in de huid en de spatiale organisatie van neuronen in de cerebrale cortex (Kenshalo & Isensee, 1983). Dit laat echter enkel toe om de positie van stimuli op het lichaam te bepalen. Om een defensieve motorische respons naar de locatie van de bedreiging te leiden, is het essentieel dat de positie van potentieel bedreigende stimuli in de externe omgeving ook bepaald wordt. De ruimte rondom ons wordt op verscheidene manieren gerepresenteerd in de hersenen, en deze verschillende representaties encoderen locaties en objecten waarin we geïnteresseerd zijn in verschillende referentiekaders (Vallar & Maravita, 2009). Elke representatie is gelinkt aan een verschillende actie of een verschillende regio in de ruimte (Fogassi et al., 1996; Graziano, Yap, & Gross, 1994; Jeannerod, Arbib, Rizzolatti, & Sakata, 1995). Deze spatiale referentiekaders of spatiale coördinatiesystemen worden gebruikt om gedrag te sturen, en er wordt aangenomen dat deze geconstrueerd worden in de pariëtale cortex. In het kader van deze doctoraatsthesis zijn voornamelijk de dissociaties van een somatotopisch versus een spatiotopisch referentiekader en van een peripersoonlijk versus extrapersoonlijk referentiekader belangrijk.

De persoonlijke ruimte (i.e. de ruimte van het lichaam) kan gerepresenteerd worden in een *somatotopisch* of een *spatiotopisch* referentiekader. Het somatotopisch referentiekader geeft een anatomische representatie van het lichaam, gebaseerd op geordende projecties van de receptieve velden¹, naar gesegregeerde subgroepen van neuronen. Met andere woorden, het is een representatie van de lichaamsdelen, zoals ze gegeven worden door de somatotopische kaart in de somatosensorische cortex. Het spatiotopisch referentiekader daarentegen, geeft een op ruimte gebaseerde representatie van het lichaam. Het is een representatie van de locatie van het lichaam en de lichaamsdelen, relatief ten opzichte van externe objecten en relatief ten opzichte van elkaar en ten opzichte van de middellijn van het lichaam (Vallar, 1997).

De externe ruimte (i.e. de ruimte buiten het lichaam) kan gerepresenteerd worden in een *peripersoonlijk* of een *extrapersoonlijk* referentiekader. Deze coderen respectievelijk de positie van stimuli dichtbij en veraf van het lichaam (Halligan & Marshall, 1991). Het peripersoonlijk referentiekader is van specifiek belang, omdat het zowel de positie van somatosensorische stimuli op het lichaamsoppervlak als de positie van stimuli in de externe ruimte (vb. visuele stimuli) encodeert, wanneer ze dichtbij het lichaam komen (Holmes & Spence, 2004; Maravita, Spence, & Driver, 2003). Het zorgt er dus voor dat de kaart van het

¹ Het receptief veld van een neuron is de regio in de ruimte waarin de aanwezigheid van een stimulus het vuren van het neuron zal veranderen.

lichaam gecoördineerd kan worden met de kaart van de externe proximale ruimte in een geïntegreerde, multisensorische representatie van het lichaam en de ruimte rondom het lichaam (Cardinali, Brozzoli, & Farnè, 2009; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981; Spence & Driver, 2004). De peripersonlijke ruimte leidt de directe manipulatie van objecten (Rizzolatti, Fadiga, Fogassi, & Gallese, 1997). Bovendien wordt er verondersteld dat de peripersonlijke ruimte cruciaal is voor de organisatie van defensieve motorische acties (Graziano & Cooke, 2006). De extrapersonlijke ruimte daarentegen, wordt gebruikt voor het exploreren van de ruimte door middel van oogbewegingen en om reikbewegingen te initiëren.

Het bestaan van een peripersonlijk referentiekader voor het lokaliseren van tactiele stimuli werd reeds uitvoerig gedocumenteerd door aan te tonen dat tactiele stimuli geïntegreerd worden met externe stimuli (vb. visuele of auditieve stimuli), wanneer deze dichtbij het lichaam aangeboden worden (voor een overzicht, zie Spence & Driver, 2004). Voor nociceptieve stimuli daarentegen heeft het meeste onderzoek zich gefocust op het beschrijven van de somatotopische organisatie van de neuronale responsen van nociceptieve en pijnlijke² stimuli (Andersson et al., 1997; Baumgärtner et al., 2010; Bingel et al., 2004; Henderson, Gandevia, & Macefield, 2007). Slechts recent zijn studies ook beginnen focussen op de mogelijkheid om pijn te lokaliseren volgens niet-somatotopische referentiekaders. Zo hebben sommige studies aangetoond dat een spatiotopisch referentiekader gebruikt wordt voor het lokaliseren van nociceptieve stimuli (Gallace, Torta, Moseley, & Iannetti, 2011; Sambo et al., 2013). Andere studies hebben gewezen op de rol van het zien van lichaamsdelen of externe visuele stimuli in het verwerken van nociceptieve stimuli (Favril, Mouraux, Sambo, & Legrain, 2014; Longo, Betti, Aglioti, & Haggard, 2009; Sambo, Forster, Williams, & Iannetti, 2012a; Sambo & Iannetti, 2013; Sambo, Liang, Cruccu, & Iannetti, 2012b; Mancini, Longo, Kammers, & Haggard, 2011; Van Ryckeghem et al., 2011). Geen van deze studies kan echter een rechtstreekse uitspraak doen over het coderen van nociceptieve stimuli in een peripersonlijk referentiekader. In sommige van deze studies was de visuele manipulatie beperkt tot het zien van het lichaam (Longo et al., 2009; Mancini et al., 2011). In andere experimenten, werden visuele stimuli niet gepresenteerd buiten de persoonlijke ruimte (Sambo et al., 2012a, 2012b; Sambo & Iannetti, 2013), of werd de

² Een onderscheid moet gemaakt worden tussen 'nociceptieve' en 'pijnlijke' stimuli. Een nociceptieve stimulus refereert naar een stimulus die de nociceptoren activeert, onafhankelijk van het feit of de stimulus ook de perceptie van pijn uitlokt. Een pijnlijke stimulus, aan de andere kant, refereert naar een stimulus die de perceptie van pijn uitlokt, onafhankelijk van het feit of deze stimulus ook de nociceptoren activeert (Loeser & Treede, 2008).

afstand van de visuele stimuli ten opzichte van het lichaam niet gemanipuleerd (Favril, Mouraux, Sambo, & Legrain, 2014; Van Ryckeghem et al., 2011).

De mogelijkheid om stimuli te lokaliseren op het lichaam en in de externe ruimte in de nabijheid van het lichaam is nochtans relevant in de context van pijn. De peripersonlijke ruimte stelt ons in staat te interageren met onze omgeving (Graziano & Cooke, 2006; Rizzolatti et al., 1997). Crossmodale interacties tussen externe en tactiele stimuli zouden ons voornamelijk in staat stellen om te grijpen naar objecten en ze te manipuleren, maar crossmodale interacties tussen externe en nociceptieve stimuli zouden de belangrijke taak hebben ons in staat te stellen potentieel bedreigende objecten, die dichterbij komen, te lokaliseren en verdedigende responsen te initiëren. Bovendien is aangetoond dat bepaalde chronische-pijnsyndromen (meer bepaald complex regionaal pijn syndroom, CRPS) geassocieerd zijn met cognitieve beperkingen die de mogelijkheid om het lichaam en de omliggende ruimte voor te stellen, veranderen (voor een overzicht, zie Legrain, Bultitude, De Paepe, & Rossetti, 2012; Legrain & Torta, 2015). Dit wijst op het belang om de spatiale perceptie te onderzoeken, niet enkel om de normale verwerking van nociceptieve stimuli beter te begrijpen, maar ook om meer inzicht te krijgen in de pathofysiologie en de behandeling van chronische pijn.

2 DOELSTELLINGEN

Het doel van deze doctoraatsthesis was om te onderzoeken hoe de hersenen een multimodaal en peripersonlijk schema van het lichaam maken om nociceptieve stimuli te lokaliseren op het lichaam, en om snel en efficiënt te reageren op fysieke bedreigingen die dichterbij het lichaam komen.

Ten eerste, hebben we onderzocht of nociceptieve stimuli inderdaad gecodeerd worden in een peripersonlijk referentiekader. We verwachtten dat, indien een peripersonlijk referentiekader gebruikt wordt voor het lokaliseren van nociceptieve stimuli, de verwerking van nociceptieve stimuli de volgende kenmerken zou hebben: (1) *multimodaal*, de verwerking zou beïnvloed worden door het voorkomen van visuele stimuli in de nabijheid van het lichaam (De Paepe, Crombez, Spence, & Legrain, 2014), (2) *spatiotopisch*, de verwerking zou afhankelijk zijn van de positie van het gestimuleerde lichaamsdeel in de externe ruimte (De Paepe, Crombez, & Legrain, 2015), en (3) *verankerd aan een lichaamsdeel*, de peripersonlijke ruimte zou spatiaal verankerd zijn aan het gestimuleerde

lichaamsdeel en zou mee bewegen met het lichaamsdeel in de ruimte (De Paepe, Crombez, & Legrain, in preparation [a]).

Ten tweede, hebben we de neurale correlaten, onderliggend aan de crossmodale interacties tussen visuele en nociceptieve stimuli in de peripersoonlijke ruimte, onderzocht met event-gerelateerde potentialen (ERPs). We verwachtten dat visuele stimuli, die gepresenteerd worden in de peripersoonlijke ruimte, de vroege sensorische-perceptuele verwerking van nociceptieve stimuli kunnen beïnvloeden (De Paepe, Crombez, & Legrain, in preparation [b]).

Ten derde, wilden we het effect van bewegende visuele stimuli op de nociceptieve verwerking onderzoeken. De visuele stimuli kwamen ofwel dichterbij de participanten, ofwel gingen ze verder weg. We verwachtten dat visuele stimuli de nociceptieve verwerking meer zouden beïnvloeden, wanneer ze dichtbij de participanten waren, dan wanneer ze nog veraf waren. Bovendien, verwachtten we dat stimuli die dichtbij komen een sterker spatiaal afhankelijk effect zullen hebben op de nociceptieve verwerking, dan stimuli die verder weg gingen (De Paepe, Crombez, & Legrain, under review).

Ten vierde, wilden we de verschillende impact van bewegende visuele stimuli op de tactiele verwerking onderzoeken voor fibromyalgie (FM) patiënten, ten opzichte van gezonde vrijwilligers. Hiermee wilden we nagaan of chronische pijn, en meer bepaald FM, spatiale perceptie kan beïnvloeden. We kozen om dit te onderzoeken bij FM patiënten, omdat deze patiënten een verhoogde respons vertonen voor pijnlijke stimuli, maar ook voor stimuli in andere modaliteiten (vb. geluid) (Crombez, Van Damme, & Eccleston, 2005; McDermid, Rollman, & McCain, 1996). Hier wilden we onderzoeken of deze overgevoeligheid bij fibromyalgie patiënten geassocieerd is met een verhoogde aandacht voor stimuli in de peripersoonlijke ruimte, of met het scannen van een groter deel van de externe ruimte om saliente of potentieel bedreigende stimuli te detecteren (De Paepe, Crombez, & Legrain, in preparation [c]).

3 BEVINDINGEN

3.1 DEEL 1

In dit deel hebben we onderzocht of nociceptieve stimuli gecodeerd worden in een peripersoonlijk referentiekader bij gezonde vrijwilligers. Dit werd onderzocht aan de hand van verschillende ‘temporal order judgment’ (TOJ) experimenten.

In **Hoofdstuk 1**, hebben we getest of de nociceptieve verwerking beïnvloed wordt door visuele stimuli die voorkomen in de nabijheid van het lichaam. Twee experimenten werden uitgevoerd, waarin participanten de temporele volgorde beoordeelden van paren van nociceptieve stimuli, waarvan één op elke hand werd aangeboden. Kort voor de eerste nociceptieve stimulus, kregen de participanten een unilaterale visuele stimulus, of bilaterale visuele stimuli te zien, ofwel dichtbij hen (i.e. in de peripersoonlijke ruimte), ofwel ver voor hen (i.e. in de extrapersoonlijke ruimte). De resultaten van deze studie toonden dat de perceptie van nociceptieve stimuli vertekend werd in het voordeel van de stimulus die aangeboden werd op de hand dichtbij de unilaterale stimulus. Dit was vooral het geval wanneer de visuele stimulus in de peripersoonlijke ruimte werd aangeboden, en in mindere mate wanneer de visuele stimulus in de extrapersoonlijke ruimte werd aangeboden. Dit suggereert dat een peripersoonlijk referentiekader gebruikt wordt voor het coderen van de positie van nociceptieve stimuli in de multisensorische ruimte.

In **Hoofdstuk 2**, onderzochten we of de positie van het gestimuleerde lichaamsdeel in de externe ruimte in rekening wordt genomen bij het verwerken van nociceptieve informatie. Twee experimenten werden uitgevoerd, waarin participanten de temporele volgorde van twee nociceptieve stimuli (één aangeboden op elke hand) moesten beoordelen, terwijl ze gevraagd werden om hun handen ofwel in de normale houding (ongekruist) te leggen, ofwel om ze te kruisen over de middellijn van het lichaam. Kort voor de eerste nociceptieve stimulus werden niet-informatieve visuele stimuli aangeboden ofwel dichtbij ofwel ver weg van het lichaam. We vonden dat de verwerking van nociceptieve stimuli, aangeboden op de hand die zich bevond in de nabijheid van een unilaterale visuele stimulus, voorrang kreeg ten opzichte van de hand die zich aan de andere kant van de unilaterale visuele stimulus bevond, ongeacht de houding van de armen (i.e. gekruist of ongekruist). Bovendien, was de invloed van de visuele stimuli kleiner wanneer ze ver van de participanten werden aangeboden, in vergelijking met wanneer ze dichtbij de participanten werden aangeboden. Tenslotte, was de temporele sensitiviteit van de participanten lager wanneer hun handen gekruist waren. Deze bevindingen zijn compatibel met het encoderen van nociceptieve stimuli in een spatiotopisch, en meer specifiek een peripersoonlijk referentiekader, waarin

de houding van de lichaamsdelen ten opzichte van elkaar en ten opzichte van andere objecten die in de nabijheid van het lichaam voorkomen in rekening wordt gebracht.

In **Hoofdstuk 3**, hebben we onderzocht of de lokalisatie van nociceptieve stimuli gebaseerd is op een spatiale representatie die verankerd is aan het gestimuleerde lichaamsdeel of eerder aan het lichaam in zijn geheel (i.e. de romp). In drie experimenten werd het effect van unilaterale visuele stimuli op de waargenomen temporele volgorde van paren van nociceptieve stimuli, waarvan één toegediend werd op elke hand, onderzocht. Een cruciaal aspect van deze studies was dat de positie van zowel de handen als van de visuele stimuli gemanipuleerd werd, zodat visuele en nociceptieve stimuli op een aanpalende of niet-aanpalende spatiale positie voorkwamen. Beoordelingen van de temporele volgorde van de nociceptieve stimuli werden vertekend ten voordele van de stimulus die werd toegediend aan de hand dichtst bij de visuele stimulus, onafhankelijk van de afstand tot het lichaam. Dit suggereert dat de mogelijkheid om de positie van nociceptieve stimuli op een specifieke lichaamsdeel te bepalen gebaseerd is op een spatiaal referentiekader dat spatiaal verankerd is aan dit lichaamsdeel en dat mee beweegt met het bewegende lichaamsdeel.

3.2 DEEL 2

In het tweede deel van deze doctoraatsthesis, wilden we de neurale correlaten onderliggend aan de crossmodale interacties tussen visuele en nociceptieve stimuli in de peripersonlijke ruimte onderzoeken met ERPs.

In **Hoofdstuk 4**, werden twee experimenten uitgevoerd met een 'exogeen crossmodaal cuing paradigma'. Participanten kregen een nociceptieve stimulus aangeboden op één van beide handen. Op sommige trials werden deze nociceptieve stimuli vervangen door tactiele stimuli (Experiment 1) of door twee nociceptieve stimuli, kort na elkaar aangeboden (Experiment 2). Kort voor de somatosensorische stimulus, werd een visuele stimulus aangeboden. Deze visuele stimulus werd ofwel gepresenteerd aan de kant van de gestimuleerde hand (congruent), ofwel aan de andere kant van de ruimte (incongruent). Bovendien werd de visuele stimulus ofwel dichtbij de handen van de participant aangeboden ofwel ver weg van de handen. Participanten kregen de opdracht te rapporteren op welke hand ze een tactiele of dubbele nociceptieve stimulus voelden, terwijl ze de enkele nociceptieve stimuli en de visuele stimuli moesten negeren. Gedragsresponsen werden geanalyseerd voor de tactiele stimuli (Experiment 1) of de dubbele nociceptieve stimuli (Experiment 2), en ERPs werden geanalyseerd voor de enkele nociceptieve stimuli. In

Experiment 1, werden tactiele stimuli sneller gediscrimineerd bij congruente dan bij incongruente trials, maar enkel wanneer de visuele stimuli aangeboden werden dichtbij (versus ver) van de handen van de participanten. ERP resultaten voor dit experiment waren niet overtuigend. In Experiment 2, vonden we geen significante gedragsresultaten, maar de ERPs waren groter in amplitude wanneer de visuele stimuli dichtbij de handen en congruent ten opzichte van de locatie van de nociceptieve stimuli werden aangeboden, in tegenstelling tot wanneer ze ver van de handen en incongruent ten opzichte van de locatie van de nociceptieve stimuli werden aangeboden. Deze grotere amplitude werd enkel terug gevonden bij de N140 component. Dit suggereert dat de locatie van visuele stimuli de nociceptieve verwerking beïnvloed door een modulatie van de elektrofyysiologische responsen compatibel met de neurale activiteit in de secundaire somatosensorische en insulaire cortices.

3.3 DEEL 3

In het derde deel van deze doctoraatsthesis waren we geïnteresseerd in de invloed van bewegende visuele stimuli op de somatosensorische verwerking.

In **Hoofdstuk 5**, hebben we bij gezonde vrijwilligers onderzocht hoe de verwerking van nociceptieve stimuli beïnvloed wordt door bewegende visuele stimuli, die ofwel dichterbij de handen van de participanten kwamen, ofwel verder ervan weg gingen. Op elke trial kwam een visuele stimulus ofwel dichterbij de linker-of rechterhand, ofwel ging deze er verder van weg. Op verschillende temporele intervallen na de start van de visuele stimulus werd een nociceptieve stimulus toegediend ofwel op de hand aan dezelfde kant van de ruimte, ofwel op de hand in het andere deel van de ruimte. Hierdoor werd de visuele stimulus op verschillende afstanden van de hand waargenomen, op het ogenblik dat de nociceptieve stimulus werd toegediend. Resultaten toonden dat reactietijden het snelst waren wanneer de visuele stimulus dichtbij de hand werd waargenomen op het moment dat de nociceptieve stimulus werd toegediend. De invloed van de visuele stimuli werd ook onderzocht over een continu spatiaal bereik (van dichtbij naar veraf). We vonden dat de visuele stimuli die dichterbij kwamen een groter spatiaal afhankelijk effect hadden op de nociceptieve verwerking dan de visuele stimuli die verder weg gingen. Deze resultaten suggereren dat het coderen van nociceptieve informatie in een peripersonlijk referentiekader een soort veiligheidsmarge rond het lichaam vormt, dat ons in staat stelt onszelf te beschermen tegen potentiële bedreigingen.

In **Hoofdstuk 6**, hebben we de verschillende impact van bewegende visuele stimuli op de tactiele verwerking vergeleken voor FM patiënten ten opzichte van gezonde vrijwilligers. Voor controleparticipanten vonden we, in overeenstemming met vorig onderzoek, dat de visuele stimuli de grootste invloed hadden op de tactiele verwerking, wanneer ze dichtbij het lichaam werden aangeboden. Voor FM patiënten was dit verschil minder duidelijk, wat mogelijks aanduidt dat FM patiënten een verhoogde aandacht hebben voor potentieel bedreigende stimuli op een verdere afstand van het lichaam. De curves die de reactietijden over een continu spatiaal bereik (van dichtbij naar veraf) bekeken, duiden aan dat FM patiënten een verhoogde aandacht hebben voor stimuli in de peripersonlijke ruimte in vergelijking met controles. Hierbij moet wel bemerkt worden dat deze verschillen enkel gevonden werden wanneer een curve gefit werd op de data. Daarom moeten de resultaten omzichtig geïnterpreteerd worden en is er nood aan verder onderzoek en replicatie.

4 CONCLUSIE

In deze doctoraatssthesi hebben we onderzocht hoe spatiale perceptie nociceptieve verwerking kan beïnvloeden. Meer specifiek, hebben we onderzocht hoe het encoderen van nociceptieve stimuli in een peripersonlijk referentiekader (een multisensorische-motorische interface tussen ons lichaam en de omgeving) ons toelaat om potentieel bedreigende stimuli in de nabijheid van ons lichaam te lokaliseren en een defensieve beweging te initiëren. Ten eerste hebben we aangetoond dat nociceptieve stimuli wel degelijk geëncodeerd worden in een peripersonlijk referentiekader. Meer specifiek hebben we gevonden dat nociceptieve verwerking (1) multimodaal is (i.e. beïnvloed wordt door het voorkomen van visuele stimuli in de nabijheid van het lichaam), (2) spatiotopisch is (i.e. afhankelijk is van de positie van het gestimuleerde lichaamsdeel in de externe ruimte), en (3) verankerd is aan het gestimuleerde lichaamsdeel en mee beweegt met het lichaamsdeel in de externe ruimte. Ten tweede, hebben we de neurale correlaten, onderliggend aan de crossmodale interacties tussen visuele en nociceptieve stimuli in de peripersonlijke ruimte, onderzocht met event gerelateerde potentialen (ERPs). We vonden evidentie voor een modulatie van nociceptieve ERPs (meer specifiek van de N140). Dit suggereert dat visuele stimuli, die gepresenteerd worden in de peripersonlijke ruimte, de vroege sensorische-perceptuele verwerking van nociceptieve stimuli in de secundaire somatosensorische en insulaire cortex kunnen beïnvloeden. Resultaten in deze experimenten varieerden echter en verdere replicatie is vereist voor definitieve conclusies getrokken kunnen worden. Ten derde, hebben we crossmodale interacties onderzocht tussen visuele en nociceptieve stimuli

onder meer ecologische condities door het effect van bewegende visuele stimuli op de nociceptieve verwerking te onderzoeken. We vonden opnieuw evidentie voor crossmodale interacties tussen visuele en nociceptieve stimuli in de peripersonlijke ruimte. Bovendien vonden we dat de visuele stimuli een sterker spatiaal afhankelijk effect hadden op de nociceptieve verwerking wanneer ze dichterbij de participanten kwamen, dan wanneer ze verder van hen weg gingen. Tenslotte, hebben we de verschillende impact van bewegende visuele stimuli op de tactiele verwerking onderzocht voor fibromyalgie (FM) patiënten ten opzichte van gezonde vrijwilligers. Resultaten waren moeilijk te interpreteren door een hoge inter-individuele variabiliteit in de reactietijdgegevens van de FM patiënten. Niettegenstaande, vonden we aanwijzingen dat FM patiënten een verhoogde aandacht hebben voor visuele stimuli die dichterbij het lichaam komen ten opzichte van gezonde vrijwilligers. Deze resultaten moeten echter gerepliceerd worden met paradigma's die geen reactietijden als primaire uitkomstmaat hebben. Bovendien kunnen toekomstige studies de onderliggende mechanismen onderzoeken van deze toegenomen aandacht voor dichterbij komende stimuli in FM patiënten.

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*“Er zou weinig van mij overblijven
indien ik alles zou moeten afstaan,
wat ik aan anderen te danken heb.”
(Johann Wolfgang von Goethe)*

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Annick

Maart, 2016

DATA STORAGE FACT SHEETS

*“By some estimates,
the data-storage curve is rocketing upward
at the rate of 800 percent per year.
Organizations are collecting so much data
they're overwhelmed.
(...) we have more items stored than
we'll ever have to allocate time for.”*

(Jim Lewis)

Data storage fact sheet (29/2/16)

% Data Storage Fact Sheet (versie 29 februari 2016)
% Data Storage Fact Sheet <Phd Annick De Paepe, Chapter 1,
Experiment 1 and 2>
% Author: Annick De Paepe
% Date: 29/02/2016

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1a. Main researcher

- name: Annick De Paepe
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Annick.DePaepe@Ugent.be

1b. Responsible ZAP (if different from the main researcher)

- name: Geert Crombez
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Geert.Crombez@UGent.be

If a response is not received when using the above contact details, please send an email to data-ppw@ugent.be or contact Data Management, Faculty of Psychology and Educational Sciences, Henri Dunantlaan 2, 9000 Ghent, Belgium.

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- De Paepe, A.L., Crombez, G., Spence, C., & Legrain, V. (2014). Mapping nociceptive stimuli in a peripersonal frame of reference: Evidence from a temporal order judgment task. *Neuropsychologia*, 56, 219-228.
- De Paepe, A.L. (2016). Mapping nociceptive stimuli in a peripersonal frame of reference: Evidence from a temporal order judgment task. PhD dissertation, Chapter 1, Experiment 1 and 2.

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% Author: Annick De Paepe
% Date: 29/02/2016

1. Contact

1a. Main researcher

- name: Annick De Paepe
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Annick.DePaepe@UGent.be

1b. Responsible ZAP (if different from the main researcher)

- name: Geert Crombez
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Geert.Crombez@UGent.be

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 - R-scripts: - Script_Lefthand_CH1.R
 - Script_Righthand_CH1.R
 - Script_Neutralhand_CH1.R
 - Script_Unilateralcues_CH2.R
 - Script_Bilateralcues_CH2.R
- file(s) containing processed data. Specify:
 - PSSandJNDfromR_CH1.txt
 - PSSandJND_FromR_CH2.txt
- file(s) containing analyses. Specify:
 - CH1_FINAL.R
 - CH1_FINAL_PLOSONE.R
 - CH2_FINAL.R
 - CH2_FINAL_PLOSONE.R
 - (R files, running these files gives the results)
- files(s) containing information about informed consent. Specify: ...
- a file specifying legal and ethical provisions. Specify: ...
- file(s) that describe the content of the stored files and how this content should be interpreted. Specify:
 - R-scripts contain additional information
- other files. Specify:
- * On which platform are these other files stored?
- individual PC
- research group file server
- other: responsible ZAP PC
- .
- * Who has direct access to these other files (i.e., without intervention of another person)?
- main researcher
- responsible ZAP
- all members of the research group
- all members of UGent
- other (specify): ...

4. Reproduction

=====

* Have the results been reproduced?: [] YES / [x] NO

* If yes, by whom (add if multiple):

- name
- address
- affiliation
- e-mail

Data storage fact sheet (29/2/16)

% Data Storage Fact Sheet (versie 29 februari 2016)
 % Data Storage Fact Sheet <Phd Annick De Paepe, Chapter 3,
 Experiment 1, 2 and 3>
 % Author: Annick De Paepe
 % Date: 29/02/2016

1. Contact

1a. Main researcher

- name: Annick De Paepe
 - address: Henri Dunantlaan 2, 9000 Gent
 - e-mail: Annick.DePaepe@UGent.be

1b. Responsible ZAP (if different from the main researcher)

- name: Geert Crombez
 - address: Henri Dunantlaan 2, 9000 Gent
 - e-mail: Geert.Crombez@UGent.be

If a response is not received when using the above contact details,
 please send an email to data-ppw@ugent.be or contact Data Management,
 Faculty of Psychology and Educational Sciences, Henri Dunantlaan 2,
 9000 Ghent, Belgium.

2. Information about the datasets to which this sheet applies

* Reference of the publication in which the datasets are reported:
 - De Paepe, A.L. (2016). Remapping nociceptive stimuli into a
 peripersonal frame of reference is spatially locked to the
 stimulated limb. PhD dissertation, Chapter 3, Experiment 1, 2 and 3.

* Which datasets in that publication does this sheet apply to?:
 All datasets reported in the publication.

3. Information about the files that have been stored

3a. Raw data

* Have the raw data been stored by the main researcher? YES /
 NO
 If NO, please justify:

* On which platform are the raw data stored?
 researcher PC
 research group file server
 research group file server via DICT
 responsible ZAP PC

* Who has direct access to the raw data (i.e., without intervention
 of another person)?
 main researcher
 responsible ZAP
 all members of the research group

- [] all members of UGent
- [] other (specify): ...

3b. Other files

- * Which other files have been stored?
 - [x] file(s) describing the transition from raw data to reported results. Specify:
 - R-scripts:
 - Script_LandR_expBOL.R
 - Script_VC_11_04.R
 - Script_HOT_11_09.R
 - [x] file(s) containing processed data. Specify:
 - PSSenJND_BOL.txt
 - [x] file(s) containing analyses. Specify:
 - Exp_BOL(congruency)_11_09.R
 - Script_VC_11_04.R
 - Script_HOT_11_09.R
 - (R files, running these files gives the results)
 - [] files(s) containing information about informed consent. Specify: ...
 - [] a file specifying legal and ethical provisions. Specify: ...
 - [x] file(s) that describe the content of the stored files and how this content should be interpreted. Specify:
 - R-scripts contain additional information
 - [] other files. Specify:
- * On which platform are these other files stored?
 - [x] individual PC
 - [x] research group file server
 - [] other: responsible ZAP PC
- .
- * Who has direct access to these other files (i.e., without intervention of another person)?
 - [x] main researcher
 - [x] responsible ZAP
 - [] all members of the research group
 - [] all members of UGent
 - [] other (specify): ...

4. Reproduction

- * Have the results been reproduced?: [] YES / [x] NO
- * If yes, by whom (add if multiple):
- name

- address
- affiliation
- e-mail

Data storage fact sheet (29/2/16)

% Data Storage Fact Sheet (versie 29 februari 2016)
% Data Storage Fact Sheet <Phd Annick De Paepe, Chapter 4,
Experiment 1 and 2>
% Author: Annick De Paepe
% Date: 29/02/2016

1. Contact

1a. Main researcher

- name: Annick De Paepe
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Annick.DePaepe@UGent.be

1b. Responsible ZAP (if different from the main researcher)

- name: Geert Crombez
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Geert.Crombez@UGent.be

If a response is not received when using the above contact details, please send an email to data-ppw@ugent.be or contact Data Management, Faculty of Psychology and Educational Sciences, Henri Dunantlaan 2, 9000 Ghent, Belgium.

2. Information about the datasets to which this sheet applies

* Reference of the publication in which the datasets are reported:
- De Paepe, A.L. (2016). Crossmodal spatial attention between vision and nociception in the peripersonal space: an ERP study. PhD dissertation, Chapter 4, Experiment 1 and 2.

* Which datasets in that publication does this sheet apply to?:
All datasets reported in the publication.

3. Information about the files that have been stored

3a. Raw data

* Have the raw data been stored by the main researcher? [] YES / [] NO

If NO, please justify:

* On which platform are the raw data stored?

[] researcher PC
[] research group file server
[] research group file server via DICT
[] responsible ZAP PC

* Who has direct access to the raw data (i.e., without intervention of another person)?

[] main researcher
[] responsible ZAP
[] all members of the research group
[] all members of UGent

[] other (specify): ...

3b. Other files

* Which other files have been stored?

- [x] file(s) describing the transition from raw data to reported results. Specify:

- R-scripts:

- Script_ERP1_behavioral_2016_05_01.R
- Script_ERP2_v1.R

- [x] file(s) containing processed data. Specify:

- ERP1_v3.sav
- ERP2analyses_V2(merged).sav

- [x] file(s) containing analyses. Specify:

- Script_ERP1_behavioral_2016_05_01.R
- Script_ERP2_v1.R
- Syntax_ERP1.sps
- Syntax_ERP2.sps

(R and SPSS files, running these files gives the results)

- [] files(s) containing information about informed consent.

Specify: ...

- [] a file specifying legal and ethical provisions. Specify: ...

- [x] file(s) that describe the content of the stored files and how this content should be interpreted. Specify:

- R-scripts and SPSS syntax contain additional information

- [] other files. Specify:

* On which platform are these other files stored?

- [x] individual PC
- [x] research group file server
- [] other: responsible ZAP PC

* Who has direct access to these other files (i.e., without intervention of another person)?

- [x] main researcher
- [x] responsible ZAP
- [] all members of the research group
- [] all members of UGent
- [] other (specify): ...

4. Reproduction

=====

* Have the results been reproduced?: [] YES / [x] NO

* If yes, by whom (add if multiple):

- name
- address
- affiliation
- e-mail

Data storage fact sheet (29/2/16)

% Data Storage Fact Sheet (versie 29 februari 2016)
% Data Storage Fact Sheet <Phd Annick De Paepe, Chapter 5,
Experiment 1>
% Author: Annick De Paepe
% Date: 29/02/2016

1. Contact

1a. Main researcher

- name: Annick De Paepe
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Annick.DePaepe@Ugent.be

1b. Responsible ZAP (if different from the main researcher)

- name: Geert Crombez
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Geert.Crombez@UGent.be

If a response is not received when using the above contact details, please send an email to data-ppw@ugent.be or contact Data Management, Faculty of Psychology and Educational Sciences, Henri Dunantlaan 2, 9000 Ghent, Belgium.

2. Information about the datasets to which this sheet applies

* Reference of the publication in which the datasets are reported:
- De Paepe, A.L. (2016). What's coming near? The influence of dynamical visual stimuli on nociceptive processing. PhD dissertation, Chapter 5, Experiment 1.

* Which datasets in that publication does this sheet apply to?:
All datasets reported in the publication.

3. Information about the files that have been stored

3a. Raw data

* Have the raw data been stored by the main researcher? [] YES / [] NO

If NO, please justify:

* On which platform are the raw data stored?

[] researcher PC
[] research group file server
[] research group file server via DICT
[] responsible ZAP PC

- * Who has direct access to the raw data (i.e., without intervention of another person)?
- main researcher
 - responsible ZAP
 - all members of the research group
 - all members of UGent
 - other (specify): ...

3b. Other files

- * Which other files have been stored?
- file(s) describing the transition from raw data to reported results. Specify:
 - R-scripts: - Script_DS_v3.R
 - file(s) containing processed data. Specify:
 - file(s) containing analyses. Specify:
 - Script_DS_v3.R
(R file, running this file gives the results)
 - files(s) containing information about informed consent. Specify: ...
 - a file specifying legal and ethical provisions. Specify: ...
 - file(s) that describe the content of the stored files and how this content should be interpreted. Specify:
 - R-script contains additional information
 - other files. Specify:
- * On which platform are these other files stored?
- individual PC
 - research group file server
 - other: responsible ZAP PC

- * Who has direct access to these other files (i.e., without intervention of another person)?
- main researcher
 - responsible ZAP
 - all members of the research group
 - all members of UGent
 - other (specify): ...

4. Reproduction

- =====
- * Have the results been reproduced?: YES / NO
- * If yes, by whom (add if multiple):
- name
 - address
 - affiliation
 - e-mail

Data storage fact sheet (29/2/16)

% Data Storage Fact Sheet (versie 29 februari 2016)
 % Data Storage Fact Sheet <Phd Annick De Paepe, Chapter 6,
 Experiment 1>
 % Author: Annick De Paepe
 % Date: 29/02/2016

1. Contact

1a. Main researcher

- name: Annick De Paepe
 - address: Henri Dunantlaan 2, 9000 Gent
 - e-mail: Annick.DePaepe@UGent.be

1b. Responsible ZAP (if different from the main researcher)

- name: Geert Crombez
 - address: Henri Dunantlaan 2, 9000 Gent
 - e-mail: Geert.Crombez@UGent.be

If a response is not received when using the above contact details,
 please send an email to data-ppw@ugent.be or contact Data Management,
 Faculty of Psychology and Educational Sciences, Henri Dunantlaan 2,
 9000 Ghent, Belgium.

2. Information about the datasets to which this sheet applies

* Reference of the publication in which the datasets are reported:
 - De Paepe, A.L. (2016). Can far become near? The effect of
 approaching visual stimuli on tactile processing in fibromyalgia
 patients and controls. PhD dissertation, Chapter 6, Experiment 1.

* Which datasets in that publication does this sheet apply to?:
 All datasets reported in the publication.

3. Information about the files that have been stored

3a. Raw data

* Have the raw data been stored by the main researcher? [] YES / []
 NO

If NO, please justify:

* On which platform are the raw data stored?

[] researcher PC
 [] research group file server
 [] research group file server via DICT
 [] responsible ZAP PC

* Who has direct access to the raw data (i.e., without intervention
 of another person)?

[] main researcher
 [] responsible ZAP
 [] all members of the research group
 [] all members of UGent

[] other (specify): ...

3b. Other files

* Which other files have been stored?

- [x] file(s) describing the transition from raw data to reported results. Specify:

- R-scripts:

- FM_transform_v5.R

- vragenlijstenFM.R

- [] file(s) containing processed data. Specify:

- [x] file(s) containing analyses. Specify:

- FM_transform_v5.R

- vragenlijstenFM.R

(R file, running this file gives the results)

- [] files(s) containing information about informed consent.

Specify: ...

- [] a file specifying legal and ethical provisions. Specify: ...

- [x] file(s) that describe the content of the stored files and how this content should be interpreted. Specify:

- R-script contains additional information

- [] other files. Specify:

* On which platform are these other files stored?

- [x] individual PC

- [x] research group file server

- [] other: responsible ZAP PC

* Who has direct access to these other files (i.e., without intervention of another person)?

- [x] main researcher

- [x] responsible ZAP

- [] all members of the research group

- [] all members of UGent

- [] other (specify): ...

4. Reproduction

=====

* Have the results been reproduced?: [] YES / [x] NO

* If yes, by whom (add if multiple):

- name

- address

- affiliation

- e-mail

